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| Application Type | BLA Supplement |
| STN | 125254/565 |
| CBER Received Date | October 28, 2015 |
| PDUFA Goal Date | August 27, 2016 |
| Division / Office | DVRPA/OVRR |
| Committee Chair | Richard Daemer, PhD |
| Clinical Reviewer(s) | Cynthia Nolletti, MD |
| Project Manager | Katherine Berkhousen, RN<br>Timothy Fritz, PhD |
| Priority Review | No |
| Reviewer Name(s) | Rong Fu, PhD |
| Review Completion Date / Stamped Date | |
| Supervisory Concurrence | Tsai-Lien Lin, PhD<br>Team Leader, Bioassay & Viral Team, VEB/DB/OBE |
| | A. Dale Horne, Dr. P.H.<br>Branch Chief, VEB/DB/OBE |
| Applicant | bioCSL Pty Ltd |
| Established Name | Influenza Vaccine |
| (Proposed) Trade Name | Afluria Quadrivalent, Influenza Vaccine |
| Formulation(s), including Adjuvants, etc | Each 0.5 mL dose of the 2014-2015 vaccine contains 15 mcg hemagglutinin from each of the following influenza strains: A/California/7/2009 (H1N1) pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Massachusetts/2/2012-like virus (B/Yamagata lineage) and B/Brisbane/60/2008-like virus (B/Victoria lineage). |
| Dosage Form(s) and Route(s) of Administration | Administered as a single dose (0.5 mL) intramuscularly into the deltoid muscle |
| Indication(s) and Intended Population(s) | Active immunization against influenza disease caused by influenza virus present in vaccine |

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## GLOSSARY

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|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| BLA | Biologics License Application |
| CI | Confidence Interval |
| CSR | Clinical Study Report |
| FAS | Full Analysis Set |
| GLM | General Linear Model |
| GMT | Geometric Mean Titer |
| HA | Hemagglutinin |
| HI | Hemagglutination Inhibition |
| IR | Information Request |
| LS | Least Squares |
| PP | Per-Protocol |
| QIV | Quadrivalent Influenza Vaccine |
| RR | Relative Risk |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCR | Seroconversion rate |
| TIV | Trivalent Influenza Vaccine |

## 1. EXECUTIVE SUMMARY

The supplement Biologics License Application (BLA) was submitted by bioCSL to seek licensure for their Afluria Quadrivalent Influenza Vaccine (bioCSL QIV), indicated for active immunization in adults 18 years of age and older against influenza disease caused by influenza virus contained in the vaccine. The application was supported by a phase 3, randomized, double-blinded, and comparator-controlled study to evaluate the immunogenicity and safety of bioCSL QIV compared with a US licensed 2014-2015 Trivalent Influenza Virus Vaccine (bioCSL TIV-1), and a TIV containing the alternate B strain (bioCSL TIV-2).

The primary objective of demonstrating the immunogenicity non-inferiority of bioCSL QIV to the bioCSL TIV comparators as measured by the Hemagglutinin Inhibition (HI) titers against influenza strains contained in the vaccine in adults ≥18 years of age was met. Specifically,

- The upper bounds of the two-sided 95% confidence interval (CI) of the geometric mean titer (GMT) ratio (bioCSL TIV/bioCSL QIV) did not exceed 1.5: the HI GMT ratios and 95% CIs for each of the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) were 0.93 (0.88, 0.99), 0.93 (0.88, 0.98), 0.87 (0.82, 0.93), and 0.95 (0.88, 1.03), respectively.
- The upper bounds of the two-sided 95% CI of the seroconversion rate (SCR) difference (bioCSL TIV-bioCSL QIV) did not exceed 10%: the HI SCR differences and 95% CIs for each of the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) were -1.1 (-4.5, 2.3), -1.7 (-5.0, 1.7), -3.2 (-7.4, 0.9), and -1.6 (-5.8, 2.5), respectively.

In addition, the same non-inferiority criteria were met for HI GMT and SCR endpoints within each of the two age cohorts (18-64 and ≥65 years) for each strain as secondary analyses, with no pre-defined multiplicity adjustment.

Regarding safety, no notable differences were found in the proportions of subjects reporting any or Grade 3 solicited local/systemic adverse events (AEs) and unsolicited AEs, or any serious adverse events (SAEs) comparing the bioCSL QIV group to bioCSL TIV groups. No cellulitis-like reaction or cellulitis at the injection site was reported. One death due to pneumonia in the bioCSL QIV group was assessed by the investigator as related to vaccination. Detailed evaluation of this death event is deferred to the clinical reviewer.

## 2. CLINICAL AND REGULATORY BACKGROUND

On September 28, 2007, bioCSL's BLA for Afluria® TIV was approved for active immunization in adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and B present in the vaccine. In October 2015, bioCSL submitted this supplement BLA to seek licensure of their QIV in adults 18 years and older for active immunization against influenza disease caused by influenza virus present in the vaccine.

The basis of this application is study CSLCT-QIV-13-01, a phase 3, randomized, multicenter, double-blinded study to evaluate the immunogenicity and safety of bioCSL QIV in comparison with a US licensed 2014-2015 TIV (bioCSL TIV-1, i.e., Afluria® TIV), and a TIV containing the alternate B strain (bioCSL TIV-2), in adults ≥18 years of age. The bioCSL QIV formulation was consistent with the 2014-2015 Afluria® TIV, with the additional alternate lineage influenza B strain, which increased the total hemagglutinin (HA) content from 45 mcg to 60 mcg per 0.5 mL dose.

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

### 5.1 Review Strategy

This review focuses on the immunogenicity and safety objectives of study CSLCT-QIV-13-01. The submitted data and Clinical Study Report (CSR) were reviewed.

### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review is primarily based on Modules 2 and 5 of STN 125254/565 (received on October 28, 2015), as well as two subsequent amendments STN 125254/565/12 (received on June 2, 2016) and STN 125254/565/17 (received on July 11, 2016) submitted by bioCSL in response to CBER's Information Requests (IRs).

### 5.3 Table of Studies/Clinical Trials

One clinical trial was submitted to support the application (Table 1).

**Table 1: Overview of Study CSLCT-QIV-13-01**

| Study Identification | Season | Country | Design | Study Arms (Number of Subjects Randomized) | Objectives |
|---|---|---|---|---|---|
| CSLCT-QIV-13-01 | 2014-2015 | US | Phase 3, randomized, double-blinded, multicenter, comparator-controlled, 18-64 years and ≥65 equally stratified. | QIV (N=1741)<br>TIV-1 (N= 871)<br>TIV-2 (N= 872) | Immunogenicity (non-inferiority, superiority to alternate B strain), safety/tolerability. |

Source: Module 2, Clinical Overview

# 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

## 6.1 Study CSLCT-QIV-13-01

### 6.1.1 Objectives

Primary Objective

- To demonstrate that vaccination with bioCSL QIV elicits an immune response that is not inferior to that of bioCSL TIV containing the same virus strains as the US licensed 2014-2015 bioCSL influenza vaccine (bioCSL TIV-1), and the TIV containing the alternate B strain (bioCSL TIV-2) among adults aged ≥18 years.

Secondary Objectives

To assess the following, among adults aged ≥18 years in two age cohorts 18-64 years and ≥65 years, as well as overall:

- To demonstrate that vaccination with bioCSL QIV elicits an immune response that is not inferior to that of bioCSL TIV-1 and bioCSL TIV-2;
- To demonstrate the immunological superiority of bioCSL QIV compared to bioCSL TIV-1 and bioCSL TIV-2 for the B strain that was not included in each TIV vaccine separately;
- To characterize the immunogenicity of bioCSL QIV, bioCSL TIV-1, and bioCSL TIV-2;
- To assess the safety and tolerability of bioCSL QIV.

### 6.1.2 Design Overview

Study subjects were randomized by age cohort (18-64 and ≥65 years; approximately equal number of subjects in each age cohort) in a 2:1:1 ratio to receive a single dose of bioCSL QIV, bioCSL TIV-1, or bioCSL TIV-2 at Day 1 (Visit 1). Further stratification within each age cohort was conducted, to obtain a maximum of 60% in one subgroup (18-49 or 50-64 years) for the younger adult cohort (18-64 years), and a minimum of 30% in the >75 years subgroup for the older adult cohort (≥65 years).

Blood samples were collected on Day 1 prior to vaccination and Day 21 (Visit 2) for immunogenicity measurements. Subjects reported solicited local and systemic symptoms and recorded temperature on a 7-day diary, and reported unsolicited AEs for the day of vaccination and the following 20 days, and any ongoing or new unsolicited AEs on a Day 22-28 diary. Subjects were instructed to contact the investigator/delegate immediately if they experienced a cellulitis-like reaction (between Day 1 and Day 28) or any signs or

symptoms of an influenza-like illness (experienced between Visit 1 and Visit 2). Monitoring for SAEs occurred for 6 months following vaccination.

6.1.3 Population

Subjects enrolled in this study were healthy males and non-pregnant females 18 years of age and older.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each subject received one 0.5 mL dose of study vaccine on Day 1 in the deltoid region of the non-dominant arm, by intramuscular injection. Each dose of the study vaccine contained 15 mcg HA from each of the strains as listed in Table 2.

**Table 2: Study Vaccine Strains**

| Influenza Strain | bioCSL QIV | bioCSL TIV-1 | bioCSL TIV-2 |
|---|---|---|---|
| A/California/7/2009 (H1N1) pdm09-like virus | ✓ | ✓ | ✓ |
| A/Texas/50/2012 (H3N2)-like virus | ✓ | ✓ | ✓ |
| B/Massachusetts/2/2012-like virus (B/Yamagata)[1] | ✓ | ✓ | |
| B/Brisbane/60/2008-like virus (B/Victoria)[2] | ✓ | | ✓ |

[1] B strain recommended for TIV.
[2] Alternate B strain to that recommended for TIV.
Source: CSR

6.1.6 Sites and Centers

The study was conducted in 31 US centers.

6.1.7 Surveillance/Monitoring

NA

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

- The co-primary endpoints were the 21-day post-vaccination HI GMT and SCR for each of the four virus strains included in the vaccines. The SCR was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a ≥4-fold increase in post-vaccination HI titer.
    - Non-inferiority criteria: for each of the four strains, the upper bound of the two-sided 95% CI on the GMT ratio (bioCSL TIV/ bioCSL QIV) ≤1.5, and the upper bound of the two-sided 95% CI of the difference in SCR (bioCSL TIV-bioCSL QIV) ≤10%.

Secondary Immunogenicity Endpoints

- The non-inferiority of bioCSL QIV compared to bioCSL TIV-1, and to bioCSL TIV-2 was assessed separately within each age cohort (18-64 and ≥65 years), by the co-primary endpoints of HI GMT and SCR for each virus strain included in the vaccines as described for the primary endpoint.

- Immunologic superiority of the alternate B strain in bioCSL QIV was assessed separately within each age cohort (18-64 and ≥65 years), and overall, by the co-primary endpoints of HI GMT and SCR for each B virus strain.
    - Superiority criteria: the lower bound of the two-sided 95% CI on the GMT ratio (bioCSL QIV/bioCSL TIV) >1, and the lower bound of the two-sided 95% CI of the difference in SCR (bioCSL QIV-bioCSL TIV) >0.
- The immunogenicity of bioCSL QIV, bioCSL TIV-1 and bioCSL TIV-2 was assessed in terms of HI GMT at Days 1 and 21, Geometric Mean Fold Increase from Day 1 to Day 21, the percentage of subjects with a titer ≥1:40 at Days 1 and 21, and SCR at Day 21, for each age cohort as well as overall.

