1. NAME OF THE MEDICINAL PRODUCT

MenQuadfi solution for injection
Meningococcal Group A, C, W and Y conjugate vaccine
MenACWY

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:

Neisseria meningitidis group A polysaccharide[1]	10 micrograms
Neisseria meningitidis group C polysaccharide[1]	10 micrograms
Neisseria meningitidis group W polysaccharide[1]	10 micrograms
Neisseria meningitidis group Y polysaccharide[1]	10 micrograms

[1]Conjugated to tetanus toxoid carrier protein 55 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The use of this vaccine should be in accordance with available official recommendations.

4.2 Posology and method of administration

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 5.1).
- Long-term antibody persistence data following vaccination with MenQuadfi are available up to 7 years after vaccination (see sections 4.4 and 5.1).
- There are no data available to indicate the need for or timing of a booster dose of MenQuadfi (see section 5.1).

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

Method of administration

For intramuscular injection only, preferably in the deltoid region or anterolateral thigh depending on the recipient's age and muscle mass.

For instructions on handling of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or after previous administration of the vaccine or a vaccine containing the same components.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

MenQuadfi should not be administered subcutaneously, intravascularly or intradermally.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable effects) and a clinical examination.

Hypersensitivity

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

Intercurrent illness

Vaccination should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, should not result in the deferral of vaccination.

Syncope

Syncope (fainting) and other anxiety-related reactions can occur following or even before any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent falling or injury and to manage syncope.

Thrombocytopenia and coagulation disorders

MenQuadfi should be given with caution to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

Protection

MenQuadfi will only protect against *Neisseria meningitidis* groups A, C, W, and Y. The vaccine will not protect against any other *Neisseria meningitidis* groups.

As with any vaccine, vaccination with MenQuadfi may not protect all vaccine recipients.

Waning of serum bactericidal antibody titres against serogroup A when using human complement in the assay (hSBA) has been reported for MenQuadfi and other quadrivalent meningococcal vaccines. The clinical relevance of this observation is unknown. However, if an individual is expected to be at particular risk of exposure to serogroup A and received a dose of MenQuadfi more than approximately one year previously, consideration may be given to administering a booster dose.

Lower hSBA geometric mean titres (GMTs) against serogroup A have been observed after a single dose of MenQuadfi was administered to toddlers who previously received serogroup C meningococcal conjugate vaccine (MenC-CRM) during infancy. Nevertheless, seroprotection rates were comparable between treatment groups (see section 5.1). The clinical relevance of this observation is unknown. This aspect might be considered for individuals at high risk for MenA infection who received MenC-CRM vaccine in their first year of life.

Immunodeficiency

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited (see section 4.5). Persons with familial complement deficiencies (for example, C5 or C3 deficiencies) and persons receiving treatments that inhibit terminal complement activation (for example, eculizumab) are at increased risk of invasive disease caused by *Neisseria meningitidis* groups A, C, W, and Y, even if they develop antibodies following vaccination with MenQuadfi. No data on immunocompromised patients are available.

Tetanus immunisation

Immunisation with MenQuadfi vaccine does not substitute for routine tetanus immunisation. Co-administration of MenQuadfi with a tetanus toxoid-containing vaccine does not impair the response to tetanus toxoid or impact the safety.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines

Injection sites on separate limbs and separate syringes must be used in the case of concomitant administration.

For ages 12-23 months, MenQuadfi can be co-administered with the measles-mumps-rubella vaccine (MMR) + varicella vaccine (V), combined diphtheria - tetanus - acellular pertussis (DTaP) vaccines, including combination DTaP vaccines with hepatitis B (HBV), inactivated poliovirus (IPV) or

Haemophilus influenzae type b (Hib) such as DTaP-IPV-HB-Hib (Hib conjugated to tetanus toxoid) vaccine and 13-valent pneumococcal polysaccharide conjugated vaccine (PCV-13).

There was no impact on the immune response to MenQuadfi when a meningococcal serogroup B vaccine was co-administered.

MenQuadfi can be administered concomitantly with PCV-13. Lower hSBA GMTs on day 30 post-dose for serogroup A have been observed when given concomitantly. The clinical relevance of this observation is unknown. As a precaution in children 12-23 months of age at high risk for serogroup A disease, consideration might be given for administration of MenQuadfi and PCV-13 vaccines separately.

For ages 10-17 years, MenQuadfi can be co-administered with diphtheria, tetanus, pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (Tdap), or Tdap and inactivated poliovirus vaccine (Tdap-IPV), and 4-valent human papillomavirus vaccine (recombinant, adsorbed) (4vHPV) or 9-valent HPV vaccine (9vHPV). However, the antibody responses to some of the antigens might be affected by the co-administration.

Meningococcal vaccine naïve children and adolescents aged 10-17 years had non inferior response for PT and lower antibody responses to FHA, PRN and FIM when Tdap vaccine was administered concomitantly with MenQuadfi and 4vHPV compared to co-administration with 4vHPV vaccine alone (immune response assessed after the full series of HPV was completed). The clinical implications of the observed pertussis antigen responses also observed with other quadrivalent meningococcal conjugate vaccines are unknown.

The co-administration of MenQuadfi with Tdap-IPV and 9vHPV in children and adolescents aged 10-17 years resulted in lower GMTs and seroresponse rates for serogroup A, lower GMTs for serogroup W, lower responses to inactivated polio types 1 and 3, diphtheria, and anti-HPV types 6 and 58 (immune response assessed after the first dose of 9vHPV) compared to when MenQuadfi was given sequentially with Tdap-IPV and 9vHPV. The clinical implication of the observed reduced titre responses is unclear. Consideration might be given for sequential administration of MenQuadfi with Tdap-IPV and 9vHPV (e.g. for children and adolescents at higher risk).

Concomitant vaccines should always be administered at separate injection sites and preferably contralateral.

Concomitant administration of MenQuadfi and other vaccines than those listed above has not been studied.

Use with systemic immunosuppressive medicinal products

It may be expected that in patients receiving immunosuppressive treatment an adequate immune response may not be elicited (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data on the use of MenQuadfi in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). MenQuadfi should be used during pregnancy only if the expected benefits for the mother outweigh the potential risks, including those for the foetus.

Breast-feeding

It is unknown whether MenQuadfi is excreted in human milk. MenQuadfi should only be used during breast-feeding when the possible advantages outweigh the potential risks.

Fertility

A developmental and reproductive toxicity study was performed in female rabbits. There were no effects on mating performances or female fertility. No study was conducted on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

MenQuadfi has no or negligible influence on the ability to drive and use machines.
However, some of the adverse reactions mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of a single dose of MenQuadfi in individuals 12 months of age and older was evaluated in clinical trials where 6 308 subjects received either a primary dose (N = 5 906) or a booster dose (N = 402) of MenQuadfi. This included 1 389 toddlers aged 12 through 23 months of age, 498 children aged 2 through 9 years, 2 289 children and adolescents aged 10 through 17 years, 1 684 adults aged 18 through 55 years, 199 older adults aged 56 through 64 years, and 249 elderly aged 65 years and older. Of these, 392 adolescents received MenQuadfi co-administered with Tdap and 4vHPV, and 589 toddlers received MenQuadfi co-administered with MMR+V (N = 189), DTaP-IPV-HB-Hib (N = 200) or PCV-13 (N = 200).

The most frequently reported adverse reactions within 7 days after vaccination with a single dose of MenQuadfi alone in toddlers 12 through 23 months of age were irritability (36.7%) and injection site tenderness (30.6%) and in ages 2 years and above were injection site pain (38.7%) and myalgia (30.5%). These adverse reactions were mostly mild or moderate in intensity.
Rates of adverse reactions after a booster dose of MenQuadfi in adolescents and adults at least 15 years of age were comparable to those seen in adolescents and adults who received a primary dose of MenQuadfi.

Rates of adverse reactions within 7 days following vaccination among toddlers were comparable when MMR+V were given concomitantly with or without MenQuadfi, and when DTaP-IPV-HB-Hib was given with or without MenQuadfi. Overall, the rates of adverse reactions were higher in toddlers who received PCV-13 given concomitantly with MenQuadfi (36.5%) than in toddlers who received PCV-13 alone (17.2%).

Children and adolescents aged 10-17 years of age were given either MenQuadfi alone (N = 171) or MenQuadfi concomitantly with Tdap-IPV and the first dose of 9vHPV (N = 116). The rates of injection site pain at the 9vHPV injection site were higher when given concomitantly with Tdap-IPV and MenQuadfi (83.6%) compared to when Tdap-IPV and 9vHPV were given without MenQuadfi (67.3%). Overall, rates and intensity of adverse reactions were comparable between these two groups.

