HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 1, 2160600
https://doi.org/10.1080/21645515.2022.2160600

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RESEARCH ARTICLE

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# Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine (MenACYW-TT) administered as a booster to adults aged ≥59 years: A phase III randomized study

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**ABSTRACT**

This 2-stage Phase III study (NCT04142242) of a recently licensed quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT) assessed the safety and immunogenicity of a booster dose in older adults (≥59 years) primed with either MenACYW-TT or a quadrivalent meningococcal polysaccharide vaccine (MPSV4). Immune persistence of MenACYW-TT and MPSV4 after primary vaccination was also evaluated. During Stage I, the participants administered MPSV4 (n = 165) or MenACYW-TT (n = 236) 3 years previously were randomized 9:2 to receive either a MenACYW-TT booster or to have blood drawn for persistence only. Participants primed with MPSV4 or MenACYW-TT 6–7 years previously had blood drawn for antibody persistence only. A serum bactericidal assay using human complement was used to measure functional antibodies against each serogroup at baseline and, for those receiving a booster, 30 days post-vaccination (D30). Proportions of participants with seroresponse (post-vaccination titers ≥1:16 when baseline titers <1:8 or ≥ 4-fold increase when baseline titers ≥1:8) were determined. Safety data were collected up to D30. Seroresponse rates for all serogroups at D30 ranged from 49.2% to 60.8% in the MPSV4-primed group, and 79.3–93.1% in the MenACYW-TT-primed group. MenACYW-TT induced sufficient seroresponses in each primed group. Geometric mean titers (GMTs) for serogroups C, W, and Y remained or trended higher than pre-vaccination levels at both 3 and 6–7 years after primary vaccination, indicating immune persistence. Safety outcomes were comparable between groups. A MenACYW-TT booster was immunogenic and well tolerated in participants aged ≥59 years regardless of previous quadrivalent meningococcal vaccine received. The greatest immune responses occurred in those primed with MenACYW-TT.

**ARTICLE HISTORY**
Received 11 August 2022
Revised 29 November 2022
Accepted 16 December 2022

**KEYWORDS**
Quadrivalent meningococcal conjugate vaccine; MenACYW-TT booster; immunogenicity; safety; older adults; elderly

## Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is a rare, rapidly progressing, and a potentially fatal infection that can result in serious sequelae for survivors.[1,2] It presents a significant public health concern worldwide, with an estimated incidence of 1.2 million cases occurring each year globally.[1,2] *N. meningitidis* has been classified into at least 12 serogroups based on its capsular polysaccharides, with the majority of disease cases caused by serogroups A, B, C, W, X, and Y.[3] The prevalence of the predominant serogroup(s) varies by time and region.[3]

While the incidence of IMD is generally highest in infants and young children, the highest case-fatality rates generally occur in older adults.[3–9] Vaccination against *N. meningitidis* with a quadrivalent (serogroup A, C, W, and Y) conjugate vaccine (MCV4) is recommended for children and adolescents in many countries, as well as for those at increased risk of the disease due to occupation or travel to endemic areas.[10–12] In particular, the Hajj pilgrimage to Mecca has been associated with outbreaks of meningococcal disease among travelers who have returned to their home countries[13,14] and therefore the Kingdom of Saudi Arabia requires visitors going on Hajj or Umrah to submit a valid vaccination certificate indicating receipt of either a quadrivalent polysaccharide meningococcal vaccine within the last 3 years, or a quadrivalent conjugate vaccine within the last 5 years.[10,14,15] This requirement stems from evidence demonstrating that protection following MCV4 vaccination may wane 3–5 years after primary vaccination.[16–19] As a significant proportion of Hajj pilgrims are elderly, it is important that safe and effective vaccines are available for this population who are at increased risk of IMD.[20,21] MPSV4 (quadrivalent meningococcal polysaccharide vaccine; Menomune®), first licensed in 1981 in several countries, including the USA, had been the only FDA-approved meningococcal vaccine in the USA for adults ≥56 years of age until its discontinuation in 2017.[10,22] The licensure of effective vaccines in this age group has been challenging due to the difficulties posed by age-related changes in the immune systems of older adults (leading to increased susceptibility to infection, reduced vaccine efficacy and more rapid waning of vaccine-induced immunity compared to younger age groups) and a general paucity of data on meningococcal vaccination in the elderly.[23,24]

MenACYW-TT (MenQuadfi®), a quadrivalent meningococcal tetanus toxoid-conjugate vaccine, is currently approved in

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**Clinical Trial Registration**: ClinicalTrials.gov: NCT04142242.
Supplemental data for this article can be accessed on the publisher's website at https://doi.org/10.1080/21645515.2022.2160600

more than 40 countries and is indicated for active immunization against IMD caused by serogroups A, C, W, and Y, in individuals aged ≥2 years in the USA, as well as in individuals aged ≥12 months in the EU and other countries. Two clinical studies (NCT02842866 and NCT01732627) specifically demonstrated that MenACYW-TT was well tolerated and immunogenic in meningococcal vaccine-naïve adults ≥56 years of age,[21,25] with study NCT02842866 demonstrating a seroresponse that was non-inferior to that of MPSV4 for all four meningococcal serogroups.[21] The immunogenicity and safety of a booster dose of MenACYW-TT in individuals primed with either MPSV4 or MenACYW-TT at ≥56 years of age had not been evaluated previously. The present study was undertaken to assess the performance of a booster dose of MenACYW-TT in older adults who had been primed with a single dose of MPSV4 or MenACYW-TT 3 years previously. Antibody persistence for up to 7 years after primary vaccination was also evaluated.

## Methods

### Study design and participants

This was a Phase III, randomized, open-label, two-stage, multicenter trial designed to assess the immunogenicity and safety of a dose of MenACYW-TT administered to participants ≥59 years of age who had received either MPSV4 or MenACYW-TT at least 3 years previously (ClinicalTrials.gov: NCT04142242). The study was conducted between October 2019 and April 2020 at 34 sites in the USA and Puerto Rico. Antibody persistence 3–7 years after primary vaccination with either MPSV4 or MenACYW-TT was also assessed.

