Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Influenza virus haemagglutinin

Proprietary Product Name: Afluria Quad

Sponsor: Seqirus Pty Ltd

First round report: March 2017

Second round report: July 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- 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 the Extract from the Clinical Evaluation Report

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

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List of common abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse Event
AESIs	Adverse Events of Special Interest
ASA	Australian Specific Annex
CBER	Center for Biologics Evaluation and Research
CDC	Centers of Disease Control and Prevention
CHMP (CPMP)	Committee for Medicinal Products for Human Use
CI	Confidence Interval
FAS	Full analysis sample
FDA	Food and Drug Administration
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GMFIs	Geometric Mean Fold Increases
GMR	Geometric mean ratio
GMTs	Geometric Mean Titres
gp	Group
HA	Haemagglutinin
HAI or HI	Haemagglutination Inhibition
IB	Investigator Brochure
ICH	International Conference on Harmonization
ILI	Influenza like Infection
IM	Intramuscular
ITT	Intention to treat
MEDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
mth(s)	month(s)
NH	Northern Hemisphere
PI	Prescribing Information
PI	Product Information
PP	Per protocol
PT	Preferred Term
QIV	Quadrivalent inactivated Influenza Vaccine
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SCF	Seroconversion Factor
SD	standard deviation
SH	Southern Hemisphere
SOC	System Organ Class
SPR	Seroprotection Rate
TDOC	sodium taurodeoxycholate
TIV	Trivalent Inactivated Influenza Vaccine
TRAE	treatment-related adverse event
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
yrs	years

1. Submission details

1.1. Submission type

The application for the registration of Seqirus' (previously named bioCSL) inactivated Quadrivalent Influenza Vaccine (Afluria Quad) for use in adults that are ≥18 years was submitted to TGA 6 October 2015 and approved 15 July 2016 (AUST R 262428). This application (PM-2016-03542-1-2) seeks to register Afluria Quad (extension on indication) for the proposed indication of active immunisation against influenza disease caused by influenza virus subtypes A and type B present in the vaccine, in persons ≥5 years of age that is, extend the indication to the age gp 5-17 years of age.

The suspension for injection includes four inactivated, split influenza virus strains (15/15/15/15µg (total 60µg)) per 0.5 mL, suspension for injection, pre-filled Syringe), two type A strain subtypes and two type B strains from separate lineages as recommended by the Australian Influenza Vaccine Committee for that season.

This dossier includes a pivotal Phase III randomised, multicentre, double blinded study to evaluate the immunogenicity and safety of Afluria Quad in comparison with a US-licensed Quadrivalent Influenza Vaccine (QIV) comparator (Fluarix Quadrivalent, GSK) in persons 5 to <18 years (Study CSLCT-QIV-13-02). The US licensed comparator QIV (Fluarix Quadrivalent, GlaxoSmithKline Vaccines) used, has been registered in Australia (Fluarix Tetra).

In addition, one supporting clinical study report (Study CSLCT-USF-10-69) was submitted, this study evaluated the safety and tolerability of Seqirus' trivalent Influenza Vaccine (TIV) in children 5 to <9 years of age. Also contained is an Addendum to the study report from the pivotal clinical trial with QIV in adults aged 18 years and older, Study CSLCT-QIV-13-01.

The 2010 formulation of Fluvax trivalent influenza vaccine (manufactured by Seqirus Pty Ltd) was associated with increased reports of febrile convulsions in children younger than 5 years. In order to provide background and context regarding the current application to seek the paediatric indication of 5 to <18 years, information relating to the use of Seqirus's TIV in children has been included: A summary of the 2010 Southern Hemisphere reports of fever and febrile seizures in children receiving TIV in Australia and New Zealand and the company's scientific investigations into these adverse events; Results from the Phase IV safety and tolerability study in children aged 5 to <9 years receiving TIV manufactured with the B strain split with 1.5% w/v TDOC (CSLCT-USF-10-69); A summary of results from earlier historical clinical safety studies in children aged 6 months to <18 years receiving TIV.

Subsequent to the submission of the Pre-submission Planning Form, the sponsorship of Afluria Quad was transferred from CSL Limited to Seqirus Pty Ltd. A notification of change to sponsorship was submitted to TGA on 10 October 2016. At the time of this submission the sponsor listed in the ARTG entry for Afluria Quad (AUST R 262428) had not yet been updated.

1.2. Drug class and therapeutic indication

This is an inactivated quadrivalent influenza vaccine containing influenza haemagglutinin antigens: Type A (H1N1)-like virus; Type A (H3N2)-like virus; Type B (Victoria lineage) and Type B (Yamagata lineage). The potency of the vaccine is expressed as the concentration of HA antigen, although neuraminidase antigen is also present. The target concentration is 15 mcg HA per strain.

1.3. Dosage forms and strengths

Afluria Quad is a quadrivalent influenza vaccine (split virion, inactivated) consisting of a clear, aqueous suspension packed in pre-filled syringes each containing 0.5 mL. The vaccine contains predominantly HA of four strains (2 x 'A'; 2 x 'B') of influenza virus.

1.4. Dosage and administration

Single 0.5mL dose annually intramuscularly (IM), or by deep subcutaneous injection, for the prevention of influenza caused by Influenza Virus, Types A and B in persons aged ≥5 yrs. Previously unvaccinated children 5 to < 9 years of age should be given 2 doses at least 4 weeks apart.

2. Background

2.1. Information on the condition being treated

Influenza, a respiratory orthomyxovirus, is a seasonal infectious disease that occurs in epidemics throughout the northern and southern hemisphere 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 (Fiore; Rothberg). During influenza epidemics, there is an increased mortality risk among older adults (age >65 yrs), people with chronic diseases, and very young children (age 0 to 12 months), as well as an increase in morbidity and hospitalisation because of influenza-associated complications (Fiore; Monto).

Influenza A and B cause most of the human disease. Influenza A viruses are divided into subtypes based on two viral external proteins, the haemagglutinin (HA) and the 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.

The influenza A or B surface glycoprotein HA is the key antigen involved in attachment of the virus to receptors on respiratory epithelial cells, whereas the NA glycoprotein is involved in release of the virus from the cell surface. During infection, the virus stimulates production of antibodies in the serum (immunoglobulin G) and nasal secretions (immunoglobulin A) to these surface glycoproteins. High levels of virus type-specific antibodies are associated with protection from disease due to infections with homologous and closely related influenza virus trains (Hay; Fiore). Novel influenza strains arise from antigenic drift due to point mutation and recombination events that occur during viral replication. These events result in the 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 (Hay).

Influenza type A is capable of major antigenic shifts when a novel HA emerges from re-assortment with an animal influenza virus. Influenza B undergoes less rapid antigenic drift that is, is generally more stable, than influenza A. When a new subtype of influenza virus emerges, all individuals are susceptible to infection except those who have lived through earlier epidemics with a related virus subtype. Infection produces immunity to the specific virus; however, the

length and extent of immunity is dependent on the degree of antigenic shift, the number of previous infections, and the immune status of the individual (Beyer).

Influenza epidemics have been associated with the circulation of type A/H3N2, type A/H1N1,

and type B viruses, either individually or together. Two genetically distinct lineages of influenza B viruses have co-circulated since 1985 (Rota). The burden of infection is largely on school age children, young adults, and the elderly (Belse). In the US, B viruses account for 24% of positive specimens and 34% of reported paediatric influenza deaths (Ambrose), however the incidence can vary dramatically between influenza seasons (range 1%-60%). The burden of influenza B appears to be the highest for children and young adults with a relative high incidence as compared to the type A strains (Grant; Olson). Influenza B causes morbidity and mortality in all age groups, however in children it appears to be a disproportionate cause of influenza related hospitalizations and deaths compared to the type A strains (Thompson).

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 trivalent 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 (Belshe). 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 2003-2004 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 lab-confirmed influenza B samples were of the lineage not included in the vaccine (Ambrose). 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.

2.2. Current treatment options

According to the WHO vaccination is the most effective way to prevent influenza and its complications and is the key public health approach in most countries around the world, including Australia. Prevention of influenza illness is achieved by annual prophylactic immunisation, the exact composition of which changes according to what are predicted to be the predominant A and B strain(s) circulating in either the Northern or Southern Hemispheres for that influenza season. In Australia, annual influenza vaccination is currently recommended for any person ≥ 6 months of age who wishes to reduce the likelihood of becoming ill with influenza, as well as a range of co-morbid conditions that place persons at risk of complications from influenza infection.

2.3. Clinical rationale

Influenza is a highly infectious disease that occurs in epidemics throughout the Northern Hemisphere (NH) and Southern Hemisphere (SH) winter months. Trivalent inactivated and live attenuated influenza vaccines have been the mainstay of influenza prevention. Each year in Australia, influenza infection affects ~5-10% of the general population, up to 20% in some years. Among Australian patients aged ≥50 years, influenza is annually associated with >3,000 deaths and >13,500 hospitalisations. Two genetically distinct lineages of influenza B viruses have co-circulated since 1985 (Rota). On average, influenza B strain accounts for approximately 25% of positive specimens in the US (Ambrose).

The burden of infection due to influenza B is largely school age children, young adults and the elderly; however, young children experience the highest mortality with 34% of reported paediatric influenza deaths in the US due to B strain infections (Belshe). Mismatches between the B strain in the vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons (Belshe). The US Centers for Disease Control and Prevention has estimated that in a season where there is a B strain mismatch, availability of QIVs could have reduced annual influenza cases (range: 2200–970,000), hospitalisation's (range: 14–8200), and deaths (range: 1–485) in the US (Reed). These findings are similar in Australia whereby data collected from 2000 to 2011 revealed poor matches with the recommended vaccine virus and the circulating B-lineage virus in 4 of the 12 years reviewed, and partial matches in 3 out of 12 influenza seasons (Barr).

The avoidance of this B strain mismatch has been one of the main drivers of the development of (and approval) of quadrivalent vaccines with representative strains of both major B strain lineages. While Afluria Quad is now approved for use in those aged 18 years and older, this application seeks to extend the indication to children aged 5 years or older, in order to minimise the effects of "B' strain mismatch in the annual vaccine, and the morbidity and mortality costs associated with this mismatch when it does occur.

2.4. Formulation

2.4.1. Formulation development

The vaccine is a clear to slightly opaque liquid containing some sediment which readily resuspends upon shaking and meets the requirements of the harmonized British Pharmacopoeia Volume IV Immunological Products Vaccines *Inactivated Influenza Vaccine (Split Virion)* and European Pharmacopeia Monograph 0158 *Influenza Vaccine (Split Virion, Inactivated)*.

The manufacturing process for QIV has been based on the process used for the manufacture of Trivalent Influenza Vaccine (TIV, Fluvax) and involves the combination of four influenza virus strains and Vaccine Diluent in suitable proportions to ensure a minimum concentration of 30 mcg/mL of the influenza virus antigen, haemagglutinin (HA), is present per strain.

The formulation process for QIV is consistent with that of TIV. The only exception is that QIV involves the combination of four rather than three influenza virus strains with Vaccine Diluent in suitable proportions to ensure a minimum concentration of 30 mcg/mL of the influenza virus antigen, haemagglutinin (HA), per strain.

This is a purified, inactivated, split virion (split virus) vaccine. Each 0.5 mL dose contains antigens for the 2017 influenza season representative of the following types:

- A/Singapore/GP1908/2015 (A/Michigan/45/2015 (H1N1) – like):15 µµg HA per dose;
- A/Hong Kong/4801/2014 (NYMC X-263B) (A/Hong Kong/4801/2014 (H3N2) – like):15 µg HA per dose;
- B/Phuket/3703/2013 (B/Phuket/3073/2013- like):15 µg HA per dose;
- B/Brisbane/46/2015 (B/Brisbane/60/2008 - like): 15 µg HA per dose.

2.4.2. Excipients

All excipients used in the manufacture of QIV are in compliance with the BP and/or Ph. Eur. and/or USP monographs.

2.5. Guidance

At pre-submission meetings held with the TGA during 2016, the sponsor discussed that data from a supportive TIV safety study (CSLCT-USF-10-69) would be included in this application. CSLCT-USF-10-69 is a Phase IV safety and tolerability study, with the primary objective to evaluate the frequency and intensity of fever in children aged 5 to <9 yrs in the 7 days after each administration of the NH 2014-2015 influenza season. This study was felt to be relevant and informative to the paediatric clinical development program for Afluria Quad, as during the SH 2010 season, there was an unexpected increase in severe fever and fever related events observed in the paediatric population, increased reports of fever events were also observed in children aged 5 to <9 yrs. Following the conclusion of the scientific investigations into the 2010 adverse events, it was thought that modification of the splitting conditions of the B strain by increasing the concentration of the splitting agent TDOC may reduce the potential for pyrogenic vaccine responses. Therefore before initiating the Afluria Quad development program in persons aged less than 18 yrs, Study CSLCT-USF-10-69 was conducted to gather a contemporary fever rate in this age group, using the NH US licensed 2014-2015 Seqirus TIV formulation where the B strain was split with a higher concentration of TDOC.

As the Afluria Quad clinical development program for the adult and paediatric studies are closely related, the paediatric clinical information from Studies CSLCT-QIV-13-02 and CSLCT-USF-10-69 have been integrated into the previously submitted and approved clinical overview and summary modules. Subsections have been created within these modules to include information from Study CSLCT-QIV-13-02 and CSLCT-USF-10-69 and existing headings amended to differentiate between the adult and paediatric sections, as required. Seqirus has also updated the section within the Clinical Overview regarding clinical lot-to-lot consistency rationale for Afluria Quad. This section now provides further explanation and clarity about demonstration of the lot-to-lot consistency for Afluria Quad, including demonstration of lot-to-lot consistency of the immune response from clinical Study CSLCT-QIV-13-01, as well a summary of the number of influenza vaccine lots assessed over several seasons and influenza virus strains in the QIV development program.

Seqirus also recently received approval from the TGA (14 November 2016) to amend the Confidence Interval (CI) interval results for Study CSLCT-QIV-13-01 (conducted in adults) listed under the Clinical Trials section of the approved Afluria Quad Product Information (PI). This minor amendment was in response to a request by the US FDA during their recent evaluation of Afluria Quad to recalculate the non-inferiority post-vaccination geometric mean titre results and 95% CI using exact methods for the difference in seroconversion rates. Although these changes have no impact on the immunogenicity results of the Study CSLCT-QIV-13-01 or any change to the overall study conclusions, the sponsor has taken the opportunity to align the tables and figures with the TGA approved PI amendment for completeness.

2.6. Evaluator's commentary on the background information

This background information provides the rationale for this product including why the sponsor is seeking extension of its use to children aged 5 yrs or older.