Adolescents and adults 13-26 years of age primed with MenQuadfi 3-6 years previously received MenQuadfi co-administered with meningococcal serogroup B vaccine (MenB), MenB (recombinant, adsorbed) (N = 93) or MenB (rDNA, component, adsorbed) (N = 92). Rates and intensity of systemic adverse reactions within 7 days following vaccination tended to be higher when MenQuadfi was given concomitantly with MenB vaccine than when MenQuadfi was given alone. The most common solicited systemic adverse reaction was myalgia, of mild intensity, which was experienced more frequently in adolescents and adults who received MenQuadfi and MenB vaccine concomitantly (MenB [recombinant, adsorbed], 65.2%; or MenB [rDNA, component, adsorbed], 63%) compared to those who received MenQuadfi alone (32.8%).

Tabulated list of adverse reactions

The following adverse reactions, as listed below, have been identified from clinical trials conducted with MenQuadfi when given alone to subjects 2 years of age and older and post-marketing surveillance. The safety profile observed in toddlers aged 12 through 23 months is presented in the paediatric population section.
The adverse reactions are listed by MedDRA system organ class and by frequency according to the following frequency categories:
Very common (≥ 1/10);
Common (≥ 1/100 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10 000 to <1/1 000);
Very rare (< 1/10 000);
Not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions following administration of MenQuadfi from clinical trials and post-marketing surveillance in subjects 2 years of age and above

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Lymphadenopathy
Immune system disorders	Very rare	Anaphylaxis
	Not known	Hypersensitivity
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
	Not known	Febrile convulsions, seizures
Gastrointestinal disorders	Uncommon	Vomiting, nausea
	Rare	Diarrhoea, stomach pain
Skin and subcutaneous tissue disorders	Rare	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Rare	Pain in extremity
General disorders and administration site conditions	Very common	Malaise
		Injection site pain
	Common	Fever
		At the injection site: swelling, erythema

	Uncommon	Fatigue
		At the injection site: pruritus, warmth, bruising, rash
	Rare	Chills, axillary pain
		At the injection site: induration

Paediatric population

The safety profile of MenQuadfi in children and adolescents 2 through 17 years of age was generally comparable to that in adults. Injection site erythema and swelling at the MenQuadfi injection site were reported more frequently in children 2 through 9 years of age (very common) than in the older age groups.

In toddlers 12 through 23 months of age, injection site erythema and swelling (very common) at the MenQuadfi injection site, vomiting (common) and diarrhoea (common), were reported more frequently than in the older age groups. The following additional reactions, as listed below in Table 2, have been reported following administration of MenQuadfi in toddlers during clinical trials and post-marketing surveillance:

Table 2: Adverse reactions following administration of MenQuadfi from clinical trials and post-marketing surveillance in subjects 12 months through 23 months

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorders	Very rare	Anaphylaxis
	Not known	Hypersensitivity
Metabolic and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Irritability
	Uncommon	Insomnia
Nervous system disorders	Very common	Drowsiness
	Not known	Febrile convulsions, seizures
Gastrointestinal disorders	Common	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria
General disorders and administration site conditions	Very common	Abnormal crying
		At the injection site: tenderness/pain, erythema, swelling
	Common	Fever
	Uncommon	At the injection site: pruritus, induration, bruising, rash

Older population

Overall, within 7 days after vaccination with a single dose of MenQuadfi, the same injection site and systemic adverse reactions were observed in older (≥ 56 years of age) and younger adults (18 through 55 years old) but at lower frequencies; except for injection site pruritus, which was more frequent (common) in older adults. These adverse reactions mostly were mild or moderate in intensity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdose with MenQuadfi is unlikely due to its presentation as a single dose vial. In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: meningococcal vaccines, ATC code: J07AH08

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.

Immunogenicity

The immunogenicity of a single dose of MenQuadfi for primary vaccination in toddlers (12-23 months of age), children and adolescents (2-17 years of age), adults (18-55 years of age) and older adults (56 years and above) was assessed in six pivotal trials and in two additional trials in toddlers (12-23 months of age) and children and adolescents (10-17 years of age). The immunogenicity of a single dose of MenQuadfi when used as a booster vaccination was assessed in one pivotal trial (subjects 15-55 years of age) and in four additional trials: two in children 3 years and 5 years after primary vaccination as toddlers 12 through 23 months of age, one in adolescents and adults 3-6 years after primary vaccination, and one in older adults 3, 5 and 6-7 years after primary vaccination at ≥ 56 years of age. In addition, clinical data on the persistence of antibody response from at least 3 years and up to 7 years after primary vaccination with MenQuadfi are available in these additional trials.

Primary immunogenicity analyses were conducted by measuring serum bactericidal activity (SBA) using human serum as the source of exogenous complement (hSBA). Rabbit complement (rSBA) data are available in subsets in all age groups and generally follows the trends observed with human complement (hSBA) data. In addition, all subjects were assessed for primary immunogenicity measured by hSBA and rSBA for serogroup C in MEQ00065 study [NCT03890367].

Immunogenicity in toddlers 12 to 23 months of age

Immunogenicity in subjects 12 through 23 months of age was evaluated in three clinical trials (MET51 [NCT02955797], MET57 [NCT03205371] and MEQ00065 [NCT03890367]).

MET51 was conducted in subjects who were either meningococcal vaccine naïve or had been primed with monovalent meningococcal C conjugate vaccines in their first year of life (see table 3).

Table 3: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-TT vaccine 30 days after vaccination of meningococcal vaccine naïve subjects only or combined (naïve + MenC primed) subjects 12 through 23 months of age (study MET51*)

Endpoint by Serogroup	MenQuadfi (95% CI) Naïve	MenACWY-TT (95% CI) Naïve	MenQuadfi (95% CI) Combined (Naïve + MenC Primed)	MenACWY-TT (95% CI) Combined (Naïve + MenC Primed)
A	N = 293	N = 295	N = 490	N = 393-394
% ≥ 1:8 (Seroprotection)**	90.8 (86.9; 93.8)	89.5 (85.4; 92.7)	90.4 (87.4; 92.9)	91.6 (88.4; 94.2)
% Seroresponse	76.8 (71.5; 81.5)	72.5 (67.1; 77.6)	76.5 (72.5; 80.2)	77.1 (72.6; 81.2)
hSBA GMT	28.7 (25.2; 32.6)	28.0 (24.4; 32.1)	29.9 (26.9; 33.2)	34.5 (30.5; 39.0)
C	N = 293	N = 295	N = 489	N = 393-394
% ≥ 1:8 (Seroprotection)**	99.3 (97.6; 99.9)	81.4 (76.4; 85.6)	99.2 (97.9; 99.8)	85.5 (81.7; 88.9)
% Seroresponse	98.3 (96.1; 99.4)	71.5 (66.0; 76.6)	97.1 (95.2; 98.4)	77.4 (72.9; 81.4)
hSBA GMT	436 (380; 500)	26.4 (22.5; 31.0)	880 (748; 1 035)	77.1 (60.7; 98.0)
W	N = 293	N = 296	N = 489	N = 393-394
% ≥ 1:8 (Seroprotection)**	83.6 (78.9; 87.7)	83.4 (78.7; 87.5)	84.9 (81.4; 87.9)	84.0 (80.0; 87.5)
% Seroresponse	67.6 (61.9; 72.9)	66.6 (60.9; 71.9)	70.8 (66.5; 74.8)	68.4 (63.6; 73.0)
hSBA GMT	22.0 (18.9; 25.5)	16.4 (14.4; 18.6)	24.4 (21.8; 27.5)	17.7 (15.8; 19.8)
Y	N = 293	N = 296	N = 488-490	N = 394-395
% ≥ 1:8 (Seroprotection)**	93.2 (89.7; 95.8)	91.6 (87.8; 94.5)	94.3 (91.8; 96.2)	91.6 (88.5; 94.2)
% Seroresponse	81.9 (77.0; 86.1)	79.1 (74.0; 83.5)	84.8 (81.3; 87.9)	78.9 (74.6; 82.9)
hSBA GMT	38.0 (33.0; 43.9)	32.2 (28.0; 37.0)	41.7 (37.5; 46.5)	31.9 (28.4; 36.0)

* Clinical trial identifier NCT02955797
N: number of subjects in the per-protocol analysis set with valid serology results. The number of subjects varies depending on the timepoints and serogroup.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met

Response in subjects previously vaccinated with MenC conjugate vaccines in their first year of life
The majority of monovalent meningococcal C conjugate vaccine primed toddlers (12 through 23 months of age) in study MET51 (NCT02955797) had hSBA titres ≥ 1:8 in the MenQuadfi group (N = 198) (≥ 86.7%) and in MenACWYTT group (N = 99) (≥ 85.7%) at D30 post-vaccination. These toddlers received during their infancy MenCTT or MenCCRM vaccines. Post-vaccination seroprotection rates

were comparable between MenQuadfi and MenACWY-TT for all serogroups regardless of the priming background.