Participants who received their primary vaccination with MPSV4 or MenACYW-TT in a Phase III study (NCT02842866), conducted from 2016 to 2017, or a Phase II study (NCT01732627) conducted in 2012, were eligible for inclusion. Details of these studies have been published previously.[21,25] Briefly, both studies involved participants aged ≥56 years (NCT02842866, n = 907; NCT01732627, n = 301) who were randomly assigned to receive a single vaccine dose of either MPSV4 or MenACYW-TT and were followed for immunogenicity and safety endpoints. Participants were excluded from the current study if they had received any vaccine in the 4 weeks preceding study enrollment (except for influenza vaccination, which could be received within 2 weeks of enrollment); had received any meningococcal vaccine since receipt of their single dose in the previous studies; had a history of meningococcal infection confirmed either clinically, serologically or microbiologically; or were at high risk for meningococcal infection during the study. Other exclusion criteria included: use of immunoglobulins, blood or blood-derived products in the 3 months prior to enrollment; immunosuppressive therapy in the preceding 6 months; long-term corticosteroid therapy; or use of oral or injectable antibiotics (due to potential interference with bioassays) within 3 days prior to the first blood sampling.

The current study involves two stages. Stage I (reported here) assessed immunogenicity and safety outcomes following a dose of MenACYW-TT administered 3 years after primary vaccination with either MPSV4 or MenACYW-TT. Antibody persistence data was also assessed 3 years and 6–7 years following primary vaccination. Stage II, which is ongoing, will assess immunogenicity and safety of a booster dose of MenACYW-TT administered approximately 5 years after primary vaccination, as well as antibody persistence; findings from Stage II will be reported separately. The study design is shown in Figure 1. Participants who had received either MPSV4 or MenACYW-TT 3 years previously were randomized in a 9:2 ratio to receive either a MenACYW-TT booster during Stage I of the study (MPSV4-primed$_{3y+booster}$ and MenACYW-TT-primed$_{3y+booster}$), or to have blood drawn for persistence (MPSV4-primed$_{3y}$ and MenACYW-TT-primed$_{3y}$, with a booster dose to be administered 2 years later, at entry into Stage II of the study). The participants who received MPSV4 or MenACYW-TT 6–7 years previously had blood drawn for persistence and did not receive a booster dose at any point during the study (MPSV4-primed$_{6\text{-}7y}$ and MenACYW-TT-primed$_{6\text{-}7y}$).

The study was approved by the appropriate independent ethics committees and institutional review boards before its initiation. The conduct of this study was consistent with standards established by the Declaration of Helsinki and compliant with the International Conference on Harmonization guidelines for Good Clinical Practice, including all local and/or national regulations, and directives. Signed and dated written informed consent was received by all participants prior to the start of the study.

### Vaccine and schedule

MenACYW-TT was given as a single 0.5-mL dose by intramuscular injection on Day 0 according to group assignment in Stage I. Each 0.5-mL dose of MenACYW-TT (Sanofi, Swiftwater, PA, USA) contained 10 µg of polysaccharide of each serogroup (A, C, W, and Y) and approximately 55 µg of tetanus toxoid protein carrier presented in solution.

### Immunogenicity

Blood samples for immunogenicity assessments by serum bactericidal antibody assay utilizing human complement (hSBA) were collected from all participants at Day 0 (baseline), and at Day 30 after vaccination for those receiving MenACYW-TT during the current study. The first 120 participants enrolled and randomized to the booster groups formed a subset of participants from whom a blood sample was also taken at Day 6 after vaccination. Antibody titers against meningococcal serogroups A, C, W, and Y were measured using an established hSBA protocol (Global Clinical Immunology, Sanofi, Swiftwater, PA, USA).[26,27] The assay had a lower limit of quantification of 1:4. Immunogenicity assessments were also made by serum bactericidal assay using baby rabbit complement (rSBA; UK Health Security Agency [formerly Public Health England], Manchester, UK).

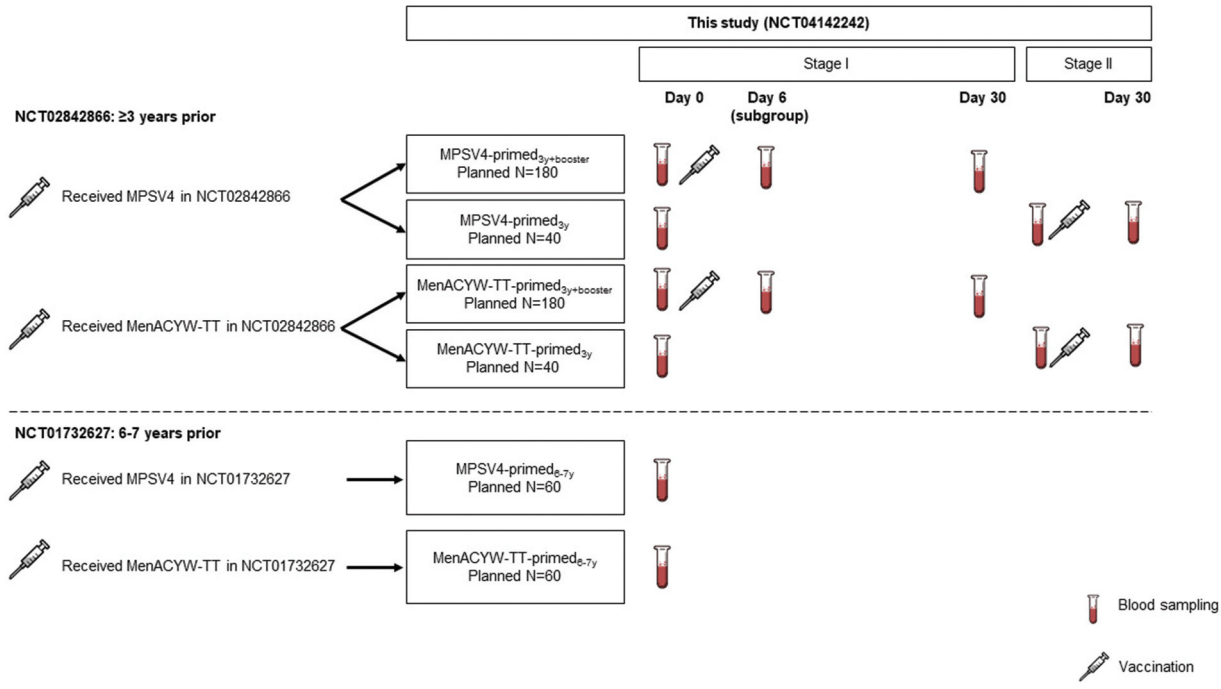


**Figure 1.** Study design.
hSBA and rSBA were used to measure antibodies against meningococcal serogroups A, C, W, and Y at baseline (Day 0) and Day 30 after the booster dose. For a subgroup of participants, antibodies were also measured 6 days after the booster.

