Immunological non-inferiority and safety of a quadrivalent inactivated influenza vaccine versus two trivalent inactivated influenza vaccines in China: Results from two studies

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ABSTRACT
A quadrivalent, split-virion influenza vaccine (Shz QIV), containing two influenza A strains, and both B lineages strains, has been developed in China. We report the safety and immunogenicity of Shz QIV in two studies: a single-center, phase I, open-label, safety trial (n=101) and a multicenter, phase III, observer-blind, randomized, safety and immunogenicity trial (n=7,106) comparing Shz QIV with two trivalent influenza vaccines (Shz TIVs; one containing a B/Victoria-like strain and the other a B/Yamagata-like strain). Participants received one dose of Shz QIV (0.5 mL), except children aged 6 months to 8 years who received one or two doses (0.25 mL or 0.5 mL) depending on previous influenza vaccination. The Shz TIV groups received one or two (0.25 mL) doses depending on previous influenza vaccination (ages 6–35 months) or a single (0.5 mL) dose (ages ≥3 years). Immunogenicity was assessed at baseline and 28 days after the last dose, with safety assessed through to 6 months. The primary objective was to demonstrate the non-inferiority of antibody responses to Shz QIV (0.25 mL and 0.5 mL) versus Shz TIVs for each strain in ages 6–35 months and ≥3 years. Overall, Shz QIV was well tolerated, and showed similar safety to the Shz TIVs. Shz QIV (0.5 mL) induced non-inferior antibody responses to all antigens versus Shz TIV, with superiority demonstrated to the non-corresponding B strain in each TIV. Shz QIV (0.25 mL) non-inferiority in those aged 6–35 months was demonstrated for both A strains and the B/Yamagata-like strain, but not the B/Victoria-like strain. In summary, Shz QIV (0.5 mL) is immunogenic and has a good safety profile.

WHO Universal Trial Numbers (UTNs): U1111-1174-4615 and U1111-1174-4698
ClinicalTrials.gov: NCT04210349 and NCT03430089

Introduction
Northern hemisphere influenza viruses circulate during the winter season in northern China, yet in southern China, influenza is prevalent throughout the year, peaking in the summer with a less pronounced peak in winter. This dual seasonal influenza pattern is unique to China.1 The burden of influenza is substantial, with an estimated influenza-associated all-cause mortality rate of 14.33/100,000 persons in China, increasing to 122.79/100,000 among those aged ≥65 years.1,2 In addition, children aged <5 years appear to have the highest rates of influenza-associated hospitalizations and related outpatient visits compared to other age groups.3 Influenza vaccination policy targeting the elderly and young children in China would help ease the burden of illness in these two vulnerable age groups.

Traditional trivalent influenza vaccines (TIVs) include two influenza A strains and either a B/Victoria-like or a B/Yamagata-like strain in a given season, meaning that protection is reduced during seasons where the circulating influenza B lineage is mismatched with the vaccine strain.3 The need for a seasonal vaccine to cover both influenza B lineages therefore prompted the development of quadrivalent influenza vaccines (QIVs), containing both B/Yamagata-like and B/Victoria-like strains. A randomized-controlled phase III study undertaken between December 2010 and October 2011 showed that in children aged 3–8 years, the absolute efficacy of QIV was 55.9% against culture-confirmed influenza, and 73.1% against moderate-to-severe influenza.4 In the 2011/12 influenza season, the WHO recommended that influenza B strains from each lineage be included in northern hemisphere vaccines.5 To date, several QIVs have been licensed for use worldwide, and many countries have replaced TIV with QIV in their national immunization programs.6

In China, Sanofi has produced a split-virion, inactivated TIV (Shz TIV) at facilities in Shenzhen for the Chinese market.
over the last decade. This vaccine is based on Sanofi’s inactivated influenza vaccine, Vaxigrip®, which is manufactured in Europe and has been licensed worldwide. Two studies undertaken in China demonstrated that Shz TIV was immunogenic and well tolerated, and helped support its widespread use in the country.⁷,⁸ In addition, a QIV formulation (Shz QIV), based on the same manufacturing process as the licensed seasonal influenza vaccine, VaxigripTetra® (Sanofi), has been developed at the Shenzhen facility, including pediatric and adult formulations. Here, we briefly describe a phase I, open-label safety study of Shz QIV in participants aged ≥6 months (including the elderly). We also report a phase III, observer-blind, randomized, safety and immunogenicity study of Shz QIV compared with two Shz TIVs (one containing a B/Victoria-like strain and the other a B/Yamagata-like strain) in the same age groups. The studies aimed to assess the safety of Shz QIV and to demonstrate the immunological non-inferiority of Shz QIV versus Shz TIV, as well as the superiority of the immune response induced by the second added B-strain.

Methods

Study designs

The phase I trial was an open-label, safety study of Shz QIV given as a single dose (in those aged ≥9 years) or 2 doses 28 days apart (in those aged ≥6 months to 8 years) at a single study center in China (Yunnan Center for Disease Control and Prevention) conducted from 22 February 2019 to 6 June 2019. Participants were sequentially enrolled in a stepwise (3-step) manner, starting in step 1 with those aged 18–60 years, in step 2 those aged 3–8 years, 9–17 years, and >60 years, and in step 3, those aged 6–35 months. A safety review was undertaken by the study Sponsor (and the safety results with conclusions were approved by an Independent Ethics Committee, an approach agreed by the Chinese Health Authority before study start) during each step to assess whether the following safety events occurred within 7 days of vaccination: Grade 3 solicited reactions of erythema, swelling, ecchymosis, induration, or fever each in more than 20% of participants per age group; Grade 3 solicited reactions of pain, headache, malaise, myalgia, or shivering each in more than 30% of participants per age group; and serious adverse events assessed related to vaccination. Progression to the next enrollment step could only occur if none of these safety criteria were met.