2.7. Scope of the clinical dossier

The submission contained the following clinical information:

- CSLCT-QIV-13-02: A Phase III, Randomised, Multicentre, Observer-Blinded, Non-inferiority Study to Evaluate the Immunogenicity and Safety of a bioCSL Quadrivalent Inactivated Influenza Virus Vaccine (bioCSL QIV) with a US-Licensed 2015-2016 Quadrivalent Inactivated Comparator Influenza Vaccine (Comparator QIV) in a Paediatric Population 5 Through 17 Years of Age;

- CSLCT-USF-10-69: A Phase IV, Multicentre, Randomised, Observer-blind, Parallel-arm Study to Evaluate the Safety and Tolerability of CSL's Influenza Virus Vaccine in Children 5 to Less Than 9 Years of Age;
- Validation (by Focus Diagnostics, Inc) of the Haemagglutination Inhibition (HAI) Test for Titrating Influenza A and B Specific Antibodies (TSOP.119.057) – [CSL: 2015-2016 Vaccine Strains that is, A/California/7/2009 (H1N1) A/South Australia/55/2014 (H3N2),B/Phuket/3073/2013, B/Brisbane/60/2008;
- Addendum to clinical study report CSLCT-QIV-13-01 (A Phase III, Randomised, Multicentre, Double-Blinded Study to Evaluate the Immunogenicity and Safety of Quadrivalent Influenza Vaccine (CSL QIV) in Comparison with a US Licensed 2014-15 Trivalent Influenza Vaccine (CSL TIV-1), and a Trivalent Influenza Vaccine Containing the Alternate B Strain (CSL TIV-2), in Adults Aged 18 years and Above. This report is not directly relevant to this application. This addendum is to report responses to requests dated 20 May 2016 by the US FDA CBER for information additional to that in the final Clinical Study Report (CSR) for Study CSLCT QIV 13 01 dated 16 July 2015.

In summary:

- The non-inferiority post-vaccination geometric mean titre (GMT) analysis results of the CSR have been updated using the model specified in the Statistical Analysis Plan (SAP), namely: Log-transformed Post-vaccination HI Titre = Vaccine + Age Gp [18-49, 50-64, 65-74, ≥75] + Sex + Vaccination History [y/n] + Log-transformed Pre-vaccination HI Titre + Site. The model specification noted above excludes the non-significant age-by-vaccine interaction term.
- Exact 95% CIs for the difference in seroconversion rates (SCRs) have been recalculated using exact methods as specified in the SAP. In addition, the table footnote regarding the method of computing the CI for the difference in SCR has been revised to read: "The exact 95% CI for the difference in seroconversion rates between CSL TIV and CSL QIV based upon the binomial distribution." As a consequence of these recalculations, the SCR results have also been updated.
- The recalculated results have no discernible impact on the non-inferiority of bioCSL QIV vs. bioCSL TIV in terms of Geometric Mean Titre (Adjusted GMT Ratios) in Adults Aged ≥18 Years (Per-Protocol Population)] and non-inferiority of bioCSL QIV vs. bioCSL TIV in terms of Seroconversion Rates (%) in adults aged ≥18 years for each Strain (Per-Protocol Population)]. There is no impact on any other immunogenicity results or any change to the overall conclusions of the study. These data will not be discussed further in this Application as they are not of direct relevance.

2.8. Paediatric data

This application seeks to extend the indication for use of Afluria Quad to children aged 5 years or older.

2.9. Good clinical practice

Approvals to undertake the clinical studies were obtained from appropriately constituted institutional ethics committees/independent research boards, in accordance with the relevant national guidelines and regulations applicable. The studies presented in this Application were conducted in accordance with GCP.

2.10. Evaluator's commentary on the clinical dossier

The main objectives of the quadrivalent paediatric clinical development programme was to demonstrate that the candidate QIV was immunogenic and safe in children aged 5-17 yrs of age.

3. Pharmacokinetics

With respect to the nature of the product, clinical pharmacology data have not been assessed. The split virion, inactivated influenza vaccine, as all vaccines, induces antibodies, which consecutively are responsible for the desired effect of the intervention, that is, protection against an infectious disease. The constituents of the vaccine itself are phagocytosed at the site of injection. Therefore, specific interaction or PK studies have not been carried out in man.

4. Immunogenicity

Efficacy and safety data arising from the pivotal study (CSLCT-QIV-13-02) is summarised below.

4.1. Overall conclusions on immunogenicity

See section 6. Efficacy (immunogenicity)

5. Dosage selection for the pivotal studies

The dose of Afluria Quad used in the pivotal paediatric study was the same as that approved for use in adults aged 18 yrs or older that is, single dose of 0.5mL IM. For previously unvaccinated children aged 5 to < 9 years, the recommended dosage is two doses at least four weeks apart.

6. Efficacy (immunogenicity)

The pivotal paediatric Study CSLCT-QIV-13-02 not an 'efficacy' study, rather the derived immunogenicity data is used as a surrogate for clinical efficacy. This is a standard approach in influenza vaccine studies. The study was designed according to the Guideline on Clinical Evaluation of New Vaccines.[1] Anti-haemagglutinin (HA) antibody response is an established correlate of protection against influenza in adults and children; therefore, HI titre was the primary outcome measure in this study.

In accordance with the guidelines indicated by EMA:

- Any HI result <10 (=undetectable);
- Sera which have a titre >=10 but <40 are considered positive but not protective;
- Sera with a titre >=40 are considered positive and protective.

6.1. Studies providing evaluable efficacy data

The pivotal Study CSLCT-QIV-13-02 provides indirect evidence of 'efficacy' through serological responses to the vaccine which have been determined, over time, and from multiple sources, to have clinical efficacy either in protecting against influenza acquisition or attenuating the course of the infection if infection is not completely prevented through vaccination.

[1] EMEA/CHMP/VWP/164653/2005

6.2. Pivotal or main efficacy studies

6.2.1. CSLCT-QIV-13-02

A Phase III, randomised, multicentre, observer-blinded, non-inferiority study to evaluate the immunogenicity and safety of a bioCSL quadrivalent inactivated influenza virus vaccine (bioCSL QIV) with a US-licensed 2015-2016 quadrivalent inactivated comparator influenza vaccine (comparator QIV) in a paediatric population 5 through 17 years of age.

6.2.1.1. Study design, objectives, locations and dates

Sponsor: bioCSL Pty Ltd.

Study design: Randomised, observer-blinded, comparator controlled study of bioCSL QIV, administered IM (into deltoid region), vs. a US-licensed 2015-2016 comparator QIV containing the same influenza strains recommended by the US FDA and the Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the 2015-2016 season. The study was conducted during the 2015-2016 NH influenza immunisation season in male/female subjects 5 to17 yrs of age. Randomisation stratified by age that is, Cohort A = subjects 5 - 8 yrs of age; Cohort B = subjects 9 - 17 yrs of age. Quota applied to ensure ≥50% were in the younger age gp (Cohort A).

Primary objective(s): To demonstrate that vaccination with bioCSL QIV elicits a non-inferior immune response to that of the comparator QIV containing the same virus strains as bioCSL QIV, among a paediatric population aged 5 to 17 yrs.

The immunogenicity of study vaccines was assessed 28 days after the last vaccine administration by measuring the HI antibody titres to the four viral strains included in the vaccine. The non-inferiority of bioCSL QIV vs. the comparator QIV was assessed by the 8 co-primary endpoints of HI geometric mean titre (GMT) and seroconversion rate (SCR) for each viral strain included in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain;
- The GMT ratio for the A/ H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);
- The difference between the SCRs** for the A/H1N1 strain;
- The difference between the SCRs for the A/H3N2 strain;
- The difference between the SCRs for the B strain (Yamagata lineage);
- The difference between the SCRs for the B strain (Victoria lineage).

* GMT ratio =geometric mean of the post-vaccination (28 days after last vaccination) HI titre for the US-licensed comparator QIV over the geometric mean of the post-vaccination HI titre for bioCSL QIV.

** Rate of seroconversion = percentage of subjects with a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or pre-vaccination HI titre ≥1:10 and a ≥4-fold increase in post-vaccination HI titre.

Secondary objective(s): To assess safety and tolerability of bioCSL QIV, among children aged 5 - 17 yrs in two age strata: 5 - 8 yrs of age, and 9 -17 yrs of age, as well as overall that is,

1. Safety assessed as the frequency and severity of:

- Solicited local adverse reactions (AR) and systemic adverse events (AEs) for 7 days after each vaccination dose;
- Cellulitis-like reaction for ≥28 days after each vaccination dose;

- Unsolicited AEs for ≥28 days after each vaccination dose;
- Serious Adverse Events (SAE) for 180 days after last vaccination dose;

2. To characterise the immunogenicity of bioCSL QIV and the comparator QIV in the two age strata, and overall. Immunogenicity assessed by: Serum HI antibody titres against the 4 influenza vaccine strains used to calculate:

- GMTs: Geometric mean of HI titres pre-vaccination (Day 1) and post-vaccination (Exit Visit);
- SCRs: % with a pre-vaccination HI titre <1:10 and a post-vaccination HI titre ≥1:40 or pre-vaccination titre ≥1:10 and a ≥4-fold increase in post-vaccination titre;
- The % with a titre ≥40 (seroprotection rates) at Day 1 and at Study Exit Visit;
- Geometric mean fold increase (GMFI)**: the geometric mean fold titre rise from Day 1 to Study Exit Visit

**GMFI in antibody titre = geometric mean of the fold increase of post-vaccination HI antibody titre over the pre-vaccination HI antibody titre.

Exploratory objectives:

1. To explore associations between any severe grade fever (and other solicited systemic AEs), after bioCSL QIV or the comparator QIV by vaccine dose and baseline characteristics;

2. To explore associations between immune response after bioCSL QIV or the comparator QIV by vaccine dose and baseline characteristics.

Locations: n=32 sites in the US

Dates: Date of first enrollment: 14 Sep 2015; Date of last visit: 13 Jun 2016.

Protocols: Version 1.0 14 May 2015; Amendment 1, version 2.0 05 Aug 2015.

6.2.1.2. Inclusion and exclusion criteria

Key Inclusion Criteria: 1. Males or females 5 - 17 yrs of age on the day of first study vaccination; 2. Parent or legally acceptable representative able to provide written informed consent and willing and able to adhere to all protocol requirements including blood draws and ability to use a Smartphone or computer to complete the eDiaries. Participant assent was also obtained if required by the applicable IRB; 3. Subject in generally good health; 4. If applicable, females of "childbearing potential" must have been abstinent or willing to use a medically accepted contraceptive regimen until ≥28 days after the last Study Vaccine. Girls under <12 years of age who had not had their first period could be considered "not of childbearing potential". Females of childbearing potential must have returned a negative urine pregnancy test result, prior to any vaccination dose with the study vaccine.

Key Exclusion Criteria: 1. History of allergic reactions to egg proteins or any components of the Study Vaccines; 2. History of serious adverse reactions to any influenza vaccines; 3. History of Guillain-Barré syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis; 4. History of licensed influenza vaccination in the last 6 months; 5. Have clinical signs of active infection and/or an oral temperature of ≥100°F (37.8°C) on the day of vaccination or within 48 hrs preceding vaccination; 6. History of any seizures, with the exception of a single febrile seizure; 7. Self-reported or known seropositivity suggestive of acute or chronic viral infection for HIV, hepatitis B or hepatitis C; 8. Known or suspected congenital or acquired immunosuppressive conditions; 9. Current or recent immunosuppressive or immunomodulatory therapy; 10. History of previous or current malignant neoplasms; 11. Administration of immunoglobulin and/or any blood products within the 3 months preceding vaccination, or planned administration during the study; 12. Vaccination with a licensed vaccine 28 days (for live or inactivated vaccines) prior to receiving the first dose of Study Vaccine, or

plans to receive any licensed vaccine prior to the Study Exit Visit; 13. Pregnant or lactating females.

6.2.1.3. Study treatments

Test Product, Dose and Mode of Administration: A single 0.5 mL dose of bioCSL QIV in a pre-filled needleless syringe given IM into the deltoid region of the arm. Each 0.5 mL dose contains 15 mcg HA from each of the following 4 influenza strains (recommended by the FDA's VRBPAC for the 2015-2016 influenza season in the US), all 4 strains were split at the upper levels of TDOC concentration (1.5% w/v):

- 15 mcg per 0.5 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
- 15 mcg per 0.5 mL dose A/Switzerland/9715293/2013 (H3N2)-like virus;
- 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage);
- 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage).

Reference Therapy, Dose and Mode of Administration: The US-licensed Comparator QIV (Fluarix quadrivalent), inactivated, split-virion, thimerosal-free, QIV, administered as one 0.5 mL IM dose into the deltoid muscle. Each 0.5 mL dose contains 15 mcg HA from each of the following 4 influenza strains (VRBPAC recommended for the 2015-2016 influenza season in the US):

- 15 mcg per 0.5 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
- 15 mcg per 0.5 mL dose A/Switzerland/9715293/2013 (H3N2)-like virus;
- 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage);
- 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage).

6.2.1.4. Efficacy variables and outcomes

Randomised using 3:1 allocation ratio to bioCSL QIV or Fluarix QIV. Stratified by age.

Study procedures: Subjects scheduled to single vaccination (Figure 1) or two-vaccination regimen (Figure 2) as clinically indicated. Overall study duration = maximum of 10 months.

Figure 1: One vaccination schedule of visits in CSLCT-QIV-13-02

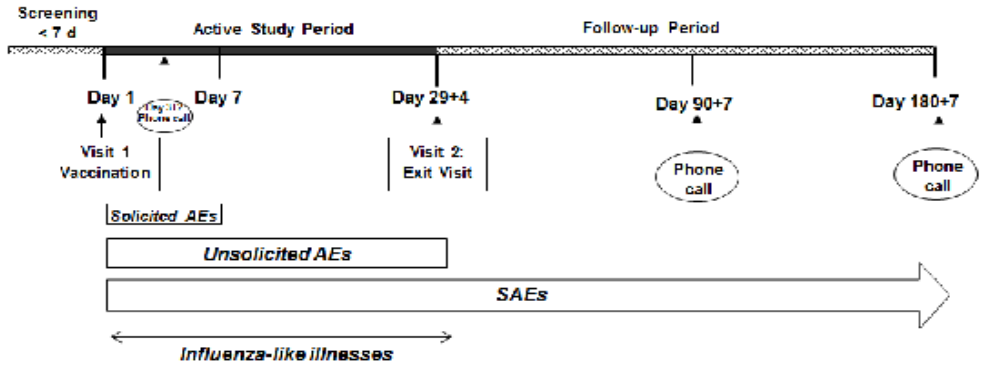


Figure 2: Two vaccination schedule of visits in CSLCT-QIV-13-02

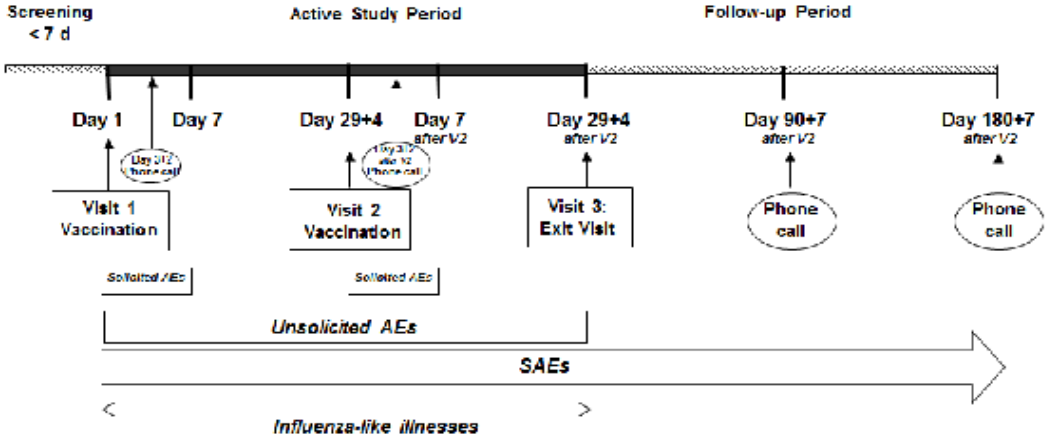


Figure 3: Schedule of assessments for participants receiving one dose of vaccine

Assessment		Visit 1	Phone call	Visit 2	Phone call	Phone call
	Pre-Study	Vaccination	Diaries Reminder	Exit Visit	SAE Follow-up	SAE Follow-up
	Day -7 to -1	Day 1	Day 3 ± 2	Day 29 ± 4	Day 90 ± 7	Day 180 ± 7
Invitation to participate	✓[1]					
Informed consent and assent *(where applicable)*	✓[1]					
Demographics and influenza vaccination history	✓[1]					
Medical history and baseline medication use	✓[1]					
Targeted physical examination *(if necessary)*	✓[1]			✓		
Body weight[3] and oral temperature		✓				
Urine pregnancy test [2]		✓		✓		
Review of eligibility criteria		✓				
Blood sample for immunogenicity testing		✓		✓		
Vaccination		✓				
Provision of study supplies and instructions		✓				
Solicited Diary review			✓	✓		
Unsolicited/Concomitant Medications Diary review				✓		
Telephone contact			✓		✓	✓
Assessment for cellulitis-like reaction, influenza-like illness *(if applicable)* [3]		←	✓	→		
Review of adverse events and concomitant medications		←	✓	→		
Review of SAEs *(if applicable)*		←	✓	→		

[1] These could be performed on or up to 7 days before the day of vaccination. [2] Female subjects of child bearing potential only. [3] Elevated oral temperature of ≥ 100.4°F (≥ 38.0°C) (or a clear history of fever/chills), and at least one flu-like symptom (including sore throat, cough, wheezing, myalgia, headache, malaise, rhinitis, dyspnea, nausea and vomiting).

