# Meningococcal serogroup C (MenC) immune response of a novel tetanus toxoid conjugate quadrivalent meningococcal vaccine (MenACYW-TT) compared to a quadrivalent (MCV4-TT) or monovalent (MenC-TT) meningococcal vaccine in healthy meningococcal vaccine-naïve toddlers


***Markus Knuf[1]*, Mika Rämet[2], Nina Breinholt Stærke[3], Yaël Thollot[4], Siham B'Chir[5], Habiba Arroum[6], Isabelle Bertrand-Gerentes[4]***

[1]Helios Dr. Horst Schmidt Kliniken Wiesbaden, Ludwig-Erhard-Straße 100, 65199 Wiesbaden, Germany (current affiliation: Klinikum Worms, Gabriel-von-Seidl-Straße 81, 67550 Worms, Germany); [2]Vaccine Research Center, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [3]Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark; [4]Sanofi Pasteur, 14 Espace Henry Vallée, 69007, Lyon, France; [5]Sanofi Pasteur, 1541 Avenue Marcel Mérieux, 69280 Marcy-l'Étoile, France; [6]Sanofi, 1 avenue Pierre Brossolette, 91385 Chilly-Mazarin, France

**presenting and corresponding author: markus.knuf@klinikum-worms.de*


## BACKGROUND AND RATIONALE

- **MenACYW-TT (MenQuadfi®):** recently-licensed quadrivalent meningococcal conjugate vaccine for use in individuals 12 months and older in the EU and some other countries
- **Changing epidemiology** of *N. meningitidis:*
  - Invasive meningococcal disease (IMD) *caused by Neisseria (N) meningitidis is unpredictable and serious*[1]
  - The distribution of meningococcal serogroups causing invasive meningococcal disease (IMD) varies geographically and with time
  - During the late 1990s, the incidence of IMD due to serogroup C increased in many EU countries, and several countries have included a monovalent MenC vaccination in their routine national immunisation programme
  - During the past decade, an increase of the incidence of IMD due to serogroups W & Y has been observed
  - In response to this change in serogroup distribution, some countries have changed their recommendations to use MenACWY conjugate vaccine in addition to or in **replacement of monovalent MenC** conjugate vaccines[2]
- A quadrivalent vaccine able to offer at least the **same protection** against MenC as a monovalent MenC vaccine supports the switch to quadrivalent vaccines in countries still recommending MenC vaccination
- MenACYW-TT has demonstrated **non-inferiority of immune response** (seroprotection) against all 4 serogroups (ACWY) in a pivotal study conducted vs MCV4-TT (Nimenrix®) in toddlers, with higher GMTs observed for serogroup C[3]
- Consequently, the current study was conducted in meningococcal vaccine-naïve toddlers (12-23 months) with the aim of:
  - Comparing the serogroup C immune response of MenACYW-TT (MenQuadfi®) *vs* MenC-TT (NeisVac-C®) and *vs* MCV4-TT (Nimenrix®) in terms of seroprotection and GMTs, and
  - Testing the non-inferiority and superiority of serogroup C immune response

## METHODS

- This was a modified phase III study (double-blind, randomized (1:1:1), parallel groups, active-controlled, multi-center trial) conducted in Denmark, Germany, and Finland
- Participants were randomly assigned to receive a single dose of either MenACYW-TT conjugate vaccine or the licensed Nimenrix® (MCV4-TT) and NeisVac-C® (MenC-TT) vaccines
- The study was conducted between September 2019 (first visit, first subject) and October 2020 (last visit, last subject)