In MenC-CRM primed subjects the GMTs for serogroup A were lower in the MenQuadfi group (N = 49) than in the MenACWY-TT group (N = 25) [12.0 (8.23; 17.5) vs 42.2 (25.9; 68.8)]. After administration of MenQuadfi seroprotection rates (hSBA titres ≥ 1:8) for subjects primed with MenC-CRM were lower but still comparable for serogroups A and W compared with those in the MenACWY-TT group [A: 68.8% (53.7; 81.3) vs 96.0% (79.6; 99.9); W: 68.1% (52.9; 80.9) vs 79.2% (57.8; 92.9)]. The rates for serogroup Y were higher but still comparable with those in the MenACWY-TT group [95.8% (85.7; 99.5) vs 80.0% (59.3; 93.2)]. The rates for serogroup C were comparable in both groups [95.7% (85.5; 99.5) vs 92.0% (74.0; 99.0)]. The clinical relevance of these results is unknown. This aspect might be considered for individuals at high risk for MenA infection who received MenC-CRM vaccine in their first year of life.

MET57 (NCT03205371) was conducted in meningococcal vaccine naïve toddlers 12 through 23 months of age to assess the immunogenicity of the concomitant administration of MenQuadfi with paediatric vaccines (MMR+V, DTaP-IPV-HB-Hib or PCV-13). Overall, the post-vaccination hSBA seroprotection rates in subjects who received MenQuadfi was high for all serogroups (between 88.9% and 100%). Seroresponse and seroprotection rates for serogroup A were comparable when MenQuadfi was co-administered with PCV-13 and alone (56.1%, [95% CI 48.9; 63.2] and 83.7% [95% CI 77.7; 88.6] vs 71.9% [95%CI 61.8; 80.6] and 90.6% [95%CI 82.9; 95.6]). There were differences in the hSBA GMTs for serogroup A when MenQuadfi was co-administered with PCV-13 (N = 196) compared with MenQuadfi administered alone (N = 96) (24.6 [95%CI 20.2; 30.1] and 49.0 [95%CI 36.8; 65.3]).) The clinical relevance of these results is unknown but this observation might be taken into consideration for individuals at high risk for MenA infection and consequently vaccinations with MenQuadfi and PCV13 might be performed separately.

MEQ00065 (NCT03890367) study was conducted in meningococcal vaccine naïve toddlers 12 through 23 months of age to assess the immunogenicity of serogroup C using hSBA and rSBA assays following administration of a single dose of MenQuadfi compared to MenACWY-TT or to MenC-TT.

Superiority of MenQuadfi was demonstrated in comparison to MenACWY-TT vaccine for the hSBA seroprotection rate and hSBA and rSBA GMTs to meningococcal serogroup C. Non-inferiority was demonstrated for the rSBA seroprotection rate to meningococcal serogroup C.

Superiority of MenQuadfi was also demonstrated in comparison to MenC-TT vaccine for the rSBA and hSBA GMTs to meningococcal serogroup C and non-inferiority was demonstrated for the rSBA and hSBA seroprotection rates to meningococcal serogroup C (see table 4).

Table 4: Comparison of hSBA and rSBA bactericidal antibody responses for serogroup C to MenQuadfi, MenACWY-TT and MenC-TT vaccines 30 days after vaccination of meningococcal vaccine naïve subjects 12 through 23 months of age (study MEQ00065*)

Endpoints	MenQuadfi (95% CI)	MenACWY-TT (95% CI)	MenC-TT (95% CI)	MenQuadfi (95% CI)	MenACWY-TT (95% CI)	MenC-TT (95% CI)
	hSBA			rSBA		
	N = 214	N = 211	N = 216	N = 213	N = 210	N = 215
% ≥ 1:8 (Seroprotection)	99.5[#§] (97.4; 100)	89.1 (84.1; 93.0)	99.5 (97.4; 100)	100[¶] (98.3; 100)	94.8 (90.8; 97.4)	100 (98.3; 100)
% Seroresponse	99.5 (97.4; 100)	83.4 (77.7; 88.2)	99.1 (96.7; 99.9)	99.5 (97.4; 100)	92.9 (88.5; 95.9)	99.5 (97.4; 100)
GMTs	515[$] (450; 591)	31.6 (26.5; 37.6)	227 (198; 260)	2 143[¥] (1 870; 2 456)	315 (252; 395)	1 624 (1 425; 1 850)

* Clinical trial identifier NCT03890367
# superiority of MenQuadfi demonstrated versus MenACWY-TT (hSBA seroprotection rates)
§ non inferiority of MenQuadfi demonstrated versus MenC-TT (hSBA seroprotection rates)
$ superiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (hSBA GMTs)
¶ non inferiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (rSBA seroprotection rates)
¥ superiority of MenQuadfi demonstrated versus MenACWY-TT and MenC-TT (rSBA GMTs)
N: number of subjects in the per-protocol analysis set with valid serology results
95% CI of the single proportion calculated from the exact binomial method

Immunogenicity in children 2 through 9 years of age

Immunogenicity in subjects 2 through 9 years of age was evaluated in study MET35 (NCT03077438) (stratified by ages 2 through 5 and 6 through 9 years) comparing seroresponses following administration of either MenQuadfi or MenACWY-CRM.

Overall, for subjects 2 through 9 years of age, immune non-inferiority, based on hSBA seroresponse, was demonstrated for MenQuadfi as compared to MenACWY-CRM for all four serogroups.

Table 5: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-CRM 30 days after vaccination in meningococcal vaccine naïve subjects 2 through 5 years and 6 through 9 years of age (study MET35*)

	2-5 years of age		6-9 years of age	
Endpoint by Serogroup	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**	**MenQuadfi (95% CI)**	**MenACWY-CRM (95% CI)**
A	N = 227-228	N = 221	N = 228	N = 237
% ≥ 1:8 (Seroprotection)	84.6 (79.3; 89.1)	76.5 (70.3; 81.9)	88.2 (83.2; 92.0)	81.9 (76.3; 86.5)
% Seroresponse	52.4 (45.7; 59.1)	44.8 (38.1; 51.6)	58.3 (51.6; 64.8)	50.6 (44.1; 57.2)
hSBA GMT	21.6 (18.2; 25.5)	18.9 (15.5; 23.0)	28.4 (23.9; 33.8)	26.8 (22.0; 32.6)
C	N = 229	N = 222-223	N = 229	N = 236
% ≥ 1:8 (Seroprotection)	97.4 (94.4; 99.0)	64.6 (57.9; 70.8)	98.3 (95.6; 99.5)	69.5 (63.2; 75.3)
% Seroresponse	94.3 (90.5; 96.9)	43.2 (36.6; 50.0)	96.1 (92.7; 98.2)	52.1 (45.5; 58.6)
hSBA GMT	208 (175; 246)	11.9 (9.79; 14.6)	272 (224; 330)	23.7 (18.2; 31.0)
W	N = 229	N = 222	N = 229	N = 237
% ≥ 1:8 (Seroprotection)	90.8 (86.3; 94.2)	80.6 (74.8; 85.6)	98.7 (96.2; 99.7)	91.6 (87.3; 94.8)
% Seroresponse	73.8 (67.6; 79.4)	61.3 (54.5; 67.7)	83.8 (78.4; 88.4)	66.7 (60.3; 72.6)
hSBA GMT	28.8 (24.6; 33.7)	20.1 (16.7; 24.2)	48.9 (42.5; 56.3)	33.6 (28.2; 40.1)
Y	N = 229	N = 222	N = 229	N = 237
% ≥ 1:8 (Seroprotection)	97.8 (95.0; 99.3)	86.9 (81.8; 91.1)	99.1 (96.9; 99.9)	94.5 (90.8; 97.0)
% Seroresponse	88.2 (83.3; 92.1)	77.0 (70.9; 82.4)	94.8 (91.0; 97.3)	81.4 (75.9; 86.2)
hSBA GMT	49.8 (43.0; 57.6)	36.1 (29.2; 44.7)	95.1 (80.2; 113)	51.8 (42.5; 63.2)

* Clinical trial identifier NCT03077438
N: number of subjects in the per-protocol analysis set with valid serology results. The number of subjects varies depending on the timepoints and serogroup.
95% CI of the single proportion calculated from the exact binomial method.

