NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA) MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
MenQuadfi - Meningococcal Vaccine, Solution for Injection in 0.5 mL Vial (MAL23076024ARZ)

ACTIVE INGREDIENT:
Neisseria Meningitides,Group A Polysaccharide 10mg
Neisseria Meningitides,Group C Polysaccharide 10mg
Neisseria Meningitides,Group Y Polysaccharide 10mg
Neisseria Meningitides,Group W-135 Polysaccharide 10mg
Tetanus toxoid carrier protein 55mg

PRODUCT REGISTRATION HOLDER:
Sanofi-Aventis (Malaysia) Sdn. Bhd

PRODUCT MANUFACTURER:
Sanofi Pasteur Inc, Pennsylvania, United States

APPROVAL DATE:
6 July 2023 (DCA 386)

1.0 BACKGROUND INFORMATION

a. MenQuadfi contains the capsular polysaccharides (PS) purified from *Neisseria meningitidis* serogroups A, C, Y and W covalently coupled to tetanus toxoid protein purified from *Clostridium tetani.*

b. The meningococcal polysaccharides in MenQuadfi are the same as those contained in the approved vaccines; Menactra® (MAL20102058ARZ) and terminated Menomune® A/C/Y/W-135 (MAL20020821ARZ).

c. The source of tetanus toxoid protein used as a carrier in MenQuadfi is the same as that used in *Haemophilus influenzae* type b Tetanus Protein Conjugate Vaccine (TETRACT-HIB VACCINE, MAL19990927A) and in the Hib portion of terminated PEDIACEL Vaccine (MAL20040144ARZ) and as the tetanus antigen in Hexaxim® (MAL13075068ARZ, DTaP2-IPV-HepB-Hib)

d. Currently DCA has registered three other vaccines containing meningococcal antigens as tabulated below.

Product Name	Amount of active ingredient	Posology
Nimenrix Powder and Solvent for Solution for Injection-tetanus (MAL13085066ACZ) PRH: Pfizer Malaysia	*Neisseria* Meningitides,Group A Polysaccharide 5mcg *Neisseria* Meningococcus C, purified polysaccharides antigen 5mcg *Neisseria* Meningitides,Group Y purified Polysaccharide 5mcg *Neisseria* meningococcus,Group W-135 Polysaccaride 5mcg Conjugated to tetanus	Infants 6 weeks to less than 6 months is 2 doses More than 6 months, adolescents and adults are single dose
Menactra Solution For Injection- purified diphtheria toxoid MAL20102058ARZ PRH: Sanofi Aventis Malaysia	Purified Meningococcal Polysaccharide Group A 4mcg Purified Meningococcal Polysaccharide Group C 4mcg Purified Meningococcal Polysaccharide Group Y 4mcg Purified Meningococcal Polysaccharide Group W135 4mcg Conjugated to purified diphtheria toxoid	9 -23 months is 2 doses 3 months apart 2 to 55 years is single dose
Menveo Powder & Solution For Solution For Injection-conjugated to CRM 197 MAL20102066ARZ PRH: GSK	Meningococcal Group C Oligosaccharide 5mcg Meningococcal Group W Oligosaccharide 5mcg Meningococcal Group Y Oligosaccharide 5mcg Meningococcal Group A Oligosaccharide 10mcg Conjugated to CRM 197 protein	Children 2-5 years: single but 2nd dose can be given 2 months apart Adults and children more than 5 years is single dose

1.1 Proposed Indication:

MenQuadfi is indicated for active immunization of individuals from the age of 12 months and older against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y.

1.2 Proposed Posology

Primary vaccination:

Individuals 12 months of age and older: One single dose (0.5 mL).

Booster vaccination:

- A single 0.5 mL dose of MenQuadfi may be used to boost subjects who have previously received a meningococcal vaccine containing the same serogroups (see section Pharmacodynamics)
- There are no data available to indicate the need for or timing of a booster dose of MenQuadfi (see section Pharmacodynamics)

Other paediatric population

The safety and immunogenicity of MenQuadfi in individuals under 12 months of age have not yet been established

1.3 Route of Administration

Intramuscular

1.4 Pharmacological Aspects

Mechanism of Action:

Anti-capsular meningococcal antibodies protect against meningococcal diseases via complement mediated bactericidal activity. MenQuadfi induces the production of bactericidal antibodies specific to the capsular polysaccharides of Neisseria meningitidis serogroups A, C, W, and Y.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- MenQuadfi contains four active substances comprising of serogroup-specific polysaccharide antigens purified from *Neisseria meningitides* Serogroup A, C, Y and W135, separately conjugated to tetanus toxoid. The original isolate of *N. meningitidis* cells, for serotypes A, C. Y and W135 received from Walter Reed Army Institute in 1970. The four serotypes used are similar to the serotypes used for the registered Menactra Vaccine.
- Tetanus toxoid produced by *Clostridium tetani* a gram-negative anaerobic bacillus that synthesized as a single polypeptide chain of 1315 amino acids. A freeze-dried strain of Clostridium tetani, derived from the Harvard 49205 strain and identified by the N° Y-IV-5A (freeze-drying date 18.10.78) was obtained from the Rijks Institute of Bilthoven (Netherlands) on November 17, 1982.

