Semi-Quantitative Benefit-Risk Assessment for a New Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-TT) in Individuals 2 Years of Age and Older

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INTRODUCTION

- Invasive meningococcal disease (IMD) remains as a global public health threat even in the scenario of highly efficacious vaccines being available
- Quadrivalent meningococcal conjugate vaccines offer protection against 4 of the clinically most important *N. meningitidis* serogroups - A, C, W, and Y causing IMD
- MenQuadfi™ (MenACYW-TT) is a new quadrivalent meningococcal conjugate vaccine that contains tetanus toxoid as carrier protein
- The vaccine is currently licensed in the US as a single dose in ages 2 years and above and is being pursued for global use in all age groups (i.e., individuals 6 weeks of age and older)
  - Biologics License Application (BLA) for MenQuadfi approved by the US FDA on 23 April 2020
- We present the structured benefit-risk assessment (sBRA) conducted by Sanofi Pasteur in support of the initial BLA for MenACYW-TT in the US
  - Qualitative approach using FDA's Benefit-risk Framework[1] outlining the key elements (Analysis of condition, Current treatment options, Benefit, and Risk and Risk Management), evidence, and uncertainties that factor into benefit-risk assessment
  - Semi-quantitative framework using data from the 5 pivotal prelicensure clinical trials in individuals 2 years of age and older **(Tables 1 and 2)**

Table 1: Overview of Pivotal Clinical Studies (ages 2 years +)[2-6]

Age Range	Trial Phase (Code)	Country	Comparator	Total Sample Size	MenACYW-TT recipients	Trial Registration
Children (2-9 years)	Phase III (MET35)[2]	USA	MenACWY-CRM (Menveo®)	1000	498	NCT03077438
Adolescents (10-17 years)	Phase II (MET50)[5]	USA	MenACWY-CRM (Menveo®)	1715	895	NCT02199691
Adolescents and Adults (10-55 years)	Phase III (MET43)[3]	USA	MenACWY-D (Menactra®)	3344	2681	NCT02842853
MCV4 primed Adolescents and Adults (≥15 years)	Phase III (MET56)[6]	USA	MenACWY-D (Menactra®)	810	402	NCT02752906
Older adults (56 years & older)	Phase III (MET49)[4]	USA	MPSV4 (Menomune®)	907	448	NCT04142242

MCV4: Quadrivalent meningococcal conjugate vaccine; MenACWY-CRM: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Menveo®); MenACWY-D: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra®); MPSV4: Meningococcal Polysaccharide Vaccine, Groups A, C, Y, W-135 Combined (Menomune® A/C/Y/W 135).

Table 2: MenACYW-TT Immunogenicity Data Summary (ages 2 years +)

Population	Comparator	Established non-inferiority vs comparator by serogroup[a]			
		A	C	W	Y
Children (2-9 years)	MenACWY-CRM	✓	✓	✓	✓
Adolescents (10-17 years)	MenACWY-D	✓	✓	✓	✓
	MenACWY-CRM	✓	✓	✓	✓
Adults (18-55 years)	MenACWY-D	✓	✓	✓	✓
Older adults (56 years & older	MPSV4	✓	✓	✓	✓
Adolescents and Adults (15 years +)[b]	MenACWY-D	✓	✓	✓	✓

[a]based on percentages of participants achieving hSBA vaccine seroresponse at Day 30 compared to baseline. Non inferiority is defined as lower bound of the 95%CI of the difference > -10%; [b]Use as a booster dose.

Safety Data Summary (ages 2 years +)

- Studies revealed no apparent safety concerns
- MenACYW-TT as a single dose has been well tolerated across all age groups
  - Overall, consistent safety profile with the known safety profile of the licensed quadrivalent meningococcal conjugate vaccines
  - Rates of SAEs were low and none were considered vaccine-related
  - No related AEs leading to study discontinuation
  - Most solicited reactions within 7 days following vaccination were Grade 1 or 2 in intensity, and resolved within 1-3 days
  - The reported AEs reflected anticipated illnesses and expected AEs in the studied age groups
  - The rates of adverse reactions after a booster dose of MenACYW-TT in adolescents and adults at least 15 years of age primed with another MCV4 were comparable to those seen among adolescents and adults who received a primary dose of MenACYW-TT
  - The safety profiles of the concomitant licensed vaccines Tdap (Adacel® [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed]) and HPV (Gardasil® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] were comparable when administered with or without MenACYW-TT in adolescents