Immunogenicity in children and adolescents 10 through 17 years of age

Immunogenicity in subjects aged 10 through 17 years of age was evaluated in three trials comparing seroresponses following administration of MenQuadfi compared to either MenACWY-CRM (MET50

[NCT02199691]) or MenACWY-DT (MET43 [NCT02842853]) or comparing seroprotection following administration of MenQuadfi compared to MenACWY-TT (MEQ00071) [NCT04490018]).

MET50 was conducted in meningococcal vaccine naïve subjects and seroresponse was evaluated following administration with either MenQuadfi alone, MenACWY-CRM alone, MenQuadfi co-administered with Tdap and 4vHPV or Tdap and 4vHPV alone.

Table 6: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-CRM 30 days after vaccination in meningococcal vaccine naïve subjects 10 through 17 years of age (study MET50*)

Endpoint by Serogroup	MenQuadfi (95% CI)		MenACWY-CRM (95% CI)	
A	N = 463		N = 464	
% ≥ 1:8 (Seroprotection)	93.5	(90.9; 95.6)	82.8	(79.0; 86.1)
% Seroresponse**#	75.6	(71.4; 79.4)	66.4	(61.9; 70.7)
hSBA GMT	44.1	(39.2; 49.6)	35.2	(30.3; 41.0)
C	N = 462		N = 463	
% ≥ 1:8 (Seroprotection)	98.5	(96.9; 99.4)	76.0	(71.9; 79.8)
% Seroresponse**#	97.2	(95.2; 98.5)	72.6	(68.3; 76.6)
hSBA GMT	387	(329; 456)	51.4	(41.2; 64.2)
W	N = 463		N = 464	
% ≥ 1:8 (Seroprotection)	99.1	(97.8; 99.8)	90.7	(87.7; 93.2)
% Seroresponse**#	86.2	(82.7; 89.2)	66.6	(62.1; 70.9)
hSBA GMT	86.9	(77.8; 97.0)	36.0	(31.5; 41.0)
Y	N = 463		N = 464	
% ≥ 1:8 (Seroprotection)	97.2	(95.2; 98.5)	83.2	(79.5; 86.5)
% Seroresponse**#	97.0	(95.0; 98.3)	80.8	(76.9; 84.3)
hSBA GMT	75.7	(66.2; 86.5)	27.6	(23.8; 32.1)

* Clinical trial identifier NCT02199691
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Post-vaccination hSBA titres ≥1:8 for subjects with pre-vaccination hSBA titres < 1:8 or at least a 4-fold increase in hSBA titres from pre- to post-vaccination for subjects with pre-vaccination hSBA titres ≥ 1:8
# Non-inferiority criterion met.

Study MET43 was performed to evaluate the immunogenicity of MenQuadfi compared to MenACWY-DT in children, adolescents and adults (10 through 55 years of age).

Table 7: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after vaccination in meningococcal vaccine naïve subjects 10 through 17 years of age (study MET43*)

Endpoint by Serogroup	MenQuadfi (95% CI)		MenACWY-DT (95% CI)	
A	N = 1 097		N = 300	
% ≥ 1:8 (Seroprotection)	96.2	(94.9; 97.2)	89.0	(84.9; 92.3)
% Seroresponse**	74.0	(71.3; 76.6)	55.3	(49.5; 61.0)
hSBA GMT	78	(71.4; 85.2)	44.2	(36.4; 53.7)
C	N = 1 097-1 098		N = 300	
% ≥ 1:8 (Seroprotection)	98.5	(97.5; 99.1)	74.7	(69.3; 79.5)
% Seroresponse**	95.6	(94.2; 96.8)	53.3	(47.5; 59.1)
hSBA GMT	504	(456; 558)	44.1	(33.7; 57.8)
W	N = 1 097		N = 300	
% ≥ 1:8 (Seroprotection)	98.3	(97.3; 99.0)	93.7	(90.3; 96.1)
% Seroresponse**	84.5	(82.2; 86.6)	72.0	(66.6; 77.0)
hSBA GMT	97.2	(88.3; 107)	59.2	(49.1; 71.3)
Y	N = 1 097		N = 300	
% ≥ 1:8 (Seroprotection)	99.1	(98.3; 99.6)	94.3	(91.1; 96.7)
% Seroresponse**	95.6	(94.2; 96.8)	85.7	(81.2; 89.4)
hSBA GMT	208	(189; 228)	80.3	(65.6; 98.2)

* Clinical trial identifier NCT02842853
N: number of subjects in the per-protocol analysis set with valid serology results. The number of subjects varies depending on the timepoints and serogroup.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

MEQ00071 was conducted in subjects who were either meningococcal vaccine naïve or had been primed with MenC vaccines before two years of age. Seroprotection was evaluated 30 days following administration with either MenQuadfi alone, MenACWY-TT alone, or MenQuadfi co-administrated with Tdap-IPV and 9vHPV.

Table 8: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-TT 30 days after vaccination in meningococcal vaccine naïve and MenC primed subjects 10 through 17 years of age (study MEQ00071*)

Endpoint by Serogroup	MenQuadfi (95% CI)	MenACWY-TT (95% CI)
A	N = 158-159	N = 159-160
% ≥ 1:8 (Seroprotection)**	97.5 (93.7; 99.3)	92.5 (87.3; 96.1)
% Seroresponse	88.0 (81.9; 92.6)	75.5 (68.0; 81.9)
hSBA GMT	78.2 (64.6; 94.7)	56.0 (44.0; 71.2)
C	N = 158-159	N = 160-161
% ≥ 1:8 (Seroprotection)**	100 (97.7; 100)	95.0 (90.4; 97.8)
% Seroresponse	99.4 (96.5; 100)	88.8 (82.8; 93.2)
hSBA GMT	2 294 (1 675; 3 142)	619 (411; 931)
W	N = 159	N = 159
% ≥ 1:8 (Seroprotection)**	100 (97.7; 100)	98.8 (95.6; 99.8)
% Seroresponse	93.1 (88.0; 96.5)	81.4 (74.5; 87.1)
hSBA GMT	134 (109; 164)	64.6 (52.5; 79.4)
Y	N = 158	N = 160
% ≥ 1:8 (Seroprotection)**	99.4 (96.5; 100)	98.1 (94.6; 99.6)
% Seroresponse	98.7 (95.5; 99.8)	88.1 (82.1; 92.7)
hSBA GMT	169 (141; 202)	84.8 (68.3; 105)

* Clinical trial identifier NCT04490018
N: number of subjects in the per-protocol analysis set with valid serology results. The number of subjects varies depending on the timepoints and serogroup.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

In an exploratory analysis in a non-random subset of participants (N = 60), the immune response and protection rates were measured 6 and 30 days following co-administration of MenQuadfi with Tdap-IPV and 9vHPV. The proportion of subjects with seroprotection for serogroup A did not increase within 6 days, whereas most of the subjects had seroprotection against serogroups C, W and Y (> 94%). After 30 days, protection rates in this subset were comparable to the full trial population reported in table 8.

Response in subjects according to MenC vaccination status
The immunogenicity of serogroup C following administration of a single dose of MenQuadfi compared to a single dose of MenACWY-TT was assessed in both meningococcal vaccine naïve and MenC primed (before two years of age) subjects (MEQ00071). Overall, the post vaccination seroresponse and hSBA GMTs against serogroup C were higher in meningococcal vaccine naive subjects who received MenQuadfi than those who received MenACWY-TT, with seroprotection rates also trending higher. No differences in antibody response were observed in MenC primed subjects between groups.

Immunogenicity in adults 18 through 55 years of age

Immunogenicity in subjects from 18 through 55 years of age was evaluated in study MET43 (NCT02842853) comparing MenQuadfi to MenACWY-DT.