The primary objective of this trial was to demonstrate "vaccine seroresponse sufficiency" to meningococcal serogroups A, C, W, and Y, 30 days after administration of a single dose of MenACYW conjugate vaccine to participants who received primary vaccination with MPSV4 vaccine 3 years earlier when they were ≥56 years old. The vaccine seroresponse was considered sufficient if the lower limit of the 1-sided 97.5% confidence interval (CI) for the proportion of participants with hSBA vaccine seroresponse against each of the four serogroups was greater than 40%. This threshold, agreed upon with the US Food and Drug Administration (FDA), was based, in part, on observed seroresponse rates following primary vaccination with MPSV4.[21]

The secondary immunogenicity objectives were to assess: the sufficiency of the vaccine seroresponse as measured by hSBA at Day 30 after MenACYW-TT vaccination in those who had received MenACYW-TT 3 years earlier; vaccine seroresponse at Day 6 after MenACYW-TT vaccination in those who had received MPSV4 or MenACYW-TT 3 years earlier (in a subset of participants); and antibody persistence at Day 0 of this study after initial vaccination with MPSV4 or MenACYW-TT 3 years or 6–7 years earlier, as measured by hSBA and rSBA.

Observational immunogenicity objectives included measurement of antibody titers (hSBA and rSBA) for each meningococcal serogroup at Day 0, Day 6 (in a subset) and Day 30; the proportion of participants with hSBA titers ≥1:4 and ≥1:8 (seroprotection); and tetanus toxoid antibody concentrations at Day 0 in all participants and at Day 30 in those who received MenACYW-TT during the current study. Seroresponse was defined as post-vaccination hSBA titers ≥1:16 for participants with pre-vaccination hSBA titers <1:8, or a ≥ 4-fold increase in hSBA titers for participants with pre-vaccination hSBA titers ≥1:8.

## Safety

Participants were observed for 30 min after vaccination, to assess the occurrence of any immediate unsolicited systemic adverse events (AEs). Information on solicited injection site (pain, erythema, swelling) and systemic (fever, headache, malaise, myalgia) reactions was collected for 7 days after vaccination in diary cards and were considered vaccine related. Participants were also asked to record information relating to any unsolicited AE from Day 0 to Day 30 (window, +14 days) in their diary cards, including the occurrence, nature, time to onset, duration, intensity, action taken, relationship to vaccination, and whether it led to early study discontinuation/termination. The same information was collected by the investigator for any serious AEs (SAEs) and AEs of special interest (generalized seizures, Guillain-Barré syndrome, and idiopathic thrombocytopenic purpura) reported up to 30 (window, +14) days post-vaccination, along with information on seriousness criteria (collected in lieu of intensity) and outcome.

## Statistical analyses

A total of 560 participants were planned to be enrolled: 180 participants each in the MPSV4-primed$_{3y+booster}$ and MenACYW-TT-primed$_{3y+booster}$ groups, 40 each in the MPSV4-primed$_{3y}$ and MenACYW-TT-primed$_{3y}$ groups, and 60 each in

the MPSV4-primed$_{6\text{-}7y}$ and MenACYW-TT-primed$_{6\text{-}7y}$ groups. Given the assumptions used for the primary immunogenicity objective (to demonstrate vaccine seroresponse sufficiency), a sample size of 120 evaluable participants per booster study group (MPSV4-primed$_{3y+booster}$ and MenACYW-TT-primed$_{3y+booster}$), was needed to achieve at least 90.0% power to detect that the lower limit of the 1-sided 97.5% CI was greater than 0.40 (proportion under the alternative hypothesis), using a 1-sided exact test with a significance level (alpha) of 0.025.

The immunogenicity analyses at Day 30 and at Day 6 were performed on the respective Per-Protocol Analysis Sets (PPAS1 for Day 30 and PPAS2 for Day 6) and in the corresponding Full Analysis Sets (FAS1 and FAS2, for Day 30 and Day 6, respectively). FAS1 and FAS2 were defined as all those who previously received MPSV4 or MenACYW-TT and who received the booster vaccine and had a valid serology result for at least one serogroup from a blood sample provided 30 days or 6 days post-vaccination, respectively. PPAS1 and PPAS2 were subsets of FAS1 and FAS2, which excluded participants with one or more major protocol deviations. The analysis of antibody persistence was performed on the FAS3 which included all participants who had a valid serology result for at least one serogroup at Day 0. Analyses were conducted for the overall population, by age subgroup (59 through 64 years of age and ≥65 years), and by sex (female and male). Subgroup analyses by race and ethnicity did not yield any meaningful results due to small numbers per subgroup.

Categorical variables were summarized and presented by frequency counts, percentages, and 95% CIs. The 1-sided 97.5% CI for the single proportion was calculated using the exact binomial method (Clopper-Pearson method). The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentages. For GMTs, 95% CIs of point estimates were calculated using normal approximation assuming they were log-normally distributed.

All safety analyses were performed on the safety analysis set (SafAS), which included all participants who had received a dose of MenACYW-TT during the current study and had safety data available. The main parameters for the safety endpoints were described by frequency counts, percentages, and 95% CIs.

Statistical analyses were conducted using SAS Version 9.4 or later.

## Results

### Study participants

A total of 471 participants were enrolled: 385 of whom had received primary vaccination with either MPSV4 or MenACYW-TT 3 years prior as participants in study NCT02842866, and 86 of whom had received primary vaccination with either MPSV4 or MenACYW-TT 6–7 years prior as participants in study NCT01732627 (Figure S1). Participants who were vaccinated 3 years previously were randomized based on priming vaccine received, either to be boosted during Stage I of the study (n = 315) or to go on to participate in Stage II (n = 70; not reported here); all participants provided a blood sample for persistence at Day 0. Participants vaccinated 6–7 years previously, provided a blood sample only and did not receive a dose of MenACYW-TT during the study (n = 86).