The phase III trial was an observer-blind, multicenter, randomized safety and immunogenicity study of Shz QIV versus Shz TIV1 (with B/Victoria-like strain) or TIV2 (with B/Yamagata-like strain) in participants aged ≥6 months, conducted from 9 January 2020 to 1 December 2020 at five Yunnan and Henan Centers for Disease Control and Prevention (CDC) sites in China. Participants aged 6 months to 8 years previously unvaccinated against influenza assigned to the Shz QIV group received two doses of vaccine 28 days apart, as did those aged 6–35 months assigned to the Shz TIV group. The remainder received one dose of their assigned vaccine. Participants aged 6–35 months were enrolled in a stepwise (2-step) manner; 20 participants were planned to be enrolled at a single center in step 1 and vaccinated with an open-label dose of Shz QIV (0.5 mL), followed by a second open-label dose 28 days later. If there was no safety signal in this cohort following an early safety review (as described in the phase I study), then subsequent participants aged 6–35 months could be randomized to receive study vaccines (see below). Enrollment of participants aged ≥3 years occurred irrespective of the 2-step enrollment in the 6–35-month age group.

The protocol and consent forms for both studies were approved by the respective Ethic Committee of Yunnan and Henan Centers for Disease Control and Prevention, and Independent Ethics Committees or local or central Institutional Review Boards. The studies were conducted following Good Clinical Practice and the Declaration of Helsinki, as well as with all local and/or national regulations and directives. All participants or parents/guardians provided informed written consent.

Study participants

Both studies were conducted with healthy individuals aged ≥6 months on the day of the respective study. Exclusion criteria included previous vaccination against influenza for the current season; receipt or planned receipt of any other vaccine within 4 weeks from and following any trial vaccination; pregnancy, lactating, or of childbearing potential and not using effective contraception; known or suspected congenital or acquired immunodeficiency; receipt of immunosuppressive therapy within the preceding 6 months; long-term systemic corticosteroid therapy within the past 3 months; or bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion.

Vaccines and schedule

Phase I study

Participants aged 6–35 months and ≥3 years received 0.25 mL and 0.5 mL doses, respectively, of Shz QIV (2018/19 Northern Hemisphere influenza season) containing, respectively, 7.5 µg or 15 µg HA each of A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, B/Colorado/06/2017-like virus, and B/Phuket/3073/2013-like virus. Those aged 6–35 months and 3–8 years received two doses of the vaccine 28 days apart (as they were considered unvaccinated due to the low coverage rate against influenza in China), and the other three age groups (aged 9–17, 18–60, and >60 years) received one dose.

Phase III study

Participants received either 0.25 mL or 0.5 mL dose of Shz QIV (2019/20 northern hemisphere influenza season containing, respectively, 7.5 µg or 15 µg HA each of A/Brisbane/02/2018, IVR-190, A/Kansas/14/2017, NYMC X-327, B/Maryland/15/2016, NYMC BX-69A, and B/Phuket/3073/2013-like strain) or Shz TIV (2019/20 northern hemisphere influenza season containing, respectively, 7.5 µg or 15 µg HA each of A/Brisbane/02/2018, IVR-190 and A/Kansas/14/2017, NYMC X-327, and either B/Maryland/15/2016, NYMC BX-69A, or B/Phuket/3073/2013-like strain). Randomization was performed by the sponsor using an interactive response
technology system. All randomized participants received one or two doses of Shz QIV or Shz TIV according to age and previous vaccination status as follows. Participants aged 6–35 months were randomly assigned to Shz QIV (0.25 mL), Shz QIV (0.5 mL), Shz TIV/Victoria lineage (0.25 mL), or Shz TIV/Yamagata lineage (0.25 mL) in a 2:2:1:1 ratio stratified by previous vaccination history, and site. Those previously unvaccinated (as determined from the participants’ self-reported vaccination histories) received two doses of their allocated vaccine 28 days apart (day 0 [D0] and day 28 [D28]), and those previously vaccinated received one dose. Those aged ≥3 years were randomly assigned to Shz QIV (0.5 mL), Shz TIV/Victoria lineage (0.5 mL), or Shz TIV/Yamagata lineage (0.5 mL) in a 2:1:1 ratio also stratified by age group, previous vaccination history, and site. Previously unvaccinated participants aged 3–8 years randomized to Shz QIV received their second dose open-label 28 days later, while the remainder in this age group, including previously vaccinated and unvaccinated participants randomized to Shz TIV/Victoria lineage or Shz TIV/Yamagata lineage, received one dose of their allocated vaccine. Those aged ≥9 years received one dose of their allocated vaccine.

Participants received the vaccine intramuscularly (in the thigh in infants aged 6–12 months or deltoid in all other participants). Vaccines were prepared and administered by unblinded staff who took no further part in the study. Subsequent assessments were performed by blinded observers. For the open-label vaccination in those aged 3–8 years who were previously unvaccinated and assigned Shz QIV, the blinding was broken at the time of the second dose.

Assessments
Safety
All participants were monitored for 30 min after vaccination for unsolicited systemic adverse events (AEs). The occurrence and severity of solicited injection site and systemic adverse reactions (ARs) were recorded by adults or by parents/guardians in diary cards for 7 days after each vaccine dose. Solicited injection site symptoms recorded were pain, erythema, swelling, induration, and ecchymosis, and solicited systemic symptoms recorded were fever, vomiting, abnormal crying, drowsiness, loss of appetite, irritability for those aged ≤23 months, or fever, headache, malaise, myalgia, and shivering in those aged ≥2 years. The intensity of unsolicited non-serious AEs (i.e., those included in the list of solicited reactions) and ARs were graded according to the National Medical Products Administration (NMPA) scale, in compliance with Chinese Guidelines. All unsolicited AEs not included in the list of solicited reactions were graded on a 3-point scale: Grade 1, no interference with activity; Grade 2, some interference with activity; and Grade 3, significant; prevents daily activity.

In the phase I study, unsolicited AEs and serious adverse events (SAEs) were monitored for 28 days after each vaccination (up to Day 56 [D56] for those who received two vaccine doses), and were assessed in terms of timing, duration, intensity, and whether they led to study discontinuation. In the phase III study, unsolicited AEs were also monitored for 28 days after each vaccination with information on SAEs collected up to 6 months after the last vaccination. The following AEs of special interest were captured as SAEs: anaphylaxis, Guillain–Barré syndrome, encephalitis/myelitis, neuritis, febrile and non-febrile convulsions, thrombocytopenia, and vasculitis. Investigators assigned the potential causal relationship in their opinion to vaccination for each unsolicited AE and SAE.

Immunogenicity
No blood samples were taken from participants in the phase I study, or those aged 6–35 months recruited in step 1 of the phase III study as these participants were enrolled for safety evaluation only.