- Validation batches for the purified bulk and for the polysaccharide tetanus toxoid conjugate concentrate has been provided for 3 batches respectively, demonstrating that the vaccine can be consistently manufactured.
- Six batches [3 validation batches and 3 comparability batches] were placed on the stability study for long term (-80°C to -60°C) for 54 months and accelerated conditions (2°C to 8°C) for 6 months. Real time study results are available for 54 months for the validation batches and demonstrate that all the test parameters are within the acceptance criteria. Real time data is available for 24 months for the comparability batches, demonstrating that all the results are within the acceptance criteria. Accelerated stability study results are available for 6 months and data is within the acceptance criteria. Stability data support the storing of the drug substance at -80°C to -60°C for 48 months.
- GMP Compliance of the drug substance manufacturer was verified by USFDA

2.1.2 Finished Product

- There are two batch sizes for the manufacture of the drug product: 55L & 275L.
- There is an overage of 20% for serogroup A and 5% for serogroup C, Y and W135.
- Process validation performed on the bulk formulation process, as well as on the formulation and filling of the drug product. Three process validation batches from the drug substance produced for the 55L was provided for formulation and filling of the drug product using 2ml vials with a 13mm stopper and 13mm flip cap. Results met the acceptance criteria for process parameters, in process criteria and critical quality attributes, demonstrating the manufacturing process and the filling process is capable of consistently producing the product.
- Validation conducted on the 275L process scale up on the bulk on four validation batches. Results consistently met the acceptance criteria demonstrating that the scale up was able to produce a consistent reproducible batch of quality.
- Stability studies conducted on the finished drug product vials to support the expiry of 48 months when stored at 2-8°C in the 2ml borosilicate glass vials are provided for 3 phase III clinical consistency/ process validation batches, three process validation batches from the 55L batch size and 275L. The study is still ongoing for the PPQ batches but is complete for 54 months for the clinical batches. All results are within the acceptance criteria, demonstrating that the vaccine is stable for 48 months at 2-8°C.

2.2 Non Clinical

- Non-clinical pharmacology and toxicology studies were conducted to demonstrate the ability of the vaccine to induce immune response.
- The toxicology studies were performed in compliance with the Good Laboratory Practices (GLP), except for the immunogenicity study phase in the repeat-dose toxicity study in rat, which was conducted in a non-GLP compliant facility that was considered to have the most appropriate expertise with evaluation of immune response to the test vaccine. Results demonstrated that the vaccine was well tolerated in mice.
- Development and reproductive toxicity study (DART study) was conducted in New Zealand White rabbits after repeated intramuscular administration of the vaccine to support use in women of childbearing potential was in GLP compliant facility. Results demonstrated that the vaccine well tolerated and specific antibodies against serogroup

C capsular polysaccharides detected in the serum of dams with transfer to fetuses and pups.

2.3 Efficacy

- Thirteen completed Phase I, Phase II and Phase III studies conducted in infants, toddlers, children, adolescents and adults were provided to support the proposed indication.
- Three Phase II trials (Studies MET44 [supportive], **MET 50** [pivotal], and MET54 [supportive]) and six pivotal Phase III studies (Studies **MET 35, MET 43, MET 49, MET51, MET 56, and MET 57**). Of the six pivotal studies, MET56 is a booster study and the other studies are primary vaccination studies.
- Summary of pivotal clinical studies conducted are as follows:

Study	Subjects	Purpose	Group 1	Group 2	Conclusion
MET 51	12 months – 2 years	Primary	MenQuadfi	Nimenrix	Non-inferior
MET 35	2-9 years	Primary	MenQuadfi	Menveo	Non inferior
MET 43	10 – 55 years	Primary	MenQuadfi	Menactra	Non inferior
		Lot to lot consistency	MenQuadfi Lot 1, Lot 2, Lot 3		Lot to lot consistency demonstrated
MET 50	10 – 17 years	Primary	MenQuadfi	Menveo	Non inferior
		Co administered with Tdap & HPV4	MenQuadfi	MenQuadfi + Tdap & HPV4	Non inferior
MET 49	≥ 56 years old	Primary	MenQuadfi	Menomune	Non inferior
MET 56	≥15 years who had received one dose of either Menactra or Menveo in the previous 4-10 years	Booster	MenQuadfi	Menactra	Non inferior
MET 57	12 months – 2years	Concomitant use with other vaccines (MMR Variella, DTaP-IPV-HebB-Hib)	MenQuadfi	DTaP-IPV-HepB-Hib MMR Variella	No clinically relevant effect on the immunogenicity of MenQuadfi or other co-administered vaccine

- The abbreviation MenACYW-TT in the clinical studies reflects MenQuadfi. The abbreviation MCV4-TT stands for Nimenrix, MenACWY-CRM / MCV4-CRM stands for Menveo, MCV4-DT stands for Menactra and MPSV4 stands for Menomune.

Study (MET51: 12 months – 2 years)

<table>
<tr><th>Study Type & Design (N)</th><th>Objective of the study</th><th>Results</th></tr>
<tr>
<td>Phase III, modified double blind, randomized, parallel- group, active controlled study

Van der Vliet D et al. (2021). Epidemiology and Infection 149, e50, 1–10

N= 918

Healthy toddlers aged 12–23 months were recruited if they were either meningococcal vaccine-naïve or if they had received at least one dose of MCC vaccine prior to 12 months of age (MCC-primed)</td>
<td>To demonstrate the non-inferiority of the antibody seroprotection to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy

To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal</td>
<td>Non- inferiority of antibody response after a single dose of MenACYW-TT in vaccine naïve or have been primed with MCC participants based on seroprotection against all four serogroups was demonstrated.

Table 3. Non-inferiority of the hSBA antibody response (seroprotection[a]) for MenACYW-TT compared with MCV4-TT at Day 30 in meningococcal vaccine-naïve or MCC-primed participants (PPAS)

