Immunogenicity, reactogenicity, and safety of inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine in healthy adults aged ≥18 years: A phase III, randomized trial

Juan Carlos Tinoco a, *, Noris Pavia-Ruz b, Aurelio Cruz-Valdez c, Carlos Aranza Doniz d, Vijayalakshmi Chandrasekaran e, Walthère Dewé f, Aixue Liu e, Bruce L. Innis e, Varsha K. Jain e

a Hospital General de Durango, Durango, Mexico
b Universidad Nacional Autonoma de Mexico, Mexico City, Mexico
c National Institute of Public Health, Cuernavaca, Morelos, Mexico
d Secretaria de Salud del Estado de Mexico, Zumpango, Mexico
e GlaxoSmithKline Vaccines, King of Prussia, PA, USA
f GlaxoSmithKline Vaccines, Rixensart, Belgium

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ABSTRACT

Background: Two influenza B lineages have been co-circulating since the 1980s, and because inactivated trivalent influenza vaccine (TIV) contains only one B strain, it provides little/no protection against the alternate B-lineage. We assessed a candidate inactivated quadrivalent influenza vaccine (QIV) containing both B lineages versus TIV in healthy adults.

Methods: Subjects received one dose of QIV (lot 1, 2, or 3) or one of two TIVs (B strain from Victoria or Yamagata lineage); randomization was 2:2:2:1:1. Hemagglutination-inhibition assays were performed 21 days post-vaccination; superiority of QIV versus TIV for the alternate B-lineage was demonstrated if the 95% confidence interval (CI) lower limit for the GMT ratio was >1.5, and non-inferiority against the shared strains was demonstrated if the 95% CI upper limit for the GMT ratio was ≤1.5. Reactogenicity and safety were assessed during the post-vaccination period. NCT01196975.

Results: Immunogenicity of QIV lots was consistent. QIV was superior to TIV for the alternate B-lineage strain, and QIV was non-inferior versus TIVs for shared strains (A/H1N1, A/H3N2, B-strain). Reactogenicity and safety profile of the QIV was consistent with seasonal influenza vaccines.

Conclusion: QIV provided superior immunogenicity for the added B strain without affecting the antibody response to the TIV strains, and without compromising safety.

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1. Introduction

Influenza is a major public health threat, and in the US, seasonal influenza epidemics account for more than 200,000 hospitalizations and more than 30,000 deaths annually [1,2]. Although influenza B is less of a public health burden than influenza A/H3N2 [2], influenza B viruses cause seasonal epidemics in adults every two to four years [3], and based on data across four seasons, clinical symptoms and hospital admission rates were similar in patients infected with influenza B compared with influenza A [4].

Two antigenically-distinct influenza B lineages (B/Victoria and B/Yamagata) emerged in the 1980s, and have co-circulated in the US since 2000. However, seasonal influenza vaccines have conventionally been trivalent, including only one B lineage, meaning...
that mismatch between the circulating influenza B virus and the vaccine strain is common. For example, between 2000 and 2010 in the US, the trivalent vaccine was mismatched for the circulating influenza B strain in six of ten seasons [5], resulting in reduced vaccine effectiveness in the mismatched years [6,7].

The huge impact of seasonal influenza vaccine mismatch with the circulating B lineage was demonstrated in Taiwan during the 2011–2012 season when the trivalent vaccine contained a B/Victoria lineage strain whereas the predominant virus was an influenza B/Yamagata strain; based on laboratory-confirmed cases of influenza in vaccinated outpatients identified over 6 months during the peak season, a test-negative case-control analysis showed that the adjusted vaccine effectiveness against influenza A was 54% (95% confidence interval: 3; 78), yet against influenza B was –66% (95% confidence interval: –132, –18) [8].