Figure 4: Schedule of assessments for participants receiving two doses of vaccine

Assessment		Visit 1	Phone call	Visit 2	Phone call	Visit 3	Phone call	Phone call
	Pre-Study	Vaccination	Diaries Reminder	Vaccination	Diaries Reminder	Exit Visit	SAE Follow-up	SAE Follow-up
	Day -7 to -1	Day 1	Day 3 ± 2	Day 29 ± 4	Day 3 ± 2 after 2nd dose	Day 29 ± 4 after 2nd dose	Day 90 ± 7 after 2nd dose	Day 180 ± 7 after 2nd dose
Invitation to participate	✓[1]							
Informed consent and assent *(where applicable)*	✓[1]							
Demographics and influenza vaccination history	✓[1]							
Medical history and baseline medication use	✓[1]							
Targeted physical examination *(if necessary)*	✓[1]			✓		✓		
Body weight[3] and oral temperature		✓		✓				
Urine pregnancy test [2]		✓		✓		✓		
Review of eligibility criteria		✓						
Blood sample for immunogenicity testing		✓				✓		
Vaccination		✓		✓				
Provision of study supplies and instructions		✓		✓				
Solicited Diary review			✓	✓	✓	✓		
Unsolicited/Concomitant Medications Diary review			✓	✓	✓	✓		
Telephone contact			✓		✓		✓	✓
Assessment for cellulitis-like reaction, influenza-like illness *(if applicable)* [3]		←	✓	→				
Review of adverse events and concomitant medications		←	✓	→				
Review of SAEs *(if applicable)*		←	✓	→				

Could be performed on or up to 7 days before the day of vaccination. [2] Female subjects of child bearing potential only. [3] Elevated oral temperature of ≥ 100.4°F (≥ 38.0°C) (or a lear history of fever/chills), and at least one flu-like symptom (including sore throat, cough, wheezing, myalgia, headache, malaise, rhinitis, dyspnea, nausea and vomiting).

Figures 3 and 4 show the schedule of assessments for subjects receiving a single or two doses of vaccine. Serological specimens were provided before first vaccination and after last vaccination. Parents/guardians recorded the occurrence of a prespecified series of local and systemic symptoms and temperature that might occur between Day 1 and Day 7 following each indicated vaccine dose in a Solicited eDiary. Any unsolicited AEs and concomitant medication use that occurred between Day 1 and the Study Exit Visit were recorded in an Unsolicited /Concomitant Medications eDiary. Subjects returned to the clinic on Day 29 following each indicated vaccine dose, for a targeted physical examination as clinically indicated, and a urine pregnancy test (if appropriate). During this visit the Solicited eDiary for Dose 1 was reviewed with the subjects, and unsolicited AEs and concomitant medications recorded reviewed and reported for the active study period (Visit 1 to Exit Visit). For one dose subjects, Visit 2 (Day 29+4) =Exit Visit. For the two-dose subjects, Visit 3 = Exit Visit. SAEs collected via a telephone call made ≥90 days after last vaccination dose and another call at 180 days after last vaccination dose.

6.2.1.5. Randomisation and blinding methods

Randomisation: via IRT to one of the 2 treatment groups in a 3:1 ratio (bioCSL QIV: QIV Comparator) and proportionally balanced in the two age strata (5 - 8 yrs and 9 - 17 yrs), with ≥50% in the 5 - 8 yrs age stratum.

Blinding: Investigational site staff, including the investigator and all personnel performing study assessments, was blinded to treatment allocation (observer-blind). The subject and parent/ guardian were also blinded to treatment allocation. As there is a visual difference between the bioCSL QIV and the Comparator QIV pre-filled syringes, personnel who prepare and administer the Study Vaccine were considered unblinded and excluded from involvement in other study procedures, with the exception of other study vaccine related activities, such as receipt, preparation and accountability management.

6.2.1.6. Analysis populations

- Full Analysis Set = all subjects whose parent(s) / guardian(s) gave informed consent and who were randomised.
- Overall Safety Population = all in the FAS who received ≥1 dose or partial dose of study vaccine and provided any evaluable follow-up safety data.
- Solicited Safety Population = all in the FAS who received ≥1 dose or partial dose of Study Vaccine and provided any evaluable data on solicited events.
- Solicited Safety Population after the First Vaccination = all randomised subjects who received the first vaccination and provided any evaluable data on solicited events after 1st vaccination.
- Solicited Safety Population after the Second Vaccination = all randomised subjects who received the 2nd vaccination and provided safety data on solicited events after 2nd vaccination.
- The Evaluable Population for immunogenicity analyses = all in the FAS who received vaccine at Visit 1, provided serology specimens which provided valid serology assay results from both Visit 1 and the Study Exit Visit (Visit 2 or 3), did not experience a lab-confirmed influenza illness between Visit 1 and the Study Exit Visit (Visit 2 or 3), and did not receive any prohibited medication during the study medically assessed as potentially impacting on immunogenicity.
- The Per-Protocol Population = all in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity.

6.2.1.7. Sample size

Designed to achieve at least 80% power to demonstrate non-inferiority for all of the 8 co-primary endpoints, seroconversion rates for 4 strains, and GMT for 4 strains using a one-sided alpha of 0.025 for each comparison in paediatric subjects from 5 -17 yrs of age. No adjustment for multiple endpoints made. For comparisons of SCRs, a non-inferiority margin of 10% (Comparator QIV - bioCSL QIV) was employed. It was assumed that the SCR for all strains for bioCSL QIV is 50% and that there is no difference between bioCSL QIV and the Comparator QIV. For comparison of GMT ratio, a non-inferiority margin of 1.5 (Comparator QIV / bioCSL QIV, equivalent to a difference on the log scale of 0.405465108) was employed. It was assumed that there is no difference between bioCSL QIV and the Comparator QIV (that is, a ratio of 1, difference on the log scale of 0) and that the SD of log (titre) is 1.4. The treatment randomisation ratio was 3:1 (bioCSL QIV: Comparator QIV). Under these assumptions and with n evaluable = 1500 in the bioCSL QIV gp and 500 in the Comparator QIV gp, the power for 4 GMT ratio endpoints was 99.95% and the power for 4 SCR endpoints was 89.70%. The overall global power of the 8 endpoints was then 89.7% x 99.95% = 89.66%. This provides a total N evaluable = 2000 (with 10% dropouts n=2222). Sample size calculations performed using SAS v9.3 and PASS v12.0.2.

6.2.1.8. Statistical methods

Primary Endpoint: In line with US influenza development guidelines, the immune response elicited by QIV was considered to be non-inferior to the US-licensed comparator QIV if, for each of the four strains the following statistical criteria were met:

- The upper bound of the two-sided 95% CI on the ratio of the GMT titres did not exceed 1.5. The GMT ratio was calculated by GMT Comparator QIV divided by GMT Seqirus QIV.
- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates did not exceed 10 percentage points. The difference in SCR was calculated by GMT Comparator QIV minus GMT Seqirus QIV.

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) was fitted on log-transformed post-vaccination HI titre (titre) as the outcome variable and terms for covariates such as vaccine, age stratum and site to acknowledge the study design and pre-vaccination titre to account for differences in pre-vaccination titres between the two treatment groups, vaccination history, nos. of doses (1 vs. 2) and gender. Potential covariate interaction effects were examined in the fit of the GLM. From the model an adjusted difference in least-square means (on the log scale) was produced with 95% confidence limits. The estimated difference and the confidence limits were back-transformed to obtain an adjusted GMT ratio with 95% confidence limits. Each of the 4 strains analysed separately. The adjusted GMT ratio was the result for which the non-inferiority assessment was based on. The measure of the unadjusted GMT ratio based on post-vaccination GMTs only, is also presented. The PP Population was the primary analysis population for the primary immunogenicity analysis; a supporting analysis was performed using the Evaluable Population according to criteria outlined in the Statistical Analysis Plan (SAP). If all 8 co-primary endpoints fulfilled non-inferiority criteria then overall non-inferiority of bioCSL QIV versus comparator QIV was concluded.

Secondary Immunogenicity Endpoints: Serum HI antibody titres against the 4 influenza vaccine strains were used to calculate:

- GMTs: Geometric mean of HI titres pre-vaccination (Day 1) and post-vaccination (Exit Visit);
- SCRs: % subjects with either a pre-vaccination HI titre <1:10 and a post-vaccination HI titre ≥ 1:40, or a pre-vaccination titre ≥1:10 and a ≥4-fold increase in post-vaccination titre;
- The % subjects with a titre ≥40 (=seroprotection) at Day 1 and at Exit Visit;
- Geometric mean fold increase (GMFI)*: Geometric mean fold titre rise Day 1 to Exit Visit

* GMFI in antibody titre is defined as the geometric mean of the fold increase of post-vaccination HI antibody titre over the pre-vaccination HI antibody titre.

For each treatment gp (each age strata, and overall), summary tables, by strain, presented for: GMT (mean and 95% CIs); seroprotection rates (nos. and % subjects) at Day 1 and Study Exit Visit; SCR (nos. and % subjects at Study Exit Visit); and GMFI (mean and 95% CIs). All secondary immunogenicity endpoint summaries described above presented overall, and by age strata, gender, race, and ethnicity.

Secondary Safety Endpoints: Secondary objectives include assessments of safety and tolerability of both vaccines, as assessed by the proportion of subjects with AEs. AEs monitored post-vaccination that is,

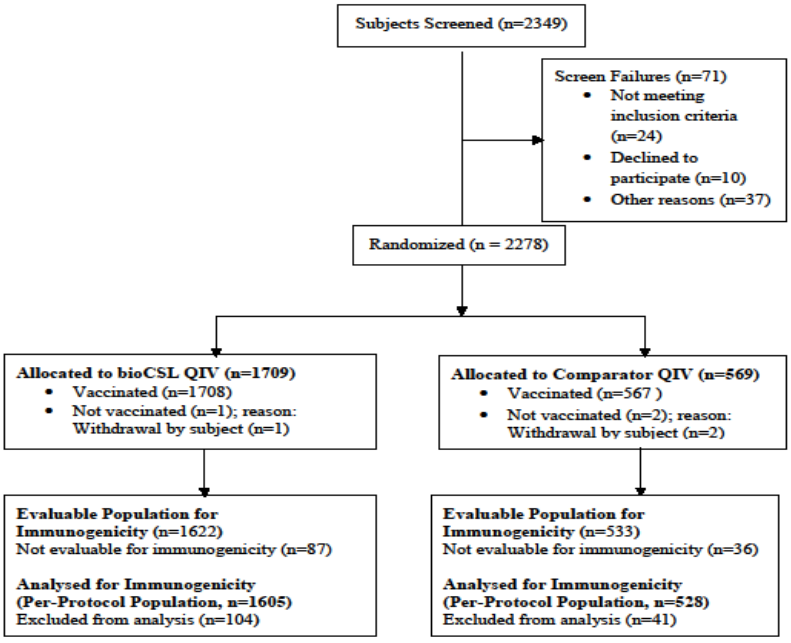
- Solicited local reactions and systemic AEs Days 1-7 inclusive after vaccination;
- Cellulitis-like reaction for ≥28 days after each vaccination dose;
- Unsolicited AEs for ≥28 days after each vaccination dose;
- SAEs for 180 days following last study vaccination dose.

The frequency and intensity of solicited and unsolicited AEs was summarised for each age and treatment gp. The proportion of subjects reporting each type of AE was presented along with percentages and CIs. Solicited local adverse reactions and systemic AEs summarised by frequency, duration and intensity. Unsolicited AEs summarised by body system, intensity and relatedness to Study Vaccine. All summaries presented overall and by maximum intensity. Analyses were made by treatment gp repeated by age strata, gender, race and ethnicity.

6.2.1.9. Participant flow

See below in Figures 5 and 6 for the immunogenicity population and safety population respectively.