Secondary Safety Endpoints

- Solicited local and systemic AEs for 7 days following vaccination;
- Cellulitis-like reaction, cellulitis, and Grade 3 injection site induration/swelling for 28 days following vaccination;
- Unsolicited AEs for 28 days following vaccination;
- SAEs for 6 months following vaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size determination

At the time of study design, the sample size was determined to achieve at least 80% power to demonstrate immunogenicity non-inferiority in each age cohort.

Immunogenicity analyses

The primary non-inferiority assessment was performed in adults ≥18 years of age on the Per-Protocol (PP) Population (see Section 6.1.10.1). For A/H1N1 and A/H3N2 strains, the two TIV groups were pooled. For B/Yamagata strain, bioCSL QIV was compared to bioCSL TIV-1; and for B/Victoria strain, bioCSL QIV was compared to bioCSL TIV-2. Each strain was analyzed separately. No multiplicity adjustment was incorporated.

- For the GMT analyses, a general linear model (GLM) was fitted for log-transformed post-vaccination HI titer versus vaccine, with adjustment covariates including age group (18-49, 50-64, 65-74, and ≥75 years), sex, influenza vaccination received prior year (Y/N), log transformed pre-vaccination titer, and site. The difference in least squares (LS) means and 95% confidence limits were estimated from the model, and back transformed to obtain the adjusted GMT ratio with 95% CIs, which were then used for the non-inferiority evaluation.
- For the SCR analyses, the differences in SCRs were presented with exact 95% CIs.

The PP Population was also used for secondary immunogenicity analyses. The secondary non-inferiority assessment by age cohort was performed in the same way as for the primary analyses, except that age group was omitted from the GLM model. For the secondary superiority assessment, bioCSL QIV was compared to bioCSL TIV-2 for the B/Yamagata strain, and to bioCSL TIV-1 for the B/Victoria strain.

Safety analyses

Safety analyses were conducted in a descriptive manner by summarizing the frequencies and percentages of subjects experiencing events. The Safety Population was used for the safety analyses (see Section 6.1.10.1).

***Reviewer's comments:***

*In the initially submitted CSR, the following key deviations from the original Statistical Analysis Plan (SAP) were identified:*

- *An age-by-vaccine interaction was added to the GLM model for the HI GMT non-inferiority analyses on overall adults ≥18 years of age.*
- *The 95% confidence limits of the SCR difference were not based on the exact method.*

*The immunogenicity results from the modified models/methods were not considered satisfactory, so an IR was issued on May 20, 2016, requesting the applicant to reanalyze the data following the SAP. Results presented in this review were based on the applicant's reanalysis, and were similar to those presented in the CSR.*

*Relative risks (RRs) were presented for some of the safety data analyses. The method to calculate the RR CIs were not explicitly stated in the SAP or CSR. Apparently the Wald method was used.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

- Full Analysis Set (FAS) comprised all subjects who provided informed consent and who were randomized to treatment. Screening failures were not included in the FAS.
- Safety Population comprised all subjects in the FAS who received at least one dose of study vaccine and provided follow-up safety data. A statement that there were no AEs constituted follow-up safety data.
- Evaluable Population consisted of subjects in the FAS who were vaccinated with the study vaccine at Visit 1, provided both pre- and post-vaccination blood samples at Visit 1 and Visit 2, did not experience a laboratory-confirmed influenza illness between Visit 1 and Visit 2, and did not receive a contraindicated medication during the study that was medically assessed as potentially impacting on the immunogenicity results.
- Per-Protocol Population included subjects in the Evaluable Population minus any subjects with deviations that were thought to potentially affect the immunogenicity results.

6.1.10.1.1 Demographics

Baseline and demographic characteristics are summarized by treatment group and overall for the FAS in Table 3. The distributions of these characteristics were well balanced

across the three treatment groups, except for a slightly higher proportion of Hispanic or Latino subjects in the bioCSL TIV-1 group compared to the bioCSL TIV-2 group.

**Table 3: Demographics and Baseline Characteristics (Full Analysis Set)**

| | bioCSL QIV | bioCSL TIV-1 | bioCSL TIV-2 | bioCSL TIV (pooled) | Overall |
|---|---|---|---|---|---|
| | N=1741 | N=871 | N=872 | N=1743 | N=3484 |
| Age (years) | | | | | |
| Mean ± SD | 58.3 ± 18.10 | 58.2 ± 18.10 | 58.3 ± 17.89 | 58.2 ± 17.99 | 58.3 ± 18.04 |
| Age Group (%) | | | | | |
| 18-49 years | 510 (29.3) | 255 (29.3) | 255 (29.2) | 510 (29.3) | 1020 (29.3) |
| 50-64 years | 361 (20.7) | 179 (20.6) | 181 (20.8) | 360 (20.7) | 721 (20.7) |
| 65-74 years | 541 (31.1) | 271 (31.1) | 270 (31.0) | 541 (31.0) | 1082 (31.1) |
| ≥75 years | 329 (18.9) | 166 (19.1) | 166 (19.0) | 332 (19.0) | 661 (19.0) |
| Sex (%) | | | | | |
| Male | 770 (44.2) | 360 (41.3) | 362 (41.5) | 722 (41.4) | 1492 (42.8) |
| Female | 971 (55.8) | 511 (58.7) | 510 (58.5) | 1021 (58.6) | 1992 (57.2) |
| Ethnicity (%) | | | | | |
| Hispanic or Latino | 84 (4.8) | 57 (6.5) | 31 (3.6) | 88 (5.0) | 172 (4.9) |
| Not Hispanic or Latino | 1653 (94.9) | 813 (93.3) | 839 (96.2) | 1652 (94.8) | 3305 (94.9) |
| Not Reported | 4 (0.2) | 1 (0.1) | 2 (0.2) | 3 (0.2) | 7 (0.2) |
| Race (%) | | | | | |
| White | 1428 (82.0) | 719 (82.5) | 722 (82.8) | 1441 (82.7) | 2869 (82.3) |
| Black or African American | 283 (16.3) | 131 (15.0) | 135 (15.5) | 266 (15.3) | 549 (15.8) |
| Asian | 12 (0.7) | 7 (0.8) | 4 (0.5) | 11 (0.6) | 23 (0.7) |
| American Indian/Alaska Native | 5 (0.3) | 4 (0.5) | 5 (0.6) | 9 (0.5) | 14 (0.4) |
| Native Hawaiian or Pacific Islander | 2 (0.1) | 4 (0.5) | 0 (0.0) | 4 (0.2) | 6 (0.2) |
| Other | 11 (0.6) | 6 (0.7) | 6 (0.7) | 12 (0.7) | 23 (0.7) |