In the phase III study, blood samples (3 mL) were taken on D0 and D56 (+7 days) from previously unvaccinated participants aged 6–35 months who received two vaccine doses, and on D0, D28 (+7 days), and D56 (+7 days) from unvaccinated participants aged 3–8 years who received two vaccine doses. Blood samples were taken pre-vaccination on D0 and on D28 (+7 days) after vaccination in all other participants who received one vaccine dose.

Serum hemagglutination-inhibition (HAI) antibody titers against each vaccine strain were measured with the HAI method using chick red blood cells. All samples were assessed at the National Institutes for Food and Drug Control (NIFDC) in China. The lower limit of quantification (LLOQ) was 1:10. Titers below this level were reported as <10 (1/dilution [dil]).

Outcomes
In the phase I study, the primary endpoint was the occurrence of serious ARs and Grade 3 unsolicited and solicited non-serious ARs occurring within 28 days after vaccination (participants aged ≥9 years) or after each and any vaccination (participants aged 6 months to 8 years). Secondary endpoints included the occurrence of unsolicited systemic AEs within 30 min of vaccination, solicited local and systemic AEs within 7 days of vaccination, unsolicited AEs within 28 days after vaccination, and SAEs including AESIs throughout the study.

In the phase III study, the primary immunogenicity endpoints were age dependent. In those aged 6–35 months, these were as follows: HAI antibody titers obtained at D0 and 28 days after the last dose (D0 and at D28 in previously vaccinated participants or D0 and D56 in previously unvaccinated participants); seroconversion, defined as a titer <10 (1/dil) at D0 and post-injection titer ≥40 (1/dil) at D28 or D56 as applicable, or titer ≥10 (1/dil) at D0 and a ≥fourfold increase in titer (1/dil) at D28 or D56, as applicable. In those aged ≥3 years, these were as follows: HAI antibody titers obtained at D0 and D28; and seroconversion at D28. The primary safety endpoints were as follows: occurrence of unsolicited AEs within 30 min of vaccination; occurrence of solicited local and systemic AEs within 7 days of each vaccination; unsolicited AEs up to 28 days after any vaccination, all SAEs and AESIs throughout the study. Secondary immunogenicity endpoints included: individual titers, individual titer ratios D28/D0 or D56/D0, as applicable, and detectable titer ≥10 (1/dil) and titer ≥40 (1/dil).
Statistics
The primary objective of the phase I study was to describe by age group the safety profile of the vaccine in terms of occurrence of serious ARs and Grade 3 unsolicited and solicited non-serious ARs after a single dose (participants aged ≥9 years) or after each and any dose administered (participants aged 6 months to 8 years). The sample size was set at 20 per age group, based on the requirements of the Chinese Health Authorities for safety surveillance; thus, a total of 100 participants was required.

In phase III study, the primary objectives were to describe the safety profile and demonstrate the non-inferiority of the immune response in terms of geometric mean titers (GMTs) and seroconversion rates achieved with Shz QIV (0.25 mL and 0.5 mL) compared with Shz TIVs (with B/Victoria-like strain or Shz TIV with B/Yamagata-like strain) for each strain, after the last dose in those aged 6–35 months or after a single (or first) dose in those aged ≥3 years. The planned sample size was set at 6,114 based on an overall power of approximately 80% to demonstrate the primary immunogenicity objectives; 20 participants aged 6–35 months were planned in step 1 for safety assessment. Such a sample size would have 88%, 97% and 94% power to demonstrate the non-inferiority of Shz QIV versus Shz TIVs in those aged 6–35 months (0.25 mL), aged 6–35 months (0.5 mL), and aged ≥3 years, respectively. The elderly (aged >60 years) group was further stratified to include 500 participants aged ≥65 years as per feedback from the Chinese Center for Drug Evaluation. The planned sample size of 500 participants aged ≥65 years would also provide an overall probability of 80% to comply with the European Medicines Agency (EMA) 1997 immunogenicity criteria.11

The Shz TIV groups were pooled for comparison with Shz QIV for the influenza A strains, and the Shz TIV/Victoria-like and Shz TIV/Yamagata-like vaccines were compared separately with QIV influenza B strains. For each strain, non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) for the ratio of GMTs was >1/1.5 and the lower limit of the 2-sided 95% CI for the difference between the seroconversion rates was >−10%. For participants aged 6–35 months, 95% CIs were calculated using log_{10}-transformed titers for GMTs. For participants aged ≥3 years, the age-stratified 95% CIs were calculated using an ANOVA model of log_{10}-transformed titers for GMTs, with age group (3–8 years, 9–17 years, 18–60 years, >60 years) as stratifying factors in the model. In all participants, 95% CIs for the seroconversion rates were calculated using the Newcombe-Wilson score method without continuity correction.12

The superiority of the antibody responses to the B strains (Shz QIV vs Shz TIV [B/Victoria-like strain or TIV [B/ Yamagata-like strain]] and to all antigens (Shz QIV 0.5 mL vs Shz QIV 0.25 mL) would be assessed as a secondary objective if the primary non-inferiority objectives were demonstrated. Superiority was demonstrated if the lower limit of the 2-sided 95% CI for the ratio of GMTs was >1 and the corresponding lower limit of the 2-sided 95% CI for the difference between the seroconversion rates was >10% for each B strain in QIV compared with the non-corresponding B strain in each Shz TIV, or Shz QIV (0.5 mL) compared with the corresponding strains in the Shz QIV (0.25 mL).

Immunogenicity in participants aged ≥65 years was assessed according to the 1997 EMA criteria.13 D28 seroconversion rate >30% and seroprotection rate >60%, and mean geometric increase >2 between D0 and D28.

The Safety Analyses Set included all participants who received ≥1 dose of the study vaccine. Safety was assessed after any dose based on the vaccine received at first dose, and after each dose based on the vaccine received at each dose. In the phase III study, this included the participants aged 6–35 months assessed for safety in step 1. The immunogenicity primary endpoints were analyzed using the Per-Protocol Set (PP) which included all participants in the Full Analysis Set (FAS) who had no relevant protocol deviations. The FAS which included all randomized participants who received ≥1 dose of the study vaccine and had a valid post-vaccination blood sample result for at least one strain, was used for the superiority assessment of the antibody responses to the B strains.

