Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

September 13, 2017

FDA Briefing Document

***Errata* - FDA Briefing Document, VRBPAC Meeting**

1. Page 4, in the first sentence of the third paragraph, change: "Safety monitoring for Zoster-006 and Zoster-022 included solicited local [injection site (IS) pain, swelling and redness] and general (fever, headache, myalgia, GI symptoms, shivering and fatigue) signs and symptoms recorded on a diary card by a **randomized** subset of subjects for seven days (Days 0 – 6) following each vaccination; unsolicited adverse events (AEs) recorded on a diary card by all subjects for 30 days following each vaccination; serious adverse events (SAEs) collected on all subjects from M0 – M14; and deaths, related SAEs and potential immune-mediated inflammatory diseases (pIMDs) collected for the duration of the studies."

to

"Safety monitoring for Zoster-006 and Zoster-022 included solicited local [injection site (IS) pain, swelling and redness] and general (fever, headache, myalgia, GI symptoms, shivering and fatigue) signs and symptoms recorded on a diary card by a subset of subjects for seven days (Days 0 – 6) following each vaccination; unsolicited adverse events (AEs) recorded on a diary card by all subjects for 30 days following each vaccination; serious adverse events (SAEs) collected on all subjects from M0 – M14; and deaths, related SAEs and potential immune-mediated inflammatory diseases (pIMDs) collected for the duration of the studies."

2. Page 4, in the second sentence of the last paragraph, change: "The breakdown of HZ case confirmation was **89.6%** by PCR and 10.6% by HZAC adjudication."

to

"The breakdown of HZ case confirmation was **89.4%** by PCR and 10.6% by HZAC adjudication."

3. Page 5, in the second sentence of the second paragraph, change: "Of subjects in the TVC, 57.9% (SHINGRIX group N = 4,457, Placebo group N = 4,464) were **randomized** to the 7-day diary card subset [stratified in an approximately 3:3:4 ratio by age (50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA, respectively)] and recorded solicited symptoms on a diary card on Days 0 – 6 following each vaccination."

to

"Of subjects in the TVC, 57.9% (SHINGRIX group N = 4,457, Placebo group N = 4,464) were **included in** the 7-day diary card subset [stratified in an approximately 3:3:4 ratio by

age (50 – 59 YOA, 60 – 69 YOA and ≥ 70 YOA, respectively)] and recorded solicited symptoms on a diary card on Days 0 – 6 following each vaccination."

4. Page 5, in the third sentence from the bottom of the second paragraph, change: "Overall by subject, any grade (Grade 3) temperature was reported by **23.5%** (0.3%) of subjects in the SHINGRIX group and 3.0% (0.1%) of subjects in the Placebo group."

to

"Overall by subject, any grade (Grade 3) temperature was reported by **21.5%** (0.3%) of subjects in the SHINGRIX group and 3.0% (0.1%) of subjects in the Placebo group."

5. Page 7, the top of the page, change: "The subject was a **90 YO male** with 10 year history of stable immune thrombocytopenia who received diagnoses of acute myeloid leukemia 75 days after Dose 1, neutropenic sepsis 97 days after Dose 1, and died (b) (6) days after Dose 1."

to

"The subject was a **male 90 years of age or older** with 10 year history of stable immune thrombocytopenia who received diagnoses of acute myeloid leukemia 75 days after Dose 1, neutropenic sepsis 97 days after Dose 1, and died (b) (6) days after Dose 1."

6. Page 9, Section 3.3: Mechanism of Action of $AS01_B$ Adjuvant, after the sentence: "$AS01_B$ adjuvant induces a local and transient activation of the innate immune system by two immune enhancers: MPL, which signals through Toll-like Receptor 4, and QS-21, which acts through as yet unknown receptor(s)."

add

The use of the saponin molecule (QS-21) purified from plant extract *Quillaja saponaria* Molina, as a component in GSK's AS01 adjuvant, has been contractually authorized to GSK by Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.

7. Page 12, Table 2: *Additional Studies - Alternative Administration Site and Specific Populations*, under the Zoster-033 column, sixth row, "Countries," change "Canada, **Estonia**"

to

"Canada, **Russian Federation**"

8. Page 16, Section: 5.1.4: Endpoints and Criteria for Study Success, second bullet, change "Safety endpoints: solicited local and general symptoms recorded by a subset of subjects **randomized to** the 7-day diary card subset for 7 days (Days 0 – 6) after each vaccination,

unsolicited AEs recorded on a diary card by all subjects during Days 0 – 29 after each vaccination, medically attended visits recorded by all subjects from M0 – M8, SAEs recorded by all subjects from M0 – 14 and SAEs judged vaccine related, SAEs related to a concurrent GSK medication/vaccination, fatal SAEs and pIMDs recorded by all subjects throughout the study."

to

"Safety endpoints: solicited local and general symptoms recorded by a subset of subjects **included in** the 7-day diary card subset for 7 days (Days 0 – 6) after each vaccination, unsolicited AEs recorded on a diary card by all subjects during Days 0 – 29 after each vaccination, medically attended visits recorded by all subjects from M0 – M8, SAEs recorded by all subjects from M0 – 14 and SAEs judged vaccine related, SAEs related to a concurrent GSK medication/vaccination, fatal SAEs and pIMDs recorded by all subjects throughout the study."