Source: Table 14.1.2.1 of CSR

***Reviewer's comments:***

*No notable differences were observed in the distribution of ethnicity between the bioCSL QIV group and each bioCSL TIV group in the Safety and PP Populations. Thus, the comparisons between them were unlikely to be biased.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

NA

6.1.10.1.3 Subject Disposition

A total of 3673 subjects were screened and of these, 3484 were randomized to study vaccines. Subject distribution in analysis populations, proportions of subjects completing the study, and reasons for discontinuation are summarized in Table 4. The most common reason for a subject in the FAS being excluded from the PP population was not having both pre- and post-vaccination blood samples (52 subjects; 1.5%).

**Table 4: Subject Disposition**

| | bioCSL QIV n (%[a]) | bioCSL TIV-1 n (%[a]) | bioCSL TIV-2 n (%[a]) | Overall n (%[a]) |
|---|---|---|---|---|
| Full Analysis Set | 1741 | 871 | 872 | 3484 |
| Safety Population | 1721 (98.9) | 864 (99.2) | 864 (99.1) | 3449 (99.0) |
| Evaluable Population | 1704 (97.9) | 857 (98.4) | 854 (97.9) | 3415 (98.0) |
| Per-Protocol Population | 1691 (97.1) | 854 (98.0) | 850 (97.5) | 3395 (97.4) |
| Completed Study | 1686 (96.8) | 852 (97.8) | 850 (97.5) | 3388 (97.2) |
| Discontinued from Study | 55 (3.2) | 19 (2.2) | 22 (2.5) | 96 (2.8) |
| Lost to Follow-Up | 46 (2.6) | 18 (2.1) | 18 (2.1) | 82 (2.4) |
| Withdrawal by Subject | 2 (0.1) | 0 | 2 (0.2) | 4 (0.1) |
| Death | 5 (0.3) | 0 | 1 (0.1) | 6 (0.2) |
| Other[b] | 2 (0.1) | 1 (0.1) | 1 (0.1) | 4 (0.1) |

[a] Percentages were based on the number of subjects in the Full Analysis Set in each group.
[b] All four subjects withdrew due to "other" reasons were not vaccinated.
Source: Table 14.1.1.1 of CSR

## 6.1.11 Efficacy Analyses

### 6.1.11.1 Analyses of Primary Endpoint(s)

Table 5 summarizes the primary analysis results on the co-primary endpoints of HI GMT and SCR for each strain in adults ≥18 years of age. The pre-specified non-inferiority criteria for the GMT ratio and SCR difference were met for all four strains.

**Table 5: Post-vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of bioCSL QIV Relative to bioCSL TIV for each Strain 21 Days Post-vaccination in Adults Aged ≥18 Years (Per-Protocol Population)**

| Strain | Post-vaccination Geometric Mean Titer[a] | | | Seroconversion Rate n (%) | | | |
|---|---|---|---|---|---|---|---|
| | bioCSL QIV[b] | Pooled TIV (A strains) or TIV-1 (B/Yamagata) or TIV-2 (B/Victoria)[c] | GMT ratio[d] (95% CI) | bioCSL QIV[b] | Pooled TIV (A strains) or TIV-1 (B/Yamagata) or TIV-2 (B/Victoria)[c] | SCR Difference[e] (95% CI) | Met both Pre-specified non-inferiority criteria[f]? |
| A/H1N1 | 302.1 | 281.1 | 0.93 (0.88, 0.99) | 656 (38.8) | 642 (37.7) | -1.1 (-4.5, 2.3) | Yes |
| A/H3N2 | 488.5 | 454.5 | 0.93 (0.88, 0.98) | 692 (40.9) | 669 (39.3) | -1.7 (-5.0, 1.7) | Yes |
| B/Yamagata | 64.1 | 56.0 | 0.87 (0.82, 0.93) | 524 (31.0) | 237 (27.8) | -3.2 (-7.4, 0.9) | Yes |
| B/Victoria | 87.6 | 83.0 | 0.95 (0.88, 1.03) | 682 (40.3) | 329 (38.7) | -1.6 (-5.8, 2.5) | Yes |