Baseline demographics for enrolled participants are summarized in Table 1. The mean age was 70 years (range 59–91 years), 62% (291/471) were female, and 90% were white. The distributions of age were comparable across the groups, with slightly different proportions for sex in each group.

### Immunogenicity following MenACYW-TT booster

Vaccine seroresponse rates in the MPSV4-primed$_{3y+booster}$ group at Day 30 for each of the serogroups ranged from 49.2% to 60.8% and met the primary objective for sufficiency (Figure 2a). Vaccine seroresponse rates in the MenACYW-TT-primed$_{3y+booster}$ group at Day 30 were higher than those seen in the MPSV4-primed$_{3y+booster}$ group, ranging from 79.3% to 93.1%, and met the secondary objective for sufficiency (Figure 2a). Vaccine seroresponse rates at Day 30 were similar across stratified age groups (56–64 years and ≥65 years) (Table S1). When stratified by sex, seroresponse rates tended to be higher in females than in males, especially for the MPSV4-primed$_{3y+booster}$ group (Table S2). In the subset of participants assessed for immunogenicity at Day 6, hSBA

**Table 1.** Baseline demographics (enrolled participants).

| Characteristic | MPSV4-primed$_{3y+booster}$ (n = 139) | MenACYW-TT-primed$_{3y+booster}$ (n = 176) | MPSV4-primed$_{3y}$ (n = 31) | MenACYW-TT-primed$_{3y}$ (n = 39) | MPSV4-primed$_{6\text{-}7y}$ (n = 26) | MenACYW-TT-primed$_{6\text{-}7y}$ (n = 60) |
|---|---|---|---|---|---|---|
| Sex, female, n (%) | 85 (61.2) | 111 (63.1) | 15 (48.4) | 27 (69.2) | 11 (42.3) | 42 (70.0) |
| Mean age (SD), years | 70.6 (7.5) | 69.8 (7.4) | 69.2 (7.1) | 69.7 (6.4) | 70.5 (5.7) | 71.4 (6.3) |
| Race, n (%) | | | | | | |
| White | 127 (91.4) | 158 (89.8) | 27 (87.1) | 32 (82.1) | 25 (96.2) | 57 (95.0) |
| Black or African American | 11 (7.9) | 16 (9.1) | 3 (9.7) | 7 (17.9) | 0 | 3 (5.0) |
| Asian | 0 | 2 (1.1) | 0 | 0 | 0 | 0 |
| Native American/Alaskan Native | 0 | 0 | 1 (3.2) | 0 | 0 | 0 |
| Mixed Origin | 1 (0.7) | 0 | 0 | 0 | 0 | 0 |
| Not reported/unknown | 0 | 0 | 0 | 0 | 1 (3.8) | 0 |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 6 (4.3) | 27 (15.3) | 5 (16.1) | 5 (12.8) | 1 (3.8) | 2 (3.3) |
| Non Hispanic or non Latino | 133 (95.7) | 149 (84.7) | 26 (83.9) | 34 (87.2) | 25 (96.2) | 58 (96.7) |

SD, standard deviation.

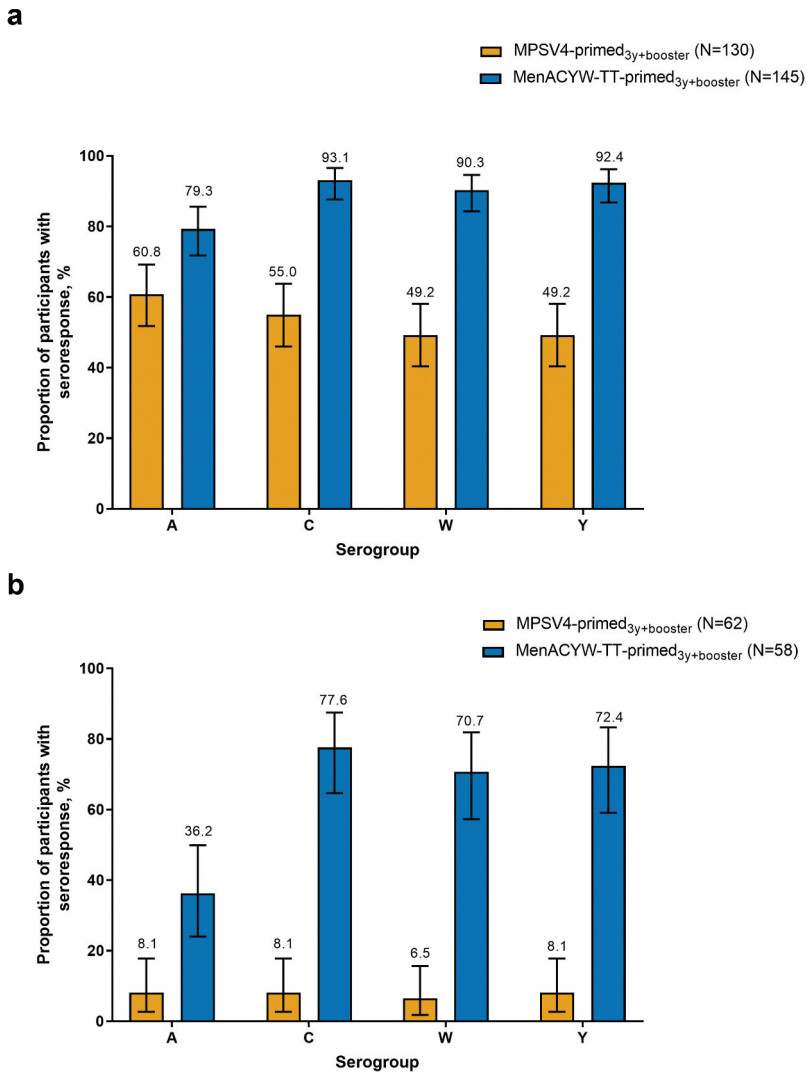


**Figure 2.** hSBA vaccine seroresponse[a] after a booster dose of MenACYW-TT at (a) Day 30 (PPAS1) for assessment of sufficiency[b] and at (b) Day 6 in a subset of participants (PPAS2).
[a]hSBA vaccine seroresponse is defined as a post-vaccination titer ≥1:16 for participants with a baseline titer <1:8, or a ≥4-fold increase in titer post-vaccination for participants with a baseline titer ≥1:8. [b]Sufficiency of the vaccine seroresponse was considered demonstrated if the lower limit of the 1-sided 97.5% confidence interval for the percentage of participants with an hSBA vaccine seroresponse against serogroups A, C, W, and Y was >40%. hSBA, serum bactericidal assay using human complement; PPAS, per-protocol analysis set.

seroresponse rates were substantially higher in the MenACYW-TT-primed$_{3y+booster}$ group than in the MPSV4-primed$_{3y+booster}$ group for all four serogroups (Figure 2b).