Results
Phase I study
The phase I study was conducted between 22 February and 6 June 2019. All enrolled participants (N = 101) received Shz QIV as planned and completed the study. The baseline characteristics of these participants are summarized in Supplement Table S1.

Shz QIV given either as a single dose or as two doses was well tolerated. There were no immediate unsolicited AEs or ARs reported (Supplement Tables S2). No AE led to study discontinuation. Pain was the most frequent solicited injection site reaction after any dose in all age groups (20–35% of participants aged up to 60 years, 10% [2/20] of those aged >60 years). Fever was the most frequent solicited systemic reaction in the two youngest age groups (50% [10/20] and 33% [7/21], respectively), as was myalgia in those aged 9–17 years (30% [6/20]); no specific solicited systemic reaction was reported by more than two participants in the two older age groups. The incidence of Grade 3 solicited reactions was low (n = 2, fever [both aged 3–8 years] and n = 1, injection site induration [18–60 years]) (Supplement Table S3). There were no Grade 3 unsolicited non-serious reactions and no serious adverse reactions within 28 days after vaccination in any of the age groups. There was 1 SAE (hand-foot-mouth disease [6–35 months]) that resolved without sequelae but was not considered to be related to vaccination.

Phase III study
The phase III study was conducted between 9 January 2020 and 1 December 2020. Following the unexpected COVID-19 outbreak in China during the conduct of this study, many participants missed their planned study visit time windows and were expected not to be compliant with the study procedures as defined in the protocol (n = 1007 impacted, i.e. had at least one major/critical protocol deviation due to COVID-19, or who did not complete the
study or 6-month follow-up). Hence, when the study was resumed, around 970 additional participants (more than 95% aged ≥3 years) were enrolled to ensure the planned evaluable sample size.

Among those aged 6–35 months, 40 participants, previously unvaccinated against influenza, were enrolled in step 1 and received the first dose of Shz QIV (0.5 mL). There was no safety concern observed in the early safety review of these first 40 participants, and vaccination proceeded to include more participants aged 6–35 months.

These participants were also included in the safety analysis set of the whole study (see below). Of these, 38 received the second dose and 20 completed the study; the reasons for discontinuation in this group were protocol deviation (45% [18/40]; due to COVID-19 pandemic) and withdrawal of consent (5% [2/40]).

A total of 7,106 (including 40 in step 1 for safety assessment) participants were enrolled and 7,066 were randomized in a modified double-blind way for immunogenicity and safety assessment; 7,088 (including those from step 1) received at least one study injection and were included in the safety analysis set. Among participants aged 6–35 months, 1,152 received Shz QIV (0.25 mL), 1,192 received Shz QIV (0.5 mL), and 1,151 received Shz TIVs; and among those aged ≥3 years, 1,799 received Shz QIV and 1,794 received Shz TIVs. The flow of participants through the study is summarized by age group and vaccination status (in age groups 6–35 months and 3–8 years) in Figure S1. Among those randomized there were 372 discontinuations (202 and 170 in the Shz QIV and Shz TIV groups, respectively); 7 (5 and 2, respectively; all in the 6–35-month age group) discontinued due to adverse events, but most (n = 204) withdrew or were withdrawn by parents/guardians (111 and 93, respectively), of which 102 were due to the COVID-19 pandemic.

The male to female proportions and ages are summarized by vaccine received in Table 1.

### Immunogenicity

For participants aged 6–35 months, the HAI antibody responses for each antigen are summarized in Supplementary Table S4 by vaccine group. Shz QIV (0.5 mL) induced non-inferior HAI antibody responses compared with the Shz TIVs to both A strains and the corresponding B strains as measured by between-group GMT ratios and differences in seroconversion rates (Tables 2 and 3). Non-inferiority was not demonstrated for Shz QIV (0.25 mL) against the B/Victoria-like strain only. Shz QIV (0.5 mL) had superior responses to the B strains not contained in the respective Shz TIV (Table 4). In addition, Shz QIV (0.5 mL) induced

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### Table 1. Baseline characteristics of the participants by vaccine received (Phase III study; safety analysis set).

| Age (year) | Sex | n (%) | Shz QIV 0.25 mL (N = 1152) | Shz QIV 0.5 mL (N = 2991) | Shz TIVs pooled (N = 2945) | All (N = 7088) |
|------------|-----|-------|---------------------------|--------------------------|--------------------------|---------------|
| 6–35 months | Male | 618 (53.6) | 1394 (46.6) | 1432 (48.6) | 3444 (48.6) | 
|           | Female | 534 (46.4) | 1597 (53.4) | 1513 (51.4) | 3644 (51.4) | 
| Missing | 0 | 0 | 0 | 0 | 0 | 
| Sex ratio: Male/Female | 1.16 | 0.87 | 0.95 | 0.95 | 

### Table 2. Non-inferiority of Shz QIV to Shz TIV using GMTs in participants aged 6–35 months after last dose (Phase III study; per protocol set).

| Antigen/strain | Shz QIV 0.25 mL/0.5 mL Shz TIVs* | Shz QIV 0.5 mL/0.5 mL Shz TIVs* |
|----------------|---------------------------------|---------------------------------|
| QIV A/H1N1 | M GMT (95% CI) | M GMT (95% CI) | Non-inferiority (95% CI) | M GMT (95% CI) | M GMT (95% CI) | Non-inferiority (95% CI) |
| A/H3N2 | | | | | | |
| B/Victoria | | | | | | |
| B/Yamagata | | | | | | |
| TIV1 A/H1N1 | 495 | 180 | 166 | 195 | 0.946 (0.854; 1.049) | 495 | 180 | 166 | 195 | 1.039 (0.940; 1.149) |
| A/H3N2 | 495 | 174 | 158 | 191 | 0.906 (0.806; 1.019) | 495 | 174 | 158 | 191 | 0.980 (0.874; 1.100) |
| B/Victoria | 495 | 91.3 | 84.9 | 98.0 | 0.701 (0.641; 0.767) | 495 | 91.3 | 84.9 | 98.0 | 0.865 (0.788; 0.950) | Yes |
| TIV2 A/H1N1 | 505 | 179 | 164 | 196 | 0.949 (0.853; 1.055) | 505 | 179 | 164 | 196 | 1.041 (0.938; 1.155) | Yes |
| A/H3N2 | 505 | 160 | 146 | 176 | 0.986 (0.878; 1.107) | 505 | 160 | 146 | 176 | 1.066 (0.951; 1.195) | Yes |
| B/Victoria | 505 | 106 | 97.0 | 115 | 0.825; 1.013 | 505 | 106 | 97.0 | 115 | 1.136 (1.025; 1.258) | Yes |
| TIVs pooled A/H1N1 | 1000 | 180 | 169 | 191 | 0.947 (0.870; 1.032) | 1000 | 180 | 169 | 191 | 1.040 (0.956; 1.131) | Yes |
| A/H3N2 | 1000 | 167 | 156 | 178 | 0.946 (0.860; 1.040) | 1000 | 167 | 156 | 178 | 1.023 (0.931; 1.123) | Yes |

* Shz TIVs means any one of the Shz TIV1, Shz TIV2 or Shz TIVs pooled group.