Figure 5: Subject Disposition in CSLCT-QIV-13-02 – Evaluable Population for immunogenicity



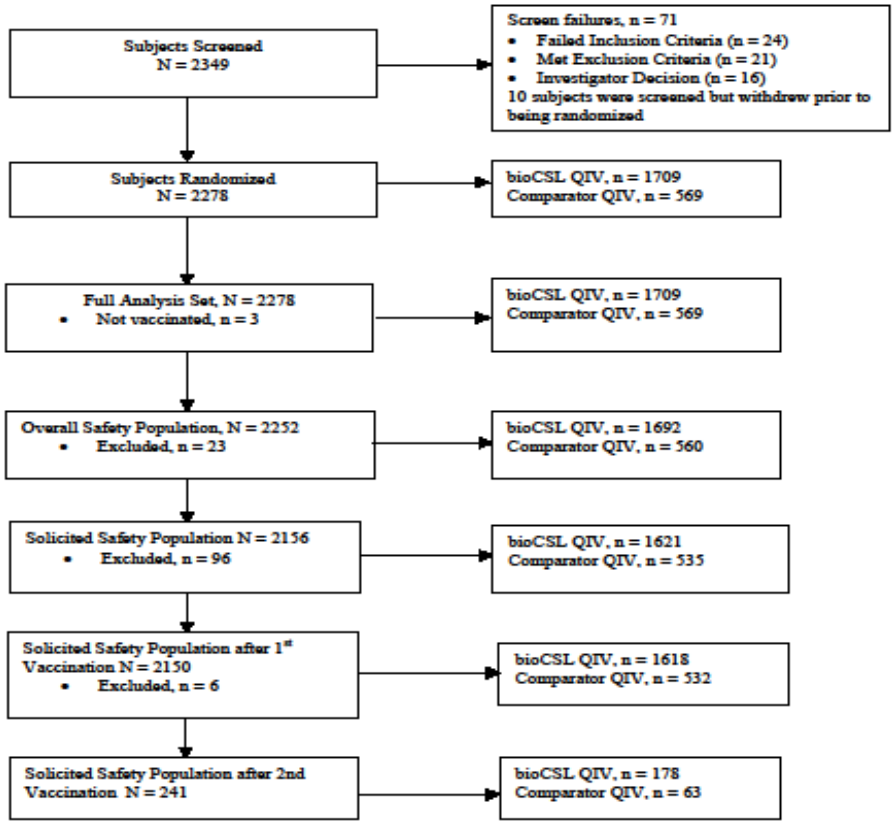
Source: Table 14.1.1.1

6.2.1.10. Major protocol violations/deviations

The Evaluable Population = 2155 subjects within the FAS who received study vaccine: 114 subjects excluded because either pre- and/or post-vaccination serology assay results were not

available; another 6 were excluded because they had received ≥1 prohibited medications potentially impacting on the immunogenicity results. PP Population included subjects in the Evaluable Population (n=2155) minus subjects with protocol deviations assessed as potentially affecting the immunogenicity results (n=22), hence the PP Population =2133 subjects.

Figure 6: Subject Disposition in CSLCT-QIV-13-02 – Evaluable Population for safety



Source: Table 14.3.1.1

6.2.1.11. Baseline data

No notable differences in demographic / baseline characteristics between the two vaccine groups in the FAS or within the age cohorts. 52.1% male and 47.9% female subjects enrolled. Majority of subjects were white (73.3%); 20.7% subjects of black or African American origin. Mean (SD) age was 9.5 yrs (3.48) (5 - 8 yrs age cohort: 6.7 yrs [1.10]; 9 -17 yrs age cohort: 12.5 yrs [2.52]). The age gp balance remained within the rules set out in the protocol, with at least 50% in the 5 - 8 yrs of age stratum. In the FAS population, 51.19% (1166 / 2278) were in this age stratum. Of the 2278 in the FAS, 1998 subjects (87.7%) had previously received an influenza vaccine in the past (bioCSL QIV: 1498 subjects; Comparator QIV: 500 subjects). 53.0% reported having received an influenza vaccine in the 2014 / 2015 NH Season during the 12 months before the study start (bioCSL QIV: 907 subjects; Comparator QIV: 300 subjects). Percentages of subjects reporting having received an influenza vaccine in the past were similar in the two age cohorts, as were percentages reporting having received influenza vaccine during the 12 months before study start.

6.2.1.12. Results for the primary efficacy outcome

Receipt of study vaccines: A total of 2275 / 2278 subjects (99.9%) received at least one vaccination with 2269/2278 subjects (99.7%) receiving vaccination according to protocol. 293 were assigned to 2 doses; 26 did not receive the 2nd vaccination and did not complete the study.

Immunogenicity results: The primary analysis was completed using the PP Population. Duplicate tables for the co-primary endpoints were also produced based on the Evaluable

Population as there was a >1% difference in the total number of subjects between the PP Population and the Evaluable Population in the 5 - 8 yrs age gp (1.67%). bioCSL QIV was shown to be non-inferior to the Comparator QIV, with all 8 co-primary endpoints met for the 4 strains in subjects 5 -17 yrs of age.

Table 1: Post-vaccination HI Antibody GMTs, SCRs, and Analyses of Non-inferiority of bioCSL QIV Relative to Comparator QIV for Each Strain 28 Days after Last Vaccination among a Paediatric Population 5 Through 17 Years of Age (Per-Protocol Population)

Strain	Postvaccination GMT		GMT Ratio [a]	Seroconversion rate (SCR) % [b]		SCR Difference [c]	Met both pre-defined non-inferiority criteria? [d]
	bioCSL QIV (n=1605)	Comparator QIV (n=528)	Comparator QIV over bioCSL QIV (95% CI)	bioCSL QIV (n=1605) (95% CI)	Comparator QIV (n=528) (95% CI)	Comparator QIV minus bioCSL QIV (95% CI)	
A/H1N1	952.6 (n=1604 [e])	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4 (n=1604 [e])	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/YAM	60.9 (n=1604 [e])	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/VIC	145.0 (n=1604 [e])	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Source: Table 14.2.1.1 and Table 14.2.2.1.

Abbreviations: A/H1N1: A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2 = A/Switzerland/9715293/2013 (H3N2)-like virus; B/YAM: B/Phuket/3073/2013-like virus (B/Yamagata lineage); B/VIC: B/Brisbane/60/2008-like virus (B/Victoria lineage); CI: confidence interval; GMT (adjusted): geometric mean titer. SCR: Seroconversion rate.

[a] GMT Ratio = Comparator QIV /bioCSL QIV. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.

[b] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.

[c] Seroconversion rate difference = Comparator QIV SCR percentage minus bioCSL QIV SCR percentage.

[d] Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the ratio of Comparator QIV /bioCSL QIV. GMT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator QIV – bioCSL QIV should not exceed 10%.

[e] Subject 8400394-0046 was excluded from the Per-Protocol Population for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (unknown prevaccination history).

6.2.1.13. Results for other efficacy outcomes

Secondary immunogenicity objectives were to characterise immunogenicity of bioCSL QIV and comparator QIV in two age strata, and overall. Immune responses were further characterised by seroprotection rates (% with HI titre ≥40), SCRs, and GMFIs by study vaccine and age cohort. Similar patterns of immune responses to those seen in subjects overall were seen within each of the two age strata for both study treatments. The post-vaccination HI GMTs for bioCSL QIV were higher for A than the B strains, and post-vaccination HI GMTs were similar between bioCSL QIV and Comparator QIV for all strains. GMFIs were similar for both age subgroups and both study vaccines. Overall for bioCSL QIV, GMFIs were: A / H1N1 7.5, A / H3N2 10.7, B / Yam 5.8 and B / Vic 8.3.

Table 2: Immune Responses (GMT and GMFI) to Each Antigen at Baseline or at 28 Days after Last Vaccination in Age Cohorts, and Overall (Per-Protocol Population)

	Subjects 5 through 8 years		Subjects 9 through 17 years		Overall	
	bioCSL QIV	Comparator QIV	bioCSL QIV	Comparator QIV	bioCSL QIV	Comparator QIV
	n=795	n=262	n=810	n=266	n=1605	n=528
A/H1N1						
Pre-V GMT (95% CI)	109.3 (98.22, 121.58)	115.1 (95.28, 138.93)	120.4 (109.29, 132.69)	124.0 (105.19, 146.29)	114.8 (106.79, 123.33)	119.5 (105.48, 135.38)
Post-V GMT (95% CI)	762.6 (713.55, 815.02)	942.5 (849.64, 1045.62)	964.8 (910.54, 1022.32)	813.4 (735.74, 899.17)	858.7 (821.46, 897.65)	875.1 (814.14, 940.59)
GMFI (95% CI)	7.0 (6.38, 7.64)	8.2 (6.85, 9.79)	8.0 (7.24, 8.87)	6.6 (5.49, 7.83)	7.5 (6.99, 8.01)	7.3 (6.46, 8.30)
A/H3N2						
Pre-V GMT (95% CI)	85.1 (77.78, 93.17)	80.0 (67.46, 94.93)	66.6 (61.50, 72.10)	65.0 (56.68, 74.57)	75.2 (70.80, 79.88)	72.1 (64.61, 80.40)
Post-V GMT (95% CI)	911.8 (846.00, 982.78)	847.9 (746.54, 963.06)	709.8 (661.38, 761.77)	804.3 (711.75, 908.81)	803.6 (763.01, 846.26)	825.6 (756.12, 901.55)
GMFI (95% CI)	10.7 (9.89, 11.60)	10.6 (9.19, 12.22)	10.7 (9.81, 11.58)	12.4 (10.63, 14.40)	10.7 (10.09, 11.31)	11.5 (10.32, 12.71)
B/YAM						
Pre-V GMT (95% CI)	9.5 (9.02, 10.07)	9.4 (8.56, 10.43)	11.7 (10.97, 12.38)	11.5 (10.31, 12.78)	10.5 (10.12, 10.99)	10.4 (9.69, 11.22)
Post-V GMT (95% CI)	51.9 (48.00, 56.07)	46.9 (41.23, 53.25)	70.8 (65.84, 76.06)	62.7 (55.52, 70.75)	60.7 (57.52, 64.01)	54.3 (49.65, 59.28)
GMFI (95% CI)	5.4 (5.04, 5.87)	5.0 (4.38, 5.62)	6.1 (5.60, 6.59)	5.5 (4.76, 6.26)	5.8 (5.44, 6.08)	5.2 (4.75, 5.71)
B/VIC						
Pre-V GMT (95% CI)	15.9 (14.76, 17.07)	14.8 (13.07, 16.79)	18.1 (16.81, 19.46)	19.2 (16.87, 21.80)	17.0 (16.10, 17.85)	16.9 (15.42, 18.46)
Post-V GMT (95% CI)	135.3 (124.37, 147.20)	120.4 (103.13, 140.48)	146.6 (135.40, 158.66)	140.9 (121.42, 163.57)	140.9 (132.97, 149.26)	130.3 (117.07, 145.06)
GMFI (95% CI)	8.5 (7.83, 9.28)	8.1 (7.00, 9.43)	8.1 (7.41, 8.86)	7.3 (6.26, 8.63)	8.3 (7.81, 8.84)	7.7 (6.92, 8.62)

Source: Table 14.2.4.1; Table 14.2.4.2; Table 14.2.5.1 and Table 14.2.5.2.
Abbreviations: HI: hemagglutination inhibition; QIV: Quadrivalent influenza vaccine; A/H1N1: A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2: A/Switzerland/9715293/2013 (H3N2)-like virus; B/YAM: B/Phuket/3073/2013-like virus (B/Yamagata lineage); B/VIC: B/Brisbane/60/2008-like virus (B/Victoria lineage); GMT (unadjusted): geometric mean titer; CI: confidence interval; GMFI: Geometric mean fold increase, defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer; Post-V: postvaccination; Pre-V: prevaccination (Baseline).

Seroconversion and seroprotection rates were similar for both age subgroups and both study treatments. Overall for bioCSL QIV, seroconversion rates and seroprotection rates were respectively: A/H1N1 66.4% and 99.7%, A/H3N2 82.9% and 99.4%, B/Yam 58.4% and 75.0% and B/Vic 72.1% and 90.3%. In general, male and female subjects showed similar pre- and post-vaccination GMTs and SCRs for both study vaccines. The study was not powered to allow comparisons between race and ethnic subgroups.

Table 3: Immune Responses (Proportion of Subjects with HI Titre ≥40 and Seroconversion Rates) to Each Antigen at Baseline or at 28 Days after Last Vaccination in Age Cohorts (Per-Protocol Population) Safety results

	Subjects 5 through 8 years		Subjects 9 through 17 years		Overall	
	bioCSL QIV n=795	Comparator QIV n=262	bioCSL QIV n=810	Comparator QIV n=266	bioCSL QIV n=1605	Comparator QIV N=528
A/H1N1						
Pre-V % HI titer ≥ 40 (95% CI)	79.5 (76.5, 82.3)	79.0 (73.6, 83.8)	83.0 (80.2, 85.5)	85.0 (80.1, 89.0)	81.2 (79.2, 83.1)	82.0 (78.5, 85.2)
Seroconversion rate* (95% CI)	67.9 (64.6, 71.2)	67.2 (61.1, 72.8)	64.8 (61.4, 68.1)	59.4 (53.2, 65.4)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)
Post-V % HI titer ≥ 40 (95% CI)	99.6 (98.9, 99.9)	99.6 (97.9, 100.0)	99.8 (99.1, 100.0)	99.6 (97.9, 100.0)	99.7 (99.3, 99.9)	99.6 (98.6, 100.0)
A/H3N2						
Pre-V % HI titer ≥ 40 (95% CI)	78.6 (75.6, 81.4)	72.9 (67.1, 78.2)	74.8 (71.7, 77.8)	75.6 (69.9, 80.6)	76.7 (74.6, 78.7)	74.2 (70.3, 77.9)
Seroconversion rate (95% CI)	83.3 (80.5, 85.8)	82.4 (77.3, 86.8)	82.6 (79.8, 85.1)	84.2 (79.3, 88.4)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)
Post-V % HI titer ≥ 40 (95% CI)	99.2 (98.4, 99.7)	98.9 (96.7, 99.8)	99.6 (98.9, 99.9)	100.0 (98.6, 100.0)	99.4 (98.9, 99.7)	99.4 (98.3, 99.9)
B/YAM						
Pre-V % HI titer ≥ 40 (95% CI)	10.1 (8.1, 12.4)	10.3 (6.9, 14.6)	15.8 (13.4, 18.5)	18.0 (13.6, 23.2)	13.0 (11.4, 14.7)	14.2 (11.3, 17.5)
Seroconversion rate (95% CI)	55.7 (52.2, 59.2)	55.3 (49.1, 61.5)	61.2 (57.8, 64.6)	54.9 (48.7, 61.0)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)
Post-V % HI titer ≥ 40 (95% CI)	69.2 (65.8, 72.4)	69.1 (63.1, 74.6)	80.6 (77.7, 83.3)	79.3 (74.0, 84.0)	75.0 (72.8, 77.1)	74.2 (70.3, 77.9)
B/VIC						
Pre-V % HI titer ≥ 40 (95% CI)	25.0 (22.1, 28.2)	24.8 (19.7, 30.5)	30.7 (27.6, 34.0)	30.8 (25.3, 36.8)	27.9 (25.7, 30.2)	27.8 (24.1, 31.9)
Seroconversion rate (95% CI)	73.6 (70.4, 76.6)	73.7 (67.9, 78.9)	70.6 (67.3, 73.7)	66.5 (60.5, 72.2)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)
Post-V % HI titer ≥ 40 (95% CI)	88.4 (86.0, 90.6)	86.6 (81.9, 90.5)	92.1 (90.0, 93.9)	90.6 (86.4, 93.8)	90.3 (88.7, 91.7)	88.6 (85.6, 91.2)

Source: Table 14.2.4.1; Table 14.2.4.2; Table 14.2.6.1 and Table 14.2.6.2.

Abbreviations: HI: hemagglutination inhibition; QIV: Quadrivalent influenza vaccine; A/H1N1: A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2 = A/Switzerland/9715293/2013 (H3N2)-like virus; B/YAM: B/Phuket/3073/2013-like virus (B/Yamagata lineage); B/VIC: B/Brisbane/60/2008-like virus (B/Victoria lineage); GMT: geometric mean titer; CI: confidence interval; V: vaccination.

*Seroconversion rate, defined as percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer.