Structured Benefit-Risk Assessment: Semi-Quantitative Analysis

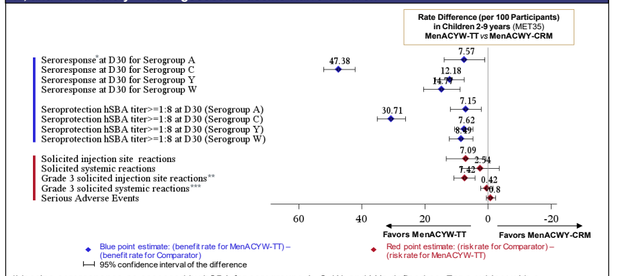
- Safety and immunogenicity of MenACYW-TT in subjects ≥2 years was evaluated in 5 pivotal randomized, active-controlled clinical trials MET35, MET43, MET50, MET49, and MET56.
  - 4,919 subjects received either a single primary dose (n=4517) or a booster dose (n=402) of MenACYW-TT
  - Serum bactericidal antibody assay using human complement (hSBA) was used to measure antibodies against representative serogroup strains at baseline and D30 after vaccination, and safety data were collected up to 6 months after vaccination
- A semi-quantitative framework **(Table 3)** was used to establish favorable and unfavorable effects of MenACYW-TT relative to comparators by age group using data from the pivotal studies:
  - *In Meningococcal vaccine-naïve participants*
  - MenACWY-CRM (Menveo®) in children 2-9 years (MET35) and adolescents 10-17 years (MET50)
  - MenACWY-D (Menactra®) in adolescents 10-17 years and adults 18-55 years (MET43)
  - MPSV4 (Menomune®) in older adults ≥ 56 years (MET49)
  - *In MCV4-primed participants*
  - MenACWY-D (Menactra®) in adolescents and adults ≥ 15 years (MET56)
- **Benefit** outcome measures
  - Vaccine seroresponse and vaccine seroprotection (titers ≥ 1:8) at D30 evaluated by serum bactericidal assay using human complement, for each serogroup
- **Risk** outcome measures
  - Rate of any solicited injection site reactions (pain, erythema and/or swelling at the injection site) within 7 days after vaccination
  - Rate of any solicited systemic reactions (fever, myalgia, headache, malaise) within 7 days after vaccination
  - Rate of any Grade 3 solicited injections reactions within 7 days after vaccination
  - Rate of any Grade 3 solicited systemic reactions within 7 days after vaccination
  - Rate of any Serious Adverse Events within 6 months after vaccination
- The differences in rates for MenACYW-TT vs Comparator were calculated along with 95% confidence intervals using Wilson score method without continuity correction