§ Non-inferiority on GMTs is concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is >0.667 for each of the comparisons applicable in this column.

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**Table 1.** Baseline characteristics of the participants by vaccine received (Phase III study; safety analysis set).

**Table 2.** Non-inferiority of Shz QIV to Shz TIV using GMTs in participants aged 6–35 months after last dose (Phase III study; per protocol set).
For participants aged ≥3 years, the HAI antibody response for each antigen is summarized in Supplementary Tables S6–S11 by vaccine group and by age subgroup (3–8 years, 9–17 years, 18–60 years, and >60 years). Shz QIV (0.5 mL) induced non-inferior HAI antibody responses compared with the Shz TIVs to both A strains and the corresponding B strains (Table 5), and had superior responses to the B strain not contained in the respective Shz TIV (Table 4).

In those aged ≥65 years, the predefined criteria for the immunogenicity of influenza vaccines (D28 seroconversion rate >30% and seroprotection rate >60%, and mean geometric increase >2 between D0 and D28) were met for all four strains in Shz QIV (Supplement Table S11).

### Safety

**Solicited ARs**

In those aged 6–35 months, the rate of injection site reactions was 14.5% (166/1148) and 16.2% (193/1190) after any dose of Shz QIV (0.25 mL) and Shz QIV (0.5 mL), respectively, and 14.4% (165/1147) after Shz TIVs (pooled group) (Table 6). Injection site tenderness/pain was the most frequently (8.9–10.5% across all vaccine groups after any dose) reported solicited injection site reaction. The rate of solicited systemic reactions was 27.6% (317/1148) and 30.4% (362/1190) after any dose of Shz QIV (0.25 mL) and Shz QIV (0.5 mL), respectively, and 27.7% (318/1147) after Shz TIVs (pooled group). Fever was the most frequently (19.7–24.4% across all vaccine groups after any dose) reported solicited systemic reaction. Grade 3 ARs were reported by ≤1% of participants (Table 7).

In those aged ≥3 years, the rate of injection site reactions was 9.9% (178/1790) after any dose of Shz QIV, and 8.0% (143/1786) after Shz TIVs (pooled group) (Table 6). Pain was the most frequently reported solicited injection reaction across all vaccine groups after any dose, occurring in 7.1–9.9% aged 3–8 years, 10.5–11.8% aged 9–17 years, 5.4–9.8% aged 18–60 years, and 2.9–3.3% aged >60 years. The rate of systemic reactions was 11.9% (213/1790) after any dose of Shz QIV, and 9.2% (164/1786) after Shz TIV (pooled group). Fever was generally the most frequently reported solicited systemic reaction across all vaccine groups after any dose, occurring in 8.2–15.5% aged 3–8 years, 8.8–12.5% aged 9–17 years, 2.7–5.8% aged 18–60 years, and 1.0–2.6% aged >60 years. Grade 3 ARs were reported by ≤0.4% of participants (Table 7).

**Unsolicited AEs/ARs**

In those aged 6–35 months, the rate of unsolicited AEs was 19.4% (223/1152) and 18.8% (224/1192) after any dose of Shz QIV (0.25 mL) and Shz QIV (0.5 mL), respectively, and 20.7% (238/1151) after TIVs (pooled group) (Table 6). Rhinorrhea was the most frequently reported unsolicited AR (0.2–0.7% across all vaccine groups after any dose). The rate of unsolicited AEs leading to study discontinuation was ≤0.3% with Shz QIV (0.25 mL or 0.5 mL) and Shz TIVs. The rate of SAEs within 28 days of vaccination was 0.7–1.6% across the vaccine groups. The most frequent SAE was pneumonia (5 [0.4%], 3 [0.3%] and 5 [0.4%] participants in the Shz QIV (0.25 mL), Shz

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**Table 5. Non-inferiority of Shz QIV to Shz TIV using seroconversion rate in participants aged 6–35 months after last dose (Phase III study per protocol set).**

| Antigen/strain | Shz QIV 0.25 mL minus Shz TIV* | Difference (%) | 95% CI | Non-inferiority§ |
|----------------|--------------------------------|----------------|--------|------------------|
| Shz QIV 0.5 mL minus Shz TIV* | n/a | n/a | n/a | no |

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**Table 3. Non-inferiority of Shz QIV to Shz TIV using seroconversion rate in participants aged 6–35 months after last dose (Phase III study per protocol set).**

| Antigen/strain | Shz QIV 0.25 mL minus Shz TIV* | Difference (%) | 95% CI | Non-inferiority§ |
|----------------|--------------------------------|----------------|--------|------------------|
| Shz QIV 0.5 mL minus Shz TIV* | n/a | n/a | n/a | no |
Table 4. Superiority of Shz QIV to Shz TIV using GMT (a) and seroconversion rates (b) against the B strains (after last dose in those aged 6–35 months) (Phase III study; Full Analysis Set).

