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Committee for Medicinal Products for Human Use (CHMP)

# Nimenrix

(meningococcal group a, c, w135 and y conjugate vaccine)

Procedure No. EMEA/H/C/000113/P46/0015
EMEA/H/C/000113/P46/0016

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

# I. EXECUTIVE SUMMARY

This report includes two article 46 procedures submitted for Nimenrix.

| P46 | Primary Study | Data submitted | eCTD sequence |
|---|---|---|---|
| P46 015 | MenACWY-TT-052 | MENACWY-TT-059 EXT:052 Y3 | 20 |
| P46 016 | MenACWY-TT-062 | MENACWY-TT-062 EXT:055 Y3 | 21 |

# II. INTRODUCTION

On 3rd September, the MAH submitted study reports for two completed paediatric studies for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Nimenrix and that there is no consequential regulatory action.

# III. SCIENTIFIC DISCUSSION

## III.1 Information on the pharmaceutical formulation used in the studies

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccine composed of *Neisseria meningitidis* serogroups A, C, W-135, Y conjugated to tetanus toxoid. Nimenrix was authorised on the 20th of April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W-135 and Y. A 0.5 ml dose of the reconstituted vaccine is used at all ages.

## III.2 Clinical aspects

### 1. Introduction

The study MenACWY-TT-059 EXT052 Y3 is a year 3 follow-up study of the primary study MenACWY-TT-052.
The study MenACWY-TT-062 EXT055 Y3 is a year 3 follow-up study of the primary study MenACWY-TT-055.

The primary phase studies, as well as the follow-up studies after 1 year, were submitted as part of the initial MAA for Nimenrix. Further follow-up of the subjects is planned up to 5 years following primary vaccination.

A variation application consisting of the full relevant data package (i.e containing several studies to update the labelling with available persistence data across all age groups) is expected to be submitted by the beginning of 2013.

### 2. Clinical studies

***GSK study report number:*** *111670*
***Study title:*** *A phase II, open, controlled, multi-center study to evaluate the long-term antibody persistence at 1 year, 3 years and 5 years after the administration of one dose of*

*GlaxoSmithKline (GSK) Biologicals' meningococcal serogroups A, C, W-135, V-tetanus toxoid conjugate (MenACWY-TT) vaccine versus one dose of sanofi-pasteur's meningococcal serogroups A, C, W-135 and Y-diphtheria toxoid conjugate vaccine (Menactra) in healthy adolescents/adults aged 10-25 years and to evaluate the safety and immunogenicity of a booster response to MenACWY-TT vaccine administered at 5 years post-primary vaccination with MenACWY-TT or Menactra and of a primary vaccination of MenACWY-TT in a newly enrolled group aged 15-<31 years.*

Note: This annex report (Annex 1) to the 111670 (MenACWYTT-059) study report presents the persistence results of serum bactericidal assays at three years after vaccination.

Study MenACWY-TT-059 was conducted in the United States. This study evaluated the immunogenicity induced by *Nimenrix* as compared to *Menactra* at 11-25 years of age in terms of the percentage of subjects with *N. meningitidis* serogroups A, C, W -135 and Y titers ≥ 1:8 as measured by hSBA (using GSK hSBA assays).

The study included 3 groups:
• ACWY-TT: MenACWY-TT (11-25 years of age)
• ACWY-DT: *Menactra* (11-25 years of age)
• ACWY<11: MenACWY-TT (10-<11 years of age)

Of the 873 subjects who were enrolled and vaccinated in study MenACWY-TT-052, 487 subjects returned for the Year 3 visit (345 subjects in the in the ACWY-TT group, 86 in the ACWY-DT group and 56 in the ACWY<11 group). In the majority of cases, the reasons for subjects not returning for the Year 3 persistence study were: the subjects had been revaccinated with a meningococcal vaccine or the subjects were lost to follow-up. Other reasons fell under the categories of withdrawal of consent or migration to another area.

The according-to-protocol immunogenicity analysis contained 473 subjects (335 in the ACWY-TT group, 84 in the ACWY-DT group and 54 in the ACWY<11 group).