<table>
<tr><th></th><th></th><th colspan="2">MenACYW-TT (N = 491)</th><th colspan="2">MCV4-TT (N = 395)</th><th colspan="2">MenACYW-TT – MCV4-TT</th></tr>
<tr><th>Serogroup</th><th>Background status</th><th>n/M</th><th>% (95% CI)</th><th>n/M</th><th>% (95% CI)</th><th>Stratified difference, % (95% CI)</th><th>Non-inferiority[b]</th></tr>
<tr><td>A</td><td>Naïve</td><td>266/293</td><td>90.8 (86.9–93.8)</td><td>264/295</td><td>89.5 (85.4–92.7)</td><td>–2.03 (–5.84–1.78)</td><td>Yes</td></tr>
<tr><td></td><td>MCC-primed</td><td>177/197</td><td>89.8 (84.8–93.7)</td><td>97/99</td><td>98.0 (92.9–99.8)</td><td></td><td></td></tr>
<tr><td>C</td><td>Naïve</td><td>291/293</td><td>99.3 (97.6–99.9)</td><td>240/295</td><td>81.4 (76.4–85.6)</td><td>12.1 (8.2–16.1)</td><td>Yes</td></tr>
<tr><td></td><td>MCC-primed</td><td>194/196</td><td>99.0 (96.4–99.9)</td><td>97/99</td><td>98.0 (92.9–99.8)</td><td></td><td></td></tr>
<tr><td>W</td><td>Naïve</td><td>245/293</td><td>83.6 (78.9–87.7)</td><td>247/296</td><td>83.4 (78.7–87.5)</td><td>0.46 (–4.37–5.28)</td><td>Yes</td></tr>
<tr><td></td><td>MCC-primed</td><td>170/196</td><td>86.7 (81.2–91.1)</td><td>84/98</td><td>85.7 (77.2–92.0)</td><td></td><td></td></tr>
<tr><td>Y</td><td>Naïve</td><td>273/293</td><td>93.2 (89.7–95.8)</td><td>271/296</td><td>91.6 (87.8–94.5)</td><td>2.24 (–1.34–6.19)</td><td>Yes</td></tr>
<tr><td></td><td>MCC-primed</td><td>189/197</td><td>95.9 (92.2–98.2)</td><td>91/99</td><td>91.9 (84.7–96.4)</td><td></td><td></td></tr>
</table>
CI, confidence interval; MCC, meningococcal C conjugate vaccine; n, number of participants with seroprotection[a]; M, number of participants with available data for the endpoint
95% CI of the single percentage calculated from the exact binomial method.
95% CI stratified on the priming status was calculated using the Wald method (normal approximation)
Weighted average difference over strata calculated using the Minimal Risk weights with the null variance method
[a]Seroprotection defined as hSBA titre ≥1:8.
[b]Non-inferiority concluded if the lower limit of the two-sided 95% CI of the overall difference of proportion stratified on the priming status is >–10%.

Non inferiority after single dose in vaccine naïve toddlers were also demonstrated in MenACYW conjugate vaccine

Table 2. Non-inferiority of the proportion of meningococcal vaccine-naïve participants who achieved hSBA vaccine seroprotection[a] at Day 30 with MenACYW-TT compared with MCV4-TT (PPAS)

<table>
<tr><th></th><th colspan="2">MenACYW-TT (N = 293)</th><th colspan="2">MCV4-TT (N = 296)</th><th colspan="2">MenACYW-TT – MCV4-TT</th></tr>
<tr><th>Serogroup</th><th>n</th><th>% (95% CI)</th><th>n</th><th>% (95% CI)</th><th>Difference, % (95% CI)</th><th>Non-inferiority[b]</th></tr>
<tr><td>A</td><td>266</td><td>90.8 (86.9–93.8)</td><td>264[c]</td><td>89.5 (85.4–92.7)</td><td>1.3 (–3.6–6.2)</td><td>Yes</td></tr>
<tr><td>C</td><td>291</td><td>99.3 (97.6–99.9)</td><td>240[c]</td><td>81.4 (76.4–85.6)</td><td>18.0 (13.6–22.8)</td><td>Yes</td></tr>
<tr><td>W</td><td>245</td><td>83.6 (78.9–87.7)</td><td>247</td><td>83.4 (78.7–87.5)</td><td>0.2 (–5.9–6.2)</td><td>Yes</td></tr>
<tr><td>Y</td><td>273</td><td>93.2 (89.7–95.8)</td><td>271</td><td>91.6 (87.8–94.5)</td><td>1.6 (–2.8–6.0)</td><td>Yes</td></tr>
</table>
CI, confidence interval; n, number of participants with seroprotection[a]; N, number of participants with available data for the endpoint.
95% CI of the single percentage calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
[a]Seroprotection defined as hSBA titre ≥1:8.
[b]The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the difference is >–10% for all four serogroups.

Conclusion:
MenACYW-TT was well tolerated and demonstrated a non-inferior immune response compared with the licensed Nimenrix vaccine when administered as a single dose to MenC vaccine primed and/or meningococcal vaccine-naïve toddlers aged 12–23 months.</td>
</tr>
</table>

	vaccine naïve toddlers Statistical Analysis Plan: For both co-primary objectives, the non-inferiority of the hSBA seroresponse for each of the serogroups, A, C, W and Y, was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the MenACYW-TT and MCV4-TT groups in terms of percentages of participants who achieved an hSBA seroresponse was >–10%, the inferiority assumption was rejected. The overall non-inferiority of each co-primary objective was demonstrated if all four individual null hypotheses were rejected.	

Study MET 35: 2 years – 9 years (vaccine naïve patients)

<table>
<tr><th>Study Type & Design (N)</th><th>Objective of the study</th><th>Results</th></tr>
<tr>
<td>Phase III, double blind, randomized parallel group, active controlled

Baccarini.C.I., et.al Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine in Healthy Meningococcal-Naïve Children 2–9 Years of Age: A Phase III, Randomized Study, Pediatr Infect Dis J: 2020;39:955–960)

Healthy meningococcal vaccine-naïve children 2-9 years

N=1000
Randomized 1:1 ratio
MenACYW-TT = 499
Menveo = 501</td>
<td>To demonstrate the non-inferiority of immune sero response following administration of a single dose of MenQuadfi relative to Menveo in terms of hSBA seroresponse to serogroups A, C, W, and Y at day 30

<u>Statistical Analysis Plan</u>:

For the primary objective, the non-inferiority of hSBA seroresponse with MenQuadfi relative to MenACWY-CRM at day 30 as tested for each of the serogroups A, C, W, and Y separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference</td>
<td>

MenQuadfi demonstrated to be non-inferior to Menveo in terms of hSBA seroresponse against all 4 serogroups at Day 30