The proportion of participants demonstrating seroprotection (hSBA titers ≥1:8) at Day 30 after booster vaccination was >80% across both groups for all four serogroups, with higher proportions in the MenACYW-TT-primed$_{3y+booster}$ group than the MPSV4-primed$_{3y+booster}$ group for serogroups C, W, and Y, and similar proportions for serogroup A (Figure S2); there was a similar trend for the proportion of participants with hSBA titers ≥1:4 (data not shown). Similar results were observed for the proportion of participants demonstrating seroprotection at Day 30 when analyzed by age (Table S4) or by sex (Table S5). Post-vaccination/pre-vaccination GMT ratios (GMTRs; Day 30/Day 0) were also higher in those who were primed with MenACYW-TT than those who were primed with MPSV4 for all four serogroups (Table S3).

The geometric mean concentration (GMC) of tetanus toxoid antibodies on Day 0 (before booster) showed some variation among the groups, with a trend for higher GMCs in the MenACYW-TT versus MPSV4 groups (Table S6). The GMCs of tetanus toxoid antibodies increased after vaccination with MenACYW-TT in the current study, to levels of 24.4 IU/mL (95% CI 19.3, 30.8) in the MPSV4-primed$_{3y+booster}$ group and 15.8 IU/mL [95% CI 13.6, 18.2]) in the MenACYW-TT-primed$_{3y+booster}$ group.

### *Persistence of immunogenicity following primary vaccination*

Persistence of immunity following primary vaccination was assessed in participants vaccinated 3 years earlier in a pooled group of those primed with MPSV4 (MSPV4-primed) and in a pooled group of those primed with MenACYW-TT

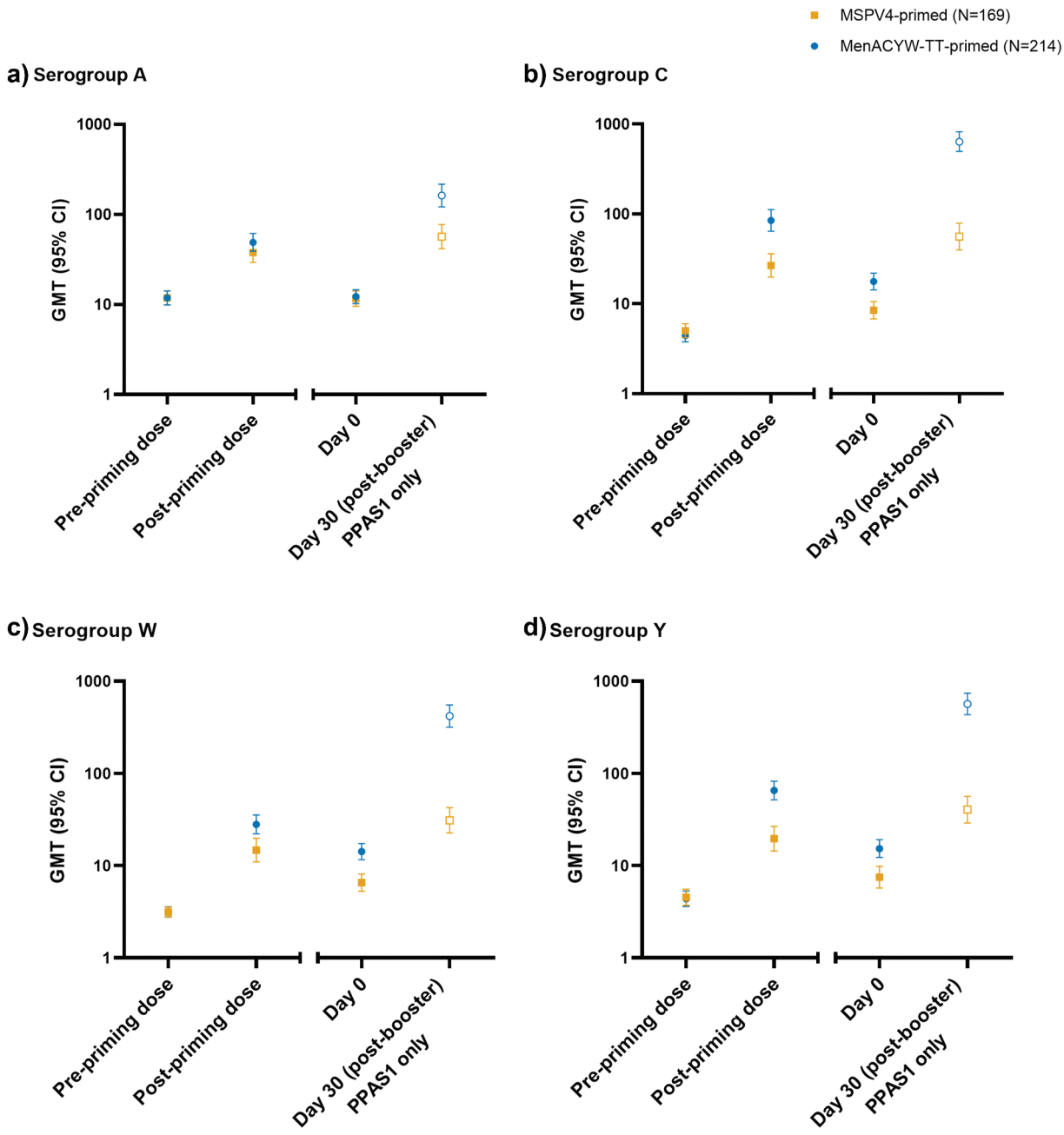


**Figure 3.** Persistence of immunity 3 years post primary vaccination: assessed by hSBA GMTs for (a) serogroup A, (b) serogroup C, (c) serogroup W and (d) serogroup Y pre- and 30 days post-vaccination in NCT02842866, and 3 years post-primary vaccination (Day 0 of this study) (FAS3), as well as after MenACYW-TT booster (Day 30 of this study) (PPAS1). Error bars represent 95% CIs. FAS, full analysis set; GMT, geometric mean titer; hSBA, serum bactericidal assay using human complement; PPAS, per-protocol analysis set.