The summary of demographic characteristics for the ATP cohort is presented below.

| | | ACWY-TT N = 335 | | ACWY-DT N = 84 | | ACWY<11 N = 54 | | Total N = 473 | |
|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age at Year 3 (years) | Mean | 17.5 | - | 17.3 | - | 13.0 | - | 16.9 | - |
| | SD | 2.70 | - | 2.41 | - | 0.19 | - | 2.86 | - |
| | Median | 17.0 | - | 17.0 | - | 13.0 | - | 17.0 | - |
| | Minimum | 14 | - | 14 | - | 12 | - | 12 | - |
| | Maximum | 28 | - | 24 | - | 14 | - | 28 | - |
| Gender | Female | 159 | 47.5 | 46 | 54.8 | 31 | 57.4 | 236 | 49.9 |
| | Male | 176 | 52.5 | 38 | 45.2 | 23 | 42.6 | 237 | 50.1 |

The percentages of subjects with hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and GMTs (ATP cohort for persistence at Year 3) are presented in the following table.

| | | | | ≥ 1:4 | | | | ≥ 1:8 | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| hSBA-MenA | ACWY-TT | PRE | 324 | 41 | 12.7 | 9.2 | 16.8 | 28 | 8.6 | 5.8 | 12.2 | 2.5 | 2.4 | 2.7 |
| | | PI(M1) | 320 | 295 | 92.2 | 88.7 | 94.9 | 292 | 91.3 | 87.6 | 94.1 | 86.2 | 73.1 | 101.7 |
| | | PI(M12) | 276 | 91 | 33.0 | 27.5 | 38.9 | 87 | 31.5 | 26.1 | 37.4 | 5.7 | 4.7 | 6.9 |
| | | PI(M36) | 316 | 124 | 39.2 | 33.8 | 44.9 | 118 | 37.3 | 32.0 | 42.9 | 6.2 | 5.2 | 7.3 |
| | ACWY-DT | PRE | 83 | 12 | 14.5 | 7.7 | 23.9 | 10 | 12.0 | 5.9 | 21.0 | 2.7 | 2.3 | 3.2 |
| | | PI(M1) | 77 | 70 | 90.9 | 82.2 | 96.3 | 70 | 90.9 | 82.2 | 96.3 | 95.6 | 65.5 | 139.5 |
| | | PI(M12) | 71 | 27 | 38.0 | 26.8 | 50.3 | 27 | 38.0 | 26.8 | 50.3 | 8.1 | 5.1 | 12.9 |
| | | PI(M36) | 79 | 38 | 48.1 | 36.7 | 59.6 | 38 | 48.1 | 36.7 | 59.6 | 10.0 | 6.5 | 15.3 |
| | ACWY<11 | PRE | 51 | 4 | 7.8 | 2.2 | 18.9 | 3 | 5.9 | 1.2 | 16.2 | 2.3 | 2.0 | 2.7 |
| | | PI(M1) | 52 | 49 | 94.2 | 84.1 | 98.8 | 48 | 92.3 | 81.5 | 97.9 | 102.2 | 68.9 | 151.5 |
| | | PI(M12) | 50 | 16 | 32.0 | 19.5 | 46.7 | 14 | 28.0 | 16.2 | 42.5 | 6.1 | 3.5 | 10.4 |
| | | PI(M36) | 52 | 24 | 46.2 | 32.2 | 60.5 | 23 | 44.2 | 30.5 | 58.7 | 9.6 | 5.6 | 16.4 |
| hSBA-MenC | ACWY-TT | PRE | 320 | 173 | 54.1 | 48.4 | 59.6 | 173 | 54.1 | 48.4 | 59.6 | 12.8 | 10.4 | 15.7 |
| | | PI(M1) | 328 | 322 | 98.2 | 96.1 | 99.3 | 322 | 98.2 | 96.1 | 99.3 | 616.1 | 493.2 | 769.7 |
| | | PI(M12) | 260 | 249 | 95.8 | 92.6 | 97.9 | 249 | 95.8 | 92.6 | 97.9 | 187.6 | 153.2 | 229.9 |
| | | PI(M36) | 319 | 297 | 93.1 | 89.7 | 95.6 | 297 | 93.1 | 89.7 | 95.6 | 119.3 | 95.5 | 149.0 |
| | ACWY-DT | PRE | 82 | 57 | 69.5 | 58.4 | 79.2 | 56 | 68.3 | 57.1 | 78.1 | 23.7 | 15.4 | 36.3 |
| | | PI(M1) | 82 | 81 | 98.8 | 93.4 | 100 | 81 | 98.8 | 93.4 | 100 | 382.1 | 248.9 | 586.5 |
| | | PI(M12) | 67 | 52 | 77.6 | 65.8 | 86.9 | 52 | 77.6 | 65.8 | 86.9 | 50.9 | 30.6 | 84.7 |
| | | PI(M36) | 81 | 69 | 85.2 | 75.6 | 92.1 | 66 | 81.5 | 71.3 | 89.2 | 54.4 | 33.8 | 87.6 |