6.2.1.14. Evaluator commentary

The study design was appropriately powered for the primary and key secondary endpoints for recipients. Although there were 293 subjects assigned to receive 2 doses at randomisation, only 267 did so. Most of the vaccinees had received influenza vaccine in the past. The immunogenicity of bioCSL QIV, measured by post-vaccination HI GMTs and SCRs, demonstrated non-inferiority to the US licensed comparator QIV, in subjects 5 - 17 yrs of age. Similar patterns of good immune responses (characterised by seroprotection rates, SCRs and GMFIs by study vaccine and by age stratum) were seen overall, and within each of the two age strata, for both study vaccines. The safety and tolerability profile of bioCSL QIV was broadly similar to the comparator QIV.

6.3. Analyses performed across trials: pooled and meta analyses

There is no pooled data or meta analyses provided in the paediatric setting.

6.4. Evaluator's conclusions on clinical efficacy

The CSLCT-QIV-13-02 study, was conducted entirely within the US over one NH flu season (2015-2016), in children aged 5-17 yrs, the majority of subjects were of white ethnicity; 51% (n=1166) in the FAS population were in the younger age group (aged 5-8 yrs). Standard methodology to demonstrate immunogenicity was utilised. The non-inferiority of Afluria Quad vs. an approved QIV was demonstrated through the eight co-primary endpoints of HI GMT and SCR for each viral strain included in the vaccines. Secondary immunogenicity findings also supported the primary endpoint conclusions. There was no difference in vaccine 'efficacy'

between the age strata. There were no safety concerns raised, the safety data is discussed in greater detail below.

7. Clinical safety

Background: In 2010, bioCSL's Southern Hemisphere TIV formulation was associated in Australia and New Zealand with increased post-marketing reports of fever and febrile seizures in children (Department of Health and Ageing 2010; CDC 2010). These reactions were predominantly in children between 6 months to <5 yrs of age. However, increased post-marketing reports of febrile reactions compared with historical averages were also observed in children 5 to <9 yrs of age (CDC 2010). Since the 2010 SH influenza vaccination season, bioCSL TIVs, including Afluria TIV, have not been approved for use in children <5 years.

Before the 2010 Southern Hemisphere Paediatric AEs, bioCSL TIV was approved for use in children from 6 months of age in several countries globally. bioCSL TIV was used in children 6 months and older in countries throughout the EU since first Marketing Authorization in 2004. This indication was also registered in Australia and New Zealand in 2007 and marketed from 2008. Additionally, approvals followed in Malaysia and Singapore (2008) and Argentina in 2009 and marketed from 2009 in these countries for use in children from 6 months of age. The 2010 SH paediatric AEs were initially detected in the third year of a government sponsored paediatric influenza vaccination program in Western Australia (WA) in which bioCSL TIV was used. During the first two years of the WA program in which similar numbers of children were vaccinated only one febrile convulsion that was temporally related to TIV vaccination was reported. Research conducted in 2010 using in-vitro modelling in a subgroup of children ≤5 years with bioCSL TIV vaccine-related febrile convulsions, showed differences in cytokine production when peripheral blood mononuclear cells were stimulated with bioCSL TIV 2010 vs. TIVs from other manufacturers (Blyth). This research demonstrated a potential clinical mechanism for the febrile AEs that is, a cytokine-mediated pyrogenic response.

An increased frequency of fever after receipt of 2009 bioCSL TIV compared to a US-licensed TIV among children 6 months to <9 yrs of age was also observed in a clinical trial conducted in the US (Brady). The AE summary results from this study for the two age groups 5 to <9 yrs and 9 to <18 yrs are also included in the Afluria TIV label. After the 2010 SH paediatric AEs, bioCSL conducted intensive scientific investigations to identify the root cause of these AEs. Reports of the investigations, results, and conclusions have been presented to key regulatory agencies in countries where bioCSL TIV is licensed, including to the US FDA, and have been published (Rockman).

The conclusions from the scientific investigations indicated that a combination of 3 key elements was predominant factors contributing to the 2010 SH paediatric AEs:

- Strain changes, in particular, replacement of all 3 virus strains in the 2009 SH vaccine formulation with the new strains for 2010 SH;
- Degraded RNA fragments that induced nuclear factor-kappa B (NF-κB), a key cellular transcription factor in cytokine production, and
- Conformation of heat-sensitive viral components, such as lipids, which appeared to facilitate RNA delivery.

Although the presence of RNA appears to be the trigger for the febrile reactions, its delivery is key to the induction of the cytokine/chemokine signal and this appears dependent on the lipid level present in the final vaccine formulation. The lipid content is inversely proportional to the concentration of the detergent sodium taurodeoxycholate (TDOC), used to disrupt the virus (Rockman). Characterisation studies conducted examined the effect of varying the concentration of TDOC, used to split the virus during manufacture, on the NF-κB activation

response. Reduction of lipids using the above process appears to reduce facilitated RNA fragment delivery into cells, decreasing the NF-κB induction associated with cytokine production. This may therefore reduce the potential for pyrogenic vaccine responses mediated by cytokines. During the scientific investigations, the highest cytokine signal in the surrogate reactogenicity assays was generated by the B strain viruses, leading bioCSL to focus on splitting conditions for B strains. Based on the available characterisation data to date, the vaccine to be used in clinical trials starting from 2014, and in commercially supplied vaccines from 2014, will have the B strain split at the upper levels of TDOC concentration (1.5% w/v), which is within bioCSL's registered splitting range for TIV.

CSLCT-QIV-13-02, described in Section 6.0 is the only study in this application that provides evaluable safety data for QIV. Study CSLCT-USF-10-69, was conducted in children aged 5-8 yrs of age, to provide contemporary data on the safety and tolerability of Seqirus TIV manufactured with 1.5%w/v splitting conditions for the B strain in children aged 5-8 yrs of age. Safety data from this study provides only indirect safety data for Afluria Quad.

Safety reporting definitions: AE = untoward medical occurrence in a clinical investigation subject given a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Unsolicited AEs coded using MedDRA version 18. The numbers (and %) experiencing at ≥1 unsolicited AEs summarised by MedDRA system organ class (SOC) and preferred term (PT), overall and by maximum severity. Severity ranked: severe >moderate >mild >unknown. All summaries presented by treatment gp (that is, bioCSL QIV/Comparator QIV/Overall), and repeated by age strata, gender, and race/ethnicity where specified.

Solicited AEs: SAE = untoward medical occurrence resulting in death/is life-threatening/requires in-patient hospitalisation/prolongation of existing hospitalisation/results in persistent or significant disability or incapacity/congenital anomaly or birth defect/important medical event/is the suspected transmission of an infectious agent via a medicinal product. SAEs, collected for 180 days and 7 days after last vaccination in CSLCT-QIV-13-02 and CSLCT-USF-10-69, respectively.

Table 4: Solicited Local Reactions captured in CSLCT-QIV-13-02 and CSTCT-USF-10-69

	Intensity Grading			
Injection Site Reaction	**None (0)**	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain	Absent	Does not interfere with daily activities	Interferes with daily activities	Prevents daily activities
Erythema	Absent	< 10 mm	≥ 10 mm to ≤ 30 mm	> 30 mm
Induration	Absent	< 10 mm	≥ 10 mm to ≤ 30 mm	> 30 mm

Source: Protocol Final Version 5.0, Table 3, Appendix 16.1.1.

Solicited systemic AEs were defined and graded as described in Table 9.5-3.

Table 5: Solicited Systemic AEs captured in CSLCT-QIV-13-02 and CSTCT-USF-10-69

	Intensity Grading			
Systemic Symptom	None (0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	< 38.0°C < 100.4°F	≥ 38.0 – < 38.5°C ≥ 100.4 – < 101.3°F	≥ 38.5 – < 39.0°C ≥ 101.3 – < 102.2°F	≥ 39.0°C ≥ 102.2°F
Nausea Vomiting Diarrhea Headache Myalgia Malaise	None	Adverse event easily tolerated by the subject, causing minimal discomfort and does not interfere with everyday activities	Adverse event sufficiently discomforting to interfere with everyday activities	Adverse event prevents normal everyday activities or requires significant medical intervention

Source: Protocol Final Version 5.0, Table 4, Appendix 16.1.1.

The intensity of unsolicited AEs was graded as follows:

- **Mild:** symptoms are easily tolerated and do not interfere with daily activities
- **Moderate:** enough discomfort to cause some interference with daily activities
- **Severe:** symptoms that prevent normal, everyday activities

- CAUSALITY OF AEs: Assessed by Investigator as related or unrelated.
- SEVERITY of AEs: Assessed by Investigator as mild, moderate, severe
- AESIs: The following AESIs were collected CSLCT-QIV-13-02, and were to be reported as medically important SAEs: Optic neuritis; encephalomyelitis; thrombocytopenia; vasculitis; Guillain-Barré syndrome; Bell's palsy; Transverse myelitis; Demyelinating disorders.

7.1. Studies providing evaluable safety data

7.1.1. Pivotal studies that assessed safety as the sole primary outcome

CSLCT-USF-10-69, described below. This is not a pivotal study; it is a supporting safety study.

7.1.2. Pivotal and/or main efficacy studies

CSLCT-QIV-13-02, immunogenicity results described above.

7.2. Studies that assessed safety as the sole primary outcome

7.2.1. Study CSLCT-USF-10-69

A Phase IV, multicentre, randomised, observer-blind, parallel-arm study to evaluate the safety and tolerability of CSL's trivalent influenza virus vaccine (CSL TIV) in children 5 to less than 9 years of age

7.2.1.1. Study design, objectives, locations and dates

Design: randomised, observer-blind, comparator-controlled, parallel-arm, multicentre study to evaluate safety and tolerability of bioCSL TIV in children 5 - 8 yrs of age. Subjects received one or two study vaccinations depending on their influenza vaccination history. A single study vaccination was scheduled if the subject received ≥2 seasonal influenza vaccinations since July 2010. Subjects were randomised to one of the two treatment groups in a 3:1 ratio (Seqirus (= CSL) TIV: Comparator QIV). This was a safety-only study, with no efficacy or immunogenicity evaluations. After each vaccination, the parents/guardians of the subjects completed a 7-day diary to record the subject's temperature and all AEs that occurred on the day of vaccination and during the subsequent six days after the day of vaccination. All medications used during this period were documented. The study was not powered to allow direct comparison between

safety and tolerability of the two study treatments. It was primarily conducted to provide contemporary data on safety and tolerability profile of Seqirus TIV manufactured with 1.5% w/v TDOC splitting conditions for the B strain, to inform the design & conduct of planned Seqirus QIV clinical development in children.

Primary objective: Evaluate frequency and intensity of fever in healthy children 5 - 8 yrs of age administered the 2014-2015 NH season formulation of bioCSL TIV, in the 7 days after each administration.

Secondary objectives:

- Frequency/intensity of fever in healthy 5 - 8 year olds administered the 2014-2015 NH season formulation of the Comparator QIV, in the 7 days after each administration;
- Describe the nature of febrile events after each bioCSL TIV or Comparator QIV vaccine;
- Safety/tolerability of bioCSL TIV in 5 – 8 year olds in the 7 days after each vaccine;
- Safety/tolerability of Comparator QIV in 5 – 8 year olds in the 7 days after each vaccine;

Exploratory: To explore the association between any and severe grade fever after administration of bioCSL TIV or the Comparator QIV by vaccine dose and baseline characteristics.

Locations: 11 sites in the USA.

Dates: 22 Sep 2014 (first subject first visit); 05 Dec 2014 (last subject last visit).

7.2.1.2. Inclusion and exclusion criteria

Key inclusions: 1. Healthy male or female subjects aged 5 - 8 years in good health at the time of first study vaccination; 2. informed consent by parent/legal guardian. Key exclusion criteria: 1. known hypersensitivity to a previous dose of influenza virus vaccine or allergy to eggs, chicken protein, neomycin, polymyxin, or any study vaccines components; 2. Clinical signs of significant active infection or an elevated oral temperature of ≥ 100.4 ºF (≥ 38.0ºC); 3. history of seizures or febrile convulsions; 4. history of GBS; 5. vaccination against influenza 6 months prior to study entry or any vaccine 14 days prior to study entry; 6. any clinical condition that would preclude reliable assessment of the subject's mental state; 7. a confirmed or suspected immunosuppressive condition; 8. treatment with radiotherapy or cytotoxic drugs or systemic glucocorticoids, immunoglobulins and/or any blood products, warfarin or other anticoagulants.

7.2.1.3. Study treatments

Trial vaccine: bioCSL TIV (2014-2015 NH season formulation), containing the following HA: A/California/7/2009 H1N1) pdm09-like virus; A/Texas/50/2012 (H3N2)-like virus; B/Massachusetts/2/2012-like virus; Batch Number: T56805. H3N2 and B strains were split at the upper levels of TDOC concentration (1.5% w/v).

Comparator: Fluzone Quadrivalent (Sanofi Pasteur), supplied in a thimerosal-free prefilled syringe containing 60 mcg HA in 0.5 mL (15 mcg of each of the four strains) for each vaccination, and injected IM into the deltoid region of the arm. Lot Number: UI169AB.

7.2.1.4. Safety variables and outcomes

Primary Safety Endpoint: Fever occurring during the 7 days after administration of bioCSL TIV assessed by the frequency and intensity of fever events.

Secondary Safety Endpoints: For fever events occurring during the seven days after each administration of bioCSL TIV or the Comparator QIV, the following characteristics were described for all fever events, and by mild, moderate and severe fever grade events, regardless of causality assessment:

- Time to event onset

- Duration
- Composite systemic fever AEs
- Fever associated with 2 or more systemic AEs
- Medical attention required
- Antipyretic use
  - Frequency/intensity of fever events during the 7 days after the Comparator QIV;
  - Frequency/intensity of fever events considered vaccine-related during the 7 days after the bioCSL TIV or Comparator QIV.

Safety and tolerability were assessed by:

- Frequency, intensity and duration of solicited local AEs occurring during the 7 days after each bioCSL TIV or Comparator QIV;
- The frequency, intensity and duration of solicited systemic AEs occurring during the 7 days after each administration of bioCSL TIV or the Comparator QIV;
- Frequency, intensity and duration of unsolicited AEs occurring during the 7 days after each administration of bioCSL TIV or the Comparator QIV;
- Incidence of SAEs occurring up to 7 days after vaccination.

7.2.1.5. Randomisation and blinding methods

≈400, 5-8 year olds, randomised 3 (bioCSL TIV):1 (Comparator QIV) allocation ratio. Observer blinded.

7.2.1.6. Analysis populations

- FAS = all subjects who were randomised to treatment.
- Overall Safety Population = all randomised subjects who received ≥1 study vaccination and provided any follow-up safety data after any vaccination.
- Safety Population after the First Vaccination =all randomised subjects who received the first vaccination and provided follow-up safety data after the first vaccination.
- Safety Population after the Second Vaccination =all randomised subjects who received the second vaccination and provided follow-up safety data after the second vaccination.

Table 6: Number and % of subjects in each Analysis Population, Study CSLCT-USF-10-69

	Seqirus TIV n (%)	Comparator QIV n (%)	Overall n (%)
Full Analysis Set (FAS)	302	100	402
Overall Safety Population	292 (96.7)	98 (98.0)	390 (97.0)
Safety Population after First Vaccination	292 (96.7)	98 (98.0)	390 (97.0)
Safety Population after Second Vaccination	120 (39.7)	39 (39.0)	159 (39.6)

Source: Module 5, Section 5.3.5.1 CSLCT-USF-10-69, Table 10.1-1, Post-Text Table 14.1.1.