Table 9: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after vaccination in meningococcal vaccine naïve subjects 18 through 55 years of age (study MET43*)

Endpoint by Serogroup	**MenQuadfi (95% CI)**		**MenACWY-DT (95% CI)**	
A	N = 1 406-1 408		N = 293	
% ≥ 1:8 (Seroprotection)	93.5	(92.1; 94.8)	88.1	(83.8; 91.5)
% Seroresponse**	73.5	(71.2; 75.8)	53.9	(48.0; 59.7)
hSBA GMT	106	(97.2; 117)	52.3	(42.8; 63.9)
C	N = 1 406-1 408		N = 293	
% ≥ 1:8 (Seroprotection)	93.5	(92.0; 94.7)	77.8	(72.6; 82.4)
% Seroresponse**	83.4	(81.4; 85.3)	42.3	(36.6; 48.2)
hSBA GMT	234	(210; 261)	37.5	(29.0; 48.5)
W	N = 1 408-1 410		N = 293	
% ≥ 1:8 (Seroprotection)	94.5	(93.2; 95.7)	80.2	(75.2; 84.6)
% Seroresponse**	77.0	(74.7; 79.2)	50.2	(44.3; 56.0)
hSBA GMT	75.6	(68.7; 83.2)	33.2	(26.3; 42.0)
Y	N = 1 408-1 410		N = 293	
% ≥ 1:8 (Seroprotection)	98.6	(97.8; 99.1)	81.2	(76.3; 85.5)
% Seroresponse**	88.1	(86.3; 89.8)	60.8	(54.9; 66.4)
hSBA GMT	219	(200; 239)	54.6	(42.3; 70.5)

* Clinical trial identifier NCT02842853
N: number of subjects in the per-protocol analysis set with valid serology results. The number of subjects varies depending on the timepoints and serogroup.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Immunogenicity in adults 56 years of age and older

Immunogenicity in adults ≥ 56 years of age (mean 67.1 years, range 56.0–97.2 years) was assessed in study MET49 (NCT02842866) comparing the immunogenicity of MenQuadfi to MenACWY polysaccharide vaccine.

Table 10: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY polysaccharide in meningococcal vaccine naïve in subjects 56 years of age and older 30 days after vaccination (study MET49*)

Endpoint by Serogroup	MenQuadfi (95% CI)		MenACWY polysaccharide (95% CI)	
A	N = 433		N = 431	
% ≥ 1:8 (Seroprotection)	89.4	(86.1; 92.1)	84.2	(80.4; 87.5)
% Seroresponse**	58.2	(53.4; 62.9)	42.5	(37.7; 47.3)
hSBA GMT	55.1	(46.8; 65.0)	31.4	(26.9; 36.7)
C	N = 433		N = 431	
% ≥ 1:8 (Seroprotection)	90.1	(86.9; 92.7)	71.0	(66.5; 75.2)
% Seroresponse**	77.1	(72.9; 81.0)	49.7	(44.8; 54.5)
hSBA GMT	101	(83.8; 123)	24.7	(20.7; 29.5)
W	N = 433		N = 431	
% ≥ 1:8 (Seroprotection)	77.4	(73.1; 81.2)	63.1	(58.4; 67.7)
% Seroresponse**	62.6	(57.8; 67.2)	44.8	(40.0; 49.6)
hSBA GMT	28.1	(23.7; 33.3)	15.5	(13.0; 18.4)
Y	N = 433		N = 431	
% ≥ 1:8 (Seroprotection)	91.7	(88.7; 94.1)	67.7	(63.1; 72.1)
% Seroresponse**	74.4	(70.0; 78.4)	43.4	(38.7; 48.2)
hSBA GMT	69.1	(58.7; 81.4)	21.0	(17.4; 25.3)

* Clinical trial identifier NCT02842866
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

Persistence of immune response and MenQuadfi booster response

Antibody persistence following primary vaccination in toddlers, adolescents and young adults, and older adults was assessed from at least 3 years and up to 7 years after primary vaccination. The immunogenicity of a MenQuadfi booster dose was also assessed.

Persistence of immune response and MenQuadfi booster response in children 4 through 5 years of age

MET62 (NCT03476135) evaluated the antibody persistence of a primary dose, immunogenicity and safety of a booster dose of MenQuadfi in children 4 through 5 years of age. These children were primed with a single dose of MenQuadfi or MenACWY-TT 3 years before as part of the phase II study MET54 when they were 12 through 23 months old. The antibody persistence prior to the MenQuadfi booster dose and the booster immune response were assessed according to the vaccine (MenQuadfi or MenACWY-TT) children had received 3 years ago (see Table 11).

For all serogroups, hSBA GMTs were higher at D30 post-primary dose than at 3 years (3Y) post-primary dose (D0 pre-booster) for MenQuadfi or MenACWY-TT. The 3Y post-primary (D0 pre-booster) GMTs were higher than the pre-primary GMTs, indicative of long-term persistence of immune response.

After the booster dose, seroprotection rates were nearly 100% for all serogroups in children primed with MenQuadfi.

Table 11: Comparison of bactericidal antibody response 30 days after booster vaccination, and persistence in children (4 through 5 years) primed with MenQuadfi or MenACWY - TT 3 years before in study MET54* – (study MET62)**

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)			MenQuadfi Booster in MenACWY-TT primed (95% CI)			MenQuadfi Booster in MenQuadfi primed + MenACWY - TT primed (95% CI)		
	Persistence[#] N = 42		Booster[$] N = 40	Persistence[#] N = 49		Booster[$] N = 44	Persistence[#] N = 91		Booster[$] N = 84
	D30- Post-primary dose	3Y Post-primary dose (D0 - Pre-booster dose)		D30 - Post-primary dose	3Y Post-primary dose (D0 - Pre-booster dose)		D30 - Post-primary dose	3Y Post-primary dose (D0 - Pre-booster dose)	
A									
% ≥ 1:8 (Seroprotection)	97.6 (87.4; 99.9)	66.7 (50.5; 80.4)	100 (91.2; 100)	89.8 (77.8; 96.6)	83.7 (70.3; 92.7)	100 (92.0; 100)	93.4 (86.2; 97.5)	75.8 (65.7; 84.2)	100 (95.7; 100)
% Seroresponse	-	-	100 (91.2; 100)	-	-	95.5 (84.5; 99.4)	-	-	97.6 (91.7; 99.7)
hSBA GMT	83.3 (63.9; 109)	11.9 (8.11; 17.4)	763 (521; 1 117)	49.6 (32.1; 76.7)	14.7 (10.7; 20.2)	659 (427; 1 017)	63.0 (48.3; 82.2)	13.3 (10.5; 17.0)	706 (531; 940)
C									
% ≥ 1:8 (Seroprotection)	100 (91.6; 100)	100 (91.6; 100)	100 (91.2; 100)	87.8 (75.2; 95.4)	57.1 (42.2; 71.2)	100 (92.0; 100)	93.4 (86.2; 97.5)	76.9 (66.9; 85.1)	100 (95.7; 100)
% Seroresponse	-	-	95.0 (83.1; 99.4)	-	-	100 (92.0; 100)	-	-	97.6 (91.7; 99.7)
hSBA GMT	594 (445; 793)	103 (71.7; 149)	5 894 (4 325; 8 031)	29.4 (20.1; 43.1)	11.6 (7.28; 18.3)	1 592 (1 165; 2 174)	118 (79.3; 175)	31.8 (21.9; 46.1)	2 969 (2 293; 3 844)
W									
% ≥ 1:8 (Seroprotection)	100 (91.6; 100)	97.6 (87.4; 99.9)	97.5 (86.8; 99.9)	95.9 (86.0; 99.5)	83.7 (70.3; 92.7)	100 (92.0; 100)	97.8 (92.3; 99.7)	90.1 (82.1; 95.4)	98.8 (93.5; 100)
% Seroresponse	-	-	97.5 (86.8; 99.9)	-	-	100 (92.0; 100)	-	-	98.8 (93.5; 100)
hSBA GMT	71.8 (53.3; 96.7)	50.0 (35.9; 69.5)	2 656 (1 601; 4 406)	40.1 (30.6; 52.6)	21.2 (14.6; 30.9)	3 444 (2 387; 4 970)	52.5 (42.7; 64.5)	31.5 (24.2; 41.0)	3 043 (2 248; 4 120)
Y									
% ≥ 1:8 (Seroprotection)	100 (91.6; 100)	97.6 (87.4; 99.9)	100 (91.2; 100)	100 (92.7; 100)	89.8 (77.8; 96.6)	100 (92.0; 100)	100 (96.0; 100)	93.4 (86.2; 97.5)	100 (95.7; 100)
% Seroresponse	-	-	100 (91.2; 100)	-	-	100 (92.0; 100)	-	-	100 (95.7; 100)

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)			MenQuadfi Booster in MenACWY-TT primed (95% CI)			MenQuadfi Booster in MenQuadfi primed + MenACWY - TT primed (95% CI)		
hSBA GMT	105 (73.9; 149)	32.5 (24.8; 42.7)	2 013 (1 451; 2 792)	75.8 (54.2; 106)	18.2 (13.8; 24.0)	2 806 (2 066; 3 813)	88.1 (69.3; 112)	23.8 (19.4; 29.1)	2 396 (1 919; 2 991)

* Clinical trial identifier MET54 – NCT03205358. The trial was conducted in toddlers 12-23 months old.
** Clinical trial identifier MET62 – NCT03476135
$ N calculated using per protocol analysis set (PPAS) with valid serology results; booster dose=D30 MET62.
# N calculated using full analysis set for persistence (FASP) with valid serology results; D30 post-primary dose=D30 MET54, 3Y Post-primary (D0 pre-booster dose)=D0 MET62.
Vaccine seroresponse: titre is < 1:8 at baseline with post-vaccination titre ≥ 1:16 or titre is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
95% CI of the single proportion calculated from the exact binomial method.