| Antigen/strain | Shz QIV | Shz TIV1 | Shz TIV2 | Shz QIV/Shz TIVs* |
|----------------|--------|---------|---------|-----------------|
|                | M GMT  | (95% CI)| M GMT  | (95% CI)        | GMT ratio | (95% CI) | Superiority§ |
| 6–35 months (QIV 0.5 mL) |        |         |         |                  |
| B/Victoria     | 1113   | 77.9    | (73.9; 82.1) | –    | –    | –    | 541 | 27.3 | (24.6; 30.2) | 2.856 | (2.576; 3.166) | Yes |
| B/Yamagata     | 1113   | 120     | (113; 127) | 546  | 23.3 | (21.0; 25.9) | –    | –    | –    | 5.145 | (4.615; 5.737) | Yes |
| ≥3 years       |        |         |         |                  |
| B/Victoria     | 1760   | 79.4    | (75.2; 83.9) | –    | –    | –    | 870 | 29.3 | (27.2; 31.6) | 2.711 | (2.475; 2.970) | Yes |
| B/Yamagata     | 1760   | 190     | (179; 201) | 881  | 73.1 | (67.2; 79.5) | –    | –    | –    | 2.591 | (2.352; 2.855) | Yes |

| Antigen/strain | Shz QIV | Shz TIV1 | Shz TIV2 | Shz QIV minus Shz TIVs* |
|----------------|--------|---------|---------|-------------------------|
|                | n/M    | %       | (95% CI)|                         |
| 6–35 months (QIV 0.5 mL) |        |         |         |                         |
| B/Victoria     | 992/1112 | 89.2   | (87.2; 91.0) | –    | –    | –    | 272/541 | 50.3 | (46.0; 54.6) | 38.93 | (34.30 ; 43.46) | Yes |
| B/Yamagata     | 1043/1112 | 93.8   | (92.2; 95.1) | 226/546 | 41.4 | (37.2; 45.7) | –    | –    | –    | 52.40 | (47.94 ; 56.66) | Yes |
| ≥3 years       |        |         |         |                         |
| B/Victoria     | 1239/1760 | 70.4   | (68.2; 72.5) | –    | –    | –    | 293/870 | 33.7 | (30.5; 36.9) | 36.72 | (32.85; 40.43) | Yes |
| B/Yamagata     | 1370/1760 | 77.8   | (75.8; 79.8) | 370/881 | 42.0 | (38.7; 45.3) | –    | –    | –    | 35.84 | (32.00; 39.57) | Yes |

M: number of participants with available data for the relevant endpoint.

*Shz TIVs means either Shz TIV1 or Shz TIV2 group displayed in the column names.

For B/Victoria strain, the immunogenicity of Shz QIV compared to Shz TIV2 group which does not contain B/Victoria strain.

For B/Yamagata strain, the immunogenicity of Shz QIV compared to Shz TIV1 group which does not contain B/Yamagata strain.

§Superiority in GMTs is observed if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is > 1 for each of the comparisons applicable in this column; superiority in seroconversion is observed if the lower limit of the 2-sided 95% CI of the difference of seroconversion rates between groups is >10% for each applicable comparison.
QIV (0.5 mL) and Shz TIVs group, respectively), all of which were considered not related to vaccination. There was a case of Grade 2 diarrhea (hospitalized and resolved) that was considered by the investigator to be related to Shz QIV (0.25 mL). One participant experienced an AESI (febrile convulsion, Grade 2) within 28 days after vaccination (Shz QIV [0.25 mL] group), but this was not considered related to study vaccination. Six participants experienced AESIs (all febrile convulsions, Grade 2–3) during 6 months of follow-up (2 each in the Shz QIV [0.25 mL], Shz QIV [0.5 mL] and Shz TIVs groups), but were not considered related to study vaccination. There were two deaths in this age group (Shz QIV [0.25 mL] and Shz TIVs groups) both unrelated to study vaccination (drowning and traffic accident).

In those aged >3 years, the rate of unsolicited AEs was 4.6% (82/1799) after any dose of Shz QIV and 4.1% (74/1794) after Shz TIVs (pooled group) (Table 6). There were 7 and 8 participants who experienced SAEs (9 and 9 SAEs, respectively) in the Shz QIV and Shz TIVs groups, respectively, within 28 days of vaccination; all were considered not related to vaccination. There were no AESIs reported within 28 days after vaccination. There were two AESIs during 6 months follow-up; Grade 2 Henoch-Schonlein purpura in the 9–17 years Shz QIV group assessed as not related, and Grade 3 immune thrombocytopenia in the >60 years Shz TIV group assessed as related to vaccination. There was one death (liver abscess and cardio-respiratory arrest) in the >60 years Shz TIV group during the 6-month follow-up, which was considered not related to the study vaccine.

### Discussion

Our Phase I study showed that Shz QIV was well tolerated by healthy Chinese participants when given either as two doses 28 days apart to those aged 6 months to 8 years or as a single dose to those aged ≥9 years. The Phase III study also showed that Shz QIV was well tolerated and had a similar safety profile to the licensed Shz TIVs in all age groups assessed. There were no safety concerns identified in any age group in both studies.

The antibody responses (GMTs and seroconversion rates) to Shz QIV (0.5 mL) for all antigens were demonstrated to be non-inferior to those achieved with Shz TIVs in those aged 6–35 months and ≥3 years, with superiority in antibody responses compared to the non-corresponding B strain in each TIV also demonstrated. Non-inferiority of Shz QIV (0.25 mL) versus Shz TIVs was demonstrated against A/H1N1, A/H3N2, and B/Yamagata in those aged 6–35 months, but this was not the case against the B/Victoria lineage strain. Superiority of Shz QIV (0.5 mL) versus Shz QIV (0.25 mL) was demonstrated for all antigens in those aged 6–35 months. Previous global studies with Vaxigrip Tetra*, a predecessor formulation of Shz QIV, had also shown that it induced non-inferior HAI antibody responses to all A strains and corresponding B strains compared with control TIVs and superior (or substantially higher) antibody responses to the non-corresponding B strains in each TIV in children 6 months to 8 years (0.25 mL for those aged 6–35 months and 0.5 mL for those aged 3–8 years) and adults.15,16
Table 6. Safety overview after any injection (Phase III study: safety analysis set).

