Administering the Second Dose of *Shingrix* After the Maximum Recommended Interval

This information is provided in response to your request for information about Shingrix® (Zoster Vaccine Recombinant, Adjuvanted).

SUMMARY

- A randomized, open label, multi-center, phase III study (N = 354), in adults ≥50 years of age assessed the immunogenicity and safety of 2 doses of *Shingrix* administered on a 0 and 2 month (0,2M; N = 119) dosing schedule compared to a 0 and 6 month (0,6M; N = 119) and a 0 and 12 month (0,12M; N = 116) dosing schedule.
- The co-primary objectives of this study were to evaluate the vaccine response rate (VRR) for anti-glycoprotein E (anti-gE) antibody concentrations 1 month post-dose 2 in the 0,6M and 0,12M groups and, if the objective was met, to demonstrate the non-inferiority in terms of anti-gE antibody concentrations 1 month post-dose 2 compared to a 0,2M schedule.
- The co-primary objective to evaluate the VRR for anti-gE antibody concentrations 1 month post-dose 2 in the 0,6M and 0,12M schedule groups was met as the lower limit (LL) of the 97.5% confidence interval (CI) was above 60% for both schedules.
- The co-primary objective of non-inferiority of the 0,6M and 0,12M schedules compared to a 0,2M schedule, in terms of anti-gE antibody concentrations 1 month post-dose 2 was met only for the 0,6M schedule. The anti-gE geometric mean concentration (GMC) ratio (0,2M/0,6M) of 1.16 (0.98-1.39) for the 0,6M group did meet the non-inferiority criterion as the UL of the 97.5% CI was below the pre-defined limit of 1.5. The anti-gE GMC ratio (0,2M/0,12M) of 1.19 (0.93-1.53) for the 0,12M group did not meet the non-inferiority criterion.
- At 12 months post-dose 2, anti-gE antibody levels remained 13.2-fold, 12.1-fold, and 11.6-fold above pre-vaccination levels in the 0,2M, 0,6M and 0,12M groups respectively.
- Pain was the most frequently reported solicited local symptom following each dose, reported by 76.5%, 79.8% and 84.5% of vaccinees in the 0,2M, 0,6M and 0,12M groups respectively. The most frequently reported solicited general symptoms after each dose were fatigue (45.5%, 52.9% and 61.2%), myalgia (52.9%, 47.9% and 55.2%) and headache (39.5%, 39.5% and 45.7%). Grade 3 fever (>39.0°C) was reported in 1 subject in the 0,2M Group and in 2 subjects in the 0,12M Group.
- The percentage of subjects reporting the occurrence of unsolicited symptoms was 22.7% in the 0,2M Group and 0,6M Group and 19.8% in the 0,12M Group. Grade 3 unsolicited symptoms were reported by 3.4% of subjects in all groups. No causally related serious adverse events (SAEs), potential immune mediated disorders (pIMDs) or herpes zoster (HZ) cases were reported from the first administered dose until the study end (12 months post-dose 2).
- *Shingrix* is not approved to be administered on schedules longer than 0 and 2-6 months.
- The Centers for Disease Control and Prevention (CDC) has published guidance on this topic. Please see below for more information.
- Important safety information is found in the attached Prescribing Information.

A randomized, open label, multinational (3 centers in US and 1 center in Estonia), phase III study (N = 354) with 3 parallel groups assessed the immunogenicity and safety of *Shingrix* (50 µg/0.5 mL)

administered intramuscularly on a 0 and 2 month (0,2M; N = 119) schedule compared to a 0 and 6 month (0,6M; N = 119) and a 0 and 12 month (0,12M; N = 116) schedule in non-immunocompromised adults ≥50 years of age.[1,2]

The co-primary objectives of the study were:

• To evaluate the VRR for anti-gE antibody concentrations 1 month post-dose 2 in the 0,6M and 0,12M groups. The objective was met if the LL of the 97.5% CI of the VRR for anti-gE antibody concentrations in the 0,6M or 0,12M groups was at least 60%.

If the first co-primary objective was met:

• To demonstrate the non-inferiority in terms of anti-glycoprotein E (gE) antibody concentrations 1 month post-dose 2 for the 0,6M and 0,12M schedules compared to a 0,2M schedule. This objective was met if the UL of the 97.5% CI for the anti-gE GMC ratio (0,2M schedule over 0,6M or 0,12M schedule) at 1 month post-dose 2 was below 1.5.

Secondary objectives included an evaluation of the persistence of anti-gE antibodies in each group 12 months post-dose 2 and the evaluation of safety and reactogenicity following administration of *Shingrix*. Solicited and unsolicited AEs were recorded for 7 and 30 days post-each dose, respectively. Serious adverse events (SAEs) and potential immune mediated disorders (pIMDs) were recorded from dose 1 to 12 months post-dose 2.

RESULTS

Immunogenicity

The first co-primary objective to evaluate the VRR was met for both groups as the lower limit of the 97.5% CI of the VRR for anti-gE antibody concentrations at 1 month post-dose 2 was above 60% for both schedules (Table 1).