| | ACWY<11 | PRE | 51 | 28 | 54.9 | 40.3 | 68.9 | 28 | 54.9 | 40.3 | 68.9 | 10.1 | 6.4 | 16.0 |
| | | PI(M1) | 52 | 52 | 100 | 93.2 | 100 | 52 | 100 | 93.2 | 100 | 1013.8 | 628.3 | 1635.9 |
| | | PI(M12) | 47 | 47 | 100 | 92.5 | 100 | 47 | 100 | 92.5 | 100 | 272.9 | 178.1 | 418.0 |
| | | PI(M36) | 54 | 52 | 96.3 | 87.3 | 99.5 | 52 | 96.3 | 87.3 | 99.5 | 140.0 | 84.5 | 232.0 |
| hSBA-MenW-135 | ACWY-TT | PRE | 293 | 79 | 27.0 | 22.0 | 32.4 | 75 | 25.6 | 20.7 | 31.0 | 5.9 | 4.7 | 7.3 |
| | | PI(M1) | 303 | 294 | 97.0 | 94.4 | 98.6 | 293 | 96.7 | 94.0 | 98.4 | 149.4 | 126.6 | 176.2 |
| | | PI(M12) | 256 | 252 | 98.4 | 96.0 | 99.6 | 252 | 98.4 | 96.0 | 99.6 | 205.6 | 177.4 | 238.2 |
| | | PI(M36) | 323 | 309 | 95.7 | 92.8 | 97.6 | 308 | 95.4 | 92.5 | 97.4 | 143.9 | 124.7 | 166.2 |
| | ACWY-DT | PRE | 72 | 36 | 50.0 | 38.0 | 62.0 | 36 | 50.0 | 38.0 | 62.0 | 18.5 | 10.5 | 32.6 |
| | | PI(M1) | 66 | 61 | 92.4 | 83.2 | 97.5 | 60 | 90.9 | 81.3 | 96.6 | 182.6 | 115.8 | 288.1 |
| | | PI(M12) | 69 | 62 | 89.9 | 80.2 | 95.8 | 62 | 89.9 | 80.2 | 95.8 | 84.3 | 55.4 | 128.3 |
| | | PI(M36) | 80 | 68 | 85.0 | 75.3 | 92.0 | 68 | 85.0 | 75.3 | 92.0 | 79.4 | 50.9 | 123.9 |
| | ACWY<11 | PRE | 46 | 5 | 10.9 | 3.6 | 23.6 | 5 | 10.9 | 3.6 | 23.6 | 3.4 | 2.2 | 5.5 |
| | | PI(M1) | 51 | 49 | 96.1 | 86.5 | 99.5 | 49 | 96.1 | 86.5 | 99.5 | 148.3 | 102.8 | 213.7 |
| | | PI(M12) | 47 | 47 | 100 | 92.5 | 100 | 46 | 97.9 | 88.7 | 99.9 | 230.2 | 167.0 | 317.3 |
| | | PI(M36) | 54 | 53 | 98.1 | 90.1 | 100 | 52 | 96.3 | 87.3 | 99.5 | 139.2 | 99.8 | 194.0 |
| hSBA-MenY | ACWY-TT | PRE | 310 | 166 | 53.5 | 47.8 | 59.2 | 163 | 52.6 | 46.9 | 58.3 | 21.1 | 16.2 | 27.5 |
| | | PI(M1) | 332 | 323 | 97.3 | 94.9 | 98.8 | 323 | 97.3 | 94.9 | 98.8 | 279.0 | 238.0 | 327.0 |
| | | PI(M12) | 282 | 278 | 98.6 | 96.4 | 99.6 | 278 | 98.6 | 96.4 | 99.6 | 298.7 | 259.2 | 344.3 |
| | | PI(M36) | 321 | 308 | 96.0 | 93.2 | 97.8 | 308 | 96.0 | 93.2 | 97.8 | 209.2 | 180.1 | 242.9 |
| | ACWY-DT | PRE | 78 | 53 | 67.9 | 56.4 | 78.1 | 53 | 67.9 | 56.4 | 78.1 | 46.6 | 27.2 | 79.9 |
| | | PI(M1) | 83 | 75 | 90.4 | 81.9 | 95.7 | 75 | 90.4 | 81.9 | 95.7 | 199.5 | 125.5 | 317.4 |
| | | PI(M12) | 72 | 66 | 91.7 | 82.7 | 96.9 | 66 | 91.7 | 82.7 | 96.9 | 133.3 | 88.8 | 200.2 |
| | | PI(M36) | 80 | 71 | 88.8 | 79.7 | 94.7 | 71 | 88.8 | 79.7 | 94.7 | 145.5 | 97.6 | 216.9 |
| | ACWY<11 | PRE | 51 | 25 | 49.0 | 34.8 | 63.4 | 24 | 47.1 | 32.9 | 61.5 | 17.2 | 8.9 | 33.2 |
| | | PI(M1) | 53 | 50 | 94.3 | 84.3 | 98.8 | 50 | 94.3 | 84.3 | 98.8 | 277.8 | 174.5 | 442.2 |
| | | PI(M12) | 51 | 51 | 100 | 93.0 | 100 | 51 | 100 | 93.0 | 100 | 303.2 | 229.9 | 399.9 |
| | | PI(M36) | 52 | 50 | 96.2 | 86.8 | 99.5 | 50 | 96.2 | 86.8 | 99.5 | 188.0 | 132.6 | 266.7 |