Persistence of immune response and MenQuadfi booster response in children 6 through 7 years of age

MEQ00073 (NCT04936685) evaluated the antibody persistence of a primary dose, immunogenicity and safety of a booster dose of MenQuadfi in children 6 through 7 years of age who had previously received a primary dose of MenQuadfi 5 years earlier as part of study MET51 when they were 12 through 23 months of age (see Table 12).

For all serogroups, the 5Y post-primary (pre-booster) GMTs were higher than the pre-primary GMTs, indicative of persistence of immune response.

After the booster dose, seroprotection rates were nearly 100% for all serogroups in children primed with MenQuadfi (98.9%, 97.7%, 100%, and 100% for serogroups A, C, W, and Y, respectively).

Table 12: Comparison of bactericidal antibody response 30 days after booster vaccination with MenQuadfi, and persistence in children (6 through 7 years) primed with MenQuadfi 5 years before in study MET51[*] – (study MEQ00073[**])

	MenQuadfi Booster in MenQuadfi primed (95% CI)		
	Persistence[#]		Booster[$] N = 88
Endpoint by Serogroup	**D30 – Post-primary dose N = 208**	**5Y Post-primary dose (D0 – Pre-booster dose) N = 208**	
A			
% ≥ 1:8 (Seroprotection)	90.4 (85.5; 94.0)	76.0 (69.6; 81.6)	98.9 (93.8; 100)
% Seroresponse	-	-	93.2 (85.7; 97.5)
hSBA GMT	28.9 (24.5; 34.0)	14.5 (12.0; 17.5)	1 143 (820; 1 594)
C			
% ≥ 1:8 (Seroprotection)	99.5 (97.4; 100)	85.1 (79.5; 89.6)	97.7 (92.0; 99.7)
% Seroresponse	-	-	97.7 (92.0; 99.7)
hSBA GMT	1 315 (1 002; 1 724)	37.6 (29.8; 47.4)	8 933 (6 252; 12 764)
W			
% ≥ 1:8 (Seroprotection)	83.7 (77.9; 88.4)	84.6 (79.0; 89.2)	100 (95.9; 100)
% Seroresponse	-	-	98.9 (93.8; 100)
hSBA GMT	25.7 (21.3; 31.0)	30.7 (24.9; 37.9)	8 656 (6 393; 11 721)
Y			
% ≥ 1:8 (Seroprotection)	92.3 (87.8; 95.5)	68.8 (62.0; 75.0)	100 (95.9; 100)
% Seroresponse	-	-	98.9 (93.8; 100)
hSBA GMT	41.6 (35.0; 49.6)	12.7 (10.5; 15.4)	3 727 (2 908; 4 776)

*Clinical trial identifier MET51 – NCT02955797. The trial was conducted in toddlers 12-23 months old.
**Clinical trial identifier MEQ00073 – NCT04936685
N calculated using full analysis set for persistence (FASP) with valid serology results; D30 post-primary dose = D30 MET51, 5Y Post-primary dose (D0 pre-booster dose)=D0 MEQ00073.
$ N calculated using per protocol analysis set (PPAS1) with valid serology results; Booster = D30 MEQ00073 5 years after primary vaccination in MET51.
Vaccine seroresponse: titre is < 1:8 at baseline with post-vaccination titre ≥ 1:16 or titre is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
95% CI of the single proportion calculated from the exact binomial method.

Response in subjects according to MenC vaccination status before priming with MenQuadfi in MET51
The antibody responses against serogroup C following administration of a booster dose of MenQuadfi were comparable regardless of MenC vaccination status during their first year of life before priming with MenQuadfi 5 years earlier in MET51.

Persistence of immune response and MenQuadfi booster response in adolescents and adults 13 through 26 years of age

MET59 (NCT04084769) evaluated the antibody persistence of a primary dose, immunogenicity and safety of a booster dose of MenQuadfi in adolescents and adults 13 through 26 years of age who had received a single dose of MenQuadfi in study MET50 or MET43 or MenACWY-CRM in study MET50 or outside of Sanofi Pasteur trials 3-6 years prior. The antibody persistence prior to the MenQuadfi booster dose and the booster immune response were assessed according to the vaccine (MenQuadfi or MenACWY-CRM) subjects had received 3-6 years previously (see Table 13).

For all serogroups, hSBA GMTs were higher at D30 post-primary dose than at 3-6 Year (3-6Y) post-primary dose (D0 pre-booster) for MenQuadfi and MenACWY-CRM primed subjects. The 3-6Y post-primary dose (D0 pre-booster) GMTs were higher than the pre-primary GMTs, indicative of long-term persistence of immune response.

After the booster dose, seroprotection rates were nearly 100% for all serogroups in adolescents and adults primed with MenQuadfi.

Table 13: Comparison of bactericidal antibody response 6 and 30 days after booster vaccination, and persistence in adolescents and adults (13 through 26 years) primed with MenQuadfi or MenACWY-CRM 3-6 years before in study MET50*, MET43 or outside of Sanofi Pasteur trials – (study MET59***)**

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)				MenQuadfi Booster in MenACWY-CRM primed (95% CI)			
	Persistence^		Booster$		Persistence^		Booster$	
	D30 – Post-primary dose N = 376	3-6Y Post-primary dose (D0 – Pre-booster dose) N = 379-380	D06 – Post-booster dose N = 46	D30 – Post-booster dose N = 174	D30 Post-primary dose N = 132-133	3-6Y Post-primary dose (D0 – Pre-booster dose) N = 140	D06- Post-booster dose N = 45	D30 – Post-booster dose N = 176
A								
% ≥ 1:8 (Seroprotection)	94.7 (91.9; 96.7)	72.8 (68.0; 77.2)	91.3 (79.2; 97.6)	99.4 (96.8; 100)	81.2 (73.5; 87.5)	71.4 (63.2; 78.7)	95.6 (84.9; 99.5)	99.4 (96.9; 100)
% Seroresponse	-	-	82.6 (68.6; 92.2)	94.8 (90.4; 97.6)	-	-	77.8 (62.9; 88.8)	93.2 (88.4; 96.4)
hSBA GMT	45.2 (39.9; 51.1)	12.5 (11.1; 14.1)	289 (133; 625)	502 (388; 649)	32.8 (25.0; 43.1)	11.6 (9.41; 14.3)	161 (93.0; 280)	399 (318; 502)
C								
% ≥ 1:8 (Seroprotection)	98.1 (96.2; 99.2)	86.3 (82.4; 89.6)	100 (92.3; 100)	100 (97.9; 100)	74.2 (65.9; 81.5)	49.3 (40.7; 57.9)	97.8 (88.2; 99.9)	100 (97.9; 100)
% Seroresponse	-	-	89.1 (76.4; 96.4)	97.1 (93.4; 99.1)	-	-	93.3 (81.7; 98.6)	98.9 (96.0; 99.9)
hSBA GMT	417 (348; 500)	37.5 (31.6; 44.5)	3 799 (2 504 ; 5 763)	3 708 (3 146; 4 369)	49.7 (32.4; 76.4)	11.0 (8.09; 14.9)	919 (500; 1 690)	2 533 (2 076; 3 091)
W								
% ≥ 1:8 (Seroprotection)	100 (99.0; 100)	88.9 (85.3; 91.9)	100 (92.3; 100)	100 (97.9; 100)	93.2 (87.5; 96.9)	76.4 (68.5; 83.2)	100 (92.1; 100)	100 (97.9; 100)
% Seroresponse	-	-	97.8 (88.5; 99.9)	97.7 (94.2; 99.4)	-	-	88.9 (75.9; 96.3)	98.9 (96.0; 99.9)