(MenACYW-TT-primed). In those who received primary vaccination 3 years earlier, baseline GMTs prior to primary vaccination were similar for both the MPSV4 and MenACYW-TT-primed groups for a given serogroup. GMTs were higher on Day 30 after primary vaccination, and then declined in the following 3 years, remaining higher than baseline for serogroups C, W and Y (Figure 3). After vaccination with MenACYW-TT in the current study, GMTs across all serogroups increased for both MPSV4-primed$_{3y+booster}$ and MenACYW-TT-primed$_{3y+booster}$ groups, with higher GMTs seen in the latter group (Figure 3). Seroprotection rates at Day 0 of this study were higher in the pooled group of MenACYW-TT-primed participants than in the pooled group of MPSV4-primed participants for serogroups C (73% vs. 48%), W (67% vs. 40%), and Y (68% vs. 41%), respectively, with similar rates seen for serogroup A (65% vs. 66%, respectively) (Figure S3a).

A similar pattern was seen in those primed 6–7 years earlier with MSPV4 or MenACYW-TT, with declines in GMTs from levels seen on Day 30 post primary dose during the subsequent 6–7 years, but remaining higher than baseline for serogroups C, W and Y for the MenACYW-TT-primed$_{6\text{-}7y}$ group (Figure 4). In the MPSV4-primed group, declines in GMTs from levels seen on Day 30 post primary dose were observed and remained higher than baseline for serogroup C, with a trend toward higher-than-

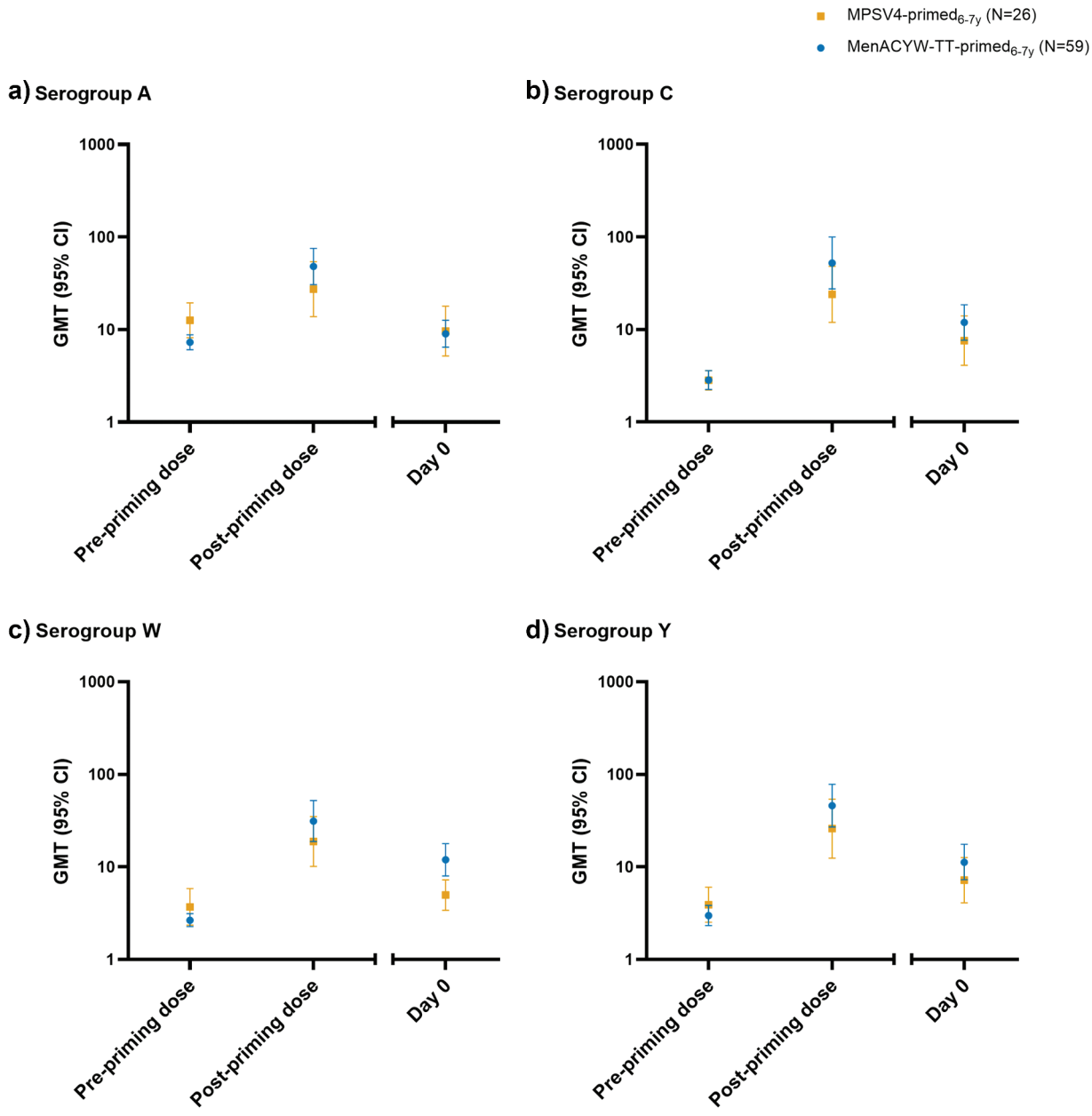


**Figure 4.** Persistence of immunity 6–7 years post primary vaccination: assessed by hSBA GMTs for (a) serogroup A, (b) serogroup C, (c) serogroup W and (d) serogroup Y pre- and 30 days post-priming vaccine dose in NCT01732627 as well as 6–7 years post-primary vaccination (Day 0 of this study) (FAS3). Error bars represent 95% CIs. FAS, full analysis set; GMT, geometric mean titer; hSBA, serum bactericidal assay using human complement; PPAS, per-protocol analysis set.

baseline levels for serogroups W and Y. At Day 0 of this study (6–7 years after primary vaccination), seroprotection rates were similar across both vaccine groups for serogroup A and trended higher in the MenACYW-TT-primed$_{6\text{-}7y}$ group than in the MPSV4-primed$_{6\text{-}7y}$ group for serogroups C, W, and Y (Figure S3b).

