SUPPLEMENTAL DIGITAL CONTENT

Immunogenicity and safety of AS03-adjuvanted H5N1 influenza vaccine in children 6–35 months of age: Results from a phase 2, randomized, observer-blind, multicenter, dose-ranging study

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Supplemental Digital Content 1. Figure

Study design

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HA, hemagglutinin; n, number of patients in each group; R, randomization

Sample size determination: Target enrollment in the study was 185 children (37 subjects per group) to achieve 34 evaluable subjects per formulation. This was based on the assumption that with a sample size of 34 evaluable subjects per formulation, standard deviation (log value) of 0.60, and a non-evaluable rate <10%, the lower limit of 95% confidence interval for the geometric mean titer (GMT) ratio would be 0.25, if the point estimate of GMT ratio of vaccine formulation to the reference (1.9μg HA/AS03B) was 0.5 (50% reduction in GMT). Based on the incidence of fever observed in children >6 months to 17 years of age in Kosalaraksa et al. (5) and with 34 evaluable subjects per group, the probability of observing at least one subject with fever ≥38°C and ≥38.5°C was >99.9% and 97.9%, assuming a fever incidence rate of 22.4% and 10.7%, respectively. The power to meet LL of 95% CI for seroconversion rate (>40%) and seroprotection rate (>70%) was 75% for any of the formulations (no type I error adjustment). Note: The first subject was enrolled on 7 July, 2016 and the last study visit was completed on 13 February, 2018. Data were locked for analysis on 25 May 2018 (Day 415). The study vaccine was an inactivated, split-virion H5N1 influenza vaccine manufactured in Québec, Canada by GSK. It contained different doses of HA from H5N1 A/Indonesia/5/2005 vaccine (0.9µg, 1.9µg, or 3.75µg) adjuvanted with AS03 (AS03B containing 5.93 mg DL-α-tocopherol, AS03C containing 2.97 mg DL-α-tocopherol, and AS03D containing DL-α-1.48 mg tocopherol).

Vaccine dose in orange color: Subjects received two priming doses of adjuvanted H5N1 vaccine (at Day 0 visit and at Day 21 visit; primary vaccination)

Vaccine dose in blue color: A single dose of unadjuvanted 3.75µg HA H5N1 antigen at the Day 385 visit (antigen challenge).

Supplemental Digital Content 2. Document

**Analyses of co-primary objectives**

1. *Immunogenicity fever index assessment*

An analysis of covariance model (ANCOVA) was fitted on the log10 transformed HI (hemagglutinin inhibition) and MN (microneutralization) antibody responses at Day 42, with the formulation as a fixed independent variable, adjusted by the log10 transformed pre-vaccination titer and age.

For vaccine-homologous HI and MN separately, an immunogenicity index (DGMT) was constructed using a desirability function based on the computed GMT (geometric mean of antibody titer) ratio (alternative formulation to reference =1.9 μg HA with AS03B, a GSK proprietary adjuvant system containing 5. mg DL-α-tocopherol and squalene in oil-in-water emulsion) and the 95% CI (confidence interval).

* DGMT was the LL (lower limit) of the 95% CI for GMT ratio
  + If the LL of the 95% CI for GMT ratio is less than 0.25 (i.e., 4- fold less than that of the reference formulation), then DGMT=0.
  + If the LL of the 95% CI for GMT ratio is greater than 1 (comparison formulation has higher GMT value than the reference formulation), DGMT=1.

Note: DGMT=1 for the reference formulation

The fever index (DR) was calculated according to body temperature measurements performed from Days 0-2 after each dose

* Any temperature <38°C (100.4°F) was assigned a value of 0. Any temperature > 40.5°C was assigned a value of 40.5.
* The highest possible temperature value per subject was 243 (6 x 40.5°C; i.e. for 3 days after Dose 1 and Dose 2);
* The lowest possible temperature value per subject was 0 (all measurements < 38.0°C (100.4°F) for 3 days after Dose 1 and Dose 2).
* For each subject, a temperature index was constructed as follows (243 minus the sum of recorded temperature values for 3 days after Dose 1 and Dose 2)/243. The average of temperature measurements for each vaccine group was calculated as the DR. A lower index value DR indicates a less desirable regimen in terms of reactogenicity. This index (D) ranged between 0 and 1 (0 = not desirable; 1 = highly desirable).

1. *Anamnestic response*

There were two separate evaluations, performed on evaluable subjects (according-to-protocol [ATP] cohort for immunogenicity at Day 392) following a booster dose:

* Point estimates and 95% CIs for MGIs (mean geometric increases) relative to Day 385 were computed for vaccine-homologous antibody titers assessed by HI at Day 392 for each formulation.
* Point estimates and 95% CIs for MGIs relative to Day 385 were computed for vaccine-homologous antibody titers assessed by MN at Day 392 for each formulation.

Supplemental Digital Content 3. Table

**Demographic characteristics with the AS03-adjuvanted H5N1 formulations (total vaccinated cohort)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **1.9 µg HA/AS03B**  **(n=38)** | **0.9 µg HA/AS03C**  **(n=37)** | **1.9 µg HA/AS03C**  **(n=38)** | **3.75 µg HA/AS03C**  **(n=37)** | **3.75 µg HA/AS03D**  **(n=35)** |
| **Age, months**  Mean ± SD  Median (range) | 21.9 ± 8.0  20.5 (8.0–35.0) | 22.6 ± 8.1  24.0 (8.0–34.0) | 21.6 ± 9.2  21.0 (7.0–35.0) | 20.8 ± 8.3  21.0 (6.0–35.0) | 20.3 ± 7.8  20.0 (6.0–34.0) |
| **Gender, n (%)**  Female  Male | 17 (44.7)  21 (55.3) | 14 (37.8)  23 (62.2) | 16 (42.1)  22 (57.9) | 23 (62.2)  14 (37.8) | 18 (51.4)  17 (48.6) |
| **Ethnicity, n (%)**  Asian-East Asian  Asian-South East  Other | 21 (55.3)  16 (42.1)  1 (2.6) | 21 (56.8)  16 (43.2)  0 (0.0) | 22 (57.9)  16 (42.1)  0 (0.0) | 21 (56.8)  16 (43.2)  0 (0.0) | 19 (54.3)  16 (45.7)  0 (0.0) |

HA, hemagglutinin; n, number of patients in the group; SD, standard deviation; AS03 is an adjuvant system containing DL-α-tocopherol and squalene in oil-in-water emulsion (AS03B containing 5.93 mg DL-α-tocopherol, AS03C containing 2.97 mg DL-α-tocopherol, and AS03D containing 1.48 mg DL-α-tocopherol).

Supplemental Digital Content 4. Table

**Summary of vaccine homologous microneutralization (MN) antibody parameters at Day 0, Day 42, Day 385 and Day 392 (Adapted according-to-protocol cohort for immunogenicity)**

|  | | **GMT** | | | **VRR** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Formulation |  | **N** | **Value** | **95% CI** | **N’** | **n’ (%)** | **95% CI** |
| **1.9 µg HA/AS03B** | Day 0 | 36 | 14.3 | 13.7–14.8 | - | - | - |
| Day 42 | 36 | 1,498.5 | 1,181.7–1,900.1 | 36 | 36 (100) | 90.3–100 |
| Day 385 | 34 | 250.3 | 197.1–318.0 | 34 | 34 (100) | 89.7–100 |
| Day 392 | 34 | 1,085.0 | 767.5–1,533.9 | 34 | 34 (100) | 89.7–100 |
| **0.9 µg HA/AS03C** | Day 0 | 32 | 14.0 | 14.0–14.0 | - | - | - |
| Day 42 | 32 | 1,214.3 | 921.3–1,600.6 | 31 | 31 (100) | 88.8–100 |
| Day 385 | 33 | 203.6 | 172.8–239.8 | 32 | 32 (100) | 89.1–100 |
| Day 392 | 33 | 969.1 | 710.1–1,322.6 | 32 | 32 (100) | 89.1–100 |
| **1.9 µg HA/AS03C** | Day 0 | 37 | 14.0 | 14.0–14.0 | - | - | - |
| Day 42 | 37 | 1,211.6 | 881.3–1,665.9 | 37 | 37 (100) | 90.5–100 |
| Day 385 | 37 | 213.8 | 175.2–260.9 | 37 | 37 (100) | 90.5–100 |
| Day 392 | 37 | 674.2 | 492.3–923.3 | 37 | 37 (100) | 90.5–100 |
| **3.75 µg HA/AS03C** | Day 0 | 29 | 14.0 | 14.0–14.0 | - | - | - |
| Day 42 | 31 | 707.1 | 533.1–937.9 | 29 | 29 (100) | 88.1–100 |
| Day 385 | 31 | 247.2 | 201.4–303.5 | 29 | 29 (100) | 88.1–100 |
| Day 392 | 31 | 681.0 | 496.3–934.4 | 29 | 29 (100) | 88.1–100 |
| **3.75 µg HA/AS03D** | Day 0 | 35 | 14.0 | 14.0–14.0 | - | - | - |
| Day 42 | 35 | 727.4 | 545.9–969.2 | 35 | 35 (100) | 90.0–100 |
| Day 385 | 32 | 198.5 | 165.1–238.7 | 32 | 32 (100) | 89.1–100 |
| Day 392 | 32 | 489.6 | 381.7–628.0 | 32 | 32 (100) | 89.1–100 |

CI, confidence interval; GMT, geometric mean antibody titer; HA, hemagglutinin; N, number of subjects with results available for GMT computation; N’, number of subjects with both pre- and post- results available for VRR calculation; n’, number of responders; VRR, vaccine response rate (defined as post-vaccination reciprocal titer of formulations that had at least 4-fold increase compared with their pre-vaccination reciprocal titer [Day 0]). AS03 is an adjuvant system containing DL-α-tocopherol and squalene in oil-in-water emulsion (AS03B containing 5.93 mg DL-α-tocopherol, AS03C containing 2.97 mg DL-α-tocopherol, and AS03D containing 1.48 mg DL-α-tocopherol).

Supplemental Digital Content 5. Table

**Descriptive statistics on the frequency of influenza-specific CD4 T-cells per million** **CD4+ T-cells expressing at least two of the following activation markers (CD40L, interleukin [IL]-2, interferon [IFN]Ɣ and tumor necrosis factor [TNF]α) (all polypositives) upon in vitro stimulation using Influenza A/Indonesia (clade 2.1.3.2) vaccine**

| Formulation |  | **N** | **Mean ± SD** |
| --- | --- | --- | --- |
| **1.9 µg HA/AS03B** | Day 0 | 20 | 164.20 ± 232.15 |
| Day 42 | 18 | 4,255.72 ± 4,758.93 |
| Day 385 | 20 | 2,519.55 ± 3,769.53 |
| Day 392 | 20 | 2,853.50 ± 3,289.31 |
| **0.9 µg HA/AS03C** | Day 0 | 19 | 111.42 ± 153.40 |
| Day 42 | 19 | 3,214.00 ± 3,446.34 |
| Day 385 | 18 | 1,507.39 ± 1,118.74 |
| Day 392 | 17 | 1,901.65 ± 2,098.05 |
| **1.9 µg HA/AS03C** | Day 0 | 17 | 207.59 ± 520.58 |
| Day 42 | 17 | 1,891.76 ± 2,679.80 |
| Day 385 | 18 | 1,949.11 ± 2,652.18 |
| Day 392 | 19 | 1,393.63 ± 1,740.16 |
| **3.75 µg HA/AS03C** | Day 0 | 18 | 340.33 ± 896.95 |
| Day 42 | 16 | 1,987.31 ± 2,042.72 |
| Day 385 | 18 | 979.67 ± 620.54 |
| Day 392 | 18 | 927.50 ± 928.30 |
| **3.75 µg HA/AS03D** | Day 0 | 19 | 582.63 ± 1,969.89 |
| Day 42 | 16 | 2,182.81 ± 2,290.70 |
| Day 385 | 17 | 1,352.35 ± 1,930.06 |
| Day 392 | 17 | 1,156.12 ± 1,140.47 |

N, number of subjects with available results for pre- and post- timepoints; SD, standard deviation

AS03 is an adjuvant system containing DL-α-tocopherol and squalene in oil-in-water emulsion (AS03B containing 5.93 mg DL-α-tocopherol, AS03C containing 2.97 mg DL-α-tocopherol, and AS03D containing 1.48 mg DL-α-tocopherol).

Supplemental Digital Content 6. Table

**Incidence of general AEs during the 7-day (Days 0-6) post-vaccination period following each dose and overall (total vaccinated cohort)**

|  | | **1.9 µg HA/AS03B** | | **0.9 µg HA/AS03C** | | **1.9 µg HA/AS03C** | | **3.75 µg HA/AS03C** | | **3.75 µg HA/AS03D** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Symptom** | **Type** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** |
| **Dose 1** | | | | | | | | | | | |
| Drowsiness | All | 38 | 15 (39.5; 24.0**–**56.6) | 37 | 10 (27.0; 13.8**–**44.1) | 38 | 7 (18.4; 7.7**–**34.3) | 37 | 10 (27.0; 13.8**–**44.1) | 35 | 11 (31.4; 16.9**–**49.3) |
| Grade 3 | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 1 (2.7; 0.1**–**14.2) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 0 (0.0; 0.0**–**9.5) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 0 (0.0; 0.0**–**9.5) | 35 | 0 (0.0; 0.0**–**10.0) |
| Irritability | All | 38 | 13 (34.2; 19.6**–**51.4) | 37 | 9 (24.3; 11.8**–**41.2) | 38 | 11 (28.9; 15.4**–**45.9) | 37 | 13 (35.1; 20.2**–**52.5) | 35 | 12 (34.3; 19.1**–**52.2) |
| Grade 3 | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 1 (2.7; 0.1**–**14.2) | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 3 (8.1; 1.7**–**21.9) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Loss of appetite | All | 38 | 12 (31.6; 17.5**–**48.7) | 37 | 5 (13.5; 4.5**–**28.8) | 38 | 9 (23.7; 11.4**–**40.2) | 37 | 10 (27.0; 13.8**–**44.1) | 35 | 8 (22.9; 10.4**–**40.1) |
| Grade 3 | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 0 (0.0; 0.0**–**9.5) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Temperature (°C) | All | 38 | 11 (28.9; 15.4**–**45.9) | 37 | 5 (13.5; 4.5**–**28.8) | 38 | 3 (7.9; 1.7**–**21.4) | 37 | 7 (18.9; 8.0**–**35.2) | 35 | 5 (14.3; 4.8**–**30.3) |
| ≥39.0 | 38 | 2 (5.3; 0.6**–**17.7) | 37 | 0 (0.0; 0.0**–**9.5) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 35 | 1 (2.9; 0.1**–**14.9) |
| Medical advice | 38 | 2 (5.3; 0.6**–**17.7) | 37 | 4 (10.8; 3.0**–**25.4) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| **Dose 2** | | | | | | | | | | | |
| Drowsiness | All (≥38℃) | 37 | 15 (40.5; 24.8**–**57.9) | 36 | 12 (33.3; 18.6**–**51.0) | 38 | 8 (21.1; 9.6**–**37.3) | 35 | 9 (25.7; 12.5**–**43.3) | 35 | 6 (17.1; 6.6**–**33.6) |
| Grade 3 | 37 | 0 (0.0; 0.0**–**9.5) | 36 | 3 (8.3; 1.8**–**22.5) | 38 | 1 (2.6; 0.1**–**13.8) | 35 | 0 (0.0; 0.0**–**10.0) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 37 | 1 (2.7; 0.1**–**14.2) | 36 | 3 (8.3; 1.8**–**22.5) | 38 | 0 (0.0; 0.0**–**9.3) | 35 | 1 (2.9; 0.1**–**14.9) | 35 | 0 (0.0; 0.0**–**10.0) |
| Irritability | All (≥38℃) | 37 | 17 (45.9; 29.5**–**63.1) | 36 | 12 (33.3; 18.6**–**51.0) | 38 | 12 (31.6; 17.5**–**48.7) | 35 | 12 (34.3; 19.1**–**52.2) | 35 | 16 (45.7; 28.8**–**63.4) |
| Grade 3 | 37 | 1 (2.7; 0.1**–**14.2) | 36 | 0 (0.0; 0.0**–**9.7) | 38 | 2 (5.3; 0.6**–**17.7) | 35 | 0 (0.0; 0.0**–**10.0) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 37 | 1 (2.7; 0.1**–**14.2) | 36 | 3 (8.3; 1.8**–**22.5) | 38 | 0 (0.0; 0.0**–**9.3) | 35 | 1 (2.9; 0.1**–**14.9) | 35 | 0 (0.0; 0.0**–**10.0) |
| Loss of appetite | All (≥38℃) | 37 | 14 (37.8; 22.5**–**55.2) | 36 | 7 (19.4; 8.2**–**36.0) | 38 | 7 (18.4; 7.7**–**34.3) | 35 | 9 (25.7; 12.5**–**43.3) | 35 | 6 (17.1; 6.6**–**33.6) |
| Grade 3 | 37 | 0 (0.0; 0.0**–**9.5) | 36 | 0 (0.0; 0.0**–**9.7) | 38 | 2 (5.3; 0.6**–**17.7) | 35 | 0 (0.0; 0.0**–**10.0) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 37 | 1 (2.7; 0.1**–**14.2) | 36 | 3 (8.3; 1.8**–**22.5) | 38 | 0 (0.0; 0.0**–**9.3) | 35 | 1 (2.9; 0.1**–**14.9) | 35 | 0 (0.0; 0.0**–**10.0) |
| Temperature (°C) | All (≥38℃) | 37 | 18 (48.6; 31.9**–**65.6) | 36 | 12 (33.3; 18.6**–**51.0) | 38 | 9 (23.7; 11.4**–**40.2) | 35 | 8 (22.9; 10.4**–**40.1) | 35 | 8 (22.9; 10.4**–**40.1) |
| ≥39.0 | 37 | 5 (13.5; 4.5**–**28.8) | 36 | 2 (5.6; 0.7**–**18.7) | 38 | 1 (2.6; 0.1**–**13.8) | 35 | 3 (8.6; 1.8**–**23.1) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 37 | 2 (5.4; 0.7**–**18.2) | 36 | 3 (8.3; 1.8**–**22.5) | 38 | 0 (0.0; 0.0**–**9.3) | 35 | 1 (2.9; 0.1**–**14.9) | 35 | 0 (0.0; 0.0**–**10.0) |
| **Overall/subject\*\*** | | | | | | | | | | | |
| Drowsiness | All (≥38℃) | 38 | 23 (60.5; 43.4**–**76.0) | 37 | 16 (43.2; 27.1**–**60.5) | 38 | 12 (31.6; 17.5**–**48.7) | 37 | 15 (40.5; 24.8**–**57.9) | 35 | 14 (40.0; 23.9**–**57.9) |
| Grade 3 | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 3 (8.1; 1.7**–**21.9) | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 0 (0.0; 0.0**–**9.5) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 4 (10.8; 3.0**–**25.4) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Irritability | All (≥38℃) | 38 | 21 (55.3; 38.3**–**71.4) | 37 | 15 (40.5; 24.8**–**57.9) | 38 | 17 (44.7; 28.6**–**61.7) | 37 | 20 (54.1; 36.9**–**70.5) | 35 | 19 (54.3; 36.6**–**71.2) |
| Grade 3 | 38 | 2 (5.3; 0.6**–**17.7) | 37 | 1 (2.7; 0.1**–**14.2) | 38 | 3 (7.9; 1.7**–**21.4) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 5 (13.5; 4.5**–**28.8) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Loss of appetite | All (≥38℃) | 38 | 20 (52.6; 35.8**–**69.0) | 37 | 10 (27.0; 13.8**–**44.1) | 38 | 12 (31.6; 17.5**–**48.7) | 37 | 17 (45.9; 29.5**–**63.1) | 35 | 10 (28.6; 14.6**–**46.3) |
| Grade 3 | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 0 (0.0; 0.0**–**9.5) | 38 | 2 (5.3; 0.6**–**17.7) | 37 | 1 (2.7; 0.1**–**14.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Medical advice | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 4 (10.8; 3.0**–**25.4) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 2 (5.4; 0.7**–**18.2) | 35 | 0 (0.0; 0.0**–**10.0) |
| Temperature (°C) | All (≥38℃) | 38 | 23 (60.5; 43.4**–**76.0) | 37 | 15 (40.5; 24.8**–**57.9) | 38 | 12 (31.6; 17.5**–**48.7) | 37 | 12 (32.4; 18.0**–**49.8) | 35 | 10 (28.6; 14.6**–**46.3) |
| ≥39.0 | 38 | 7 (18.4; 7.7**–**34.3) | 37 | 2 (5.4; 0.7**–**18.2) | 38 | 1 (2.6; 0.1**–**13.8) | 37 | 4 (10.8; 3.0**–**25.4) | 35 | 1 (2.9; 0.1**–**14.9) |
| Medical advice | 38 | 4 (10.5; 2.9**–**24.8) | 37 | 6 (16.2;6.2**–**32.0) | 38 | 0 (0.0; 0.0**–**9.3) | 37 | 3 (8.1; 1.7**–**21.9) | 35 | 0 (0.0; 0.0**–**10.0) |

\*\*Overall/subject is based on the primary vaccination series i.e. dose 1 and dose 2.

AE, adverse events: CI, confidence interval; HA, hemagglutinin; N, number of subjects with results available; n, number of subjects reporting AE.

AS03 is an adjuvant system containing DL-α-tocopherol and squalene in oil-in-water emulsion (AS03B containing 5.93 mg DL-α-tocopherol, AS03C containing 2.97 mg DL-α-tocopherol, and AS03D containing 1.48 mg DL-α-tocopherol).

Supplemental Digital Content 7. Table

**Global summary of Medically Attended Events (MAEs) and Adverse Events of Special Interest (AESIs) reported during the entire study period (Total vaccinated cohort)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1.9 µg HA/AS03B** | | **0.9 µg HA/AS03C** | | **1.9 µg HA/AS03C** | | **3.75 µg HA/AS03C** | | **3.75 µg HA/AS03D** | |
|  | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** | **N** | **n (%; 95% CI)** |
| Subjects with at least one unsolicited symptom with MAE reported | 38 | 29 (76.3; 59.8-88.6) | 37 | 28 (75.7; 58.8-88.2) | 38 | 33 (86.8; 71.9-95.6) | 37 | 27 (73.0; 55.9-86.2) | 35 | 26 (74.3; 56.7-87.5) |
| Subjects with at least one unsolicited symptom with AESI reported | 4 (10.5; 2.9-24.8) | 3 (8.1; 1.7-21.9) | 3 (7.9; 1.7-21.4) | 2 (5.4; 0.7-18.2) | 2 (5.7; 0.7-19.2) |

N, number of subjects with at least one administered dose; n (%), number (percentage) of subjects reporting the symptom at least once; CI, confidence interval.

Supplemental Digital Content 8. Figure

Focus on the Patient SectionA screenshot of a cell phone

Description automatically generated