7.2.1.7. Sample size

In previous clinical studies of bioCSL TIV, the proportion of subjects 5 through 8 yrs of age who reported fever was between 9.8% and 16.2%. Based on 300 subjects in the bioCSL TIV gp, if the rate was observed to be 16% the width of a 95% CI was to be 8.5%.

7.2.1.8. Statistical methods

Descriptive: The safety population was used in the assessment of AEs. Summary statistics presented for continuous variables, by way of n, mean, SD, median, minimum and maximum and gp frequencies and % for categories of categorical variables. Percentages calculated using total

subjects per treatment gp. 95% CIs provided for descriptive statistics. The 95% CI for % were exact CIs based upon the binomial distribution. Statistics displayed for: bioCSL TIV, Comparator QIV, Overall. For primary and secondary safety endpoints statistics were displayed for: bioCSL TIV or Comparator QIV: After first and second vaccination, Overall.

7.2.1.9. Participant flow

See above.

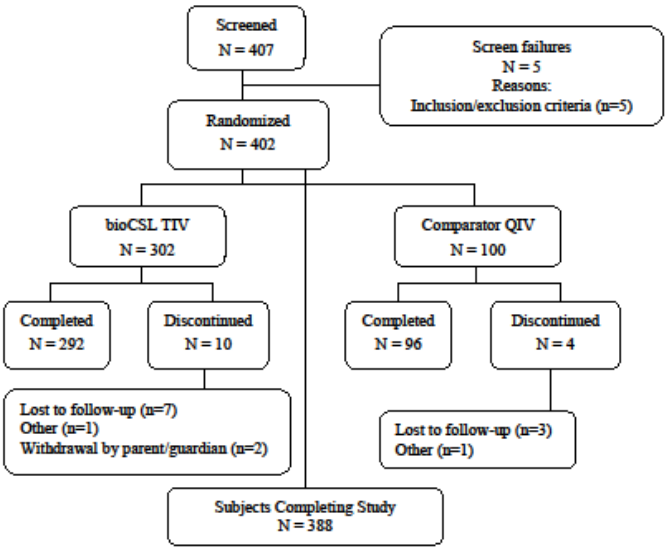
7.2.1.10. Major protocol violations/deviations

No major protocol deviations relating to inclusion/exclusion criteria occurred. 53 subjects had 70 major protocol deviations mainly due to 'out-of-window' diary return or diary not completed/returned, missed study visits and informed consent errors. Two subjects were randomised to the two-vaccination gp in error; however they only received one vaccination. Some subjects had ≥1 protocol deviation. On medical review of concomitant medications, there were no vaccinations reported, and no evidence that prophylactic antipyretics were given on the day of vaccination.

7.2.1.11. Baseline data

The mean (SD) age was 6.6 (1.04) yrs ranging from 5 to 8 years old. There were slightly more male subjects than female subjects overall (52.0% male; 48.0% female). Majority of subjects were white (71.4%), with 22.4% subjects black or African American, 5.0% 'other', 0.5% Asian, 0.5% Native Hawaiian or Pacific Islander and 0.2% American Indian/Alaska Native. The mean (SD) pre-vaccination temperature of all randomized subjects in the FAS was 98.15 ºF (0.626) (range: 95.7 to 99.7 ºF). No differences >10% were noted between the vaccine groups in the distribution of sex, ethnicity and race, with exception of the subjects who were black or African American (bioCSL TIV: 19.5%; Comparator QIV: 31.0%).

Figure 7: Subject Disposition in CSLCT-USF-10-69



Source: Post-text Table 14.1.1 (Section 14.1) and Listing 16.2.1.1 (Appendix 16.2.1)

7.2.1.12. Results for the primary safety outcome

Overall fever rate (during 7 days after vaccination) with bioCSL TIV was 8.2%; most fever event(s) were considered related. Severe fever event(s) occurred in 2.1% of subjects and related severe fever event(s) occurred in 1.7% of subjects. The proportion of subjects who had any fever event with ≥2 solicited systemic AEs was 3.4% (fever with ≥1 solicited systemic AE was 4.5%); subjects who had a severe fever event with ≥2 solicited systemic AE was 1.4% (severe fever with ≥1 solicited systemic AE was 1.7%). Mean onset for all fevers (mild, moderate, severe) was on Day 2 and lasted 1 to 3 days.

Direct comparison with Comparator QIV could not be made as this study was not sufficiently powered; however, fever rates were similar between the vaccine groups (proportion of subjects in the Comparator QIV gp: overall fever rate: 9.2%; severe fever: 4.1%; related fever: 5.1%; severe related fever: none reported; overall fever with ≥2 solicited systemic AE: 4.1%; overall fever with ≥1 solicited systemic AE: 6.1%). Exploratory analyses performed with adjustment for covariates including age, sex, weight, vaccine dose or previous vaccination in order to evaluate the contribution of these factors to fever outcomes, no association was found.

Table 7: Proportion with Fever Event, Related Fever Event or Composite Solicited Systemic Fever AEs by Intensity during the 7 Days after bioCSL TIV Vaccination (CSLCT-USF-10-69)

	Percentage (%)[a] of subjects reporting a fever event: bioCSL TIV		
	Overall N = 292 [b]	After first vaccination N = 292 [c]	After second vaccination N = 120 [d]
≥ 1 Fever Event	8.2	8.2	0
Mild [e]	4.1	4.1	0
Moderate [f]	2.1	2.1	0
Severe [g]	2.1	2.1	0
≥ 1 Related Fever Event	7.5	7.5	0
Mild	4.1	4.1	0
Moderate	1.7	1.7	0
Severe	1.7	1.7	0
Fever + ≥ 1 Solicited Systemic AEs	4.5	4.5	0
Mild	1.0	1.0	0
Moderate	1.7	1.7	0
Severe	1.7	1.7	0
Fever + ≥ 2 Solicited Systemic AEs	3.4	3.4	0
Mild	1.0	1.0	0
Moderate	1.0	1.0	0
Severe	1.4	1.4	0
Fever + ≥ 2 GI Symptoms (Nausea/Vomiting/Diarrhea)	1.0	1.0	0
Mild	0.3	0.3	0
Moderate	0	0	0
Severe	0.7	0.7	0
Fever + ≥ 2 non-GI Symptoms (Headache/Myalgia/Malaise)	2.1	2.1	0
Mild	0.7	0.7	0
Moderate	1.0	1.0	0
Severe	0.3	0.3	0
Fever + ≥ 1 GI Symptom and ≥ 1 non-GI Symptom	2.1	2.1	0
Mild	1.0	1.0	0
Moderate	0	0	0
Severe	1.0	1.0	0

[a] Proportion of subjects with a fever event, related fever event or composite solicited systemic fever AEs by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom. Excludes subjects with missing intensity information for the whole 7 days.
[b] N = number of subjects in the Overall Safety Population (after any vaccination) for the bioCSL TIV group.
[c] N = number of subjects in the Safety Population After the First Vaccination for the bioCSL TIV group.
[d] N = number of subjects in the Safety Population After the Second Vaccination for the bioCSL TIV group.
[e] Mild fever: ≥ 100.4 to < 101.3° F (≥ 38.0 to < 38.5° C).
[f] Moderate fever: ≥ 101.3 to < 102.2° F (≥ 38.5 to < 39.0° C).
[g] Severe fever: ≥ 102.2° F (≥ 39.0° C).

7.2.1.13. Results for other safety outcomes

See below.

Table 8: Solicited and Unsolicited AE after bioCSL TIV Vaccination in CSLCT-USF-10-69

	Percentage (%)[a] of subjects experiencing AEs: bioCSL TIV		
	Overall N = 292 [b]	After first vaccination N = 292 [c]	After second vaccination N = 120 [d]
One or more AEs	76.0	72.6	48.3
Solicited local adverse reactions [e]	70.2	65.8	46.7
Solicited systemic AEs	40.8	37.3	23.3
Unsolicited AEs	14.0	13.0	5.0
One or more related AEs	75.0	71.2	46.7
Solicited local adverse reactions	70.2	65.8	46.7
Solicited systemic AEs	33.9	31.2	18.3
Unsolicited AEs	4.1	4.1	0.8
SAEs	0.3	0.3	0
Related SAEs	0.3	0.3	0
Discontinuation due to an AE	0	0	0
Deaths	0	0	0

[a] Proportion of subjects based on the number of subjects in the respective group.
[b] N = number of subjects in the Overall Safety Population (after any vaccination) for the bioCSL TIV group.
[c] N = number of subjects in the Safety Population After the First Vaccination for the bioCSL TIV group.
[d] N = number of subjects in the Safety Population After the Second Vaccination for the bioCSL TIV group.
[e] All solicited local events were considered to be related.

No deaths or AEs leading to study withdrawal. No AEs triggering the halting rules in either vaccine gp. One SAE (severe delirium febrile) occurred on Day 3 post bioCSL TIV and was resolved the same day. The SAE was assessed as 'listed/expected' and vaccine related. Although the event of 'delirium febrile' did not meet halting criteria at the time and did not trigger study halt, the Data and Safety Monitoring Board (DSMB) Chair was notified of the event via email communication one day after initial receipt of the SAE. After unblinding, the event was re-reviewed later by the sponsor and reassessed as 'unlisted/unexpected', which would have halted the study pending DSMB review according to the protocol. However, as noted above, the DSMB Chair was provided the initial case details and informed of additional follow-up clinical information.

Solicited local AR occurred in most subjects (bioCSL TIV: 70.2% and Comparator QIV: 68.4%) and of mild intensity (bioCSL TIV: 49.8% and Comparator QIV: 46.9%). A higher proportion reported local AR after the first vaccination in both vaccine groups. Most local AR reported after bioCSL TIV started on Day 1 and lasted 1- 2 days. Mean duration of pain, redness and swelling was longer following the 1st vaccination compared with 2nd in both vaccine groups. In the Comparator QIV gp, most reactions started on Day 1 and lasted 2 - 3 days. The most common solicited local AR was pain (bioCSL TIV: 64.4% and Comparator QIV: 57.1%) and persisted for a mean (SD) duration of 2 days in both vaccine groups (bioCSL TIV: 1.7 days [0.84]; Comparator QIV: 1.9 days [0.93]).

Solicited systemic AEs occurred in 40.8% (bioCSL TIV) and 44.9% (Comparator QIV). A higher proportion of subjects reported solicited systemic AEs after the first vaccination. The most common solicited systemic AE was myalgia (bioCSL TIV: 24.3% and Comparator QIV: 23.5%) and headache (bioCSL TIV: 14.7% and Comparator QIV: 23.5%). Malaise and diarrhoea more commonly reported (by >10% subjects) in the Comparator QIV gp.

Most solicited systemic events reported by the bioCSL TIV gp began on/after Day 2 (except myalgia, which started on Day 1) and lasted 1-2 days. Average onset day for solicited systemic AEs was Day 1, 2 or 3 (myalgia and diarrhoea: average onset Day 1; headache, malaise & vomiting: average onset Day 2; nausea & fever: average onset Day 3). The duration of events was slightly longer after Comparator QIV (1-3 days).

Unsolicited AEs experienced within 7 days post-vaccination were reported in 14.0% in the bioCSL TIV gp and in 22.4% in Comparator QIV gp. Cough more commonly reported (4.1%) in the bioCSL TIV gp and oropharyngeal pain and abdominal pain more commonly reported (3.1%) with Comparator QIV. Higher proportions reported unsolicited AEs after 1st vs. 2nd vaccination in both vaccine groups.

7.2.1.14. Evaluator commentary

CSLCT-USF-10-69 provided safety data on Seqirus TIV manufactured with 1.5% w/v TDOC splitting conditions for the B strain. Vaccination with bioCSL TIV and Comparator QIV was generally safe and well tolerated in 5 - 8 year olds. The study was underpowered for a proper comparison with the Comparator QIV. Overall fever rate and severe fever rate was 8.2% and 2.1%, respectively with bioCSL TIV. Similar rates were observed in the Comparator QIV gp with an overall fever rate and severe fever rate of 9.2% and 4.1%, respectively. Fever events deemed related occurred in 7.5% recipients of bioCSL TIV and 5.1% vaccinated with Comparator QIV. Severe related fever events occurred in 1.7% of subjects vaccinated with bioCSL TIV vs. none with Comparator QIV. Few events occurred in either vaccine gp which required medical attention or for which antipyretics were given. No statistically significant association between fever outcomes and age, sex, weight, vaccine dose, previous vaccination. When considering historical fever rates in previous paediatric clinical studies in 5 - 8 year olds vaccinated with Seqirus TIV overall and severe fever rates were lower in children vaccinated with the 2014-2015 NH TIV manufactured using 1.5% TDOC splitting conditions for the B strain.

7.3. Patient exposure Children and adolescents aged 5-17 years of age

As this is an application seeking approval of Afluria Quad in children/adolescents aged 5-17 yrs of age, the safety data in adults is not of direct relevance. See below for a summary of the safety populations in CSLCT-QIV-13-02.

Table 9: Number and % of Subjects in Each Analysis Population, Study CSLCT-QIV-13-02

Analysis Populations	Seqirus QIV (n = 1709)	Comparator QIV (n= 569)	Total (N = 2278)
Full Analysis Set, n (%)	1709 (100)	569 (100)	2278 (100)
Overall Safety Population, n (%)	1692 (99.0)	560 (98.4)	2252 (98.9)
Solicited Safety Population, n (%)	1621 (94.9)	535 (94.0)	2156 (94.6)
Solicited Safety Population After 1st Vaccination, n (%)	1618 (94.7)	532 (93.5)	2150 (94.4)
Solicited Safety Population After 2nd Vaccination, n (%)	178 (10.4)	63 (11.1)	241 (10.6)

Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 11.1-1, Post-Text Table 14.1.1.1.

7.4. Adverse events

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

7.4.1.1. Integrated safety analyses

There is no integrated safety analysis; safety data arises from one Study CSLCT-QIV-13-02.

7.4.1.2. Pivotal and/or main efficacy Study CSLCT-QIV-13-02

Unsolicited Adverse Events in Children 5 to 17 yrs of age

Unsolicited AEs reported by 15.1% of subjects overall, 15.9% in the Seqirus QIV vs. 12.5% in Comparator QIV gp. Unsolicited AEs considered vaccine related, reported in a higher proportion in the Seqirus QIV gp vs. Comparator QIV gp (3.8% vs. 2.0% respectively).

Intensity (Seqirus QIV gp) =mild (8.8% subjects) or moderate (6.4% subjects); 0.7% of subjects reported severe intensity unsolicited AEs. Similar rates observed in the two age strata.

The majority in the Comparator QIV gp reporting unsolicited AEs reported events with a maximum intensity of mild (5.5% subjects) or moderate (5.9% subjects); 1.1% of subjects reported unsolicited AEs of severe intensity.

No related unsolicited AE were reported by ≥1% of subjects in either vaccine gp. Most common related unsolicited AEs (≥0.1% to <0.5% of overall subjects) were cough, oropharyngeal pain, rhinorrhoea, nasal congestion, vomiting, headache, pyrexia, injection site warmth.