The persistence of rSBA GMTs was also seen in those primed with MPSV4 or MenACYW-TT 3 years (Table S7) or 6–7 years earlier (Table S8); where titers increased following primary vaccination, declined over time, but remained or trended higher than those seen at baseline for serogroups C, W, and Y.

## *Safety*

The safety profile of MenACYW-TT when administered to participants who were previously primed with either MPSV4 or MenACYW-TT is shown in Table 2. The incidence of solicited injection site and systemic reactions were similar regardless of the previous vaccine received and were comparable to those observed following primary vaccination with MenACYW-TT in NCT02842866 (Table 2). The most common solicited injection site reaction was pain (21.2% MPSV4-primed$_{3y+booster}$ vs 16.7% MenACYW-TT-primed$_{3y+booster}$), followed by erythema (7.3% MPSV4-primed$_{3y+booster}$ vs 3.7% MenACYW-TT-primed$_{3y+booster}$) and swelling (4.6% MPSV4-primed$_{3y+booster}$ vs 3.7% MenACYW-TT-primed$_{3y+booster}$). Myalgia was the most common solicited systemic reaction (19.9% MPSV4-primed$_{3y+booster}$ vs 21.6% MenACYW-TT-primed$_{3y+booster}$), followed by headache (13.9% MPSV4-primed$_{3y+booster}$ vs 18.5% MenACYW-TT-primed$_{3y+booster}$) and malaise (14.6% MPSV4-primed$_{3y+booster}$ vs 13.6%

**Table 2.** The safety profile of MenACYW-TT administered as a booster dose or as a primary vaccination dose.

| | Number of participants (%) experiencing ≥ 1 event following: | | |
|---|---|---|---|
| | MPSV4-primed$_{3y+booster}$ (N = 151) | MenACYW-TT-primed$_{3y+booster}$ (N = 162) | Previous vaccination with MenACYW-TT [g] (n = 448) |
| Immediate unsolicited AE (within 30 min) | 0 | 0 | 1 (0.2) |
| Solicited injection site reaction[a] (within 7 days) | 38 (25.2) | 32 (19.8) | 118 (26.6)[c] |
| Solicited systemic reaction[b] (within 7 days) | 37 (24.5) | 50 (30.9) | 138 (31.2)[d] |
| Unsolicited non-serious AE (within 30 days) | 20 (13.2) | 32 (19.8) | 65 (14.5) |
| SAE (within 30 days) | 2 (1.3)[e] | 1 (0.6)[f] | 3 (0.7) |
| Death (within 30 days) | 0 | 0 | 0 |

[a]Solicited injection site reactions = pain, erythema, swelling.
[b]Solicited systemic reactions = fever, headache, malaise, myalgia.
[c]118 of 442 participants with data available.
[d]138 of 442 participants with data available.
[e]Diverticulitis (n = 1) and transient ischemic attack (n = 1) – both considered unrelated to vaccination.
[f]Epithelioid mesothelioma (n = 1) – considered unrelated to vaccination.
[g]Participants who received MenACYW-TT vaccination in study NCT02842866.
AE, adverse event; SAE, serious adverse event.

MenACYW-TT-primed$_{3y+booster}$). The majority of solicited reactions were of mild or moderate intensity and resolved spontaneously within 3 days of onset.

There were no immediate AEs (within 30 min of vaccination), no AEs of special interest, no discontinuations due to an SAE or other AE, and no deaths reported during the study. A total of three SAEs were experienced within 30 days of vaccination (diverticulitis and transient ischemic attack [TIA], each n = 1, in the MPSV4-primed$_{3y+booster}$ group; and epithelioid mesothelioma in one MenACYW-TT-primed$_{3y+booster}$ participant), none of which were considered to be vaccine-related by the investigator. The participant experiencing the TIA in the current study was an 84-year-old woman who had also experienced an SAE (non-ST elevation myocardial infarction [NSTEMI]) three years earlier in Study NCT02842866, within 25 days of being vaccinated with MPSV4. The NSTEMI in study NCT02842866 was considered to be unrelated to vaccination by the investigator. Of note, this participant's past medical history was significant for a cerebrovascular accident and carotid artery bypass graft procedure (in 2016), diabetes mellitus type 2, hypertension, and dyslipidemia.

## Discussion

This Phase III study demonstrated that MenACYW-TT was immunogenic and well tolerated in adults ≥59 years of age who had been primed at least 3 years prior with either MPSV4 or MenACYW-TT. The study met its objectives of demonstrating the sufficiency of the vaccine seroresponse following a MenACYW-TT booster in those primed with MPSV4 and in those primed with MenACYW-TT 3 years previously. High seroresponse rates (>79%) and high seroprotection rates (>93%) were achieved 30 days after MenACYW-TT vaccination among participants primed with MenACYW-TT. These results in older adults supplement findings from previous Phase III MenACYW-TT booster studies that demonstrated seroprotection rates of >99% among adolescents and younger adults (15–59 years of age) primed 4–10 years earlier with an MCV4[28] and seroprotection rates of 100% following a booster of MenACYW-TT in children 4–5 years of age who had been primed as toddlers.[29]

The definition of sufficiency for the vaccine seroresponse in this study was made in agreement with the US Food and Drug Administration – with the lower limit of the 1-sided 97.5% CI for the proportion of participants with hSBA vaccine seroresponse at 30 days post-vaccination being >40% for each of the four serogroups. The decision regarding the 40% threshold was made due to the seroresponse rates seen 30 days after primary vaccination with MPSV4 in trial NCT02842866, which ranged from 42.5% to 49.7%,[21] and the ability of MenACYW-TT to induce booster responses as observed in other studies.[28,29]