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)				MenQuadfi Booster in MenACWY-CRM primed (95% CI)			
	Persistence^		Booster$		Persistence^		Booster$	
	D30 – Post-primary dose N = 376	3-6Y Post-primary dose (D0 – Pre-booster dose) N = 379-380	D06 – Post-booster dose N = 46	D30 – Post-booster dose N = 174	D30 Post-primary dose N = 132-133	3-6Y Post-primary dose (D0 – Pre-booster dose) N = 140	D06- Post-booster dose N = 45	D30 – Post-booster dose N = 176
A								
hSBA GMT	82.7 (73.6; 92.9)	28.8 (25.1; 33.0)	1 928 (1 187 ; 3 131)	2 290 (1 934; 2 711)	45.1 (34.3; 59.4)	14.9 (11.9; 18.6)	708 (463; 1 082)	2 574 (2 178; 3 041)
Y								
% ≥ 1:8 (Seroprotection)	97.9 (95.9; 99.1)	81.8 (77.5; 85.5)	97.8 (88.5; 99.9)	100 (97.9; 100)	88.7 (82.1; 93.5)	52.1 (43.5; 60.7)	100 (92.1; 100)	100 (97.9; 100)
% Seroresponse	-	-	95.7 (85.2; 99.5)	98.9 (95.9; 99.9)	-	-	91.1 (78.8; 97.5)	100 (97.9; 100)
hSBA GMT	91.0 (78.6; 105)	21.8 (18.8; 25.1)	1 658 (973; 2 826)	2 308 (1 925; 2 767)	36.1 (27.2; 47.8)	8.49 (6.50; 11.1)	800 (467; 1 371)	3 036 (2 547; 3 620)

*MET50 – The study was conducted in adolescents (10-17 years of age).
**MET43 – The study was conducted in children, adolescents and adults (10-55 years of age).
***MET59 – NCT04084769
$N calculated using per protocol analysis set (PPAS 1 and 2) with valid serology results; post-booster dose=D06 or D30 of MET59
^N calculated using full analysis set for persistence (FASP) with valid serology results. The number of subjects varies depending on the timepoints and serogroup; post-primary dose=D30 MET50 or MET43, 3-6 Y post-primary dose (pre-booster dose)=D0 MET59.
Vaccine seroresponse: titre is < 1:8 at baseline with post-vaccination titre ≥ 1:16 or titre is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
95% CI of the single proportion calculated from the exact binomial method.

Persistence of immune response and MenQuadfi booster response in adults 59 years of age and older

MEQ00066 (NCT04142242) evaluated the antibody persistence of a primary dose, immunogenicity, and safety of a booster dose of MenQuadfi in adults ≥ 59 years of age who had received a single dose of MenQuadfi or MenACWY-PS ≥ 3 years previously in study MET49 or MET44.

3-year persistence

The antibody persistence prior to the MenQuadfi booster dose and the booster immune response were assessed according to the vaccine (MenQuadfi or MenACWY-PS) subjects had received 3 years previously in MET49 (Table 14).

For all serogroups, hSBA GMTs were higher at D30 post-primary dose than at 3 Year (3Y) post-primary dose (D0 pre-booster) for both MenQuadfi-primed and MenACWY-PS-primed adults. In addition, for both primed groups, the 3 Year (3Y) post-primary dose (pre-booster) GMTs were higher than the pre-primary GMTs for serogroups C, W and Y (indicative of long-term persistence of immune response for these serogroups) and were comparable for serogroup A.

Table 14: Comparison of bactericidal antibody response 6 and 30 days after booster vaccination, and persistence in adults (≥ 59 years) primed with MenQuadfi or MenACWY-PS 3 years before in study MET49* – (study MEQ00066#)

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)				MenQuadfi Booster in MenACWY-PS primed (95% CI)			
	Persistence^		Booster$		Persistence^		Booster$	
	D30 – Post-primary dose N = 214	3Y Post-primary dose (D0 - Pre-booster dose) N = 214	D06 – Post-booster dose N = 58	D30 – Post-booster dose N = 145	D30 Post-primary dose N = 169	3Y Post-primary dose (D0 - Pre-booster dose) N = 169	D06 – Post-booster dose N = 62	D30 – Post-booster dose N = 130
A								
% ≥ 1:8 (Seroprotection)	89.6 (84.7; 93.4)	65.0 (58.2; 71.3)	91.4 (81.0; 97.1)	93.8 (88.5; 97.1)	85.7 (79.5; 90.6)	65.7 (58.0; 72.8)	72.6 (59.8; 83.1)	87.7 (80.8; 92.8)
% Seroresponse	-	-	36.2 (24.0; 49.9)	79.3 (71.8; 85.6)	-	-	8.1 (2.7; 17.8)	60.8 (51.8; 69.2)
hSBA GMT	48.9 (39.0; 61.5)	12.2 (10.2; 14.6)	43.7 (26.5; 71.9)	162 (121; 216)	37.7 (29.3; 48.7)	11.6 (9.53; 14.1)	13.1 (9.60; 17.8)	56.6 (41.5; 77.2)
C								
% ≥ 1:8 (Seroprotection)	88.2 (83.1; 92.2)	73.4 (66.9; 79.2)	98.3 (90.8; 100)	99.3 (96.2; 100)	71.4 (64.0; 78.1)	47.9 (40.2; 55.7)	51.6 (38.6; 64.5)	85.3 (78.0; 90.9)
% Seroresponse	-	-	77.6 (64.7; 87.5)	93.1 (87.7; 96.6)	-	-	8.1 (2.7; 17.8)	55.0 (46.0; 63.8)
hSBA GMT	84.8 (64.0; 112)	17.7 (14.3; 21.9)	206 (126; 339)	638 (496; 820)	26.7 (19.8; 36.0)	8.47 (6.76; 10.6)	11.1 (7.17; 17.1)	56.0 (39.7; 78.9)
W								
% ≥ 1:8	78.8	66.8	89.7	98.6	60.1	39.6	46.8	80.8

Endpoint by Serogroup	MenQuadfi Booster in MenQuadfi primed (95% CI)				MenQuadfi Booster in MenACWY-PS primed (95% CI)			
	Persistence^		Booster$		Persistence^		Booster$	
	D30 – Post-primary dose N = 214	3Y Post-primary dose (D0 - Pre-booster dose) N = 214	D06 – Post-booster dose N = 58	D30 – Post-booster dose N = 145	D30 Post-primary dose N = 169	3Y Post-primary dose (D0 - Pre-booster dose) N = 169	D06 – Post-booster dose N = 62	D30 – Post-booster dose N = 130
(Seroprotection)	(72.6; 84.1)	(60.1; 73.1)	(78.8; 96.1)	(95.1; 99.8)	(52.3; 67.6)	(32.2; 47.4)	(34.0; 59.9)	(72.9; 87.2)
% Seroresponse	-	-	70.7 (57.3; 81.9)	90.3 (84.3; 94.6)	-	-	6.5 (1.8; 15.7)	49.2 (40.4; 58.1)
hSBA GMT	28.0 (22.2; 35.3)	14.2 (11.6; 17.4)	118 (64.0; 216)	419 (317; 553)	14.7 (11.0; 19.8)	6.54 (5.28; 8.11)	9.89 (6.45; 15.2)	31.0 (22.6; 42.6)
Y								
% ≥ 1:8 (Seroprotection)	92.5 (88.0; 95.6)	68.2 (61.5; 74.4)	94.8 (85.6; 98.9)	100 (97.5; 100)	65.5 (57.8; 72.6)	40.8 (33.3; 48.6)	45.2 (32.5; 58.3)	81.5 (73.8; 87.8)
% Seroresponse	-	-	72.4 (59.1; 83.3)	92.4 (86.8; 96.2)	-	-	8.1 (2.7; 17.8)	49.2 (40.4; 58.1)
hSBA GMT	65.3 (51.8; 82.2)	15.3 (12.3; 19.1)	151 (83.4; 274)	566 (433; 740	19.6 (14.4; 26.7)	7.49 (5.72; 9.82)	11.1 (6.31; 19.4)	40.5 (29.0; 56.4)

* Clinical trial identifier: NCT02842866
# Clinical trial identifier: NCT04142242
^N calculated using full analysis set for persistence (FASP) with valid serology results; Post primary dose=D30 of MET49, 3Y post-primary dose (Pre-booster dose)=D0 of MEQ00066
$N calculated using per protocol analysis Set 2 and 1 (PPAS2 and PPAS1) with valid serology results. Post booster dose=D06 or D30 of MEQ00066
Vaccine seroresponse - titre is < 1:8 at baseline with post-vaccination titre ≥ 1:16 or titre is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
95% CI of the single proportion calculated using the exact binomial method.