No clinically significant differences noted in those reporting unsolicited AEs based on sex, race, or ethnicity in either vaccine gp.

7.4.1.3. Treatment related adverse events (adverse drug reactions) CSLCT-QIV-13-02

Solicited Local Adverse Reactions in Children 5 to <9 yrs of age

After Any Vaccination: Solicited local AR after any vaccination, experienced by 57.2% in Seqirus QIV and 54.0% in Comparator QIV gp. In both study vaccine groups, pain>redness > swelling were reported. The most common local AR was injection site pain (Seqirus QIV: 51.3%, Comparator QIV: 49.6%). Injection site redness and swelling were experienced by >10% of subjects (Seqirus QIV: 19.4% (redness), 15.3% (swelling), respectively; Comparator QIV: 18.6% (redness), 12.4% (swelling), respectively). Most solicited local ARs were mild in both groups. Moderate swelling and redness were experienced by a slightly higher proportion of the Seqirus QIV gp (7.0% and 5.1%, respectively) vs. Comparator QIV gp (4.0% and 2.6%, respectively). A

similar pattern was observed for severe swelling and redness (Seqirus QIV: 3.4% and 3.5%, respectively and Comparator QIV: 2.2% and 1.8%, respectively). Severe solicited local AR occurred in 5.5% of the Seqirus QIV gp and 4.0% of the Comparator QIV.

After the First Vaccination: After the first vaccination, the proportion of subjects experiencing any of the solicited local adverse reactions was similar between the study vaccine groups. Solicited local adverse reactions after the first vaccination were experienced by 55.1% of subjects who received Seqirus QIV and by 53.1% of subjects who received Comparator QIV. In both study vaccine groups, pain, redness and swelling were reported in decreasing order of frequency. Severe intensity local adverse reactions were experienced by 4.8% of subjects in the 5 to < 9 years age stratum after the first vaccination (5.2% of subjects who received Seqirus QIV and 3.7% of subjects who received Comparator QIV. These severe local adverse reactions included pain, redness and swelling. All solicited local adverse reactions (pain, swelling, and redness), experienced in either vaccine group, had a mean onset between Day 1 and Day 2. The mean duration of pain and swelling was similar between vaccine groups (1.7 days in both and 1.8 days in both, respectively). The mean duration of redness was slightly longer in the Seqirus QIV group (1.9 days) than in the Comparator QIV group (1.5 days).

One subject who received Seqirus QIV experienced a cellulitis-like reaction during the study. This subject experienced Grade 3 pain, Grade 3 swelling (up to 78 mm), and Grade 3 redness (up to 78 mm) concurrently from Day 3 to Day 7 after the first vaccination into the deltoid muscle of the right arm. The reaction was assessed by the Investigator and confirmed not to be cellulitis.

All solicited local AR (pain, swelling, redness), had a mean onset between Days 1-2; mean duration for all solicited local AR was <2 days, and similar between vaccine groups.

After the Second Vaccination: Solicited local AR less frequent after the 2nd vaccination than 1st, but numbers receiving a 2nd vaccine were much smaller. After the 2nd vaccination, 37.1% (Seqirus QIV) and 34.9% (Comparator QIV) experienced solicited local AR. Injection site pain and redness were less frequently experienced after the 2nd vaccination than the 1st in both study vaccine groups. The proportion of subjects in the 5 - 8 yrs age gp experiencing pain and redness after a 2nd vaccination decreased to 34.8% and 9.6%, respectively (from 49.0% and 19.1%, respectively after the 1st vaccination) in the Seqirus QIV gp. Similar findings observed in the Comparator QIV gp. After the 2nd vaccination, the proportion reporting moderate and severe injection site swelling was slightly higher in the Seqirus QIV gp (5.1% and 2.2%, respectively) compared with the Comparator QIV (none reported).

Table 10: Maximum Intensity of Solicited Local Reactions Experienced after Vaccination by Subjects 5 to 8 yrs of age (Solicited Safety Population), Study CSLCT-QIV-13-02

	Seqirus QIV (n=829)				Comparator QIV (n=274)				RR (95% CI)[a]
%[b] of subjects with:	Mild	Mod-erate	Severe	All grades	Mild	Mod-erate	Severe	All grades	
Local Reactions After Any Vaccination[c]									
Any	39.2	12.4	5.5	57.2	41.0	8.8	4.0	54.0	1.06 (0.93, 1.20)
Pain	42.1	8.3	0.8	51.3	42.1	6.6	0.7	49.6	1.03 (0.90, 1.18)
Swelling	4.9	7.0	3.4	15.3	6.2	4.0	2.2	12.4	1.23 (0.87, 1.76)
Redness	10.9	5.1	3.5	19.4	14.2	2.6	1.8	18.6	1.04 (0.79, 1.39)
Local Reactions After the First Vaccination[c]									
	Seqirus QIV (n=826)				**Comparator QIV (n=271)**				
Any	38.7	11.1	5.2	55.1	40.0	9.3	3.7	53.1	1.04 (0.91, 1.18)
Pain	40.9	7.3	0.8	49.0	41.9	6.3	0.7	49.1	1.00 (0.87, 1.15)
Swelling	4.7	6.3	3.0	14.0	6.3	4.1	2.2	12.5	1.12 (0.78, 1.60)
Redness	11.4	4.5	3.3	19.1	14.0	2.6	1.5	18.1	1.06 (0.79, 1.41)
Local Reactions After the Second Vaccination[c]									
	Seqirus QIV (n=178)				**Comparator QIV (n=63)**				
Any	24.7	10.1	2.2	37.1	31.7	1.6	1.6	34.9	1.06 (0.72, 1.56)
Pain	28.1	6.7	0	34.8	28.6	1.6	0	30.2	1.15 (0.75, 1.77)
Swelling	3.9	5.1	2.2	11.2	4.8	0	0	4.8	2.36 (0.73, 7.67)
Redness	3.9	4.5	1.1	9.6	7.9	0	1.6	9.5	1.00 (0.41, 2.43)

[a] Relative risk (RR) for Seqirus QIV compared to Comparator QIV = proportion of subjects with a given symptom in the Seqirus QIV group/proportion of subjects with a given symptom in the Comparator QIV group. If the value 1 is not in the range of the confidence interval (CI), it can be concluded that the proportions are significantly different in the two groups, and that there is an increased risk in one group compared to the other.
[b] Proportion of subjects based on the number of subjects in the respective group.
[c] Local adverse reactions: Severe (Grade 3) pain is that which prevents daily activity; Swelling and redness: Any = >0 mm diameter, Severe (Grade 3) = >30 mm diameter.
Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 12.2.2.2-1, Post-Text Table 14.3.1.2.2; Table 14.3.1.2.3; Table 14.3.1.2.4.

Solicited local AR in children/adolescents 9 to 17 yrs of age

In the 9 to <18 yrs age gp, the proportion experiencing any solicited local AR after vaccination was slightly higher in the Seqirus QIV gp (54.9%) than Comparator QIV gp (50.2%). In both study vaccine groups, pain, redness and swelling were reported in decreasing order of frequency. The most common local AR experienced was injection site pain, more frequently reported in the Seqirus QIV gp (Seqirus QIV: 51.5%, Comparator QIV: 45.2%); maximum intensity was mild, in the majority. Severe local AR (pain, redness, swelling) reported by 3.3% after vaccination (3.2% Seqirus QIV; 3.8% Comparator QIV). Overall, solicited local AR had a mean onset between Day 1 and 2; most resolved within 2 days, and similar between vaccine groups.

Solicited systemic adverse events in Children 5 to 8 yrs of age

After Any Vaccination: Solicited systemic AEs after any vaccination were experienced by 27.6% (Seqirus QIV) and 26.3% (Comparator QIV) subjects. Most frequently experienced in the Seqirus QIV gp was headache (12.3%; Comparator QIV: 10.6%) followed by myalgia (9.8%; Comparator QIV: 11.3%). Malaise and fatigue, nausea, diarrhoea, fever, and vomiting were reported in decreasing order of frequency. Any fever and severe fever (≥39.0°C) was reported by 4.5% and 1.2% of subjects who received Seqirus QIV and by 3.6% and 0.7% of subjects who received Comparator QIV, respectively. Solicited systemic AEs with a maximum intensity of mild or moderate were experienced by the majority. The mean onset for solicited systemic events was generally between Day 2 - 4, and mean duration for all AEs was <2 days. Mean onset for headache, the most frequently experienced systemic AE, was Day 2.7 in Seqirus QIV gp and Day 3.3 in Comparator QIV gp; mean duration 1.3 and 1.6 days respectively. The mean onset for myalgia, the next most frequently experienced systemic AE, was Day 1.8 (Seqirus QIV) and Day 1.9 (Comparator QIV); mean duration 1.6 and 1.5 days respectively. The mean onset for fever was on Day 3.0 in the Seqirus QIV gp and on Day 3.5 in the Comparator QIV gp; mean duration 1.2 and 1.3 days respectively.

After the First Vaccination: In the 5 to 8 yrs age stratum, solicited systemic AEs after 1st vaccination were experienced by 25.5% (Seqirus QIV) and 24.0% (Comparator QIV) subjects.

The most frequently experienced solicited systemic AE was headache (Seqirus QIV: 11.3%; Comparator QIV: 9.6%). Myalgia, malaise and fatigue, nausea, diarrhoea, fever and vomiting reported in decreasing order of frequency. Solicited systemic AEs with maximum intensity of mild/moderate were experienced by the majority. Similar frequencies of moderate or severe solicited systemic AEs observed after Seqirus QIV vs. Comparator QIV. Solicited systemic AEs maximum intensity or severe were experienced by 1.6% (Seqirus QIV) and by 1.5% (Comparator QIV).

Seqirus QIV was associated with earlier onset of solicited systemic AEs than Comparator QIV (with the exception of vomiting), and most solicited systemic AEs resolved within 3 days. Mean onset for solicited systemic events was between Day 2 – 4; mean duration for all AEs was <2 days. The mean onset for headache, the most frequently experienced solicited systemic AE, was on Day 2.8 (Seqirus QIV) and Day 3.3 (Comparator QIV); mean duration 1.3 and 1.6 days respectively. The mean onset for myalgia, the next most frequently experienced solicited systemic AE, was Day 1.8 in both vaccine groups; mean duration 1.6 and 1.5 days respectively. The mean onset for fever was Day 3.1 (Seqirus QIV) and Day 3.5 (Comparator QIV); mean duration 1.2 and 1.4 days respectively.

After the Second Vaccination: In the 5 - 8 yrs age gp, solicited systemic AEs (overall and for each AE) were less frequent after the 2nd vaccination than after the 1st vaccination for all AEs except vomiting (overall, Seqirus QIV and Comparator QIV) and fever (Comparator QIV). Solicited systemic AEs after the 2nd vaccination were experienced by 16.9% of subjects who received Seqirus QIV and by 19.0% of subjects who received Comparator QIV. In both study vaccine groups, the most frequently experienced solicited systemic AEs were headache (Seqirus QIV: 6.7%; Comparator QIV: 7.9%) and malaise and fatigue (Seqirus QIV: 5.6%; Comparator QIV: 1.6%). Diarrhoea, myalgia and nausea were experienced in decreasing order of frequency in the Seqirus QIV gp. The mean times to first onset were earlier in the Seqirus QIV gp than Comparator QIV gp; duration of solicited systemic AEs similar between the vaccine groups. The majority in the 5 – 8 yrs age gp reported solicited systemic AEs of mild/moderate intensity. There were no severe solicited systemic AEs reported. After the 2nd vaccination, proportions reporting each of the solicited systemic AEs were not significantly different between the study vaccine groups.

Table 11: Maximum Intensity of Solicited Systemic AEs Experienced after Vaccination by Subjects 5 to 8 Years of Age (Solicited Safety Population), CSLCT-QIV-13-02

	Seqirus QIV (n=829)				Comparator QIV (n=274)				RR (95% CI)[a]
%[b] of subjects with:	Mild	Mod-erate	Severe	All grades	Mild	Mod-erate	Severe	All grades	
Systemic AEs After Any Vaccination[c]									
Any	17.9	8.1	1.6	27.6	15.0	9.9	1.5	26.3	1.05 (0.84; 1.32)
Headache	8.7	3.4	0.1	12.3	6.2	4.0	0.4	10.6	1.16 (0.79; 1.72)
Myalgia	7.2	2.4	0.1	9.8	8.8	2.2	0.4	11.3	0.86 (0.58; 1.28)
Malaise and Fatigue	4.6	3.9	0.4	8.8	2.6	3.3	0	5.8	1.51 (0.89; 2.55)
Nausea	3.7	3.1	0.1	7.1	4.0	4.4	0	8.4	0.85 (0.53; 1.35)
Diarrhoea	4.3	0.8	0	5.2	3.3	0.4	0	3.6	1.42 (0.72; 2.79)
Fever	1.9	1.3	1.2	4.5	1.5	1.5	0.7	3.6	1.22 (0.62; 2.43)
Vomiting	0.8	1.3	0.2	2.4	1.5	2.9	0	4.4	0.55 (0.27; 1.11)
Systemic AEs After the First Vaccination[c]									
	Seqirus QIV (n=826)				**Comparator QIV (n=271)**				
Any	16.6	7.3	1.6	25.5	14.4	8.1	1.5	24.0	1.07 (0.84; 1.36)
Headache	7.9	3.2	0.1	11.3	5.5	3.7	0.4	9.6	1.17 (0.78; 1.77)
Myalgia	7.3	2.2	0.1	9.6	8.1	2.2	0.4	10.7	0.89 (0.60; 1.34)
Malaise and Fatigue	4.0	3.8	0.4	8.1	2.6	3.0	0	5.5	1.47 (0.85; 2.52)
Nausea	3.8	2.8	0.1	6.8	3.7	3.7	0	7.4	0.92 (0.56; 1.50)
Diarrhoea	3.6	0.8	0	4.5	3.0	0.4	0	3.3	1.35 (0.66; 2.76)
Fever	1.7	1.1	1.2	4.0	1.1	1.1	0.7	3.0	1.35 (0.63; 2.89)
Vomiting	0.8	1.1	0.2	2.2	1.5	1.5	0	3.0	0.74 (0.32; 1.68)
Systemic AEs After the Second Vaccination[c]									
	Seqirus QIV (n=178)				**Comparator QIV (n=63)**				
Any	11.2	5.6	0	16.9	11.1	7.9	0	19.0	0.88 (0.48; 1.62)
Headache	5.6	1.1	0	6.7	6.3	1.6	0	7.9	0.85 (0.31; 2.32)
Malaise and Fatigue	5.1	0.6	0	5.6	0	1.6	0	1.6	3.54 (0.46, 27.10)
Diarrhoea	3.4	0.6	0	3.9	1.6	0	0	1.6	2.48 (0.31, 19.74)
Myalgia	1.7	1.7	0	3.4	6.3	0	0	6.3	0.53 (0.15; 1.82)
Nausea	1.7	1.7	0	3.4	1.6	3.2	0	4.8	0.71 (0.18; 2.75)
Fever	1.1	1.1	0	2.2	1.6	1.6	0	3.2	0.71 (0.13; 3.77)
Vomiting	1.1	1.1	0	2.2	0	6.3	0	6.3	0.35 (0.09; 1.37)

[a]Relative risk (RR) for Seqirus QIV compared to Comparator QIV = proportion of subjects with a given symptom in the Seqirus QIV group/proportion of subjects with a given symptom in the Comparator QIV group. If the value 1 is not in the range of the confidence interval (CI), it can be concluded that the proportions are significantly different in the two groups, and that there is an increased risk in one group compared to the other.
[b]Proportion of subjects based on the number of subjects in the respective group.
[c]Systemic adverse events: Fever: Mild (Grade 1) = ≥ 38.0°C to < 38.5°C, Moderate (Grade 2) = ≥ 38.5 to < 39.0°C, Severe (Grade 3) = ≥ 39.0°C; Severe (Grade 3) for all other adverse events is that which prevents daily activity.
Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 12.2.2-3, Post-Text Table 14.3.1.3.2; Table 14.3.1.3.3; Table 14.3.1.3.4.