The inclusion of an influenza B strain from both the Victoria and Yamagata lineages in a quadrivalent vaccine could improve protection against influenza B, and could reduce the burden of seasonal influenza illness, hospitalization, and death [9]. As such, for the first time, the World Health Organization (WHO) recommended B strains from both lineages for use in vaccines for the 2012–2013 season in the Northern Hemisphere [10]. There are currently four quadrivalent vaccines approved in the US, produced by three manufacturers (MedImmune, Sanofi Pasteur, GlaxoSmithKline Vaccines) [11]. A live attenuated quadrivalent vaccine has been assessed in children aged 2–17 years [12], and in adults aged 18–49 years [13], and in each study was found to provide non-inferior immune responses compared with a live attenuated trivalent influenza vaccine. Inactivated quadrivalent influenza vaccines have been showed to be immunogenic for all four vaccine strains, with superior or non-inferior immunogenicity for the additional B strain compared with TIV, without interfering with antibody responses to the three shared strains in children aged 3–17 years [14,15], and in adults [16,17].

In this Phase III, double-blind, randomized study we assessed the immunogenicity, reactogenicity, and safety of a candidate inactivated quadrivalent split viral influenza vaccine (QIV). The aim of the study was to evaluate the immunological consistency of three QIV lots, the superiority of antibody responses against the B strains in the QIV versus TIVs containing the alternate B lineage, and the non-inferior immunogenicity for QIV and TIV against shared influenza A and B strains.

2. Methods

This Phase III, randomized, double-blind study compared the immunogenicity of QIV and TIV in adults. Reactogenicity and safety was also assessed. The study was conducted in Canada, Mexico, and the US. Eligible subjects were aged ≥18 years, were in stable health, and had not received any non–registered drug or vaccine within 30 days or any investigational or approved influenza vaccine within six months of the first visit. All subjects provided written informed consent.

The study protocol, any amendments, informed consent and other information requiring pre-approval were reviewed and approved by national, regional, or investigational center Institutional Review Boards. The study was conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and all regulatory requirements. clinicaltrials.gov NCT01196975.

2.1. Vaccines and randomization

Subjects were scheduled to receive a single dose of either a licensed seasonal TIV (FluLaval™, GlaxoSmithKline Vaccines) or a candidate QIV. All vaccines contained 15 µg of hemagglutinin antigen (HA) of influenza A/H1N1 (A/California/7/2009) and A/H3N2 (A/Victoria/210/2009), as recommended by WHO for the 2010/11 influenza season. The TIV contained 15 µg HA of an influenza B strain from the Victoria lineage (B/Brisbane/60/2008 [B lineage recommended for 2010/11 season by WHO]) or the Yamagata lineage (B/Florida/4/2006) and the QIV contained 15 µg HA of both influenza B strains. The TIVs and QIV were given as a 0.5 mL dose; the TIVs contained 0.50 µg thimerosal and the QIV was thimerosal-free. All vaccines were manufactured by GlaxoSmithKline (GSK) Biologics in Quebec, Canada.

Randomization was performed by the study sponsor using a blocking scheme, and treatment allocation at the investigator site was performed using a central randomization system on the internet. Subjects were randomized 2:2:2:1:1 to receive QIV (lot 1, 2, or 3), TIV-B Victoria (TIV-Vic) or TIV-B Yamagata (TIV-Yam). Groups had an equal distribution of subjects aged 18–64 years versus ≥65 years and a minimization algorithm was used to account for country, and influenza vaccination in the previous season. Subjects received one dose of vaccine in the deltoid of the non-dominant arm. All personnel and subjects were blind to the vaccine allocation.

2.2. Assessments and objectives

2.2.1. Immunogenicity

Blood was collected for serological testing on or just before vaccination (Day 0) and then 21 and 180 (sub-cohort) days post-vaccination (Day 21, and Day 180, respectively). Hemagglutination inhibition (HI) antibody titers against the vaccine strains were assessed at GlaxoSmithKline Vaccines central laboratory using validated assay methods as previously described [18].