[a] Adjusted GMT Model: Log-transformed Post-vaccination HI Titer = Vaccine + Age Group (18-49, 50-64, 65-74, ≥75) + Sex + Vaccination History (y/n) + Log-transformed Pre-vaccination HI Titer + Site.
[b] bioCSL QIV, N=1691
[c] For A strains, bioCSL QIV was compared to Pooled TIV (N=1704); for B/Yamagata, bioCSL QIV was compared to TIV-1 (N=854); for B/Victoria, bioCSL QIV was compared to TIV-2 (N=850).
[d] GMT Ratio = bioCSL TIV/bioCSL QIV
[e] SCR difference = bioCSL TIV-bioCSL QIV
[f] Non-inferiority criteria: the upper bound of the two-sided 95% CI of the GMT ratio ≤1.5; the upper bound of the two-sided 95% CI of the SCR difference ≤10%.
Source: Table 11.4-1 and Table 14.2.2.1.1 of the IR response submitted in STN 125254/565/12

### 6.1.11.2 Analyses of Secondary Endpoints

Non-inferiority analyses by age cohort

The co-primary endpoints of HI GMT and SCR for each strain were assessed separately within each age cohort (18-64 and ≥65 years). The non-inferiority criteria for GMT ratio and SCR difference were met for all four strains, as shown in Table 6. Generally, the

immune response induced by bioCSL QIV was lower in older adults (≥65 years) compared to younger adults (18-64 years) for all strains.

**Table 6: Post-vaccination HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of bioCSL QIV Relative to bioCSL TIV for each Strain 21 Days Post-vaccination by Age Cohort (Per-Protocol Population)**

| | Post-vaccination Geometric Mean Titer[a] | | | Seroconversion Rate n (%) | | | |
|---|---|---|---|---|---|---|---|
| Strain | bioCSL QIV | Pooled TIV (A strains) or TIV-1 (B/ Yamagata) or TIV-2 (B/ Victoria)[b] | GMT ratio[c] (95% CI) | bioCSL QIV | Pooled TIV (A strains) or TIV-1 (B/ Yamagata) or TIV-2 (B/ Victoria)[b] | SCR Difference[d] (95% CI) | Met both Pre-specified non-inferiority criteria[e]? |
| 18-64 years[f] | | | | | | | |
| A/H1N1 | 432.7 | 402.8 | 0.93 (0.85, 1.02) | 428 (51.3) | 415 (49.1) | -2.1 (-6.9, 2.7) | Yes |
| A/H3N2 | 569.1 | 515.1 | 0.91 (0.83, 0.99) | 470 (56.3) | 437 (51.7) | -4.6 (-9.4, 0.2) | Yes |
| B/Yamagata | 92.3 | 79.3 | 0.86 (0.76, 0.97) | 382 (45.7) | 175 (41.3) | -4.5 (-10.3, 1.4) | Yes |
| B/Victoria | 110.7 | 95.2 | 0.86 (0.76, 0.98) | 481 (57.6) | 223 (53.0) | -4.6 (-10.5, 1.2) | Yes |
| ≥65 years[g] | | | | | | | |
| A/H1N1 | 211.4 | 199.8 | 0.95 (0.88, 1.02) | 228 (26.6) | 227 (26.4) | -0.2 (-5.0, 4.5) | Yes |
| A/H3N2 | 419.5 | 400.0 | 0.95 (0.89, 1.02) | 222 (25.9) | 232 (27.0) | 1.1 (-3.7, 5.8) | Yes |
| B/Yamagata | 43.3 | 39.1 | 0.90 (0.84, 0.97) | 142 (16.6) | 62 (14.4) | -2.2 (-8.0, 3.6) | Yes |
| B/Victoria | 66.1 | 68.4 | 1.03 (0.94, 1.14) | 201 (23.5) | 106 (24.7) | 1.2 (-4.6, 7.0) | Yes |

[a] Adjusted GMT Model: Log-transformed Post-vaccination HI Titer = Vaccine + Sex + Vaccination History (y/n) + Log-transformed Pre-vaccination HI Titer + Site.
[b] For A strains, bioCSL QIV was compared to Pooled TIV; for B/Yamagata, bioCSL QIV was compared to TIV-1; for B/Victoria, bioCSL QIV was compared to TIV-2.
[c] GMT Ratio = bioCSL TIV/bioCSL QIV
[d] SCR difference = bioCSL TIV-bioCSL QIV
[e] Non-inferiority criteria: the upper bound of the two-sided 95% CI of the GMT ratio ≤1.5; the upper bound of the two-sided 95% CI of the SCR difference ≤10%.
[f] 18-64 years: bioCSL QIV N=835, Pooled TIV N=845, TIV-1 N=424, TIV-2 N=421.
[g] ≥65 years: bioCSL QIV N=856, Pooled TIV N=859, TIV-1 N=430, TIV-2 N=429.
Source: Table 14.2.4.1 of CSR and Table 14.2.4.2.1 of the IR response submitted in STN 125254/565/12

Superiority analyses of the alternate B strain, overall and by age cohort

Immunologic superiority of the alternate B strain in bioCSL QIV was assessed separately within each age cohort (18-64 and ≥65 years), and overall, by the co-primary endpoints of HI GMT and SCR for each B virus strain. As shown in Table 7, the superiority criteria were met for both B strains in adults ≥18 years, as well as within each age cohort.

**Table 7: Post-vaccination HI Antibody GMTs, SCRs, and Analyses of Superiority of bioCSL QIV Relative to bioCSL TIV for the Alternate B Strain Overall in Adults ≥18 Years and by Age Cohort (Per-Protocol Population)**