<table>
<tr><th></th><th colspan="2">MenACYW-TT (n = 458)</th><th colspan="2">MenACWY-CRM (n = 460)</th><th>MenACYW-TT–MenACWY-CRM</th></tr>
<tr><th>Serogroup</th><th>n/M</th><th>% (95% CI)</th><th>n/M</th><th>% (95% CI)</th><th>Difference, % (95% CI)</th></tr>
<tr><td>A</td><td>252/455</td><td>55.4 (50.7-60.0)</td><td>219/458</td><td>47.8 (43.2-52.5)</td><td>7.6 (1.1-14.0)</td></tr>
<tr><td>C</td><td>436/458</td><td>95.2 (92.8-97.0)</td><td>219/458</td><td>47.8 (43.2-52.5)</td><td>47.4 (42.2-52.2)</td></tr>
<tr><td>W</td><td>361/458</td><td>78.8 (74.8-82.5)</td><td>294/459</td><td>64.1 (59.5-68.4)</td><td>14.8 (8.9-20.5)</td></tr>
<tr><td>Y</td><td>419/458</td><td>91.5 (88.5-93.9)</td><td>364/459</td><td>79.3 (75.3-82.9)</td><td>12.2 (7.7-16.7)</td></tr>
</table>
[a]hSBA vaccine seroresponse was demonstrated if a participant had prevaccination titers <1:8, then the postvaccination titer had to be ≥1:16, or for a participant with a prevaccination titer ≥1:8, the postvaccination titer had to be at least 4-fold greater than the prevaccination titer; 95% CIs of the single proportion was calculated from the exact binomial method.
CI, confidence interval; PPAS, Per Protocol Analysis Set; n, number of participants who achieved an hSBA vaccine seroresponse; M, number of participants with available data for the endpoint; N, number of participants in the PPAS.
The overall noninferiority would be demonstrated if the lower limit of the 2-sided 95% CI is > –10% for all 4 serogroups.

The number of patients with hSBA titters more than 4 fold increase from baseline to day 30 are higher in the MenQuadfi arm than in the Menveo arm. Serogroup C, W and Y demonstrated a higher hSBA seroresponse in MenQuadfi than Menveo, with a similar proportion of patients achieving seroresponse against serogroup A.

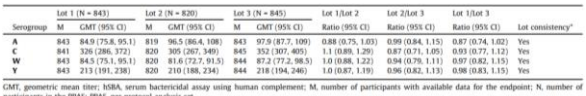
<table>
<tr><th></th><th></th><th colspan="2">MenACYW-TT (n = 458)</th><th colspan="2">MenACWY-CRM (n = 460)</th></tr>
<tr><th>Serogroups</th><th>Time Point</th><th>n/M</th><th>% (95% CI)</th><th>n/M</th><th>% (95% CI)</th></tr>
<tr><td>A</td><td>Day 0</td><td>225/457</td><td>49.2 (44.6-53.9)</td><td>224/460</td><td>48.7 (44.0-53.4)</td></tr>
<tr><td></td><td>Day 30</td><td>394/456</td><td>86.4 (82.9-89.4)</td><td>363/458</td><td>79.3 (75.3-82.9)</td></tr>
<tr><td>C</td><td>Day 0</td><td>56/458</td><td>12.2 (9.4-15.6)</td><td>59/459</td><td>12.9 (9.9-16.3)</td></tr>
<tr><td></td><td>Day 30</td><td>448/458</td><td>97.8 (96.0-98.9)</td><td>308/459</td><td>67.1 (62.6-71.4)</td></tr>
<tr><td>W</td><td>Day 0</td><td>90/458</td><td>19.7 (16.1-23.6)</td><td>93/460</td><td>20.2 (16.6-24.2)</td></tr>
<tr><td></td><td>Day 30</td><td>434/458</td><td>94.8 (92.3-96.9)</td><td>396/459</td><td>86.3 (82.8-89.3)</td></tr>
<tr><td>Y</td><td>Day 0</td><td>54/458</td><td>11.8 (9.0-15.1)</td><td>57/460</td><td>12.4 (9.5-15.8)</td></tr>
<tr><td></td><td>Day 30</td><td>451/458</td><td>98.5 (96.9-99.4)</td><td>417/459</td><td>90.8 (87.8-93.3)</td></tr>
</table>
CI, confidence interval; M, number of participants with a valid serology result for the particular serogroup and time point; n, number of participants experiencing the endpoint.
Titers ≥1:8 were considered seroprotective.

Conclusion:
The results demonstrate that MenQuadfi is non inferior to Menveo in vaccine naïve patients aged between 2 -9 years old and is well tolerated
</td>
</tr>
</table>

	between the 2-seroresponse rates was greater than –10%, the inferiority hypothesis was rejected.	

Study MET 43- vaccine naïve patients 10-55years

Study Type & Design (N)	Objective of the study	Results
Phase III, randomized, modified double blind active controlled *Dhingra.M.S.et.al Immunogenicity, safety and inter-lot consistency of a meningococcal conjugate vaccine (MenACYW-TT) in adolescents and adults: A Phase III randomized study; Elseview 2020; Volume 38, (33) 5194-5201* Randomized 3:3:3:2 3344 healthy vaccine naïve adolescent and adults 10-55 years 500 subjects 18-55 years 300 subjects 10-17 years N=902 MenQuadfi N=895 MenQuadfi N=906 MenQuadfi N=641 Menactra	1. To demonstrate the immune lot consistency of the antibody responses to meningococcal serogroups A, C, Y & W following administration of a single dose of MenQuadfi with respect to hSBA geometric mean titers 2. To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y & W following administration of a single dose of MenQuadfi compared to those observed following the administration of single dose of Menactra. <u>Statistical Analysis Plan</u> Equivalence was demonstrated if for each pairwise assessment the 2-sided 95% confidence interval (CI) of the GMTR was between 0.5 and 2 for all three pairs.	• Lot to lot consistency was demonstrated across the three lots at Day 30 based on hSBA GMTR for each serogroup • Non-inferiority of MenQuadfi to Menactra was demonstrated based on the proportion of participants achieving hSBA vaccine seroresponse in the MenQuadfi (pooled lots) group versus the Menactra group [difference between groups]. serogroup A: 19.1 [95% CI: 14.8, 23.5] serogroup C: 40.9 [95% CI: 36.7, 45.0] serogroup W: 19.1 [95% CI: 14.9, 23.3] serogroup Y: 18.1 [95% CI:14.5, 21.9]) Non inferiority was demonstrated in the hSBA vaccine sero response for both adults (18-55 years) and adolescents (10 – 17 years old) for each sero group, with higher seroresponse in adolescents to serogroup C **Conclusion:** The study demonstrated immune consistency of three commercial lots of MenQuadfi and non-inferiority of antibody response with MenQuadfi compared with Menactra in vaccine naïve adolescents and adults aged 10-55 years.