The primary objective was to assess the lot-to-lot consistency of three QIV lots based on GMTs at Day 21 post-vaccination. Secondary objectives were to evaluate: the superiority of GMTs at Day 21 for QIV versus TIV-Vic against the Yamagata B strain, and QIV versus TIV-Yam against the Victoria B strain (i.e. B strains absent from each TIV); and the non-inferiority of GMTs at Day 21 for QIV versus TIV-Vic + TIV-Yam against all four strains, QIV versus TIV-Vic against the Victoria B strain, and QIV versus TIV-Yam against the Yamagata B strain (i.e. shared strains). Immunogenicity was described at Day 0, 21, and 180 (sub-cohort) including GMTs, seroprotection rate (SPR; proportion with post-vaccination titer ≥1:40), seroconversion rate (SCR; proportion with antibody titer <1:10 at baseline and with post-vaccination titer of ≥1:40, or pre-vaccination titer of ≥1:10 and a ≥4-fold post-vaccination increase in titer), and seroconversion factor (SCF; geometric mean of the ratio between pre-vaccination and post-vaccination reciprocal HI titers). Subjects with HI antibody titers of ≥1:10 were considered to be seropositive. Immunogenicity was also assessed according to US Center for Biologics Evaluation and Research (CBER) licensure criteria.

2.2.2. Reactogenicity and safety

The occurrence and intensity of solicited adverse events (AEs) was recorded by subjects on diary cards and included local symptoms (pain, redness, and swelling) and general symptoms (arthralgia, fatigue, gastrointestinal symptoms, headache, generalised myalgia, shivering, and fever). Unsolicited AEs were assessed prospectively at each study visit. Injection site reactions were considered to be related to the vaccine and investigators provided causality assessments for solicited general symptoms and unsolicited events.

Reactogenicity and safety outcome measures (secondary objectives) were local and general solicited adverse events during the 7-day post-vaccination period, unsolicited AEs during the 21-day post-vaccination period, and medically attended events (MAEs) and serious adverse events (SAEs) during the 6 months study period.
2.3. Sample size and statistical analyses

The target sample size for the QIV group was 400 subjects assigned to each of the three QIV lots; assuming 6% will be non-evaluable and equivalence among the lots, 375 evaluable subjects per lot would have 92% power using Bonferroni’s adjustment to meet the consistency criterion. The target sample size for each TIV group was 200 subjects, giving 190 evaluable subjects assuming 5% will be non-evaluable. A sample of 1125 for QIV and 190 for TIV would have ~99% power to meet the criteria for superiority against alternate-lineage B strains, and ~99% and ~96% power to demonstrate non-inferiority against shared A strains and shared B strains, respectively (each calculation based on a 1-sided, 2-sample t-test for a difference of means, α = 2.5%). To fulfill CBER licensure criteria with ~99% power using Bonferroni’s adjustment in the QIV group, each age stratum (18–64 and ≥65 years) would need at least 562 evaluable subjects.

HI antibody responses were described as the anti-log of the arithmetic mean of the log-10 transformed inverse geometric mean titers (GMT). In the lot-to-lot consistency, superiority, and non-inferiority analyses, GMTs at Day 21 were computed by fitting an ANCOVA model, including vaccine group as a fixed effect and pre-vaccination antibody titer as a covariate. Lot-to-lot consistency was based on adjusted GMT ratios for pairwise comparisons of QIV lots (lot 1/lot 2, lot 1/lot 3, lot 2/lot 3) for each strain; the pair with the largest GMT ratio for each strain was evaluated, and lot-to-lot consistency was demonstrated if the 2-sided 95% CI limit was between 0.67 and 1.5 for all four strains. Superiority of QIV versus each TIV group for the alternate lineage B strain was demonstrated if the lower limit of the 2-sided 95% CI on the adjusted GMT ratio (QIV/TIV) at Day 21 was ≥1.5 for both comparisons. Non-inferiority for QIV versus TIV-Vic+TIV-Yam for A strains, and versus TIV-Vic and TIV-Yam for the B Victoria and B Yamagata strains, respectively, was demonstrated if the lower limit of the 2-sided 95% CI on the adjusted GMT ratio (TIV/QIV) at Day 21 was ≤1.5.

Based on descriptive analyses, immunogenicity parameters were tabulated with 95% CIs at Day 0, 21, and 180 (sub-cohort), and CBER licensure criteria for immunogenicity of influenza vaccines were assessed at Day 21 and Day 180; the criteria were fulfilled if the lower limit of the 2-sided 95% CI on the SCR was ≥40% (aged 18–64 years) or ≥30% (aged ≥65 years), and the lower limit of the 2-sided 95% CI on the SPR was ≥70% (aged 18–64 years) and ≥60% (aged ≥65 years) [19]. The immunogenicity analyses were performed on the according-to-protocol (ATP) immunogenicity cohort including all eligible subjects without protocol deviation who had serological data available at a given time point. The Day 180 analyses were performed on an ATP sub-cohort (immunogenicity persistence cohort).