9. Page 23, in the first and second sentences of Section 5.1.10: Safety Results, Solicited symptoms, change "Solicited symptoms were collected for 7 days (Days 0 – 6) on a **randomized** subset of subjects with a planned age stratification of 3:3:3:1 for the 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA age strata. Approximately 58% of the subjects in the TVC were **randomized to** this subset (SHINGRIX group N = 4,457, Placebo group N = 4,464)."

to

"Solicited symptoms were collected for 7 days (Days 0 – 6) on a subset of subjects with a planned age stratification of 3:3:3:1 for the 50 – 59, 60 – 69, 70 – 79 and ≥ 80 YOA age strata. Approximately 58% of the subjects in the TVC were **included in** this subset (SHINGRIX group N = 4,457, Placebo group N = 4,464)."

10. Page 25, Table 12: *Incidence of solicited general symptoms reported during the 7-day (Days 0 – 6) post-vaccination period overall/subject (Zoster-006 TVC Diary card – EOS analysis)*, in the row: "Temperature – any grade" change "SHINGRIX group n (%): 940 (**23.5%**)"

to

"SHINGRIX group n (%): 940 (**21.5%**)."

11. Page 29, in the third sentence of Section 5.2: Study Zoster-022, change: "The DLP for the Final HZ efficacy analysis (time point for primary efficacy analysis) was 01-JUL-2014, and the DLP for the EOS database freeze was 12-OCT-2015."

to

"The DLP for the database freeze was 12-OCT-2015."

12. Page 38, in the second sentence of the second paragraph, change the sentence: "A post-hoc tabulation performed by the applicant of the proportions of subjects in the 7-day diary card subset reporting unsolicited AEs during the 30-day post-vaccination period indicated that **27.1%** and **25.8%** of subjects overall in the 7-day diary card subset in the SHINGRIX and Placebo groups, respectively, reported at least one unsolicited AE during the 30-day post-vaccination period."

to

"A post-hoc tabulation performed by the applicant of the proportions of subjects in the 7-day diary card subset reporting unsolicited AEs during the 30-day post-vaccination period indicated that **26.0%** and **26.1%** of subjects overall in the 7-day diary card subset in the SHINGRIX and Placebo groups, respectively, reported at least one unsolicited AE during the 30-day post-vaccination period."

13. Page 42, in the second sentence of the second paragraph under Table 29, change: "The subject, a **90 YO male** with a past medical history of stable immune thrombocytopenia for approximately 10 years prior to vaccination, was noted to be pancytopenic 72 days after Dose 1, and diagnosed with acute myeloid leukemia (AML) on the basis of a bone marrow biopsy 75 days after Dose 1.

to

"The subject, a **male 90 years of age or older** with a past medical history of stable immune thrombocytopenia for approximately 10 years prior to vaccination, was noted to be pancytopenic 72 days after Dose 1, and diagnosed with acute myeloid leukemia (AML) on the basis of a bone marrow biopsy 75 days after Dose 1."

14. Pages 42 – 43, in the second sentence under *Broader pooling analysis*, change: "No subjects in the broader pooled analysis (ex-Zoster-006 and Zoster-022) died within the 30 day post last vaccination period. **Six** subjects died from first dose to 365 days last vaccination and an additional **three** subjects died during the whole post-vaccination period."

to

"No subjects in the broader pooled analysis (ex-Zoster-006 and Zoster-022) died within the 30 day post last vaccination period. **Five** subjects died from first dose to 365 days last vaccination and an additional **four** subjects died during the whole post-vaccination period."

15. Page 48, in the second sentence under *Convulsions*, change: "Available **narratives** were reviewed; of these subjects two had alternative etiologies for their event (intracranial aneurysm, acute subdural hematoma after a fall) and two had a prior history of convulsions."

to

"Available **data** were reviewed; of these subjects two had alternative etiologies for their event (intracranial aneurysm, acute subdural hematoma after a fall) and two had a prior history of convulsions."

16. Page 48, in the second sentence under *Supraventricular tachyarrhythmias,* change: "For signal detection purposes, CBER analyzed the proportions of subjects in the main pooling reporting events in the narrow Cardiac arrhythmia SMQ, Tachyarrhythmias sub-SMQ and Supraventricular tachyarrhythmias sub-SMQ as unsolicited AEs during the 30-day post-vaccination period or MAEs during M0-**M14**, and did not detect a difference for events in these narrow SMQs during those time periods."

to

"For signal detection purposes, CBER analyzed the proportions of subjects in the main pooling reporting events in the narrow Cardiac arrhythmia SMQ, Tachyarrhythmias sub-SMQ and Supraventricular tachyarrhythmias sub-SMQ as unsolicited AEs during the 30-day post-vaccination period or MAEs during M0-**M8**, and did not detect a difference for events in these narrow SMQs during those time periods.