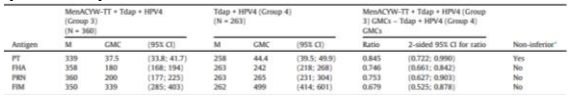
	Lot 1 (N = 843)		Lot 2 (N = 820)		Lot 3 (N = 845)		Lot 1/Lot 2	Lot 2/Lot 3	Lot 1/Lot 3	
Serogroup	M	GMT (95% CI)	M	GMT (95% CI)	M	GMT (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Lot consistency[a]
A	843	84.9 (75.8, 95.1)	819	96.5 (86.4, 108)	843	97.9 (87.7, 109)	0.88 (0.75, 1.03)	0.99 (0.84, 1.15)	0.87 (0.74, 1.02)	Yes
C	841	326 (286, 372)	820	305 (267, 349)	845	352 (307, 405)	1.1 (0.89, 1.29)	0.87 (0.71, 1.05)	0.93 (0.77, 1.12)	Yes
W	843	84.5 (75.1, 95.1)	820	81.6 (72.7, 91.5)	844	87.2 (77.2, 98.5)	1.0 (0.88, 1.22)	0.94 (0.79, 1.11)	0.97 (0.82, 1.15)	Yes
Y	843	213 (191, 238)	820	210 (188, 234)	844	218 (194, 246)	1.0 (0.87, 1.19)	0.96 (0.82, 1.13)	0.98 (0.83, 1.15)	Yes

GMT, geometric mean titer; hSBA, serum bactericidal assay using human complement; M, number of participants with available data for the endpoint; N, number of participants in the PPAS; PPAS, per protocol analysis set.
[a]Lot consistency was demonstrated if for each pair of lots and each antigen, the 2-sided 95% CI for the ratio of GMTs lies between 0.5 and 2.

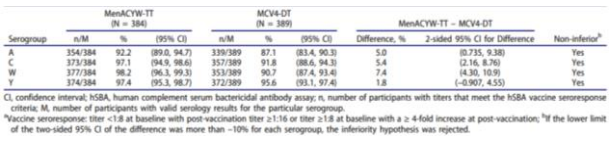
3 lots of MenQuadfi was used to demonstrate consistency	The inferiority assumption was rejected for each serogroup if the lower limit of the 2-sided 95% CI of the difference between MenACYW-TT (pooled lots) versus MCV4-DT was greater than –10%	

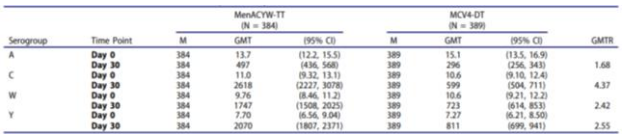
Study MET 50- co administered with Tdap vaccine naïve

Study Type & Design (N)	Objective of the study	Results
Phase II, open label, randomized, parallel group *Chang.L.J., et.al., A Phase II, randomized, immunogenicity and safety study of a quadrivalent meningococcal conjugate vaccine, MenACYW-TT, in healthy adolescents in the United States., Vaccine 38(2020) 3560-3569* 1715 Vaccine naïve adolescents aged 10-17 years Randomized into 5:5:4:3 (GP1)MenQuadfi =499 (GP2) Menveo = 500 (GP3)MenQuadfi + HPV4 = 391 (GP4)Tdap HPV4 = 296	To evaluate the antibody responses to the antigens present in MenACYW conjugate vaccine when MenACYW conjugate vaccine given alone compared to those when Menveo® is given alone. **Statistical Analysis Plan** 1. For the primary objective, the non-inferiority of MenQuadfi alone compared to vaccination with Menveo alone was assessed in terms of hSBA vaccine seroresponse for each serogroup A, C, W, and Y for Group 1 vs Group 2. 2. Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10%, the inferiority	Primary Endpoint: The percentages of subjects with an hSBA vaccine seroresponse were higher in Group 1 than in Group 2 for all serogroups: Sero group A: 75.6% (350/463) in Group 1 and 66.4% (308/464) in Group 2 Serogroup C: 97.2% (449/462) in Group 1 and 72.6% (336/463) in Group 2 Sero group Y: 97.0% (448/462) in Group 1 and 80.8% (375/464) in Group 2 Sero group W: 86.2% (399/463) in Group 1 and 66.6% (309/464) in Group 2 **Group 1 MenACYW (N=463) / Group 2 MENVEO (N=464) / Group 1 - Group 2 P1 - P2** **Serogroup** — **n/M** — **P1 (%)** — **(95% CI)** — **n/M** — **P2 (%)** — **(95% CI)** — **Difference (%)** — **2-sided 95% CI for Difference** A — 350/463 — 75.6 — (71.4; 79.4) — 308/464 — 66.4 — (61.9; 70.7) — 9.2 — (3.4; 15.0) C — 449/462 — 97.2 — (95.2; 98.5) — 336/463 — 72.6 — (68.3; 76.6) — 24.6 — (20.3; 29.0) Y — 448/462 — 97.0 — (95.0; 98.3) — 375/464 — 80.8 — (76.9; 84.3) — 16.2 — (12.3; 20.2) W — 399/463 — 86.2 — (82.7; 89.2) — 309/464 — 66.6 — (62.1; 70.9) — 19.6 — (14.2; 24.8) Secondary Endpoint: 2. **MenQuadfi administered concomitantly with Tdap and HPV4** - The immune response for each serogroup was non-inferior compared to MenQuadfi alone. MenACYW-TT (Group 1) N = 463 / MenACYW-TT + Tdap + HPV4 (Group 3) N = 360 / MenACYW-TT + Tdap + HPV4 (Group 3) – MenACYW-TT (Group 1) **Serogroup** — **n/M** — **%** — **n/M** — **%** — **Difference, %** — **2-sided 95% CI for Difference** — **Non-inferior†** A — 350/463 — 75.6 — 290/360 — 80.6 — 5.0 — (−0.8; 10.5) — Yes C — 449/462 — 97.2 — 350/360 — 97.2 — 0.0 — (−2.5; 2.4) — Yes W — 399/463 — 86.2 — 302/360 — 83.9 — −2.3 — (−7.3; 2.6) — Yes Y — 448/462 — 97.0 — 344/360 — 95.6 — −1.4 — (−4.3; 1.2) — Yes M, number of participants with valid serology results for the particular serogroup n, number of participants with titers that meet the hSBA vaccine seroresponse criteria PPAS 1, per protocol analysis set 1 * Vaccine seroresponse: titer is <1:8 at baseline with post-vaccination titer ≥ 1:8 or titer is ≥ 1:8 at baseline with a ≥4-fold increase at post-vaccination † If the lower limit of the 2-sided 95% CI of the difference is more than −10% for each serogroup, the inferiority hypothesis was rejected **3. Non-inferiority of diphtheria, tetanus, pertussis and HPV antigens** - the proportion of participants who achieved ≥ 1.0IU/ml anti tetanus or anti diphtheria antibody concentration at Day 30 , after Tdap administration, MenQuadfi and HPV4 (97.8%)