The frequency of solicited and unsolicited adverse events was tabulated with 95% CIs. Unsolicited AEs were assessed in all vaccinated subjects with available diary cards (reactogenicity cohort).
and unsolicited adverse events were assessed in all vaccinated subjects (total vaccinated cohort; TVC).

3. Results

3.1. Subjects

The first subject was enrolled on 1 October 2010 and the last study contact was on 21 June 2011. There were 1703 subjects enrolled, of which 1272 received QIV (423, 424, 425 received lot 1, 2, and 3, respectively), and 213 received TIV-Vic and 218 TIV-Yam. A total of 1655 subjects completed the study and there were 48 withdrawals of which 6 were associated with an SAE (Fig. 1). The groups were balanced for baseline demographics and clinical characteristics (Table 1). The mean age in the QIV, TIV-Vic, and TIV-Yam groups was 50.0 years, 50.8 years, and 49.6 years, respectively. About 70% of each group had received seasonal influenza vaccines during one of the previous three seasons.

3.2. Immunogenicity

The limits of the two-sided 95% CI for the adjusted GMT ratios at Day 21 among the three lots of QIV were between 0.67 and 1.5 for each of the four strains, and the criteria for lot-to-lot consistency were met.

Superior immunogenicity was shown for QIV versus TIV-Vic for the Yamagata B strain and versus TIV-Yam for the Victoria B strain; the lower limit of the 95% CI for the GMT ratio of QIV/TIV-Vic for B/Florida/4/2006 was 1.90 and for Q-IV/TIV-Yam for B/Brisbane/60/2008 was 2.11. Non-inferior immunogenicity was shown for QIV versus each TIV for the shared vaccine strains (Table 2).

In the QIV group, the lower limits of 95% CI for SPR were ≥70% or ≥60% for all four vaccine strains in the 18–64 and ≥65 years strata, respectively, fulfilling CBER criteria (Fig. 2). The 95% CI for the SCR was ≥40% for all four vaccine strains in the 18–64 years stratum, and ≥30% for A/H1N1, A/H3N2, and the Yamagata lineage B strain in the ≥65 years stratum, fulfilling CBER criteria (Fig. 2). The SCR for the Victoria lineage B strain in the ≥65 years stratum was 31.2% (95% CI: 26.7, 36.0).

QIV, TIV-Vic, and TIV-Yam were highly immunogenic against each vaccine strain in each group overall at Day 21. At Day 180, seropositivity rates were 88.3–100% in the QIV group, 97.3–100% in the TIV-Vic group and 83.3–100% in the TIV-Yam group (Table 3).

3.3. Reactogenicity and safety

Injection site pain was the most frequent local solicited symptom and was reported by 59.5% (750/1260) of the QIV group, and 44.7% (93/208) of the TIV-Vic, and 41.2% (89/216) of the TIV-Yam group; grade 3 pain was reported by 1.7%, 1.0% and 1.4% of the QIV, TIV-Vic, and TIV-Yam groups, respectively (Fig. 3). Other local events were uncommon (Fig. 3). Fatigue, headache, and muscle aches were the most frequently reported solicited general symptoms in all groups (Fig. 3). Fatigue was reported by 21.5% (271/1260) of the QIV group, and 21.6% (45/208) and 17.1% (37/216) of the TIV-Vic and TIV-Yam groups, respectively. The incidence of grade 3 solicited general symptoms was <1% in each group.

During the 21-day post-vaccination period, at least one unsolicited AE was reported by 19.2% (244/1272) of the QIV group, and 22.5% (48/213) and 23.4% (51/218) of the TIV-Vic and TIV-Yam groups, respectively. The most frequent unsolicited AEs were oropharyngeal pain, cough, and nasopharyngitis, occurring at a frequency of 1.7–2.8%. Grade 3 unsolicited AEs were reported by 26 (2.0%), 6 (2.8%), and 7 (3.2%) of the QIV, TIV-Vic and TIV-Yam groups, respectively.