Table 1. VRR for Anti-gE at One Month Post-Dose 2 in 0,6M and 0,12M Groups (ATP Cohort for Immunogenicity)[1]

		VRR*			
				97.5%CI	
Group	**N**	**n**	**%**	**LL†**	**UL**
0,6M	114	110	96.5	**90.4**	99.2
0,12M	110	104	94.5	**87.6**	98.3

97.5% CI = Exact 97.5% confidence interval; anti-gE = Anti-glycopteotein E; ATP cohort for immunogenicity = According to protocol cohort for immunogenicity included all subjects who had met all eligibility criteria, complied with the procedures and intervals defined in the protocol, did not meet any of the criteria for elimination during the study and for whom data concerning immunogenicity outcome measures were available; LL = Lower Limit; N = Number of subjects with both pre- and post-vaccination results available; n/% = Number/percentage of responders; UL = Upper Limit; VRR = Vaccine response rate

*Vaccine response defined as:

• For initially seronegative subjects, antibody concentration at 1 month post-vaccination ≥ 4 fold the cut-off for Anti-gE (97 mIU/mL)

• For initially seropositive subjects, antibody concentration at 1 month post-vaccination ≥ 4 fold the pre-vaccination antibody concentration

†The objective was met if the lower limit of the 97.5% confidence interval (CI) of the VRR for anti-gE antibody concentrations in the 0,6M or 0,12M schedule groups was at least 60%

The second co-primary objective to demonstrate non-inferiority compared to the 0,2M dosing schedule was met for the 0,6M dosing schedule as the UL of the 97.5% CI for the anti-gE GMC ratio (0,2M Group over 0,6M Group) was below 1.5. The objective was not met for the 0,12M dosing schedule (Table 2).

Table 2- See Appendix

Persistence of the immune response

The persistence of antibodies to gE was evaluated in each group, 1 and 12 months post-dose 2. Anti-gE antibody levels remained at least 11.6-fold above pre-vaccination levels for 12 months post-dose 2 irrespective of the vaccination schedule (Table 3).

Table 3. GMCs of Anti-gE at Pre-vaccination and Month 1 and Month 12 Post-Dose 2 of *Shingrix* Given on 0,2 Month, 0,6 Month and 0,12 Month schedules (Adapted ATP cohort for immunogenicity) [(1)]

			GMC (mIU/ml)		
				95%CI	
Group	**Timepoint**	**N**	**Value**	**LL**	**UL**
0,2M	PRE	118	1079.1	891.9	1305.5
	Month 1*	118	44,376.3	39,697.0	49,607.2
	Month 12*	117	14,245.4	12,450.8	16,298.6
0,6M	PRE	114	1066.1	891.3	1275.3
	Month 1*	114	38,153.7	34,205.8	42,557.3
	Month 12*	115	12,911.5	11,412.7	14,607.2
0,12M	PRE	110	1019.4	858.6	1210.2
	Month 1*	111	37,435.8	30,813.8	45,480.8
	Month 12*	110	11,892.1	10,236.4	13,815.6

95% CI = 95% Confidence interval; Adapted ATP cohort for immunogenicity = Adapted ATP cohort for immunogenicity: Adapted according to protocol cohort including all evaluable subjects for whom the pre-vaccination and one month post dose 2 time point data were obtained from ATP cohort for immunogenicity and 12 months post-dose 2 time point data were obtained from ATP cohort for persistence; GMC = Geometric mean antibody concentration calculated on all subjects; LL = Lower Limit; N = Number of subjects with available results; PRE = Pre-vaccination; UL = Upper Limit
*Post-Dose 2

Reactogenicity and Safety

Solicited local and general symptoms were reported at similar rates among the 3 study groups, by 89.9%, 89.1%, and 92.2% of subjects in the 0,2M, 0,6M and 0,12M Groups, respectively. Reactions were transient (median duration: 1–4 days) and mostly mild to moderate.[(1,2)] Pain was the most frequently reported solicited local symptom during the 7-day post-vaccination period after each dose. Fatigue, myalgia and headache were the most frequently reported solicited general symptoms (Table 4).

The percentage of subjects reporting the occurrence of unsolicited symptoms within the 30-day (Days 0-29) post-vaccination period was 22.7% in the 0,2M and 0,6M Group and 19.8% in the 0,12M Group. Grade 3 unsolicited symptoms were reported by 3.4% of subjects in all groups.[(1,2)]

Two fatal SAEs (cerebral hemorrhage and cardiovascular disorder) were reported in the study from 30 days post last vaccination up to the study end. These fatal events were assessed by the investigator as not causally related to vaccination. No causally related serious SAEs, pIMDs or HZ cases were reported from the first administered dose until the study end (12 months post dose 2).[(1,2)]

Table 4. Number (%) of Subjects Reporting Solicited Local and General Symptoms During the 7-day (Days 0-6) Post-Vaccination Period Across Doses (Total Vaccinated Cohort)[1]