| | Post-vaccination Geometric Mean Titer[a] | | | Seroconversion Rate n (%) | | | |
|---|---|---|---|---|---|---|---|
| Strain | bioCSL QIV | TIV-2 (B/Yamagata) or TIV-1 (B/Victoria)[b] | GMT ratio[c] (95%CI) | bioCSL QIV | TIV-2 (B/Yamagata) or TIV-1 (B/Victoria)[b] | SCR Difference[d] (95%CI) | Met both Pre-specified superiority criteria[e]? |
| ≥18 years[f] | | | | | | | |
| B/Yamagata | 62.9 | 42.7 | 1.47 (1.38,1.57) | 524 (31.0) | 133 (15.6) | 15.3 (11.2,19.4) | Yes |
| B/Victoria | 86.9 | 55.4 | 1.57 (1.45,1.70) | 682 (40.3) | 173 (20.3) | 20.1 (16.0,24.1) | Yes |
| 18-64 years[g] | | | | | | | |
| B/Yamagata | 89.9 | 53.8 | 1.67 (1.50,1.87) | 382 (45.7) | 96 (22.8) | 22.9 (17.1,28.6) | Yes |
| B/Victoria | 113.5 | 64.3 | 1.76 (1.55,2.01) | 481 (57.6) | 123 (29.0) | 28.6 (22.9,34.2) | Yes |
| ≥65 years[h] | | | | | | | |
| B/Yamagata | 43.8 | 33.6 | 1.30 (1.21,1.40) | 142 (16.6) | 37 (8.6) | 8.0 (2.2,13.8) | Yes |
| B/Victoria | 64.1 | 46.3 | 1.38 (1.27,1.51) | 201 (23.5) | 50 (11.6) | 11.9 (6.0,17.6) | Yes |

[a] Adjusted GMT Model (≥18 years): Log-transformed Post-vaccination HI Titer = Vaccine + Age Group (18-49, 50-64, 65-74, ≥ 75) + Sex + Vaccination History (y/n) + Log-transformed Pre-vaccination HI Titer + Site + Age Group*Vaccine. Adjusted GMT Model (each age cohort): Log-transformed Post-vaccination HI Titer = Vaccine + Sex + Vaccination History (y/n) + Log-transformed Pre-vaccination HI Titer + Site.
[b] For B/Yamagata, bioCSL QIV was compared to TIV-2; for B/Victoria, bioCSL QIV was compared to TIV-1.
[c] GMT Ratio = bioCSL QIV/bioCSL TIV
[d] SCR difference = bioCSL QIV - bioCSL TIV
[e] Superiority criteria: the lower bound of two-sided 95% CI of the GMT ratio >1; the lower bound of two-sided 95% CI of the SCR difference >0.
[f] ≥18 years: bioCSL QIV N=1691; TIV-1 N=854; TIV-2 N=850.
[g] 18-64 years: bioCSL QIV N=835; TIV-1 N=424; TIV-2 N=421.
[h] ≥65 years: bioCSL QIV N=856; TIV-1 N=430; TIV-2 N=429.
Source: Table 14.2.4.3 of CSR and Table 14.2.4.4.1 of the IR response submitted in STN 125254/565/12

***Reviewer's comments:***

*While the superiority criteria were met for both age cohorts, the treatment effect of bioCSL QIV in eliciting an immune response tended to be higher in the younger age cohort than in the older age cohort.*

6.1.11.3 Subpopulation Analyses

Analyses of the co-primary endpoints were also performed by sex, race, and ethnicity. For the subgroups of male, female, white, and Not Hispanic or Latino subjects, the upper bounds of the two-sided 95% CI for the GMT ratio (bioCSL TIV/bioCSL QIV) did not exceed 1.5 and the upper bounds of the two-sided 95% CI for the SCR difference (bioCSL TIV-bioCSL QIV) did not exceed 10%. Other race and ethnicity subgroups had sample sizes too small to support meaningful statistical analyses.

A summary of the post-vaccination HI titers by subgroup is provided in Table 8. The results show that, among subjects who received bioCSL QIV:

- females had slightly higher post-vaccination HI GMT and SCR than males for each strain;
- the post-vaccination HI GMTs and SCRs were higher in black or African Americans compared to white subjects;

- Hispanic or Latino subjects showed higher post-vaccination HI GMTs and SCRs than Not Hispanic or Latino subjects.

**Table 8: Post-vaccination HI Antibody GMTs and SCRs for bioCSL QIV Recipients by Sex, Race, and Ethnicity in Adults ≥18 Years (Per-Protocol Population)**

| Strain | Female | Male | White | Black or African American | Hispanic or Latino | Not Hispanic or Latino |
|---|---|---|---|---|---|---|
| | N=950 | N=741 | N=1397 | N=265 | N=79 | N=1608 |
| Post-vaccination GMT | | | | | | |
| A/H1N1 | 293.1 | 250.2 | 251.0 | 412.4 | 571.0 | 264.1 |
| A/H3N2 | 452.5 | 413.2 | 422.0 | 503.6 | 587.8 | 430.1 |
| B/Yamagata | 62.1 | 58.7 | 56.3 | 88.6 | 114.6 | 58.6 |
| B/Victoria | 78.4 | 76.1 | 74.6 | 93.3 | 101.4 | 76.2 |
| Seroconversion rate % (95% CI) | | | | | | |
| A/H1N1 | 40.5 (37.4, 43.7) | 36.6 (33.1, 40.2) | 36.9 (34.4, 39.5) | 48.3 (42 1, 54 5) | 69.6 (58.2, 79.5) | 37.3 (34.9, 39.7) |
| A/H3N2 | 42.8 (39.7, 46.1) | 38.5 (34.9, 42.1) | 37.7 (35.1, 40.3) | 57.7 (51 5, 63.8) | 63.3 (51.7, 73.9) | 39.8 (37.4, 42.2) |
| B/Yamagata | 32.4 (29.5, 35.5) | 29.1 (25.9, 32.6) | 29.4 (27.0, 31.9) | 40.0 (34 1, 46 2) | 60.8 (49.1, 71.6) | 29.5 (27.3, 31.8) |
| B/Victoria | 43.2 (40.0, 46.4) | 36.7 (33.2, 40.3) | 38.2 (35.6, 40.8) | 50.6 (44.4, 56.7) | 63.3 (51.7, 73.9) | 39.2 (36.8, 41.6) |

Source: Tables 14.2.4.5, 14.2.4.6, 14.2.4.9, 14.2.4.10, 14.2.4.13, and 14.2.4.14 of CSR

6.1.11.4 Dropouts and/or Discontinuations

Please refer to Table 4 for the distribution of subjects who prematurely discontinued the study.