During the 6-month follow-up, at least one MAE was reported by 25.9% (330/1272) of the QIV group, and 23.9% (51/218) and 29.4% (64/218) of the TIV-Vic and TIV-Yam, respectively. The most frequent MAEs were sinusitis (2.1–3.2%) and upper respiratory tract infection (0.9–2.3%). During the 6-month follow-up, at least one

Table 1
Demographic characteristics at baseline in the total vaccinated cohort.

<table>
<thead>
<tr>
<th></th>
<th>QIV N = 1272</th>
<th>TIV Victoria lineage N = 213</th>
<th>TIV Yamagata N = 218</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD; median; range)</td>
<td>50.0 (19.5; 50.0; 18–97)</td>
<td>50.8 (18.5; 51.0; 18–87)</td>
<td>49.6 (19.3; 49.0; 18–91)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>491 (38.6)</td>
<td>88 (41.3)</td>
<td>80 (36.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>781 (61.4)</td>
<td>125 (58.7)</td>
<td>138 (63.3)</td>
</tr>
<tr>
<td>Hispanic/Latino ethnicity, n (%)</td>
<td>466 (36.6)</td>
<td>76 (35.7)</td>
<td>79 (36.4)</td>
</tr>
<tr>
<td>Not Hispanic/Latino ethnicity, n (%)</td>
<td>806 (63.4)</td>
<td>137 (64.3)</td>
<td>138 (63.6)</td>
</tr>
<tr>
<td>Heritage/race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European heritage/Caucasian</td>
<td>764 (60.1)</td>
<td>122 (57.3)</td>
<td>129 (59.2)</td>
</tr>
<tr>
<td>Arabic/north American heritage/Caucasian</td>
<td>13 (1.0)</td>
<td>4 (1.9)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (0.01)</td>
<td>4 (0.01)</td>
<td>4 (0.01)</td>
</tr>
<tr>
<td>African heritage/African American</td>
<td>40 (3.1)</td>
<td>7 (3.3)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>American Indian or native Alaskan</td>
<td>5 (0.4)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>434 (34.1)</td>
<td>76 (35.7)</td>
<td>75 (34.4)</td>
</tr>
</tbody>
</table>

QIV, inactivated quadrivalent influenza vaccine; SD, standard deviation; TIV, inactivated trivalent influenza vaccine.
SAE was reported by 2.8% (35/1272) of the QIV group, and 1.4% (3/213) and 3.2% (7/218) of the TIV-Vic and TIV-Yam groups, respectively (Supplementary Table 1). None of the SAEs were considered to be vaccine related.

4. Discussion

This Phase III, randomized, double-blind study of healthy adults aged ≥18 years showed that QIV was immunologically superior versus TIV for the alternate-lineage B strain, and was non-inferior for the influenza strains shared in the QIV and TIVs. HI antibody responses were also shown to be consistent between three lots of QIV, thus demonstrating manufacturing consistency of the candidate vaccine. Our results show that in people aged ≥18 years, QIV offers improved immunogenicity against the additional B strain without affecting antibody responses to existing strains compared with conventional TIVs; therefore, our study supports a switch from conventional TIV to QIV with the aim of improving protection against influenza B disease.

The immunogenicity and safety findings reported for this QIV which was manufactured in Canada are consistent with a previous report of an inactivated QIV produced by the same company using a different process at facilities in Germany [16]. The results add to the growing evidence in both children and adults which shows that live attenuated and inactivated QIVs provide similar immune responses against shared vaccine strains versus TIV with added protection against the additional B strain [12–17].

We showed that each of the vaccines elicited strong HI antibody responses against the A/H1N1 and A/H3N2 vaccine strains, and against B/Brisbane/60/2008 (Victoria) and/or against B/Florida/4/2006 (Yamagata). SCRs and SPRs against each vaccine strain were considered to be high, and immune responses were slightly stronger against influenza A than influenza B strains with QIV and both TIVs. The persistence of antibody responses was assessed six months after vaccination in a sub-cohort of subjects, and whereas immune responses decreased at 6 months in each vaccine group relative to those measured at day 21 after vaccination, they remain notably increased above baseline levels. In the QIV group, antibody persistence at 6 months appeared to be more robust against the influenza B strains with SPRs of 94.9% and 99.6% against B/Victoria and B/Yamagata, respectively, compared with SPRs of 66.5% and 64.6% against A/H1N1 and A/H3N2, respectively. Antibody levels were decreased against the influenza A strains at 6 months post-vaccination, and the clinical significance of this is uncertain.
Table 3
Descriptive immunogenicity based on HI assays in the QIV and TIV groups in the ATP immunogenicity persistence cohort.