The differences between ACWY-TT and ACWY-DT groups in percentages of subjects with titers equal to or above the cut-off values of 1:4 and 1:8 and the GMT ratios 3 years after the primary vaccination are shown in the tables below.

| | | | | | | | | Difference in percentage (ACWY-TT minus ACWY-DT) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ACWY-TT | | | ACWY-DT | | | | 95% CI | |
| Antibody | Type | N | n | % | N | n | % | % | LL | UL |
| hSBA-MenA | 1:4 | 316 | 124 | 39.2 | 79 | 38 | 48.1 | -8.86 | -20.99 | 3.18 |
| | 1:8 | 316 | 118 | 37.3 | 79 | 38 | 48.1 | -10.76 | -22.87 | 1.27 |
| hSBA-MenC | 1:4 | 319 | 297 | 93.1 | 81 | 69 | 85.2 | 7.92 | 0.95 | 17.56 |
| | 1:8 | 319 | 297 | 93.1 | 81 | 66 | 81.5 | 11.62 | 3.93 | 21.76 |
| hSBA-MenW-135 | 1:4 | 323 | 309 | 95.7 | 80 | 68 | 85.0 | 10.67 | 3.90 | 20.29 |
| | 1:8 | 323 | 308 | 95.4 | 80 | 68 | 85.0 | 10.36 | 3.56 | 20.00 |
| hSBA-MenY | 1:4 | 321 | 308 | 96.0 | 80 | 71 | 88.8 | 7.20 | 1.33 | 16.17 |
| | 1:8 | 321 | 308 | 96.0 | 80 | 71 | 88.8 | 7.20 | 1.33 | 16.17 |

| | | | | | Adjusted GMT ratio (ACWY-TT / ACWY-DT) | | |
|---|---|---|---|---|---|---|---|
| | ACWY-TT | | ACWY-DT | | | 95% CI | |
| Anti body | N | Adjusted GMT | N | Adjusted GMT | Value | LL | UL |
| hSBA-MenA | 316 | 7.2 | 79 | 11.6 | 0.62 | 0.41 | 0.92 |
| hSBA-MenC | 319 | 107.6 | 81 | 49.1 | 2.19 | 1.33 | 3.62 |
| hSBA-MenW-135 | 323 | 119.7 | 80 | 65.4 | 1.83 | 1.27 | 2.63 |
| hSBA-MenY | 321 | 204.2 | 80 | 141.4 | 1.44 | 1.01 | 2.06 |

No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation were reported from the last visit in the MenACWY-TT-052 study up to 3 years after vaccination.

***Discussion on clinical aspects***

The GMTs for MenC, MenW-135 and MenY at the Year 3 persistence time point remained above pre-vaccination titers. The MenA GMTs had decreased markedly to almost baseline levels at Year 1 persistence time point and remained at a similar level at Year 3 persistence time point.

Exploratory evaluations suggested that the ACWY-TT group had statistically significantly higher hSBA MenC, MenW-135 and MenY titers ≥1:8 compared to the ACWY-DT group. Exploratory evaluations of the ratio of the GMTs suggested that the ACWY-DT group had statistically significantly higher hSBA MenA GMTs compared to the ACWYTT-group and that the ACWY-TT group had statistically significantly higher hSBA MenC, Men W-135 and MenY GMTs compared to the ACWY-DT group.

In the current approved Summary of Product Characteristics (SmPC) for *Nimenrix,* results from the 1 year persistence of study MenACWY -TT -059 are presented. There is also a statement that “Studies with Nimenrix have shown a rapid waning (as measured at 12 months post-dose onwards) of serum bactericidal antibody titres against MenA when using human complement in the assay (hSBA). The clinical relevance of the rapid waning of hSBA MenA antibody titres is unknown.”