6.1.11.5 Exploratory and Post Hoc Analyses

NA

6.1.12 Safety Analyses

**Solicited local and systemic adverse events**

Table 9 summarizes the solicited local and systemic AEs within 7 days of vaccination by treatment group and by age cohort. The proportions of subjects reporting any solicited local or systemic AEs were similar across treatment groups. In treatment groups of bioCSL QIV, bioCSL TIV-1, and bioCSL TIV-2, Grade 3 solicited local AEs were reported in <1% of subjects, and Grade 3 solicited systemic AEs were reported in 2.0%, 1.6%, and 2.3% of subjects, respectively. Subjects receiving bioCSL QIV tended to be more likely to experience headache than subjects receiving bioCSL TIV-1 overall (RR=1.35; 95% CI: 1.08-1.68), as well as in younger adults 18-64 years of age (RR=1.43; 95% CI: 1.10-1.85). No other individual solicited local or systemic AEs showed imbalanced distributions comparing bioCSL QIV to bioCSL TIV-1 or bioCSL TIV-2.

Generally, the proportion of subjects in the bioCSL QIV group experiencing each solicited local or systemic AE was higher in younger adults (18-64 years) compared to older adults (≥65 years), with the exception of redness (2.9% versus 4.2%).

**Table 9: Percentage[a] of Subjects with Solicited Local or Systemic Adverse Events within 7 Days of Vaccination in Adults ≥18 Years and by Age Cohort (Safety Population)**

| | Overall (≥18 years) | | | 18-64 years | | | ≥65 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | bioCSL QIV N= 1721 | bioCSL TIV-1 N= 864 | bioCSL TIV-2 N= 864 | bioCSL QIV N= 854 | bioCSL TIV-1 N= 428 | bioCSL TIV-2 N= 430 | bioCSL QIV N= 867 | bioCSL TIV-1 N= 436 | bioCSL TIV-2 N= 434 |
| Local | | | | | | | | | |
| Any | 644 (37.4) | 299 (34.6) | 316 (36.6) | 413 (48.4) | 189 (44.2) | 221 (51.4) | 231 (26.6) | 110 (25.2) | 95 (21.9) |
| Pain | 622 (36.1) | 286 (33.1) | 309 (35.8) | 409 (47.9) | 187 (43.7) | 218 (50.7) | 213 (24.6) | 99 (22.7) | 91 (21.0) |
| Redness | 61 (3.5) | 21 (2.4) | 23 (2.7) | 25 (2.9) | 12 (2.8) | 12 (2.8) | 36 (4.2) | 9 (2.1) | 11 (2.5) |
| Swelling/Lump | 60 (3.5) | 18 (2.1) | 22 (2.5) | 32 (3.7) | 10 (2.3) | 15 (3.5) | 28 (3.2) | 8 (1.8) | 7 (1.6) |
| Systemic | | | | | | | | | |
| Any | 498 (28.9) | 245 (28.4) | 235 (27.2) | 327 (38.3) | 156 (36.4) | 154 (35.8) | 171 (19.7) | 89 (20.4) | 81 (18.7) |
| Myalgia | 328 (19.1) | 161 (18.6) | 157 (18.2) | 218 (25.5) | 100 (23.4) | 104 (24.2) | 110 (12.7) | 61 (14.0) | 53 (12.2) |
| Headache | 258 (15.0) | 96 (11.1) | 116 (13.4) | 185 (21.7) | 65 (15.2) | 82 (19.1) | 73 (8.4) | 31 (7.1) | 34 (7.8) |
| Malaise | 114 (6.6) | 61 (7.1) | 62 (7.2) | 76 (8.9) | 39 (9.1) | 40 (9.3) | 38 (4.4) | 22 (5.0) | 22 (5.1) |
| Nausea | 73 (4.2) | 41 (4.7) | 36 (4.2) | 59 (6.9) | 33 (7.7) | 27 (6.3) | 14 (1.6) | 8 (1.8) | 9 (2.1) |
| Chills | 58 (3.4) | 28 (3.2) | 26 (3.0) | 41 (4.8) | 19 (4.4) | 20 (4.7) | 17 (2.0) | 9 (2.1) | 6 (1.4) |
| Vomiting | 17 (1.0) | 4 (0.5) | 13 (1.5) | 13 (1.5) | 4 (0.9) | 10 (2.3) | 4 (0.5) | 0 (0.0) | 3 (0.7) |
| Fever[b] | 11 (0.6) | 8 (0.9) | 4 (0.5) | 9 (1.1) | 4 (0.9) | 2 (0.5) | 2 (0.2) | 4 (0.9) | 2 (0.5) |

[a] Percentages were based on the number of subjects of the Safety Population in the respective group.
[b] Fever: ≥38°C
Source: Table 14.3.1.2.1, Table 14.3.1.2.2, Table 14.3.1.3.1, and Table 14.3.1.3.2 of CSR

***Reviewer's comments:***

*The upper 95% confidence bound of the RR of headache (bioCSL QIV versus bioCSL TIV-1) shown in above text was less than 2, suggesting a relative low degree of increase in the risk. The evaluation of whether this increase was clinically meaningful is deferred to the clinical reviewer.*

**Cellulitis-like reactions, cellulitis, and Grade 3 injection site induration/swelling**

Very low proportions of subjects (5 [0.3%] in bioCSL QIV versus 1 [0.1%] in bioCSL TIV-2; 2 [0.1%] in the 18-64 age cohort versus 4 [0.2%] in the ≥65 years cohort) experienced Grade 3 injection site swelling/induration. No subject experienced a cellulitis-like reaction or cellulitis at the injection site during the study.