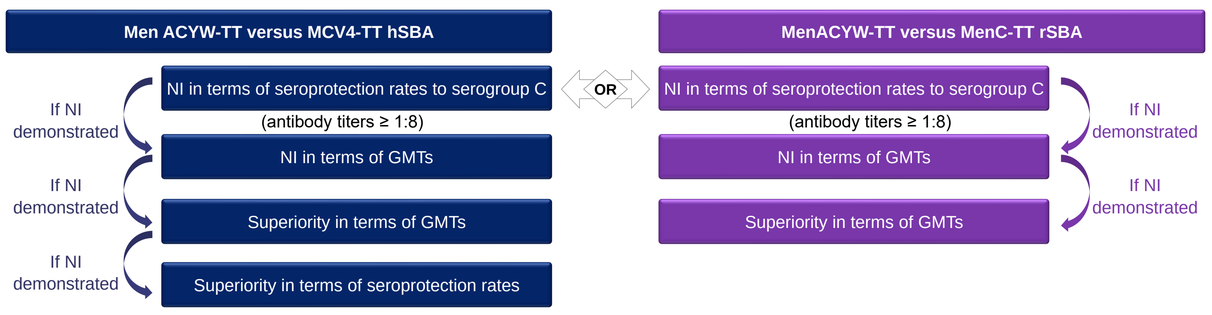
**Immunogenicity assessment:**

- Serum bactericidal assays with human complement (hSBA) and baby rabbit complement (rSBA) were used to measure antibodies against the serogroup C at baseline (Day 0 [D0]) and 30 days post-vaccination (D30)

**Primary and secondary objectives:**

- The immunogenicity of serogroup C of MenACYW-TT has been compared to that of MCV4-TT and to that of MenC-TT
- Sequential testing approach (described in **Figure 1**):
  The testing approach was done in parallel and used a step-by-step approach for the 2 comparators (vs MCV4-TT and vs MenC-TT)
  - Overall, the primary objective for the study will be met if, objective 1) non-inferiority of the seroprotection rate versus MCV4-TT as measured by hSBA, is demonstrated OR objective 2) non-inferiority of the seroprotection rate versus MenC-TT measured by rSBA, is demonstrated
  - Overall, the secondary objective for the study will be met if, objective 1) non-inferiority of the seroprotection rate versus MCV4-TT as measured by rSBA, is demonstrated OR objective 2) non-inferiority of the seroprotection rate versus MenC-TT as measured by hSBA, is demonstrated

**Figure 1:** Sequential testing approach for primary and secondary immunogenicity objectives




- **Seroprotection rates (SPR):**
  - The non-inferiority of seroprotection rates (≥ 1:8) is demonstrated if the lower limit of the two-sided 97.5% confidence interval (CI) of the difference between the SPR of MenACYW-TT minus the SPR of the comparator vaccine is > -10%
  - The superiority in terms of seroprotection rates is demonstrated if the lower limit of the two-sided 97.5% CI of the difference between the SPR of MenACYW-TT minus the SPR of the comparator vaccine is > 0%
- **GMTs:**
  - The non-inferiority of GMTs is demonstrated if the lower limit of the two-sided 97.5% CI of the ratio of GMTs (calculated as the GMTs of MenACYW-TT divided by the GMTs of the comparator vaccine ) is > 1/1.5
  - The superiority in terms of GMTs is demonstrated if the lower limit of the two-sided 97.5% CI of the ratio of GMTs (calculated as the GMTs of MenACYW-TT divided by the GMTs of the comparator vaccine ) is > 1

**Safety assessment**

- Safety data collected for 30 days (+14 days) after the vaccine administration:
  - The interval for solicited adverse events (AEs) was between D0 and D7
  - Collection of solicited reactogenicity included daily measurement of body temperature and injection site redness and swelling, as well as recording of the intensity for injection site pain, appetite lost, irritability, vomiting, abnormal crying and drowsiness
  - Unsolicited AEs, Adverse Events of Special Interest (AESIs: generalized seizures, Kawasaki disease, Idiopathic thrombocytopenic purpura and Guillain-Barré syndrome), and Serious Adverse Events (SAEs) were collected throughout the study from D0 to D30

## RESULTS

707 healthy meningococcal vaccine naïve subjects aged 12 to 23 months were randomized in 29 sites –98.4% of subjects completed the trial (**Table 1**)