<table>
<thead>
<tr>
<th>Seropositive</th>
<th>GMT</th>
<th>SCR</th>
<th>SPR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%; 95% CI)</td>
<td>n/N (%; 95% CI)</td>
<td>n/N (%; 95% CI)</td>
</tr>
<tr>
<td>0</td>
<td>142/257 (55.3; 48.9, 61.4)</td>
<td>159/257 (61.9; 55.6, 67.8)</td>
<td>207/257 (80.5; 75.2, 85.2)</td>
</tr>
<tr>
<td>21</td>
<td>248/257 (96.5; 93.5, 98.4)</td>
<td>247/256 (96.5; 93.4, 98.4)</td>
<td>257/257 (100; 98.6, 100)</td>
</tr>
<tr>
<td>180</td>
<td>227/257 (88.3; 83.8, 92.0)</td>
<td>241/257 (93.8; 90.1, 96.4)</td>
<td>257/257 (100; 98.6, 100)</td>
</tr>
<tr>
<td>TIV-</td>
<td>0</td>
<td>23/37 (62.2; 44.8, 77.5)</td>
<td>23/37 (62.2; 44.8, 77.5)</td>
</tr>
<tr>
<td>Vic</td>
<td>21</td>
<td>36/37 (97.3; 85.8, 99.9)</td>
<td>31/37 (83.1; 72.9, 93.0)</td>
</tr>
<tr>
<td>180</td>
<td>36/37 (97.3; 85.8, 99.9)</td>
<td>37/100 (33.3; 23.3, 45.6)</td>
<td>37/100 (33.3; 23.3, 45.6)</td>
</tr>
<tr>
<td>TIV-</td>
<td>0</td>
<td>23/42 (54.8; 38.7, 70.2)</td>
<td>23/37 (62.2; 44.8, 77.5)</td>
</tr>
<tr>
<td>Yam</td>
<td>21</td>
<td>38/42 (90.5; 77.4, 97.3)</td>
<td>42/60 (77.0; 70.6, 80.3)</td>
</tr>
<tr>
<td>180</td>
<td>35/42 (83.3; 68.6, 93.0)</td>
<td>42/53 (28.9, 71.0)</td>
<td>42/53 (28.9, 71.0)</td>
</tr>
</tbody>
</table>

ATP, according-to-protocol; CI, confidence interval; GMT, geometric mean titer; HI, Hemagglutination inhibition; TIV-Vic, inactivated trivalent influenza vaccine Victoria lineage B strain; TIV-Yam, inactivated trivalent influenza vaccine Yamagata lineage B strain; QIV, inactivated quadrivalent influenza vaccine.

Descriptive analyses were also performed to further assess the immunogenicity of QIV according to age. The median age was 50.0 years (18–91 years) overall, with an equal distribution of subjects aged 18–64 years versus ≥65 years in each group. In subjects aged 18–64 years in the QIV group, the vaccine fulfilled CBER licensure criteria for immunogenicity against all four vaccine strains, but in the ≥65 years stratum, the criteria was fulfilled for A/H1N1, A/H3N2, and influenza B/Victoria, but the SCR criteria for influenza B/Yamagata was not met. However, the proportion of subjects aged ≥65 years who had pre-vaccination antibody titers of ≥1.40 against the strain from the B/Yamagata lineage was relatively high (87.4%), compared with the pre-vaccination SCR in the younger stratum (77.0%). In two of the three preceding influenza seasons, a Yamagata lineage B strain was recommended for use in TIVs for annual vaccination in people aged ≥65 years in the Northern Hemisphere, and this may have accounted for the relatively high baseline antibody levels in older subjects in our study. A tabulation of SCR by prior influenza vaccination status in the ≥65 years stratum in our study showed that the SCR met the CBER criterion in 34 subjects without influenza vaccination in the past three seasons, whereas in 363 subjects who had received influenza vaccine in the past three seasons, licensure criteria against the Yamagata lineage B strain were not met (data not shown).