***GSK study report number:*** *112021*
***Study title:*** *A phase II, open, multi-center study to evaluate the long-term antibody persistence at 1 year, 3 years and 5 years after the administration of one or two doses of GlaxoSmithKline (GSK) Biologicals' meningococcal serogroups A, C, W-135, Y-tetanus toxoid conjugate (MenACWY-TT) vaccine in healthy toddlers at 9-12 months of age, and to evaluate the safety and immunogenicity of a booster dose of MenACWY-TT administered 5 years post-primary vaccination and of a primary vaccination of MenACWY-TT in a newly enrolled group, aged 5-6 years, as a naive control.*

Note: This annex report (Annex 1) to the 112021 (MenACWYTT-062) study report presents the persistence results of serum bactericidal assays at three years after vaccination.

Study MenACWY-TT-062 was conducted in the United States. This study evaluated antibody persistence at 3 years after vaccination with either one dose of *Nimenrix* at 12 months of age (ACWY-l group) or two doses of *Nimenrix* at 9 and 12 months of age (ACWY-2 group). Samples collected 3 years after vaccination in this study were tested using GSK hSBA and rSBA assay performed at the Health Protection Agency, UK (HPA).

Of the 347 subjects vaccinated in study MenACWY-TT-055, 202 subjects returned for the Year 3 visit (98 in the ACWY-1 group and 104 in the ACWY-2 group). In the majority of cases, the reasons for subjects not returning for the Year 3 persistence study were: the subjects were not willing to participate in the study or the subjects were lost to follow-up. Other reasons fell under the categories of withdrawal of consent, migration to another area or non-participation of the study site.

The ATP cohort for persistence Year 3 analysis contained 186 subjects, including 86 subjects in the ACWY-1 group and 100 subjects in the ACWY-2 group.

The summary of demographic characteristics for the ATP cohort is presented below.

| | | ACWY-1 N = 86 | | ACWY-2 N = 100 | | Total N = 186 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age at Year 3 (months) | Mean | 48.5 | - | 48.5 | - | 48.5 | - |
| | SD | 1.06 | - | 1.04 | - | 1.05 | - |
| | Median | 48.0 | - | 48.0 | - | 48.0 | - |
| | Minimum | 47 | - | 47 | - | 47 | - |
| | Maximum | 53 | - | 51 | - | 53 | - |
| Gender | Female | 40 | 46.5 | 53 | 53.0 | 93 | 50.0 |
| | Male | 46 | 53.5 | 47 | 47.0 | 93 | 50.0 |

The percentages of subjects with hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and GMTs (ATP cohort for persistence at Year 3) are presented in the following table.