**Table 1:** Subject disposition and demographic characteristics

| | Group 1 MenACYW – TT | Group 2 MCV4-TT | Group 3 MenC-TT | Total |
|---|---|---|---|---|
| **Number of subjects Randomized** | 232 | 235 | 240 | **707** |
| **Vaccinated** | 230 | 232 | 239 | **701** |
| **Completed trial** | 228 | 229 | 239 | **696** |
| **Age (months)** mean (SD) | 16.5 ± 3.27 | 16.6 ± 3.48 | 16.7 ± 3.45 | **16.6 ± 3.40** |
| **Female / Male** | 115 / 117 | 108 / 127 | 109 / 131 | **332 / 375** |
| **Enrollment by country** | | | | |
| **Denmark** | 36 | 36 | 36 | **108** |
| **Finland** | 102 | 105 | 106 | **313** |
| **Germany** | 94 | 94 | 96 | **286** |
| **hSBA PPAS** | 214 | 211 | 216 | **641** |
| **rSBA PPAS** | 213 | 210 | 215 | **638** |
| **SafAS** | 230 | 232 | 239 | **701** |

PPAS: Per protocol Analysis
SafAS: Safety Analysis Set

**Primary immunogenicity results:**

- **Comparison of MenACWY-TT vs MCV4-TT: (Table 2)**

**Table 2:** hSBA seroprotection rates (≥1:8) and hSBA GMTs of serogroup C at D30 following a single dose of MenACYW-TT *vs* MCV4-TT
*hSBA PPAS*

| | MenACYW-TT (N= 214) | | MCV4-TT N= 211 | | MenACYW-TT vs MCV4-TT | | Conclusion |
|---|---|---|---|---|---|---|---|
| **Seroprotection rate (≥1:8)** | 99.5 % | (95%CI) (97.4 ; 100) | 89.1 % | (95%CI) (84.1; 93.0) | Difference 10.43 % | (97.5%CI) (5.68; 16.20) | Non inferiority : YES Superiority : YES |
| **GMTs** | 515 | (95%CI) (450 ; 591) | 31.6 | (95%CI) (26.5 ; 37.6) | Ratio 16.3 | (97.5%CI) (12.7; 21.0) | Non inferiority : YES Superiority : YES |

- **Comparison of MenACWY-TT vs MenC-TT: (Table 3)**

**Table 3:** rSBA seroprotection rates (≥1:8) and rSBA GMTs of serogroup C at D30 following a single dose of MenACYW-TT vs MenC-TT
*rSBA PPAS*

| | MenACYW-TT (N= 213) | | MenC-TT (N= 215) | | MenACYW-TT vs MenC-TT | | Conclusion |
|---|---|---|---|---|---|---|---|
| **Seroprotection rate (≥1:8)** | 100 % | (95%CI) (98.3 ; 100) | 100 % | (95%CI) (98.3; 100) | Difference 0.0 % | (97.5%CI) (-2.30; 2.28) | Non inferiority : YES |
| **GMTs** | 2143 | (95%CI) (1870 ; 2456) | 1624 | (95%CI) (1425; 1850) | Ratio 1.32 | (97.5%CI) (1.06; 1.64) | Non inferiority : YES Superiority : YES |

**Secondary immunogenicity results:**

- **Comparison of MenACWY-TT vs MCV4-TT : (Table 4)**

**Table 4:** rSBA seroprotection rates (≥1:8) and rSBA GMTs of serogroup C at D30 following a single dose of MenACYW-TT vs MCV4-TT
*rSBA PPAS*

| | MenACYW-TT (N= 213) | | MCV4-TT (N= 210) | | MenACYW-TT vs MCV4-TT | | Conclusion |
|---|---|---|---|---|---|---|---|
| **Seroprotection rate (≥1:8)** | 100 % | (95%CI) (98.3 ; 100) | 94.8 % | (95%CI) (90.8; 97.4) | Difference 5.24 % | (97.5%CI) (1.83; 9.85) | Non inferiority : YES |
| **GMTs** | 2143 | (95%CI) (1870 ; 2456) | 315 | (95%CI) (252; 395) | Ratio 6.80 | (97.5%CI) (5.04; 9.18) | Non inferiority : YES Superiority : YES |