	assumption was rejected 3. The proportion of participants achieving hSBA vaccine seroresponse, anti-tetanus seroprotection, anti-diphtheria seroprotection or HPV4 seroconversion was considered non-inferior if the lower limit of the 2-sided 95% confidence intervals (CIs) of the percentage difference between the 2 groups was >–10%. 3. Pertussis antigen geometric mean concentrations (GMCs) and HPV antibody GMTs in Group 3 were considered non-inferior to those in Group 4 if the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the two groups was >2/3 for each antigen.	was non-inferior to Tdap and HPV alone (98.9%)  If the lower limit of the 2-sided 95% CI of the ratio is more than 2/3, the inferiority hypothesis is rejected **Conclusion:** This study demonstrated that non-inferior to Menveo. The percentage of participants achieving hSBA seroresponse after 30 days was higher in the MenQuadfi group than in the Menveo group. Co-administration of MenQuadfi had no safety concerns raised and antibody response to diphtheria, tetanus and PT antigens were non-inferior to the group 4 alone.

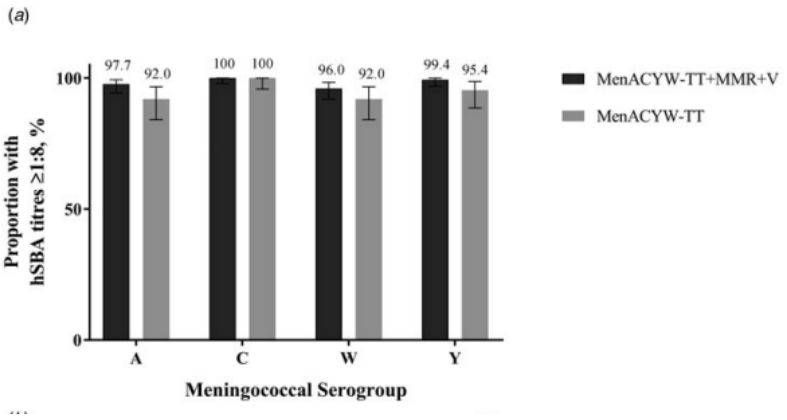
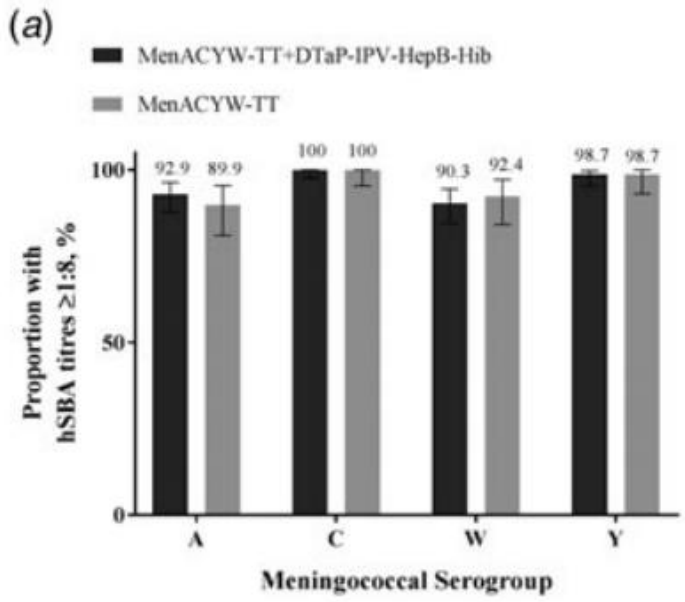
Study MET 56- booster dose