| | | | | ≥ 1:4 | | | | ≥ 1:8 | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| **Antibody** | **Group** | **Timing** | **N** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** |
| hSBA-MenA | ACWY-1 | PI(M4) | 83 | 71 | 85.5 | 76.1 | 92.3 | 65 | 78.3 | 67.9 | 86.6 | 24.7 | 17.9 | 34.0 |
| | | PI(M12) | 71 | 15 | 21.1 | 12.3 | 32.4 | 14 | 19.7 | 11.2 | 30.9 | 3.3 | 2.6 | 4.2 |
| | | PI(M36) | 82 | 14 | 17.1 | 9.7 | 27.0 | 14 | 17.1 | 9.7 | 27.0 | 3.5 | 2.6 | 4.6 |
| | ACWY-2 | PI(M1) | 92 | 59 | 64.1 | 53.5 | 73.9 | 52 | 56.5 | 45.8 | 66.8 | 10.9 | 8.0 | 14.8 |
| | | PII(M4) | 95 | 84 | 88.4 | 80.2 | 94.1 | 84 | 88.4 | 80.2 | 94.1 | 45.1 | 33.8 | 60.3 |
| | | PII(M12) | 85 | 21 | 24.7 | 16.0 | 35.3 | 20 | 23.5 | 15.0 | 34.0 | 3.8 | 2.9 | 4.9 |
| | | PII(M36) | 96 | 19 | 19.8 | 12.4 | 29.2 | 16 | 16.7 | 9.8 | 25.6 | 3.4 | 2.7 | 4.3 |
| hSBA-MenC | ACWY-1 | PI(M4) | 84 | 78 | 92.9 | 85.1 | 97.3 | 78 | 92.9 | 85.1 | 97.3 | 145.5 | 105.7 | 200.1 |
| | | PI(M12) | 76 | 65 | 85.5 | 75.6 | 92.5 | 65 | 85.5 | 75.6 | 92.5 | 57.4 | 38.8 | 85.1 |
| | | PI(M36) | 81 | 59 | 72.8 | 61.8 | 82.1 | 57 | 70.4 | 59.2 | 80.0 | 31.2 | 18.9 | 51.6 |
| | ACWY-2 | PI(M1) | 90 | 81 | 90.0 | 81.9 | 95.3 | 81 | 90.0 | 81.9 | 95.3 | 90.3 | 64.6 | 126.1 |
| | | PII(M4) | 95 | 95 | 100 | 96.2 | 100 | 95 | 100 | 96.2 | 100 | 1084.6 | 859.1 | 1369.2 |
| | | PII(M12) | 88 | 80 | 90.9 | 82.9 | 96.0 | 80 | 90.9 | 82.9 | 96.0 | 65.8 | 46.9 | 92.5 |
| | | PII(M36) | 94 | 69 | 73.4 | 63.3 | 82.0 | 68 | 72.3 | 62.2 | 81.1 | 29.8 | 18.9 | 47.0 |
| hSBA-MenW-135 | ACWY-1 | PI(M4) | 76 | 39 | 51.3 | 39.6 | 63.0 | 36 | 47.4 | 35.8 | 59.2 | 11.0 | 7.0 | 17.2 |
| | | PI(M12) | 74 | 63 | 85.1 | 75.0 | 92.3 | 63 | 85.1 | 75.0 | 92.3 | 90.8 | 55.5 | 148.5 |
| | | PI(M36) | 86 | 54 | 62.8 | 51.7 | 73.0 | 54 | 62.8 | 51.7 | 73.0 | 29.0 | 18.0 | 46.9 |
| | ACWY-2 | PI(M1) | 84 | 16 | 19.0 | 11.3 | 29.1 | 15 | 17.9 | 10.4 | 27.7 | 3.3 | 2.6 | 4.2 |
| | | PII(M4) | 99 | 98 | 99.0 | 94.5 | 100 | 98 | 99.0 | 94.5 | 100 | 1088.4 | 856.2 | 1383.5 |
| | | PII(M12) | 88 | 88 | 100 | 95.9 | 100 | 88 | 100 | 95.9 | 100 | 212.1 | 167.8 | 268.3 |
| | | PII(M36) | 97 | 82 | 84.5 | 75.8 | 91.1 | 82 | 84.5 | 75.8 | 91.1 | 63.9 | 44.0 | 92.8 |
| hSBA-MenY | ACWY-1 | PI(M4) | 82 | 50 | 61.0 | 49.6 | 71.6 | 46 | 56.1 | 44.7 | 67.0 | 16.4 | 10.5 | 25.5 |
| | | PI(M12) | 78 | 61 | 78.2 | 67.4 | 86.8 | 60 | 76.9 | 66.0 | 85.7 | 46.5 | 29.1 | 74.2 |
| | | PI(M36) | 85 | 53 | 62.4 | 51.2 | 72.6 | 53 | 62.4 | 51.2 | 72.6 | 22.0 | 14.0 | 34.5 |
| | ACWY-2 | PI(M1) | 93 | 36 | 38.7 | 28.8 | 49.4 | 35 | 37.6 | 27.8 | 48.3 | 6.9 | 4.8 | 9.9 |
| | | PII(M4) | 99 | 98 | 99.0 | 94.5 | 100 | 98 | 99.0 | 94.5 | 100 | 451.0 | 360.2 | 564.8 |
| | | PII(M12) | 92 | 86 | 93.5 | 86.3 | 97.6 | 86 | 93.5 | 86.3 | 97.6 | 86.6 | 64.5 | 116.2 |
| | | PII(M36) | 95 | 59 | 62.1 | 51.6 | 71.9 | 59 | 62.1 | 51.6 | 71.9 | 20.5 | 13.6 | 30.8 |

The percentages of subjects with rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and GMTs (ATP cohort for persistence at Year 3) are presented in the following table.