| Participants experiencing at least one: | Shz QV 0.25 mL (N=1152) | Shz QV 0.5 mL (N=1192) | Shz TIVs Pooled (N=1151) | Shz QV (N=1799) | Shz TIVs Pooled (N=1794) |
|----------------------------------------|--------------------------|------------------------|--------------------------|-----------------|----------------------------|
| **Within 30 minutes after any injection** | | | | | |
| Immediate unsolicited AE | 2/1152 (0.2) (0.0; 0.6) | 2/1192 (0.2) (0.0; 0.6) | 2/1151 (0.2) (0.0; 0.6) | 1/1799 <0.1 | 1/1794 <0.1 (0.0; 0.3) |
| Immediate unsolicited AR | 2/1152 (0.2) (0.0; 0.6) | 2/1192 (0.2) (0.0; 0.6) | 0/1150 (0) (0; 0.6) | 1/1799 <0.1 | 0/1794 0 (0.0; 0.2) |
| **Within solicited period after any injection** | | | | | |
| Solicited reaction | 340/1148 (33.2; 37.9) | 470/1190 (39.5) (36.7; 42.3) | 401/1147 (35.0) (32.2; 37.8) | 335/1790 (18.7) | 335/1790 (18.7) (16.9; 20.6) |
| Solicited injection site reaction | 166/1148 (14.5; 16.6) | 193/1190 (16.2) (14.2; 18.4) | 165/1147 (14.4) (12.4; 16.6) | 178/1790 (9.9) | 178/1790 (9.9) (8.6; 11.4) |
| Tenderness/pain | 121/1148 (10.5; 12.5) | 124/1190 (10.4) (8.7; 12.3) | 104/1147 (9.1) (7.5; 10.9) | 158/1790 (8.8) | 158/1790 (8.8) (7.6; 10.2) |
| Eythema | 55/1148 (4.8; 6.6) | 74/1190 (6.2) (4.9; 7.7) | 64/1147 (5.6) (4.3; 7.1) | 32/1790 (1.8) | 32/1790 (1.8) (1.2; 2.5) |
| Swelling | 9/1148 (0.8; 1.5) | 16/1190 (1.3) (0.8; 2.2) | 8/1146 (0.7) (0.3; 1.4) | 14/1790 (0.8) | 14/1790 (0.8) (0.4; 1.3) |
| Induration | 3/1148 (0.3; 0.8) | 5/1190 (0.4) (0.1; 1.0) | 4/1146 (0.3) (0.1; 0.9) | 4/1790 (0.2) | 4/1790 (0.2) (0.1; 0.6) |
| Ecchymosis | 6/1148 (0.5; 1.1) | 5/1190 (0.4) (0.1; 1.0) | 1/1146 <0.1 | 3/1790 (0.2) | 3/1790 (0.2) (0.0; 0.5) |
| **Solicited systemic reaction** | | | | | |
| Fever | 317/1148 (27.6; 30.3) | 362/1190 (30.4) (27.8; 33.1) | 318/1147 (27.7) (25.2; 30.4) | 213/1790 (11.9) | 213/1790 (11.9) (10.4; 13.5) |
| Aggravation | 226/1148 (19.7; 22.1) | 290/1190 (24.4) (22.0; 26.9) | 253/1147 (22.1) (19.7; 24.6) | 154/1796 (8.6) | 154/1796 (8.6) (7.3; 10.0) |
| | | | | | |
| **Within 28 days after any injection** | | | | | |
| Unsolicited AE | 223/1152 (19.4; 21.6) | 224/1192 (18.8) (16.6; 21.1) | 238/1151 (20.7) (18.4; 23.1) | 82/1799 (4.6) | 74/1794 (4.1) (3.5; 5.2) |
| Unsolicited AR | 30/1152 (2.6; 3.7) | 30/1192 (2.5) (1.7; 3.6) | 34/1151 (3.0) (2.1; 4.1) | 10/1799 (0.6) | 6/1794 (0.3) (0.1; 0.7) |
| AE leading to discontinuation | 3/1152 (0.3; 0.8) | 2/1192 (0.2) (0.0; 0.6) | 2/1151 (0.2) (0.0; 0.6) | 0/1799 0 | 0/1794 0 (0.2) |
| SAE | 13/1152 (1.1; 1.9) | 8/1192 (0.7) (0.3; 1.3) | 18/1151 (1.6) (0.9; 2.5) | 7/1799 (0.4) | 8/1794 (0.4) (0.2; 0.8) |
| Death | 1/1152 <0.1 | 0/1192 0 | 0/1151 <0.1 | 0/1799 0 | 0/1794 0 (0.2) |
| AESI | 1/1152 <0.1 | 0/1192 0 | 0/1151 0 | 0/1799 0 | 0/1794 0 (0.2) |
| **During 6-month follow-up period** | | | | | |
| SAE | 13/1152 (1.1; 1.9) | 16/1192 (1.3) (0.8; 2.2) | 21/1151 (1.8) (1.1; 2.8) | 21/1799 (1.2) | 22/1794 (1.2) (0.7; 1.8) |
| Death | 0/1152 0 | 0/1192 0 | 0/1151 0 | 0/1799 0 | 0/1794 0 (0.2) |
| AESI | 2/1152 (0.2; 0.6) | 2/1192 (0.2) (0.0; 0.6) | 0/1151 0 | 1/1799 <0.1 | 0/1794 <0.1 (0.0; 0.3) |
| **During the study** | | | | | |
| SAE | 26/1152 (2.3; 3.3) | 24/1192 (2.0) (1.3; 3.0) | 39/1151 (3.4) (2.4; 4.6) | 26/1799 (1.4) | 30/1794 (1.7) (1.1; 2.4) |
| Death | 1/1152 <0.1 | 0/1192 0 | 1/1151 <0.1 | 0/1799 0 | 0/1794 <0.1 (0.0; 0.3) |
| AESI | 3/1152 (0.3; 0.8) | 2/1192 (0.2) (0.0; 0.6) | 2/1151 (0.2) (0.0; 0.6) | 1/1799 <0.1 | 1/1794 <0.1 (0.0; 0.3) |