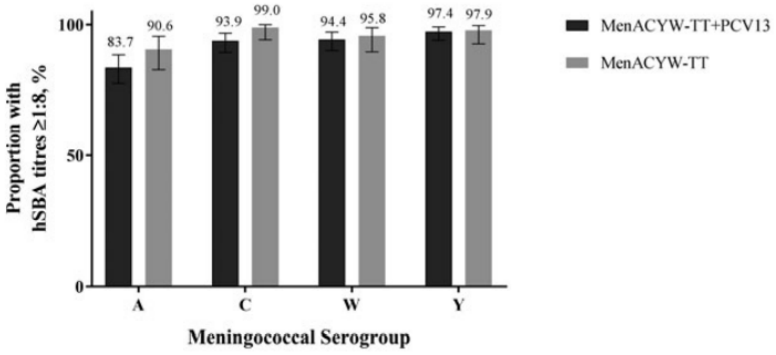
Study Type & Design (N)	Objective of the study	Results
Phase III, modified double blind randomized parallel group, active control *Anez.G.et.al., Immunogenicity and safety of a booster dose of a quadrivalent meningococcal*	To demonstrate the non-inferiority of the MenQuadfi booster vaccine seroresponse to meningococcal serogroups A, C, W, and Y measured by hSBA at Day 30 in MCV4-primed (Menactra or Menveo)	• Non-inferiority was demonstrated for MenQuadfi compared with Menactra booster as the proportion of participants achieving the hSBA at day-30 post vaccination. 

tetanus toxoid-conjugate vaccine (MenACYW-TT) in adolescents and adults: a Phase III randomized study Human Vaccines & Immunotherapeutics 2020, VOL. 16, NO. 6, 1292–1298 Healthy adolescents and adults aged 15 years and above who had received one dose of either Menactra or Menveo at age 10 years or older, 4 -10 years previously Randomized 1:1 ratio to receive either booster dose of MenACYW- TT or Menactra MenQuadfi: 403 Menactra: 407	participants compared with Menactra booster. **Statistical analysis Plan:** If the lower limit of the two-sided 95% confidence interval (CI) of the difference in vaccine seroresponse for a given serogroup between the two study groups was more than –10%, then the inferiority assumption for that serogroup was rejected.	• Baseline titers were comparable. At day 30, hSBA GMTs for all serogroups were higher than for both groups. The hSBA titers after MenQuadfi was higher than after Menactra booster dose.  MenACYW-TT (N = 384) / MCV4-DT (N = 389) Serogroup | Time Point | M | GMT | (95% CI) | M | GMT | (95% CI) | GMTR A | **Day 0** | 384 | 13.7 | (12.2, 15.5) | 389 | 15.1 | (13.5, 16.9) | **Day 30** | 384 | 497 | (436, 568) | 389 | 296 | (256, 343) | 1.68 C | **Day 0** | 384 | 11.0 | (9.32, 13.1) | 389 | 10.6 | (9.10, 12.4) | **Day 30** | 384 | 2618 | (2227, 3078) | 389 | 599 | (504, 711) | 4.37 W | **Day 0** | 384 | 9.76 | (8.46, 11.2) | 389 | 10.6 | (9.21, 12.2) | **Day 30** | 384 | 1747 | (1508, 2025) | 389 | 723 | (614, 853) | 2.42 Y | **Day 0** | 384 | 7.70 | (6.56, 9.04) | 389 | 7.27 | (6.21, 8.50) | **Day 30** | 384 | 2070 | (1807, 2371) | 389 | 811 | (699, 941) | 2.55 **Conclusion:** The study demonstrate the MenQuadfi booster dose, administered 4–10 y after a priming MCV4 (Either Menactra or Menveo) vaccination at age ≥10 y, was immunogenic and well tolerated.

<u>Study</u> <u>MET 57- concomitant use with other vaccines</u>

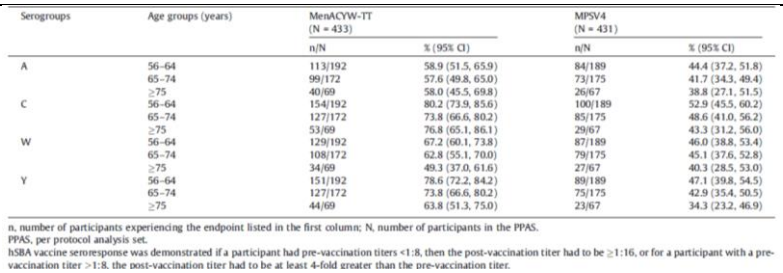
Study Type & Design (N)	Objective of the study	Results
Phase III, open label, randomized, active controlled Dhingra MS et al (2021). Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine administered	To evaluate the immunogenicity and safety of MenACYW-TT when Co administered with routinely used paediatric vaccines in South Korea, Thailand, Mexico and Russian Federation, according to	<u>Thailand and Korea – MenQuadfi + MMR, Varicella</u> • When co- administered, the proportion of participants with seroprotection to each serogroup was comparable between the groups at Day 30. • hSBA GMTs increased from baseline to Day 30 and were comparable between the groups at Day 30

concomitantly with other paediatric vaccines in toddlers: a phase III randomized study. *Epidemiology and Infection* 149, e90, 1–10. Healthy meningococcal vaccine naïve toddlers 12 -23 months Healthy toddlers aged 15–23 months who had not received the third dose of PCV13 randomized in a 2:1 ratio to MenACYW-TT and PCV13 or PCV13 alone. N= 1183 South Korea: 213 Mexico: 400 Russia: 400 Thailand:170 Randomized 2:1:1 to receive either MenACYW-TT and co-administered	the local immunization programme To determine immune response against all four meningococcal serogroups as measured by hSBA before vaccination and at Day 30 after vaccination	 • At day 30, the anti-measles, mumps, rubella and varicella antibodies all increased from baseline and were comparable between the groups. <u>Mexico: MenQuadfi with DTaP-IPV-HepB-Hib</u> • For both MenACYW-TT co-administered with DTaP-IPV-HepBHib and MenQuadfi groups, the proportion of participants with seroprotection to each meningococcal serogroup increased from baseline and was comparable between the groups at Day 30  • The geometric mean concentration for individual antigens after Day 30 had increased and were comparable <u>Russia: MenQuadfi with PCV13</u>

vaccines , MenACYW-TT alone or co administered vaccines alone Russia: healthy meningococcal vaccine-naïve toddlers aged 12–14 months and 16–23 months were assigned to the MenACYW-TT alone group		• The proportion of participants with seroprotection for each serogroup was comparable between the groups at Day 30. hSBA titers had increased from baseline to Day 30.  **Conclusion:** The study demonstrated that there was no clinically relevant effect on the immunogenicity of MenQuadfi or the other co-administered vaccines.