The safety analysis in our study showed that the most frequent injection site reaction was pain (>41% of subjects in each vaccine group) and the most frequent solicited general events were headache and muscle ache (~20% of each vaccine group). During the 6-month follow-up, the rate of SAEs was low in all vaccine groups, and no SAE was considered to be vaccine-related. Overall, the reactogenicity and safety profile of QIV was consistent with the established profile of seasonal influenza vaccines, suggesting that inclusion of an additional 15 μg of antigen in the candidate QIV did not compromise safety compared with TIV.

Although this study provides evidence of the viability of the candidate QIV, the limitation of the trial is that immunogenicity is a surrogate of protection; further studies are needed to evaluate if covering both influenza B lineages improves vaccine efficacy, and to establish if QIV reduces the burden of influenza versus TIV, as previously suggested by modelling studies [9]. Natural exposure to influenza viruses was a potential confounding factor as enrollment may have coincided with increased influenza activity. In Mexico, the influenza season started in July 2010, peaked in late-December
and was over by January 2011, in Canada the season peaked in early January 2011, and in the US, the season peaked in mid-February 2011 [20]. Subjects were enrolled in early October 2010 and enrollment continued into mid-December, meaning that in the US and Canada, the majority of blood samples were taken before peak-season, thus limiting the impact of natural exposure. The sub-cohort in Mexico may have been exposed to natural influenza virus infection between vaccination and 21-day blood sampling, although such exposure is likely to have been limited to about 5% of the sub-cohort. In addition, in Mexico, transmission was nearly entirely associated with A/H3N2, and in the US and Canada, A/H3N2 was also the predominant virus; pre-vaccination antibody titers to A/H3N2 were low (GMTs 13.9–16.0) and did not suggest discernible immune responses to natural exposure [20]. Furthermore, because this was a randomized, controlled study, any boost to the immunogenicity of the sub-cohort by natural infection is expected to be similar among the treatment arms and, therefore, the analysis of the confirmatory objectives would not have been confounded. Indeed, there was no evidence to suggest that the study was limited by this phenomenon.

In conclusion, the results confirm the manufacturing consistency of the candidate QIV, and shows that compared with TIV, QIV provides superior immunogenicity against the additional B strain and non-inferior immunogenicity against the shared strains.

Authors’ contributions

All authors participated in the implementation of the study including substantial contributions to conception and design, the gathering of the data, or analysis and interpretation of the data. Bruce Innis, Varsha Jain, and Aixue Liu led the clinical team at GlaxoSmithKline group of companies and were involved in all phases of the study. Juan Carlos Tinoco, Noris Pavia-Ruz, Aurelio Cruz-Valdez, and Carlos Aranza Doniz coordinated the study at the investigator site. Vijayalakshmi Chandrasekaran and Walthère Dewé conducted the statistical analysis. All the authors revised the manuscript critically for important intellectual content and approved the final version before submission.

Financial disclosure

GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis (ClinicalTrials.gov Identifier: NCT01196975). GlaxoSmithKline Biologicals SA also took in charge all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and the corresponding author had final responsibility to submit for publication.

Trade mark ownership

FluLava™ is a trade mark of the GlaxoSmithKline group of companies.

Conflicts of interest statement

Bruce Innis, Aixue Liu, Walthère Dewé, Vijayalakshmi Chandrasekaran, and Varsha Jain are employees of GlaxoSmithKline group of companies. Bruce Innis, Aixue Liu, Walthère Dewé, and Varsha Jain report ownership of stock options. Walthère Dewé reports grants received for travel/accommodation/meeting expenses unrelated to present activities from GlaxoSmithKline group of companies. Varsha Jain received support for travel to meetings for the study and provision of administrative support to his institution from GlaxoSmithKline group of companies. Noris Pavia-Ruz reports grants pending to his institution from GlaxoSmithKline group of companies. Aurelio Cruz-Valdez, Carlos Aranza Doniz, and Juan Carlos Tinoco report no conflict of interest.

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