n: number of participants experiencing the endpoint listed in the first column.
M: number of participants with available data for the relevant endpoint.
Intensity scales based on the Chinese NMFA scale classification.
*Assessed infants aged < 23 months.
†Assessed in those aged ≥ 2 years.
Currently in China, there are eight approved QIVs (including Sinovac Biotech, Beijing; and Hualan Biotech, Xinxiang, China) which are licensed for use in individuals aged ≥3 years and one approved in individuals aged 6 to 35 months (Hualan Biotech). The national pharmacopoeia of China recommends that children aged <3 years receive the 0.25 mL dose (containing 7.5 μg hemagglutinin per virus strain) of any influenza vaccine, while globally a 0.5 mL dose (containing 15 μg hemagglutinin per virus strain) of influenza vaccine is more widely recommended in this age group. Our study showed that the safety profiles of Shz QIV (0.25 mL) and Shz QIV (0.5 mL) were similar after the first and the second injections in those aged 6–35 months, suggesting that the increased dose does not compromise safety in this age group. HAI antibody responses were slightly higher for Shz QIV (0.5 mL) than Shz QIV (0.25 mL) and non-inferiority of the 0.25 mL dose for the B/Victoria-like strain was not shown. In addition, Shz QIV (0.5 mL) induced superior antibody responses to all corresponding strains compared with Shz QIV (0.25 mL), suggesting that Shz QIV (0.5 mL) may be a better option in children aged 6–35 months. The findings for the 0.25 mL dose are similar to those previously observed in China with the currently approved QIV (Sinovac Biotech, Beijing), in 2,320 children aged 6–35 months, QIV (0.25 mL) was non-inferior to TIVs for the influenza A strains and the B/Yamagata lineage strain, but non-inferiority was not shown for the B/Victoria lineage strain. The safety, immunogenicity and efficacy of QIV inactivated influenza vaccine, Vaxigrip Tetra, has been previously confirmed for the 0.5 mL dose in participants aged 6–35 months worldwide, and our safety and immunogenicity findings with Shz QIV, which is based on Vaxigrip Tetra, in Chinese participants are in line with those observations.

Children aged 3–8 years received one or two doses of Shz QIV (0.5 mL) in our study based on prior influenza vaccination status. In those who were previously unvaccinated, the second dose of Shz QIV elicited higher HAI antibody responses than after the first, suggesting that a schedule of two doses, 4 weeks apart would be more appropriate for previously unvaccinated children in this age range. However, the Chinese national pharmacopoeia recommends that children aged 3–8 years receive one dose irrespective of previous influenza vaccination history, which is inconsistent with guidelines by the Chinese Center for Disease Control and Prevention and the World Health Organization and the Advisory Committee on Immunization Practices (ACIP) in the USA.

In older adults aged ≥65 years, Shz QIV elicited robust HAI antibody responses and seroconversion rates were high against all of the vaccine strains, fulfilling the EMA 1997 criteria for immunogenicity of influenza vaccines in the elderly.

HAI antibody titers are generally accepted as the best indicator of protection against influenza, but have limitations as surrogate endpoints since their correlation with protection may differ by vaccine type and formulation, as well as age and health status of the volunteer population. In addition, although the 0.67 non-inferiority margin for GMT ratios and 10% for seroconversion rate differences are commonly (implicitly recommended) used, a meta-analysis of published trials concluded that publications do not provide a clear rationale for

### Table 7. Summary of solicited AR, within 7 days after any injection

| n/M | ≥3 years | 6–35 months |
|-----|----------|-------------|
| Shz QIV 0.25 mL | n/M | 95% CI | n/M | 95% CI |
| n | 403/1148 | (0.1, 0.2) | 35.3 | (0.1, 0.2) |
| Solicited reaction | | | | |
| Graded solicited reaction | | | | |
| Grade 3 solicited reaction | | | | |
| Solicited systemic reaction | | | | |
| Grade 3 systemic reaction | | | | |

Intensity scale based on the Chinese WHO scale classification.

Note: Data are for Chinese residents.
In conclusion, Shz QIV (0.5 mL) elicited non-inferior HAI antibody responses against all corresponding A and B strains compared to the licensed Shz TIVs in a healthy Chinese participants aged ≥6 months, including the elderly. Moreover, Shz QIV (0.5 mL) elicited superior HAI antibody responses to that of the non-corresponding B strain in each TIV. These results suggest that QIV (0.5 mL) would provide broader protection against seasonal influenza than TIVs in those aged ≥6 months in China. The safety profile of Shz QIV was also similar to that of the licensed Shz TIVs, and no safety concerns were observed in any age group. Our observations in children aged 6–35 months supports the use of QIV 0.5 mL in this age group.

Acknowledgments

The authors thank the FSQ01/FSQ02 study group for their contributions to the successful conduct of the study: Lili Huang; Xiaolong Li; Qiang Liu; Hongzhuan Luo; Qinfen Lv; Meihui Su; Zhiqiang Xie; Huacheng Xia; Wangyang You; Wei Zhang; Youmei Zheng; Guangjie Zhu; Zhongyi Zhang; Huiqian Zhang; Karina Abalos; Yann-Joel Beyer; Michael Zhang; Catherine Moreau; Cathy Deng; Camille Salamand; Cynthia Tabar; Rui Ao; Tamala Mallett Moore; Alexandra Jouve; and Carina Frago; Rongna A; Erah Jean Baria; Salamand Camille; Xu Cao; Danette Cathcart; Anne-Laure Chabanon; Nong Chen; Huimei Feng; Anne-Isabelle Fontvieille; Audrey Hagenbach; Huan He; Ajinkya Inamdar; Helene Janosczyk; Angelina Lau; Celine Petit; Wilhelm Philipp; Stephanie See; Laurence Serradell-Vallejo; Anne Tourault; Shuyu Wu; Meng Yan; Chenyan Yue; Xinwei Zhang; Hui Zhang; Yuanju Zhu; Jianfen Li; Haiyan Mao; Haitao Yang; Yang Yang; Xiang Yi; Zhixiang Du; Lizhen Guo; Kai Wang.

Editorial assistance with the preparation of the manuscript was provided by Richard Glover, inScience Communications, Springer Healthcare Ltd, Chester, UK, and was funded by Sanofi. The authors also thank Isabel Grégoire for editorial assistance and manuscript coordination on behalf of Sanofi.

Author’s contributions

XQL, JP, SX, BL, NL, JD, SIS, and IDB contributed to the conceptual design of the study; All authors contributed to data acquisition and/or data analysis/interpretation, and participated in the drafting and/or revision of this report, approved the final version and are accountable for its accuracy and integrity.

Disclosure statement

JP, OS, NL, JD, SIS, and IDB are employees of Sanofi and may hold shares and/or stock options in the company. BL and JH were employees of Sanofi at the time of these studies. XL and SY are employees of Yunnan Province Center for Disease Control and Prevention, Yunnan Province, SX and YW are employees of Henan Province Center for Disease Control and Prevention, Henan Province, SL and CZ are employees of National Institutes for Food and Drug Control, Beijing, all in China, and were contracted by Sanofi to conduct this research.

Funding

This work and studies were funded by Sanofi.

Data availability statement

Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi’s data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

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