5-year persistence
A subset of subjects (N = 52) who were assessed for antibody persistence at 3 years and did not receive the booster dose were re-assessed for antibody persistence at 5 years at which time they received a booster dose of MenQuadfi. In MenQuadfi-primed subjects, hSBA GMTs for serogroups C, W and Y 5Y post-primary dose trended higher than the pre-priming GMTs (and were comparable for serogroup A). Following the MenQuadfi booster dose, seroprotection rates were 100% for serogroups A, C, and Y, and 95.0% for serogroup W in subjects primed with MenQuadfi and 87.5%, 62.5%, 87.5% and 68.8% for serogroups A, C, W and Y, respectively, for those primed with MenACWY-PS. Additionally, hSBA

GMTs were higher and seroresponse rates were higher or trended higher for all serogroups in subjects primed with MenQuadfi compared to those primed with MenACWY-PS.

6-7 year persistence
The antibody persistence was assessed according to the vaccine (MenQuadfi or MenACWY-PS) subjects had received 6-7 years previously in study MET44 (Table 15).

For all serogroups, hSBA GMTs were higher at D30 post-primary dose than at 6-7 Year (6-7Y) post-primary dose for MenQuadfi-primed adults. The 6-7Y post-primary GMTs were higher than the pre-primary GMTs for serogroup C, W, and Y in MenQuadfi-primed adults, indicative of long-term persistence of immune response for these serogroups, and were comparable for serogroup A.

Table 15: Comparison of bactericidal antibody persistence in adults (≥ 59 years) primed with MenQuadfi or MenACWY-PS 6-7 years before in MET44^ – (study MEQ00066[#])

	MenQuadfi primed (95% CI)		**MenACWY-PS primed (95% CI)**	
Endpoint by Serogroup	**D30 - Post-primary dose$** **N = 59**	**6-7Y Post-primary dose#** **N = 59**	**D30 - Post-primary dose$** **N = 26**	**6-7Y Post-primary dose#** **N = 26**
A				
% ≥ 1:8 (Seroprotection)	91.4 (81.0; 97.1)	55.9 (42.4; 68.8)	76.9 (56.4; 91.0)	50.0 (29.9; 70.1)
GMT	48.0 (30.6; 75.4)	9.00 (6.44; 12.6)	27.3 (13.8; 54)	9.64 (5.18; 17.9)
C				
% ≥ 1:8 (Seroprotection)	74.1 (61.0; 84.7)	59.3 (45.7; 71.9)	76.9 (56.4; 91.0)	42.3 (23.4; 63.1)
GMT	52.2 (27.4; 99.7)	11.9 (7.67; 18.5)	23.9 (11.9; 48.1)	7.58 (4.11; 14.0)
W				
% ≥ 1:8 (Seroprotection)	75.9 (62.8; 86.1)	66.1 (52.6; 77.9)	73.1 (52.2; 88.4)	38.5 (20.2; 59.4)
GMT	31.2 (18.8; 52.0)	11.9 (7.97; 17.8)	18.8 (10.1; 34.9)	4.95 (3.39; 7.22)
Y				
% ≥ 1:8 (Seroprotection)	81.0 (68.6; 90.1)	59.3 (45.7; 71.9)	73.1 (52.2; 88.4)	46.2 (26.6; 66.6)
GMT	45.8 (26.9; 78.0)	11.2 (7.24; 17.5)	25.9 (12.4; 53.8)	7.19 (4.09; 12.6)

^Clinical trial identifier: NCT01732627
[#]Clinical trial identifier: NCT04142242
N: number of subjects in full analysis set for persistence (FASP) with valid serology results.
$ Post primary dose=D30 of MET44
# 6-7Y Post-primary dose=D0 of MEQ00066
95% CI of the single proportion calculated from the exact binomial method.

Booster response in adolescents and adults at least 15 years of age primed with other MenACWY vaccines

Study MET56 (NCT02752906) compared the immunogenicity of a booster dose of MenQuadfi with a booster dose of MenACWY-DT in subjects at least 15 years of age. These subjects were primed with a

quadrivalent meningococcal conjugate vaccine (MenACWY-CRM (11.3%) or with MenACWY-DT (86.3%)) 4 to 10 years earlier.

At baseline, hSBA seroprotection and GMT were similar for serogroups A, C, W, and Y.

Table 16: Comparison of bactericidal antibody responses to MenQuadfi and MenACWY-DT 30 days after booster vaccination in subjects at least 15 years of age primed with MenACWY-CRM or MenACWY-DT 4 to 10 years earlier (study MET56*)

Endpoint by Serogroup	**MenQuadfi (95% CI)**		**MenACWY-DT (95% CI)**	
A	**N = 384**		**N = 389**	
% ≥ 1:8 (Seroprotection)	100.0	(99.0; 100.0)	99.0	(97.4; 99.7)
% Seroresponse**	92.2	(89.0; 94.7)	87.1	(83.4; 90.3)
hSBA GMT	497	(436; 568)	296	(256; 343)
C	N = 384		N = 389	
% ≥ 1:8 (Seroprotection)	99.5	(98.1; 99.9)	99.0	(97.4; 99.7)
% Seroresponse**	97.1	(94.9; 98.6)	91.8	(88.6; 94.3)
hSBA GMT	2 618	(2 227; 3 078)	599	(504; 711)
W	N = 384		N = 389	
% ≥ 1:8 (Seroprotection)	100.0	(99.0; 100.0)	99.7	(98.6; 100.0)
% Seroresponse**	98.2	(96.3; 99.3)	90.7	(87.4; 93.4)
hSBA GMT	1 747	(1 508; 2 025)	723	(614; 853)
Y	N = 384		N = 389	
% ≥ 1:8 (Seroprotection)	99.7	(98.6; 100.0)	99.5	(98.2; 99.9)
% Seroresponse**	97.4	(95.3; 98.7)	95.6	(93.1; 97.4)
hSBA GMT	2 070	(1 807; 2 371)	811	(699; 941)

* Clinical trial identifier NCT02752906
N: number of subjects in the per-protocol analysis set with valid serology results.
95% CI of the single proportion calculated from the exact binomial method.
** Non-inferiority criterion met.

The European Medicines Agency has deferred the obligation to submit the results of trials within one or more subsets of the paediatric population under 12 months of age (see 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a developmental and reproductive toxicity study in female rabbits.

The administration of MenQuadfi to female rabbits at a full human dose showed no effects on mating performance, female fertility, no teratogenic potential, and no effect on pre- or post-natal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate (E 262)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. At the end of this period, MenQuadfi should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

Solution in a Type I borosilicate clear glass vial with a 13 mm chlorobutyl stopper and a flip off seal.

Pack of 1, 5 or 10 single dose (0.5 mL) vials.
Pack of 1 single dose (0.5 mL) vial co-packaged with 1 single use empty luer-lok syringe (polypropylene) with a plunger-stopper (synthetic elastomer), and 2 separate needles (stainless steel) with needle-shield (polypropylene).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The vaccine should be inspected visually for any particulate matter and/or variation of physical aspect (or discolouration) prior to administration. In the event of either being observed, discard the vaccine.

Preparation

Pack of 1, 5 or 10 single dose (0.5 mL) vials
Remove the vial flip off seal and using a suitable syringe and needle, withdraw 0.5 mL of solution from the vial, ensuring no air bubbles are present before injection.

Pack of 1 single dose (0.5 mL) vial co-packaged with 1 single use empty syringe and 2 needles
Specific instructions for luer-lok syringe

To attach the needle to the syringe, gently twist the needle clockwise into the syringe until slight resistance is felt. Before injection, remove the vial flip off seal and withdraw 0.5 mL of solution from the vial, ensuring no air bubbles are present. A new needle should be used to administer the vaccine.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1483/001
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EU/1/20/1483/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2020
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.