| | | | | ≥ 1:8 | | | | ≥ 1:128 | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| rSBA-MenA | ACWY-1 | PI(M12) | 5 | 2 | 40.0 | 5.3 | 85.3 | 0 | 0.0 | 0.0 | 52.2 | 10.6 | 2.0 | 56.5 |
| | | PI(M36) | 83 | 38 | 45.8 | 34.8 | 57.1 | 23 | 27.7 | 18.4 | 38.6 | 18.4 | 12.0 | 28.3 |
| | ACWY-2 | PII(M12) | 9 | 6 | 66.7 | 29.9 | 92.5 | 2 | 22.2 | 2.8 | 60.0 | 21.8 | 5.9 | 80.5 |
| | | PII(M36) | 97 | 44 | 45.4 | 35.2 | 55.8 | 24 | 24.7 | 16.5 | 34.5 | 16.6 | 11.3 | 24.3 |
| rSBA-MenC | ACWY-1 | PI(M12) | 5 | 2 | 40.0 | 5.3 | 85.3 | 0 | 0.0 | 0.0 | 52.2 | 7.0 | 2.3 | 21.4 |
| | | PI(M36) | 83 | 27 | 32.5 | 22.6 | 43.7 | 18 | 21.7 | 13.4 | 32.1 | 13.2 | 8.6 | 20.2 |
| | ACWY-2 | PII(M12) | 9 | 4 | 44.4 | 13.7 | 78.8 | 0 | 0.0 | 0.0 | 33.6 | 8.0 | 4.0 | 16.2 |
| | | PII(M36) | 97 | 30 | 30.9 | 21.9 | 41.1 | 15 | 15.5 | 8.9 | 24.2 | 10.6 | 7.4 | 15.0 |
| rSBA-MenW-135 | ACWY-1 | PI(M12) | 5 | 2 | 40.0 | 5.3 | 85.3 | 2 | 40.0 | 5.3 | 85.3 | 21.1 | 1.2 | 381.1 |
| | | PI(M36) | 83 | 36 | 43.4 | 32.5 | 54.7 | 24 | 28.9 | 19.5 | 39.9 | 19.4 | 12.3 | 30.6 |
| | ACWY-2 | PII(M12) | 9 | 6 | 66.7 | 29.9 | 92.5 | 2 | 22.2 | 2.8 | 60.0 | 23.5 | 5.7 | 96.6 |
| | | PII(M36) | 95 | 35 | 36.8 | 27.2 | 47.4 | 23 | 24.2 | 16.0 | 34.1 | 14.6 | 9.7 | 21.8 |
| rSBA-MenY | ACWY-1 | PI(M12) | 5 | 2 | 40.0 | 5.3 | 85.3 | 0 | 0.0 | 0.0 | 52.2 | 10.6 | 2.0 | 56.5 |
| | | PI(M36) | 83 | 39 | 47.0 | 35.9 | 58.3 | 21 | 25.3 | 16.4 | 36.0 | 19.6 | 12.7 | 30.1 |
| | ACWY-2 | PII(M12) | 9 | 8 | 88.9 | 51.8 | 99.7 | 1 | 11.1 | 0.3 | 48.2 | 23.5 | 8.3 | 66.2 |
| | | PII(M36) | 98 | 45 | 45.9 | 35.8 | 56.3 | 24 | 24.5 | 16.4 | 34.2 | 16.7 | 11.5 | 24.3 |

The differences between ACWY-2 and ACWY-1 groups in percentages of subjects with hSBA titers equal to or above the cut-off values of 1:4 and 1:8 and the GMT ratios 3 years after the primary vaccination are shown in the tables below.

| | | | | | | | | Difference in percentage (ACWY-2 minus ACWY-1) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ACWY-2 | | | ACWY-1 | | | | 95% CI | |
| Antibody | Type | N | n | % | N | n | % | % | LL | UL |
| hSBA-MenA | 1:4 | 96 | 19 | 19.8 | 82 | 14 | 17.1 | 2.72 | -9.09 | 14.14 |
| | 1:8 | 96 | 16 | 16.7 | 82 | 14 | 17.1 | -0.41 | -11.91 | 10.68 |
| hSBA-MenC | 1:4 | 94 | 69 | 73.4 | 81 | 59 | 72.8 | 0.56 | -12.52 | 13.91 |
| | 1:8 | 94 | 68 | 72.3 | 81 | 57 | 70.4 | 1.97 | -11.38 | 15.52 |
| hSBA-MenW-135 | 1:4 | 97 | 82 | 84.5 | 86 | 54 | 62.8 | 21.75 | 9.13 | 34.15 |
| | 1:8 | 97 | 82 | 84.5 | 86 | 54 | 62.8 | 21.75 | 9.13 | 34.15 |
| hSBA-MenY | 1:4 | 95 | 59 | 62.1 | 85 | 53 | 62.4 | -0.25 | -14.30 | 13.92 |
| | 1:8 | 95 | 59 | 62.1 | 85 | 53 | 62.4 | -0.25 | -14.30 | 13.92 |

| | | | | | GMT ratio (ACWY-2 / ACWY-1) | | |
|---|---|---|---|---|---|---|---|
| | ACWY-2 | | ACWY-1 | | | 95% CI | |
| Anti body | N | GMT | N | GMT | Value | LL | UL |
| hSBA-MenA | 96 | 3.4 | 82 | 3.5 | 0.97 | 0.68 | 1.40 |
| hSBA-MenC | 94 | 29.8 | 81 | 31.2 | 0.96 | 0.49 | 1.87 |
| hSBA-MenW-135 | 97 | 63.9 | 86 | 29.0 | 2.20 | 1.21 | 4.00 |
| hSBA-MenY | 95 | 20.5 | 85 | 22.0 | 0.93 | 0.51 | 1.70 |