Table 3: Structured Benefit-Risk Assessment: Descriptive framework

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	IMD is a serious bacterial infection caused by *Neisseria meningitidis*. Almost all cases of IMD are caused by one of six serogroups (A, B, C, W, X, Y) that vary in prevalence based on temporal, geographic, and age group risk factors. The overall case-fatality ratio for meningococcal disease is 10-15%, while meningococcal sepsis is fatal in up to 40% of cases. 10% to 20% of IMD survivors experience permanent sequelae, including limb amputation, deafness, and skin necrosis requiring skin grafting, cognitive deficits, and seizure disorders. Throughout the world, IMD rates peak especially among infants and adolescents/young adults (0-24 years old).	The public health impact of meningococcal infection underscores the need for effective vaccines and their optimal use. In the US, reductions in the incidence of meningococcal among adolescents suggest an impact of the MCV4 vaccine program in this age group.
Current Treatment Options	**Treatment:** A range of antibiotics can treat the infection, including penicillin, ampicillin and ceftriaxone. **Chemoprophylaxis** (Antibiotics) is indicated for close contacts of patients with meningococcal disease. **Vaccines:** Two MCV4s (Menactra® and Menveo®), which protect against serogroups A, C, Y, and W, and 2 serogroup B vaccines (Bexsero® and Trumenba®) are currently available for use in the USA for active immunization against meningococcal disease in various age groups.	While there are other vaccines available, MenQuadfi is expected to offer the broadest age indication.
Benefit	**Protection from IMD** • Higher immune response (based on seroprotective levels) for serogroups C, W, and Y vs all other MCV4 vaccines across all age groups • Demonstrated immunogenicity in ages 56 years above • Demonstrated co-administration with HPV vaccine in males and females **Herd protection effect; Fully liquid formulation** Uncertainties: Long-term persistence of the immune response after primary vaccination with MenQuadfi, and immunogenicity of a booster in individuals primed with MenQuadfi	MenQuadfi is expected to further decrease the incidence of IMD associated with vaccine serogroups due to demonstrated immunogenicity in broader age range and generally higher immune response. MenQuadfi is expected to limit the disease transmission in unvaccinated individuals due to the herd immunity effect. Convenience: ease of administration due to fully liquid presentation, and the potential to reduce administration errors.
Risk / Risk Management	**Most common reactions** (≥ 10%) reported in the pivotal studies: In all ages 2 years and above: pain at the injection site, myalgia, malaise, and headache. Additional very common reactions in children 2-9 years of age: erythema and swelling at the injection site. All were non-serious and self-limited. **No important identified risks** discovered to date during the development program for MenQuadfi. **No cases of the important potential risks** (Anaphylaxis, Guillain-Barré syndrome, Bell's palsy) in the pivotal studies (within the accepted risk intervals). **Other risk** includes vasovagal syncope following injection procedure Uncertainties: Safety of a booster in individuals primed with MenQuadfi	MenQuadfi is well tolerated and has a favorable safety profile across all age groups. The most common reported AEs and important potential risks are the same as the current MCV4 vaccines. Management of these risks through routine pharmacovigilance activities and routine risks minimization measures. Studies to assess immunogenicity and further characterize the safety profile of a booster dose of MenQuadfi in individuals primed with MenQuadfi have been initiated/planned.

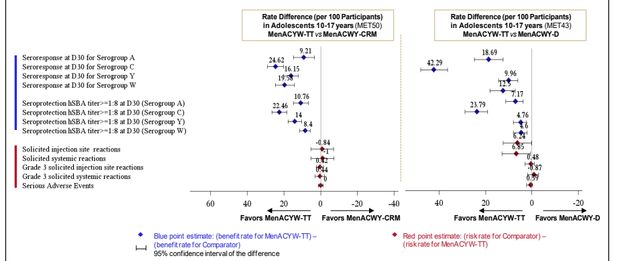
IMD: Invasive meningococcal disease

Figure 1: Forest plots of hSBA vaccine immune response against meningococcal serogroups A, C, W, and Y and safety – Meningococcal Vaccine-Naïve Children



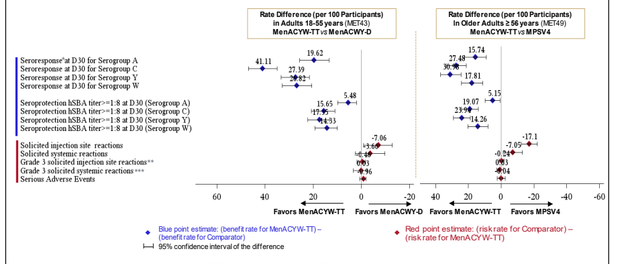
*Vaccine seroresponse as assessed by hSBA for serogroups A, C, W, and Y is defined as: For a subject with a pre-vaccination titer <1:8, the post-vaccination titer must be ≥1:16; For a subject with a pre-vaccination titer ≥1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer; **Grade 3 injection site pain: Unable to perform usual activities; Grade 3 injection site erythema or swelling: ≥ 50 mm; ***Grade 3 myalgia, headache or malaise: Prevents daily activity; Grade 3 fever: ≥ 102.1°F (39.0°C)

Figure 2: Forest plots of hSBA vaccine immune response against meningococcal serogroups A, C, W, and Y and safety – Meningococcal Vaccine-Naïve Adolescents