		0,2M Group N = 119		0,6M Group N = 119		0,12M Group N = 116	
Symptom	**Type**	**n**	**%**	**n**	**%**	**n**	**%**
Local symptoms							
Pain	Any	91	76.5	95	79.8	98	84.5
	Grade 3	7	5.9	6	5.0	12	10.3
Redness (mm)	Any	48	40.3	50	42.0	53	45.7
	>100	2	1.7	0	0.0	1	0.9
Swelling (mm)	Any	26	21.8	28	23.5	39	33.6
	>100	0	0.0	0	0.0	0	0.0
General symptoms							
Fatigue	Any	54	45.4	63	52.9	71	61.2
	Grade 3	7	5.9	5	4.2	4	3.4
	Related	49	41.2	58	48.7	66	56.9
Gastrointestinal symptoms*	Any	27	22.7	20	16.8	27	23.3
	Grade 3	3	2.5	2	1.7	1	0.9
	Related	26	21.8	17	14.3	21	18.1
Headache	Any	47	39.5	47	39.5	53	45.7
	Grade 3	2	1.7	4	3.4	5	4.3
	Related	41	34.5	38	31.9	45	38.8
Myalgia	Any	63	52.9	57	47.9	64	55.2
	Grade 3	7	5.9	4	3.4	3	2.6
	Related	57	47.9	52	43.7	59	50.9
Shivering	Any	37	31.1	35	29.4	48	41.4
	Grade 3	4	3.4	3	2.5	3	2.6
	Related	34	28.6	29	24.4	43	37.1
Temperature (°C)†	Any	32	26.9	32	26.9	33	28.4
	>39.0	1	0.8	0	0.0	2	1.7
	Related	31	26.1	31	26.1	30	25.9

95%CI = Exact 95% confidence interval; Any = occurrence of any general symptoms regardless of their intensity grade or relationship to vaccination; ATP = According to protocol; Grade 3 symptoms = Symptoms that prevented normal activity; LL = Lower limit, N = Number of subjects with at least one documented dose; n/% = Number/percentage of subjects reporting the symptom at least once when the intensity was maximum; Related = General symptom assessed by the investigator as causally related to vaccination; Total Vaccinated cohort = cohort including all subjects with at least one study vaccine administered; UL = Upper limit
*Gastrointestinal symptoms means nausea, vomiting, diarrhea and/or abdominal pain
†Temperature is defined on oral, axillary, rectal or tympanic

PUBLISHED RECOMMENDATIONS FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

The CDC has published recommendations from the Advisory Committee on Immunization Practices (ACIP) on this topic.[3]

"Following the first dose of RZV [Recombinant Zoster Vaccine; CDC abbreviation for *Shingrix*], the second dose should be given 2–6 months later. The vaccine series need not be restarted if more than 6 months have elapsed since the first dose; however, the efficacy of alternative dosing regimens has not been evaluated, data regarding the safety of alternative regimens are limited, and individuals might remain at risk for herpes zoster during a longer than recommended interval between doses 1 and 2."

Additional information has been published by the CDC in supplement to the Morbidity and Mortality Weekly Report (MMWR).[4]

"CDC does not recommend substituting another shingles vaccine for the second dose if Shingrix is not available. A series started with Shingrix must be completed with Shingrix..."

CDC LINK INFORMATION

Please refer to http://www.cdc.gov/mmwr/ for the most current information with regards to immunization practices and guidelines from CDC.

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCE(S)

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Appendix

Table 2. Adjusted GMC Ratios of 0,2M Group over 0,6M and 0,12 M Groups at 1 Month Post-Dose 2 (ATP Cohort for Immunogenicity) [(1)]

0,2M Group				0,6M Group				Adjusted GMC Ratio (0,2M /0,6M)		
		97.5% CI				97.5% CI			97.5% CI	
N	Adjusted GMC	LL	UL	N	Adjusted GMC	LL	UL	Value	LL	UL*
118	44.352.6	39.208.5	50.171.5	114	38.137.8	33.642.5	43.233.7	1.16	0.98	**1.39**
0,2M Group				0,12M Group				Adjusted GMC Ratio (0,2M /0,12M)		
		97.5% CI				97.5% CI			97.5% CI	
N	Adjusted GMC	LL	UL	N	Adjusted GMC	LL	UL	Value	LL	UL*
118	44.201.0	37.183.6	52.542.7	110	37.019.9	30.945.7	44.286.3	1.19	0.93	**1.53**

97.5% CI = 97.5% Confidence interval; Adjusted GMC = Geometric mean antibody concentration adjusted for baseline concentration and group age; Anti-gE = anti-glycoprotein E; ATP cohort for immunogenicity = According to protocol cohort for immunogenicity included all subjects who had met all eligibility criteria, complied with the procedures and intervals defined in the protocol, did not meet any of the criteria for elimination during the study and for whom data concerning immunogenicity outcome measures were available ; LL = Lower limit; N = Number of subjects with both pre- and post-vaccination results available; UL = Upper limit.
*Non-inferiority objective was met if the upper limit of the 97.5% CI for the anti-gE GMC ratio (0,2M schedule over 0,6M or 0,12M schedule) at one month post-dose 2 was below 1.5.