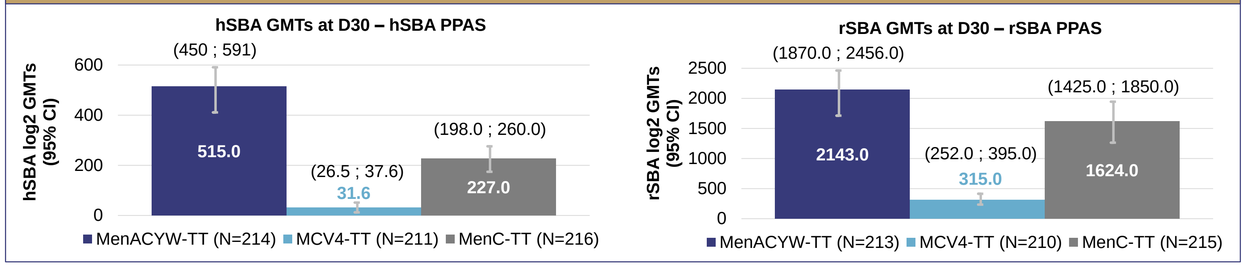
- **Comparison of MenACWY-TT vs MenC-TT : (Table 5)**

**Table 5:** hSBA seroprotection rates (≥1:8) and hSBA GMTs of serogroup C at D30 following a single dose of MenACYW-TT vs MenC-TT
*hSBA PPAS*

| | MenACYW-TT (N= 214) | | MenC-TT (N= 216) | | MenACYW-TT vs MenC-TT | | Conclusion |
|---|---|---|---|---|---|---|---|
| **Seroprotection rate (≥1:8)** | 99.5 % | (95%CI) (97.4 ; 100) | 95.7 % | (95%CI) (97.4 ; 100) | Difference -0.0 % | (97.5%CI) (-2.71; 2.67) | Non inferiority : YES |
| **GMTs** | 515 | (95%CI) (450; 591) | 227 | (95%CI) (198; 260) | Ratio 2.27 | (97.5%CI) (1.82;2.84) | Non inferiority : YES Superiority : YES |

- In the **Figure 2**, the GMTs of serogroup C at D30 following a single dose of MenACYW-TT, MCV4-TT or MenC-TT, measured with hSBA or rSBA are presented

**Figure 2:** hSBA & rSBA GMTs of serogroup C at D30 following a single dose of MenACYW-TT , MCV4-TT or MenC-TT

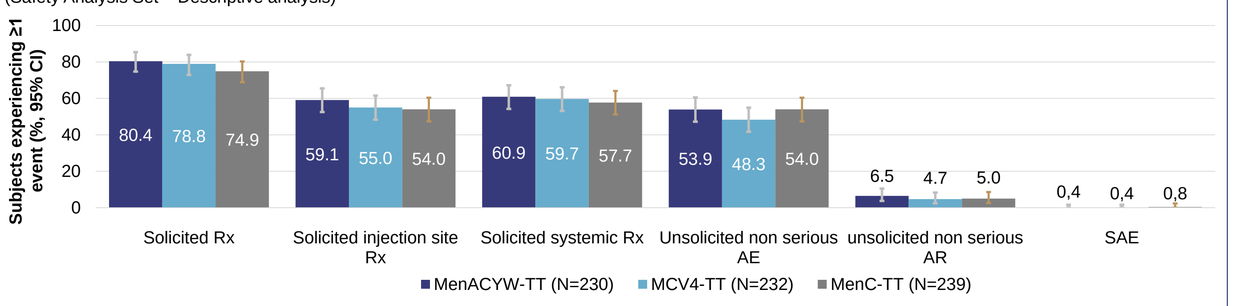



**Summary of safety findings**

- The safety profile of a single dose of MenACYW-TT was comparable to MCV4-TT and MenC-TT
- Overall, the safety profile was comparable between vaccine groups in terms of solicited and unsolicited adverse reactions (**Figure 3** with solicited reactions (solicited injection site reactions and solicited systemic reactions) observed in 80.4% of the MenACYW-TT group, 78.8% of the MCV4-TT group, and 74.9% of the MenC-TT group
  The proportion of participants who reported at least 1 unsolicited adverse reaction (AR) was 6.5% (15/230) in the MenACYW-TT group, 4.7% (11/232) in the MCV4-TT group, and 5.0% (12/239) in the MenC-TT group
- No immediate unsolicited AEs were reported within 30 minutes of vaccination in any group
- No study vaccine related SAEs and no deaths in either the MenACYW-TT or MCV4-TT and MenC-TT groups were reported