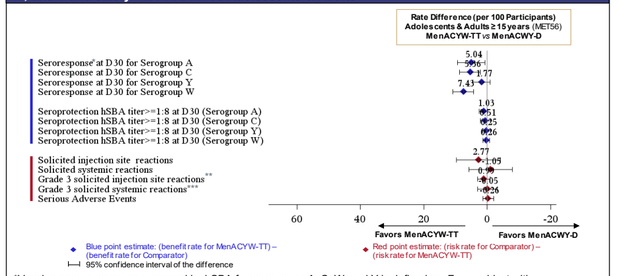
*Vaccine seroresponse as assessed by hSBA for serogroups A, C, W, and Y is defined as: For a subject with a pre-vaccination titer <1:8, the post-vaccination titer must be ≥1:16; For a subject with a pre-vaccination titer ≥1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer; **Grade 3 injection site pain: Prevents daily activity; Grade 3 injection site erythema or swelling: > 100 mm; ***Grade 3 myalgia, headache or malaise: Prevents daily activity; Grade 3 fever: ≥ 102.1°F (39.0°C)

Figure 3: Forest plots of hSBA vaccine immune response against meningococcal serogroups A, C, W, and Y and safety – Meningococcal Vaccine-Naïve Adults & Older Adults



*Vaccine seroresponse as assessed by hSBA for serogroups A, C, W, and Y is defined as: For a subject with a pre-vaccination titer <1:8, the post-vaccination titer must be ≥1:16; For a subject with a pre-vaccination titer ≥1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer; **Grade 3 injection site pain: Prevents daily activity; Grade 3 injection site erythema or swelling: > 100 mm; ***Grade 3 myalgia, headache or malaise: Prevents daily activity; Grade 3 fever: ≥ 102.1°F (39.0°C)

Figure 4: Forest plots of hSBA vaccine immune response against meningococcal serogroups A, C, W, and Y and safety - MCV4-Primed Adolescents & Adults



*Vaccine seroresponse as assessed by hSBA for serogroups A, C, W, and Y is defined as: For a subject with a pre-vaccination titer <1:8, the post-vaccination titer must be ≥1:16; For a subject with a pre-vaccination titer ≥1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer; **Grade 3 injection site pain: Prevents daily activity; Grade 3 injection site erythema or swelling: > 100 mm; ***Grade 3 myalgia, headache or malaise: Prevents daily activity; Grade 3 fever: ≥ 102.1°F (39.0°C)

Summary of semi-quantitative results

- For all **benefit criteria**, and in all age groups, rate differences favored MenACYW-TT in meningococcal vaccine-naïve individuals
  - Immune response differences were more pronounced for serogroup C
- Differences showed favorable (seroresponse criteria) or comparable (seroprotection criteria) effects for MenACYW-TT in adolescents and adults previously primed with another MCV4 (MenACWY-D or MenACWY-CRM)
- For the **risk criteria**, overall, rate differences showed comparable effects between MenACYW-TT and the comparator MCV4s (MenACWY-D or MenACWY-CRM) in children, adolescents and adults
  - Favorable effects for **MenACYW-TT** vs **MenACWY-CRM** in meningococcal-vaccine naïve children for the solicited injection site reactions, including for Grade 3 injection site reactions; comparable effects between both vaccines in adolescents
  - Favorable effects for **MenACWY-D** vs **MenACYW-TT** in meningococcal-vaccine naïve adults for the solicited injection site reactions, with no associated increase in Grade 3 reactions; comparable effects between both vaccines in meningococcal-vaccine naïve adolescents and MCV4-primed adults and adolescents
- Rate differences for solicited reactions, particularly for injection site reactions, favored MPSV4 in older adults
  - The differences in composition between the vaccines (conjugated for **MenACYW-TT**, and non-conjugated for **MPSV4**) are expected to have contributed to the differences
  - No associated increase in Grade 3 injection site or systemic reactions

CONCLUSIONS

- **Across all age groups, the benefit risk profile of MenACYW-TT is considered favorable relative to the comparator meningococcal licensed vaccines in individuals ≥ 2 years.**
- There is strong evidence towards benefit of MenACYW-TT based on the robust and consistent immunogenicity across all the age groups with non-inferior immune response for all serogroups versus the control vaccines; and higher immune response for serogroups C, W, and Y (based on hSBA seroprotective levels).
- No safety concerns were identified; the most common reactions were non-serious, self-limited, and the same as those observed with the licensed MCV4s.
- Ease of administration of MenACYW-TT due to fully liquid presentation.

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