Solicited systemic adverse events in children 9 - 17 yrs of age

Solicited systemic AEs experienced by 34.1% (Seqirus QIV) and by 28.7% (Comparator QIV) subjects. In both study vaccine groups, the most frequently experienced solicited systemic AE was headache (Seqirus QIV: 18.8%; Comparator QIV: 14.6%). Myalgia, malaise and fatigue, nausea, diarrhoea, fever and vomiting were reported in decreasing order of frequency for Seqirus QIV.

A higher frequency of some solicited systemic AEs seen with Seqirus QIV than Comparator QIV, particularly headache, myalgia, and malaise and fatigue. Fever was experienced by 2.1% who received Seqirus QIV and by 0.8% who received Comparator QIV. A significant difference for myalgia between two vaccines was observed in this age stratum. Seqirus QIV subjects were 1.5 times more likely to experience myalgia after vaccination vs. Comparator QIV (RR: 1.50; 95% CI 1.03, 2.19). The majority experienced solicited systemic AEs with maximum intensity of mild/moderate. Severe intensity solicited systemic AEs were reported by 1.4% and 0.8% in the Seqirus QIV and Comparator QIV groups respectively. Severe fever was experienced by 0.5% in the Seqirus QIV gp. There were no severe fevers experienced in the Comparator QIV gp. Seqirus QIV was associated with similar onset of solicited systemic AEs as Comparator QIV, except for fever. Mean onset for fever was Day 2.1 (Seqirus QIV) and Day 4.0 in the Comparator QIV gp; mean duration was 1.2 and 1.0 days respectively. Most solicited systemic AEs resolved in less than 2 days.

Table 12: Maximum Intensity of Solicited Systemic AEs Reported after Vaccination by Subjects 9 to 17 Years of Age (Solicited Safety Population), Study CSLCT-QIV-13-02

	Seqirus QIV (n=792)				Comparator QIV (n=261)				RR [95% CI][a]
%[b] of subjects with:	Mild	Mod-erate	Severe	All grades	Mild	Mod-erate	Severe	All grades	
Systemic AEs After Vaccination[c]									
Any	20.2	12.5	1.4	34.1	17.2	10.7	0.8	28.7	1.19 (0.96; 1.47)
Headache	12.0	6.4	0.4	18.8	8.8	5.4	0.4	14.6	1.29 (0.93; 1.79)
Myalgia	11.6	4.8	0.3	16.7	7.7	3.1	0.4	11.1	1.50 (1.03; 2.19)
Malaise and fatigue	5.3	4.3	0.4	10.0	5.4	2.3	0	7.7	1.30 (0.81; 2.08)
Nausea	4.9	2.8	0	7.7	4.2	3.8	0	8.0	0.96 (0.59; 1.54)
Diarrhoea	4.4	1.0	0	5.4	2.7	1.5	0	4.2	1.29 (0.67; 2.46)
Vomiting	1.3	0.5	0	1.8	0.8	1.5	0	2.3	0.77 (0.30; 1.98)
Fever	1.1	0.5	0.5	2.1	0.4	0.4	0	0.8	2.80 (0.65,12.04)

[a]Relative risk (RR) for Seqirus QIV compared to Comparator QIV = proportion of subjects with a given symptom in the Seqirus QIV group/proportion of subjects with a given symptom in the Comparator QIV group. If the value 1 is not in the range of the confidence interval (CI), it can be concluded that the proportions are significantly different between the two groups, and that there is an increased risk in one group compared to the other.
[b]Proportion of subjects based on the number of subjects in the respective group.
[c]Systemic adverse events: Fever: Mild (Grade 1) = ≥ 38.0°C to < 38.5°C, Moderate (Grade 2) = ≥ 38.5 to < 39.0°C, Severe (Grade 3) = ≥ 39.0°C; Severe (Grade 3) for all other adverse events is that which prevents daily activity.
Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 12.2.2-4, Post-Text Table 14.3.1.3.2.

7.4.2. Deaths and other serious adverse events in CSLCT-QIV-13-02

DEATHS: None. SAEs: 10 subjects (8 in the Seqirus QIV gp (0.5%) and 2 in the Comparator QIV gp (0.4%)) with 13 SAEs. Subject narratives for all SAEs are provided. One SAE (influenza) was assessed as related to study vaccine by the sponsor (but not by the Investigator) and the majority of SAEs were reported by subjects in the 9 to <18 yrs age stratum. AESI: None.

7.4.3. Discontinuations due to adverse events in CSLCT-QIV-13-02

No subjects discontinued due to an AE CSLCTQIV-13-02.

7.5. Issues in CSLCT-QIV-13-02 with possible regulatory impact

7.5.1. Liver function, liver toxicity, renal function, renal toxicity, other clinical chemistry, haematology and haematological toxicity

Not assessed.

7.5.2. Electrocardiograph findings and cardiovascular safety

Not applicable, not assessed.

7.5.3. Vital signs and clinical examination findings

None revealed.

7.5.4. Immunogenicity and immunological events

None revealed.

7.5.5. Serious skin reactions

One subject who received Seqirus QIV experienced a 'cellulitis-like reaction'. This subject experienced Grade 3 pain, Grade 3 swelling (up to 78mm), and Grade 3 redness (up to 78mm) concurrently from Day 3 -7 after 1st vaccination into right deltoid muscle. Investigator assessed and confirmed not cellulitis.

7.6. Other safety issues

7.6.1. Safety in special populations

Not assessed.

7.6.2. Safety related to drug-drug interactions and other interactions

Not assessed.

7.7. Post marketing experience

Not applicable.

7.8. Evaluator's overall conclusions on clinical safety

Safety data was provided for Afluria Quad from a single study conducted during the NH 2015-2016 season, CSLCT-QIV-13-02. In this study, the Seqirus QIV contained the 4 influenza strains split with a higher concentration of TDOC. In total, 874 children aged 5-8 years and 834 children/adolescents aged 9-17 years received at least 1 dose of Afluria Quad. Fever rates were comparable to the QIV comparator, in both age groups. There was a slight excess of local injection site reactions (pain/swelling/redness) in the younger age group compared to the comparator QIV, although these resolved quickly. There was also a slight excess of severe solicited local adverse reactions in the Seqirus QIV recipients versus Comparator QIV. One Seqirus QIV patient (aged 8) had a 'cellulitis like reaction' with grade 3 pain/swelling/redness which lasted through to Day 7 post vaccination. In the older age group myalgia was 1.5 fold more likely to be experienced in the Seqirus QIV recipients. Although relatively small numbers of subjects received a second vaccine on study, there was no evidence that receipt on the second vaccine was associated with an excess of solicited local and systemic side-effects, or unsolicited adverse events; in general the second vaccine was better tolerated. CSLCT-USF-10-69 provided supportive safety data for Seqirus TIV (2014-2015 NH season product) in which the H3N2 and B strains were split at the upper levels of TDOC concentration. In total there were 292 children aged 5-8 years in the safety analysis set for 1st vaccination. When considering historical fever rates in previous paediatric clinical studies (CSLCT-USF-07-36, CSLCT-USF-06-29 and CSLCT-FLU-04-05) in the same age group, overall and severe fever rates were lower in children vaccinated with the Seqirus TIV manufactured using higher TDOC splitting conditions for the H3N2 and B strains.

The clinical reviewer notes the reporting of an SAE ('severe delirium febrile') which was reported as 'expected' and then later reassessed as 'unlisted/unexpected'. This event was reported to the DSMB Chair. In summary, with respect to the safety data arising from Study CSLCT-QIV-13-02, Afluria Quad appears to have an acceptable safety profile in both age groups enrolled.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

See table below.

Table 13: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
1. Afluria Quad in the proposed usage provides non-inferior 'coverage' (antibody seroconversion and other	1. Data are robust, study design appropriate with adequate power, standard immunogenicity

Indication	
Benefits	**Strengths and Uncertainties**
standard measures of immunogenicity) against all 4 influenza strains contained in the vaccine vs. an approved US Comparator QIV. 2. Safety profile of this QIV is similar to the comparator QIV. 3. Safety data from the CSLCTUSF-10-69 study is supportive, although it used a TIV vaccine, with 2 of the 3 strains split with the higher concentrations of TDOC.	endpoints 2. Safety data provided for only 874 in the younger age group (5-8 years), I feel uncertain with this new QIV and with all 4 split with the higher percentages of TDOC, that this is sufficient immunogenicity and safety data. 3. While the safety data from the CSLCTUSF-10-69 study is reassuring, it did not use Afluria Quad, and is underpowered for the comparator arm. No immunogenicity data provided in this study. 4. Other QIV flu vaccines available, so this QIV will not fill a 'gap in the market'.

8.2. First round assessment of risks

See table below.

Table 14: First round assessment of risks

Risks	Strengths and Uncertainties
1. No data on the immunogenicity and safety profile in immunocompromised patients as these subjects were specifically excluded from participation; 2. Data supplied is over one NH season, in one country, predominantly children of white ethnicity enrolled, only 874 younger children aged 5-8 years exposed, are these data representative for a new formulation of QIV? 3. Hardly any data for the QIV in subjects of Asian ethnicity, this is of direct relevance to Australia. 4. No data for the QIV in Australian indigenous ethnicity – this is of direct relevance to Australia.	1. Flagged in the PI; as detailed in the RMP. Other routine measures including monitoring and reporting of post-marketing safety data and signal detection in the immunocompromised.

8.3. First round assessment of benefit-risk balance

While the data arising from this single Study CSLCT-QIV-13-02, demonstrate that Afluria Quad appears safe and immunogenic against all 4 influenza strains (2 x 'A' and 2 x 'B') in the younger and the older children enrolled in the study, the evaluator has a number of concerns:

- The study took place over just one NH season;
- The study enrolled predominantly children of white ethnicity, and hardly any children of Asian ethnicity were enrolled, this is of direct relevance to Australia;
- Overall, only 874 younger children (aged 5-8 years) have been exposed to Afluria Quad with all 4 strains split with higher levels of TDOC; do we know that future lots will be as immunogenic and safe?
- While CSLCTUSF-10-69 is a supportive study providing safety information without any immunogenicity data in the 5-8 year old age group, the TIV vaccine used in this study contained the H3N2 and B/Massachusetts/02/2012 (B Yamagata) strains split with higher concentrations of TDOC, the H1N1 strain was split with lower, more 'usual' concentrations of TDOC. While no safety signals of concern were revealed when comparing febrile reactions to historical data from older TIV formulations, these data would have been more compelling if the study was properly powered for the Comparator (a US registered QIV), and if the TIV vaccine had included all 3 strains split with higher concentrations of TDOC.
- The evaluator is aware that there is an ongoing study of Afluria Quad in children between the ages of 6-6-59 months, CSLCT-QIV-15-03, which is due to report in 3rd Quarter of 2017. The safety and immunogenicity data for different lot(s) of Afluria Quad (containing A/California/7/2009 (H1N1); A/Hong Kong/4801/2014 (H3N2); B/Phuket/3073/2013 (B Yamagata); B/Brisbane/60/2008; (B Victoria)), albeit in a slightly younger age group, will provide further important data of this QIV in children, albeit in a younger age group. The evaluator thinks the data arising from CSLCT-QIV-15-03 will compliment that already provided in CSLCT-QIV-13-02 and provide a broader immunogenicity and safety profile in the paediatric.

9. First round recommendation regarding authorisation

The evaluator does not recommend authorisation.

10. Clinical questions

10.1. Efficacy

None.

10.2. Safety

None.

10.3. Additional expert input

None required.

11. Second round evaluation

The sponsor submitted further documentation in June 2017. This documentation comprised, a cover letter, response to request for information, updated PI, CMI, Mock ups of the 1x and 10x carton and, Australian Specific Annex of the Risk Management Plan incorporating TGA's recommendations.

Included in this response is a response to the specific concerns raised above**.** The evaluator acknowledges this thoughtful response to the concerns. The evaluator is especially reassured by the following:

- The sponsor has provided a comprehensive of quality assurance that includes targeted splitting of all influenza strains included in QIV with 1.5% w/v TDOC, and a control strategy to ensure optimised lipid clearance. The non-clinical reviewer will need to comment on the adequacy of this response and the plan going forward, as this is beyond the remit of the Clinical Reviewer's expertise.
- The plans to not market Seqirus QIV for the indication aged 5 years and above, until the SH 2019 season, which will allow the review of further data arising from the following studies:
  - post marketing reports from the US 2018/2019 season;
  - safety surveillance for reactogenicity in Australia;
- Study CSLCT-QIV-15-03 has completed enrollment and the active study period, during the latter immunogenicity data, solicited and unsolicited data has been collected. The study is in follow-up to collect all SAE through to the 180 days post vaccination. The sponsor, in their response, has indicated that the Data Safety Monitoring Board for this study has not indicated any concerns re safety, and this is reassuring. It is planned to present these data from the active study period to the TGA in July 2017.

The evaluator has amended most of the report based on omissions/errors/oversights/requests for clarification of wording pointed out by the sponsor.

However, the evaluator has not updated the inclusion and exclusion criteria, as the evaluator has deliberately included what they consider to be 'key' criteria. The sponsor also requested that the evaluator update the inclusion and exclusion criteria for completeness for Study CSLCT-USF-10-69; however, the evaluator has not amended these since the evaluator has included what they consider to be the key inclusions and exclusions for this study.

The Reviewer notes the detailed explanation by the sponsor for the 'febrile delirium', and the sequence of events was consistent with the initial reporting of the serious event as 'expected' when in fact it was 'unexpected.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

Predicated upon further safety data as planned, including data from Study CSLCT-QIV-15-03, the benefit for the use of this QIV may be favourable in those aged 5 years and older.

12.2. Second round assessment of risks

As above, the sponsor has provided some reassurances in their response, including the lack of any safety concerns in Study CSLCT-QIV-15-03, but TGA will still need to review these data. This is planned in July 2017.

12.3. Second round assessment of benefit-risk balance

The evaluator may be in favour of benefit, predicated upon further safety data including data from Study CSLCT-QIV-15-03 indicating no concerning safety signal.

13. Second round recommendation regarding authorisation

No recommendation at this juncture; further safety data will be provided in the younger age group enrolled in Study CSLCT-QIV-15-03 to TGA in July 2017.[2]

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au