**Figure 3:** Safety overview following MenACYW-TT , MCV4-TT and MenC-TT vaccination in toddlers (12-23 months)

(Safety Analysis Set – Descriptive analysis)




Solicited Rx reported within 7 days; Unsolicited AE, unsolicited AR and SAEs reported within 30 days.
AE, adverse event; AR, adverse reaction; N, number of participants in the safety analysis set; Rx, reaction; SafAS, safety analysis set; SAEs, serious adverse event

## CONCLUSIONS

- **The trial met all primary and secondary objectives:**
  - **MenACYW-TT vs MCV4-TT administered as a single dose in meningococcal vaccine-naïve toddlers:**
    - **Superiority of serogroup C hSBA seroprotection rates and non inferiority of serogroup C rSBA seroprotection rates**
    - **Superiority of serogroup C hSBA & rSBA GMTs**
  - **MenACYW-TT vs MenC-TT administered as a single dose in meningococcal vaccine-naïve toddlers:**
    - **Non-inferiority of serogroup C rSBA & hSBA seroprotection rates**
    - **Superiority of serogroup C rSBA & hSBA GMTs**
- **This study showed that MenACYW-TT elicited a robust immune response against serogroup C without safety concerns. The safety profile is comparable for all 3 vaccines**
- **MenACYW-TT induced a superior immune response to serogroup C compared to the licensed MCV4-TT and MenC-TT vaccines when administered as a single dose to meningococcal vaccine-naïve toddlers aged 12–23 months**
  **These results supports the switch from monovalent MenC to MenACWY vaccination, providing reassurance that protection against MenC can be maintained with MenACYW-TT vaccine**
- **The use of quadrivalent meningococcal vaccines offers the advantage of broadening the protection against other serogroups and contribute to address the public health need with regard to a changing and unpredictable epidemiology**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- The study was sponsored by Sanofi Pasteur


## AUTHORS AND CONFLICT OF INTEREST

- MK serves as NCI and PI in clinical studies and Consultant for GSK, Pfizer, Baxter, Novartis, Astra Zeneca, MedImmune, Sanofi Pasteur, MSD, Jansen, Takeda, BioNTech and others. He perceived activities as official duties and did not personally receive any fees from companies. There is also no target agreement with his employer in this regard
- MR serves as NCI and/or PI SI in clinical studies for GSK, Pfizer, AstraZeneca, MedImmune, Sanofi Pasteur, MSD, Jansen, and others. He has not personally received any fees from companies. The institution was reimbursed for study costs
- NBS serves as PI and SI in clinical studies with Pfizer, Gilead and Sanofi Pasteur. She has not personally received any fees from companies. The institution was reimbursed for study costs
- IBG, YT, SB, and HA are employees of Sanofi Pasteur and may hold shares and/or stock options in the company

## REFERENCES


1. Booy R et al. Recent changes in the epidemiology of Neisseria meningitidis serogroup W across the world, current vaccination policy choices and future strategies. Human Vaccines & Immunotherapeutics 2019,15(2): 470-480
2. Presa J, Findlow J, Vojicic J, Williams S, Serra L. Epidemiologic Trends, Global Shifts in Meningococcal Vaccination Guidelines, and Data Supporting the Use of MenACWY-TT Vaccine: A Review. Infect Dis Ther 2019; 8:307-33
3. van der Vliet D, Vesikari T, Sandner B, Martinon-Torres F, Muzsay G, Forsten A, et al. Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT) vs. a licensed quadrivalent meningococcal tetanus toxoid-conjugate vaccine in meningococcal vaccine-naive and meningococcal C conjugate vaccine-primed toddlers: a phase III randomised study. Epidemiol Infect 2021; 149:e50



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