Although the sufficiency objectives were met for each primed group, hSBA seroresponse rates after booster vaccination were higher at Day 30 and at Day 6 among those who had previously received MenACYW-TT than those primed with MPSV4. This pattern was also seen for seroprotection rates and for GMTs. Three years after primary vaccination, hSBA GMTs declined in both priming vaccine groups; however, GMTs for serogroups C, W, and Y remained or trended higher than pre-vaccination levels, indicative of immune persistence. A large proportion of participants maintained titers consistent with seroprotection 3 years after primary vaccination, with seroprotection persisting, albeit to a lesser extent, up to 6–7 years. As seen at both Day 6 and Day 30, responses and seroprotection rates tended to be higher in those primed with MenACYW-TT than in those primed with MPSV4. These differences are expected for a protein conjugate vaccine given in series[21,25,30,31] and are believed to be due to differences in the induction of T- and B-cell responses.[32,33]

While the primary objectives of our study were based on hSBA, we used both hSBA and rSBA to assess the remaining endpoints. This ensured alignment with the differing preferences for data used for licensure purposes worldwide. The first MCV4 was licensed by the US Food and Drug Administration in 2005 based on rSBA data,[34,35] MCV4-CRM was licensed in Europe primarily on the basis of

hSBA data,[35,36] and MCV4-TT was approved based primarily on rSBA results, but the submission also included hSBA data.[35,37]

The reactogenicity profile of a MenACYW-TT booster as observed in this study was acceptable, and not influenced by the nature of the priming vaccine received 3 years previously. Rates of AEs following booster vaccination were similar to those observed after primary vaccination in adults ≥56 years of age. No vaccine-related SAEs were reported, which is consistent with findings from a previous study of MenACYW-TT also conducted in adults ≥56 years of age.[21] SAE data were collected up to 30 days post-vaccination, which is equivalent to the period used in study NCT01732627, but differs from the follow-up period used in study NCT02842866 where safety data were collected up to 6 months post-vaccination.[21,25]

Meningococcal polysaccharide vaccines have a number of limitations, including relatively short-term protection, lack of potential to induce herd protection, and the risk of immune hyporesponsiveness following repeated doses. On the other hand, the conjugation of polysaccharide antigens to a protein carrier may prevent the acquisition of meningococci, reducing carriage. Furthermore, meningococcal conjugate vaccines can induce T-cell-dependent immune responses, which may result in higher antibody titers, longer duration of the immune response, and enhanced immunologic memory, which allows for a booster response. As a result, the use of a conjugate vaccine is generally preferred over polysaccharide vaccines for both priming and booster doses.[21,25] As IMD is particularly life threatening for older adults,[3–9] the potential for conjugate vaccines in this population to reduce IMD morbidity and mortality is of interest. Recent evidence indicated that MenACYW-TT is suitable for use in this population to prevent IMD caused by serogroups A, C, W, and Y.[21,25] MenACYW-TT is currently the only available MCV4 in the USA licensed for adults ≥56 years of age.[23] It is also licensed for use in other countries and regions. The safety and immunogenicity data from this study support the use of MenACYW-TT as a booster in older adults at continued risk for infection due to *N meningitidis* because of occupation or travel who received either MPSV4 or MenACYW-TT as their primary dose at least 3 years earlier. In addition, this study adds to the body of data demonstrating the ability of MenACYW-TT to elicit booster responses in persons previously primed with MenACYW-TT, without any new safety concerns identified.

In those participants who received a MenACYW-TT vaccination during this study, an increase in GMCs of tetanus toxoid antibodies was also seen, likely due to the presence of the tetanus toxoid carrier protein. The GMCs of tetanus toxoid antibodies tended to be higher after primary vaccination with MenACYW-TT than after primary vaccination with MPSV4. Although the increase in GMCs is noteworthy, the clinical significance of these findings is not yet well understood. Of note, MenACYW-TT is not indicated for active immunization against tetanus. Similar increases have been seen in other studies of MenACYW-TT,[29,38] and for other conjugate vaccines.[32]

There was a misallocation of participants that resulted in 15 participants being assigned to groups that were inconsistent with the priming vaccine received. These participants underwent immunogenicity analysis as a part of FAS1 (these misallocated subjects were not included in PPAS1) with their assigned groups, while safety analysis was done based on the priming vaccine received, in accordance with the protocol and statistical analysis plan established before the study was initiated. In response to the misallocation of participants, a sensitivity analysis was performed, which revealed no effect on immunogenicity results due to this misassignment. While 139 participants were enrolled in the MPSV4-primed$_{3y+booster}$ group and 176 in the MenACYW-TT-primed$_{3y+booster}$ group, exceeding the threshold of 120 participants required in each group to evaluate the primary immunogenicity objective, this sample size was not sufficient to draw conclusions on subgroup analyses conducted by race or ethnicity.

In conclusion, this study demonstrates sufficiency of the vaccine seroresponse following a MenACYW-TT booster in those primed with MPSV4 (primary objective) and in those primed with MenACYW-TT (secondary objective). It also provides important data on the persistence of the immune response at 3 and up to 7 years after primary vaccination with either MPSV4 or MenACYW-TT in older adults. The MenACYW-TT booster was well tolerated regardless of the priming vaccine received.

## Acknowledgments

The authors would like to thank all the participants who volunteered to take part in the study; all the investigators and their site staff; and the MEQ00066 Sanofi team, who designed and coordinated the conduct of the study. Editorial assistance with preparation of the manuscript was provided by Nicola Truss PhD, of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Sanofi. Manuscript coordination and editorial support were provided by Anirban Sanyal, PhD (Sanofi).

## Author contributions

CAR, AS, KG, and PO contributed to the concept or design of the study. JJ contributed to data acquisition. CAR, JJ, AS, KG, and PO contributed to data analysis or interpretation. All authors critically revised the manuscript, gave final approvals, and are accountable for its accuracy and integrity.

## Disclosure statement

CAR, AS, KG and PO are current employees of Sanofi and may hold shares/stocks in Sanofi. JJ reports no conflicts of interest.

## Funding

The study was sponsored by Sanofi.

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## Data availability statement

Qualified researchers may request access to patient-level data and related study documents including 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 study participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/

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