**Unsolicited adverse events**

Overall, unsolicited AEs were experienced in similar proportions of subjects in all three vaccine groups. The proportions of subjects experiencing Grade 3 unsolicited AEs were relatively low in all three vaccination groups, with no notable differences between bioCSL QIV and bioCSL TIV-1 (or bioCSL TIV-2) groups. The proportion of subjects experiencing any unsolicited AE was similar in the 18-64 years age cohort compared with the ≥65 years age cohort.

***Reviewer's comments:***

*In the CSR, it appears that all treatment emergent unsolicited AEs that occurred during the entire study period were included for analyses. An IR was sent to request analyses of*

*unsolicited AEs focusing only on events that occurred within 28 days of vaccination. Only slight changes were observed from the reanalyses. Please refer to the clinical review for detailed coverage of unsolicited AEs.*

6.1.12.1 Methods

Please refer to Section 6.1.9.

6.1.12.3 Deaths

There were 6 deaths reported during the study (5 [0.3%] in bioCSL QIV and 1 [0.1%] in bioCSL TIV-2). One death due to pneumonia in the ≥65 years age cohort in the bioCSL QIV group was assessed by the investigator as related to the vaccine. Please refer to the clinical review for detailed evaluation of this death event.

6.1.12.4 Nonfatal Serious Adverse Events

The overall SAEs were reported in 39 (2.3%) subjects receiving bioCSL QIV, 14 (1.6%) subjects receiving bioCSL TIV-1, and 13 (1.5%) subjects receiving bioCSL TIV-2. Although the incidence rate of SAE was slightly higher in the bioCSL QIV group compared to the other two TIV groups, there was no notable difference. Three non-fatal SAEs (asthma, pancreatitis acute, and hypoxia) experienced in 2 (0.1%) subjects receiving bioCSL QIV were assessed by the investigator as related to study vaccine (one in each age cohort, respectively). Overall, more subjects aged ≥65 years experienced SAEs compared to subjects aged 18-64 years (3.0% versus 0.8%).

***Reviewer's comments:***

*According to the reviewer's calculation, non-fatal SAEs were reported in 34 (2.0%) subjects in the bioCSL QIV group, as compared to 14 (1.6%) subjects in the bioCSL TIV-1 group and 13 (1.5%) subjects in the bioCSL TIV-2 group during the study.*

6.1.12.5 Adverse Events of Special Interest (AESI)

No AESIs were reported in this study.

6.1.12.6 Clinical Test Results

No routine safety laboratory evaluations of hematology, biochemistry, wound swab, or blood culture were conducted during this study.

6.1.12.7 Dropouts and/or Discontinuations

No subjects discontinued due to an AE. Given that the proportion of subjects who withdrew from the study was low (2.8%) and similar across treatment groups, missing data were not expected to have significant impact on the interpretation of safety analysis results.

# 10. CONCLUSIONS

## 10.1 Statistical Issues and Collective Evidence

Immunogenicity

In summary, the primary objective of demonstrating the immunogenicity non-inferiority of bioCSL QIV to the bioCSL TIV comparators for influenza strains contained in the vaccine in adults ≥18 years of age was met. Specifically,

- The upper bounds of the two-sided 95% CI of the GMT ratio (bioCSL TIV/bioCSL QIV) did not exceed 1.5: the HI GMT ratios and 95% CIs for each of the four strains (A/H1N1, A.H3N2, B/Yamagata, and B/Victoria) were 0.93 (0.88, 0.99), 0.93 (0.88, 0.98), 0.87 (0.82, 0.93), and 0.95 (0.88, 1.03), respectively.
- The upper bounds of the two-sided 95% CI of the SCR difference (bioCSL TIV-bioCSL QIV) did not exceed 10%: the HI SCR differences and 95% CIs for each of the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) were -1.1 (-4.5, 2.3), -1.7 (-5.0, 1.7), -3.2 (-7.4, 0.9), and -1.6 (-5.8, 2.5), respectively.

In addition, the same non-inferiority criteria were met for HI GMT and SCR endpoints within each of the two age cohorts (18-64 and ≥65 years) for each strain as secondary analyses. For another secondary analysis of the immunologic superiority of the alternate B strain, the pre-specified superiority criteria were also met. No pre-defined multiplicity adjustment was applied to the secondary analyses.

Safety

Overall, no major safety concerns were identified from the statistical perspective.

- The proportions of subjects reporting any solicited local or systemic AEs appeared balanced across treatment groups. Grade 3 solicited local AEs were reported in less than 1% of subjects, and Grade 3 solicited systemic AEs were reported in 1.6%-2.3% of subjects across treatment groups.
- The proportions of subjects reporting any unsolicited AEs were similar across treatment groups.
- Grade 3 injection site swelling/induration was reported in a very low proportion of bioCSL QIV group recipients (0.3%), as well as in bioCSL TIV recipients (0-0.1%). No cellulitis-like reaction or cellulitis at the injection site was reported.
- A slightly higher proportion of subjects reported SAEs in the bioCSL QIV group compared to the bioCSL TIV groups (2.3% versus 1.5%-1.6%), with no notable difference across treatment groups.
- Six deaths were reported during the study, with 5 (0.3%) subjects in the bioCSL QIV group, and 1 (0.1%) subject in the bioCSL TIV-2 group. One death due to pneumonia in the bioCSL QIV group was assessed by the investigator as related to vaccination.

## 10.2 Conclusions and Recommendations

No major statistical issues were identified with respect to the immunogenicity or safety analyses in this submission. The submitted data suggest that the primary non-inferiority immunogenicity objective was met.