The differences between ACWY-2 and ACWY-1 groups in percentages of subjects with rSBA titers equal to or above the cut-off values of 1:8 and 1:128 and the GMT ratios 3 years after the primary vaccination are shown in the tables below.

| | | | | | | | | Difference in percentage (ACWY-2 minus ACWY-1) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | ACWY-2 | | | ACWY-1 | | | | 95% CI | |
| Antibody | Type | N | n | % | N | n | % | % | LL | UL |
| rSBA-MenA | 1:8 | 97 | 44 | 45.4 | 83 | 38 | 45.8 | -0.42 | -14.92 | 14.04 |
| | 1:128 | 97 | 24 | 24.7 | 83 | 23 | 27.7 | -2.97 | -16.03 | 9.86 |
| rSBA-MenC | 1:8 | 97 | 30 | 30.9 | 83 | 27 | 32.5 | -1.60 | -15.31 | 11.93 |
| | 1:128 | 97 | 15 | 15.5 | 83 | 18 | 21.7 | -6.22 | -18.03 | 5.17 |
| rSBA-MenW-135 | 1:8 | 95 | 35 | 36.8 | 83 | 36 | 43.4 | -6.53 | -20.77 | 7.86 |
| | 1:128 | 95 | 23 | 24.2 | 83 | 24 | 28.9 | -4.71 | -17.83 | 8.27 |
| rSBA-MenY | 1:8 | 98 | 45 | 45.9 | 83 | 39 | 47.0 | -1.07 | -15.54 | 13.40 |
| | 1:128 | 98 | 24 | 24.5 | 83 | 21 | 25.3 | -0.81 | -13.68 | 11.75 |

| | | | | | GMT ratio (ACWY-2 / ACWY-1) | | |
|---|---|---|---|---|---|---|---|
| | ACWY-2 | | ACWY-1 | | | 95% CI | |
| Anti body | N | GMT | N | GMT | Value | LL | UL |
| rSBA-MenA | 97 | 16.6 | 83 | 18.4 | 0.90 | 0.51 | 1.59 |
| rSBA-MenC | 97 | 10.6 | 83 | 13.2 | 0.80 | 0.46 | 1.38 |
| rSBA-MenW-135 | 95 | 14.6 | 83 | 19.4 | 0.75 | 0.41 | 1.37 |
| rSBA-MenY | 98 | 16.7 | 83 | 19.6 | 0.85 | 0.48 | 1.50 |

No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation were reported from the last visit in MenACWY-TT-055 up to 3 years after vaccination.

***Discussion on clinical aspects***

Three years after vaccination in study MenACWY-TT-055, the percentages of subjects with persistent hSBA MenA, MenC and Men Y titers ≥ 1:8 were comparable in both groups. However, the percentage of subjects with persistent hSBA MenW-135 titers ≥ 1:8 was higher in subjects that received two doses (84.5%) as compared with only one dose (62.8%).

In both groups, the GMTs decreased three years after vaccination compared to one year after vaccination and were comparable between the two groups (overlapping CIs); however, an exploratory analysis showed a ratio of 2.2 (with a 95%CI that did not contain 1) for the hSBA MenW-135 titers in favour of the two-dose regimen. The hSBA MenA GMTs were below the assay cut-off at both Year 1 and 3 persistence timepoints (ranged between 3.3 and 3.8 across groups and Year 1 and 3 persistence timepoints) for both groups, indicating that the majority of subjects did not retain hSBA MenA antibodies.

Three years after vaccination in study MenACWY-TT-055, the percentages of subjects with persistent HPA rSBA titers ≥ 1:8 and ≥ 1:128 for all serogroups were comparable in both study groups.

The HPA rSBA GMTs were comparable in both groups for the four meningococcal serogroups (ranged between 10.6 and 19.6 across study groups and the four serogroups). Since the rSBA titers during the vaccination and Year 1 persistence phases were tested with the GSK rSBA

assay, antibody kinetics and decay from the Year 1 to the Year 3 timepoints could not be directly assessed.

In conclusion, the difference between the two groups regarding hSBA MenW-135 titers observed at Year 1 persisted at Year 3 but was not supported by the rSBA titers results. Likewise, the discrepancy between GSK hSBA and rSBA MenA titers observed at year 1 was also observed at Year 3 with the HPA rSBA assay.

# IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH has provided updated (Year 3) persistence data from two studies showing progressive GMTs decrease over time. There is no unexpected information compared to the results reported at Year 1 but these should be updated in the SmPC. The MAH intends to submit a variation beginning of 2013 when all 3-year persistence data are available across all age groups. This position is supported.

- **Recommendation**

☒ **Fulfilled**

No further action required

# V. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable