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

Authors: Joon Hyung Kim1, Mamadou Drame1,Thanyawee Puthanakit2,Nan-Chang Chiu3,Khuanchai Supparatpinyo4, Li-Min Huang5, Cheng-Hsun Chiu6, Po-Yen Chen7,Kao-Pin Hwang8, Jasur Danier1, Damien Friel9, Bruno Salaun10, Wayne Woo1, David W. Vaughn11, Bruce Innis12, Anne Schuind1,a

Affiliations:

1GSK, Rockville, MD, USA

2Center of Excellence in Pediatric Infectious Diseases and Vaccines, and Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

3Mackay Children’s Hospital, Taipei, Taiwan

4Chiang Mai University, Chiang Mai, Thailand

5National Taiwan University Hospital, Taipei, Taiwan

6Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

7Taichung Veterans General Hospital, Taichung, Taiwan

8China Medical University Hospital, PhD, Taichung, Taiwan

9GSK, Wavre, Belgium

10GSK, Rixensart, Belgium

11GSK, Rockville, MD, USA (current: Bill & Melinda Gates Foundation, Seattle, WA, USA)

12PATH, Washington, DC, USA

a current affiliation: PATH, Washington, DC, USA

**Corresponding author**: Joon Hyung Kim**,** GSK, Rockville, MD, USA

Supplemental Digital Content 1. Figure

Study design



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 ± SDMedian (range) | 21.9 ± 8.020.5 (8.0–35.0) | 22.6 ± 8.124.0 (8.0–34.0) | 21.6 ± 9.221.0 (7.0–35.0) | 20.8 ± 8.321.0 (6.0–35.0) | 20.3 ± 7.820.0 (6.0–34.0) |
| **Gender, n (%)**FemaleMale | 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 AsianAsian-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 Section