Study MET 49 – older adults ≥ 56

Study Type & Design (N)	Objective of the study	Results
Phase III, modified double blind, randomized parallel group, active controlled *Jaramilo.et.al., Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine*	To demonstrate non-inferiority of MenQuadfi compared with Menomune in seroresponse to each serogroup A, C, Y, W measure by hSBA at baseline and	• MenQuadfi was non-inferior for the participants achieving seroresponse for serogroups A, C, Y and W. MenACYW-TT (N = 433) / MPSV4 (N = 431) / MenACYW-TT – MPSV4 Serogroup | N | % (95% CI) | n | % (95% CI) | Difference, % (95% CI) | Non-inferiority A | 252 | 58.2 (53.4, 62.9) | 183 | 42.5 (37.7, 47.3) | 15.7 (9.08, 22.2) | Yes C | 334 | 77.1 (72.9, 81.0) | 214 | 49.7 (44.8, 54.5) | 27.5 (21.2, 33.5) | Yes W | 271 | 62.6 (57.8, 67.2) | 193 | 44.8 (40.0, 49.6) | 17.8 (11.2, 24.2) | Yes Y | 322 | 74.4 (70.0, 78.4) | 187 | 43.4 (38.7, 48.2) | 31.0 (24.6, 37.0) | Yes PPAS, per protocol analysis set; n, number of participants who achieved an hSBA vaccine seroresponse; N, number of participants in the PPAS. hSBA vaccine seroresponse was demonstrated if a participant had pre-vaccination titers <1:8, then the post-vaccination titer had to be ≥1:16, or for a participant with a pre-vaccination titer ≥1:8, the post-vaccination titer had to be at least 4-fold greater than the pre-vaccination titer; 95% CIs of the single proportion was calculated from the exact binomial method; 95% CIs of the difference was calculated using the Wilson Score method without continuity correction. The overall non-inferiority would be demonstrated if the lower limit of the 2-sided 95% CI is >−10% for all four serogroups. • The proportion of participants achieving hSBA seroresponse for A, C, Y, W at day 30 was comparable. There was higher response rates in participants aged 56-64 for serogroup C and Y in the MenQuadfi group as compared to the Menomune

(MenACYW-TT) in ≥ 56 years olds: A Phase III randomized study. Vaccine: 2020 N=906 healthy adults aged ≥ 56 years old Randomized 1:1 to receive MenACYW-TT or Menomune	Day 30 in adults aged ≥ 56 years **Statistical Analysis plan** If the lower limit of the 2-sided 95% CI of the difference between the two proportion was ≥ 10%, then inferiority was rejected.	 **Conclusion:** The study demonstrate non-inferiority of MenQuadfi compared to Menomune in terms of hSBA seroresponse in adults older than 56 years old.

Serogroups	Age groups (years)	MenACYW-TT (N = 433)		MPSV4 (N = 431)	
		n/N	% (95% CI)	n/N	% (95% CI)
A	56–64	113/192	58.9 (51.5, 65.9)	84/189	44.4 (37.2, 51.8)
	65–74	99/172	57.6 (49.8, 65.0)	73/175	41.7 (34.3, 49.4)
	≥75	40/69	58.0 (45.5, 69.8)	26/67	38.8 (27.1, 51.5)
C	56–64	154/192	80.2 (73.9, 85.6)	100/189	52.9 (45.5, 60.2)
	65–74	127/172	73.8 (66.6, 80.2)	85/175	48.6 (41.0, 56.2)
	≥75	53/69	76.8 (65.1, 86.1)	29/67	43.3 (31.2, 56.0)
W	56–64	129/192	67.2 (60.1, 73.8)	87/189	46.0 (38.8, 53.4)
	65–74	108/172	62.8 (55.1, 70.0)	79/175	45.1 (37.6, 52.8)
	≥75	34/69	49.3 (37.0, 61.6)	27/67	40.3 (28.5, 53.0)
Y	56–64	151/192	78.6 (72.2, 84.2)	89/189	47.1 (39.8, 54.5)
	65–74	127/172	73.8 (66.6, 80.2)	75/175	42.9 (35.4, 50.5)
	≥75	44/69	63.8 (51.3, 75.0)	23/67	34.3 (23.2, 46.9)

n, number of participants experiencing the endpoint listed in the first column; N, number of participants in the PPAS.
PPAS, per protocol analysis set.
hSBA vaccine seroresponse was demonstrated if a participant had pre-vaccination titers <1:8, then the post-vaccination titer had to be ≥1:16, or for a participant with a pre-vaccination titer >1:8, the post-vaccination titer had to be at least 4-fold greater than the pre-vaccination titer.

Safety

- In the clinical trials, similar adverse events reporting rates were observed. The most common solicited injection site reactions in 12 to 23 months was injection site tenderness, erythema and swelling while in the 2- 9 years of age and 10 years and older was injection site pain, erythema and swelling.
- The solicited systemic reactions reported in 12 – 23 months of age were fever, vomiting, crying abnormal, drowsiness, appetite lost and irritability while in the 2 years and older were fever, headache, malaise and myalgia.
- The nature and frequency of the reported events were consistent with those expected after vaccination and are comparable with the comparator vaccines

3.0 CONCLUSION

In all the clinical studies provided, the primary endpoint demonstrate a higher immune response rate for MenQuadfi compared to the other quadrivalent meningococcal vaccines. The vaccine is well tolerated with no safety concerns identified. The benefit risk ratio for this product is favorable.

Drug Control Authority (DCA) on the 386th meeting on 6th July 2023 has decided to approve the registration of this product with the following indication:

MenQuadfi is indicated for active immunization of individuals from the age of 12 months and older against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y