RESPONSE TO FDA COMMENTS ON SAFETY DATED NOVEMBER 10, 2021

The Sponsor acknowledges FDA Comments on SAFETY (in **BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Postmarketing Reports of Herpes Zoster

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following requests for additional information:

ITEM 1:
The FDA is reviewing reports of herpes zoster post receipt of the Moderna Covid-19 Vaccine given the imbalance seen in review of Clinical Trial data in support of the Spikevax BLA (STN 125752/2).

Please provide an update to your previous analysis of postmarketing reports received by Moderna on cases of Herpes Zoster post receipt of Moderna Covid-19 Vaccine. In this report, please include to following:

- Case counts (serious, non-serious) by U.S. and global origin,
- Time to onset (median and range) post-vaccination by dose, demographics (sex and age [median and range])
- An updated observed to expected analysis, overall and stratified by age (<18 year, 18-64 years, >= 65 Years).

Please provide your assessment of this potential safety signal and the occurrence of herpes zoster following receipt of Moderna Covid-19 vaccine.

Sponsor Response

Herpes Zoster

1.1 Source of the New Information

The ModernaTX clinical database and global safety database were queried for valid, clinical, and spontaneous case reports received from HCP, HA, consumers and literature, cumulatively since IBD, worldwide, that were reported for SPIKEVAX.

1.2 Background Relevant to the Investigation

ModernaTX, Inc was requested by the FDA to assess cumulative post-marking reports of herpes zoster after receipt of the SPIKEVAX.

Herpes zoster, also known as zoster or as shingles, is characterized by painful, unilateral vesicular eruption, usually in a restricted dermatomal distribution (thoracic and lumbar most

commonly) corresponding to involved sensory ganglion with acute neuritis. Primary infection with varicella zoster virus (VZV) is a necessary prerequisite for herpes zoster, and occurs nearly universally in childhood, in populations in which varicella vaccination is not widely implemented as part of the pediatric immunization schedule. Following varicella infection, VZV localizes in the dorsal root ganglia, remaining dormant, often for decades. In an immunocompetent host, the rash is infectious until lesions crust over in ~7-10 days. Less than 20% of subjects with a rash have systemic symptoms such as fever, malaise, headache, or fatigue. Pain is frequently reported as "throbbing", "burning" or "stabbing". Prodromal pain that precedes the rash by 2-3 days occurs in 75% of patients. Herpes zoster complications includes: post-herpetic neuralgia (most common), herpes zoster ophthalmicus, acute retinal necrosis, Ramsay Hunt syndrome, Aseptic meningitis, encephalitis, peripheral motor neuropathy, myelitis, Guillain-Barre syndrome, stroke, bacterial infections, cutaneous or visceral organ dissemination which can be life threatening (Dworkin 2007, Yawn 2007).

Age and immune status are the primary risk factors for zoster. The risk of zoster, severe manifestations, and complications all dramatically increase with increased age, possibly as a consequence of immune senescence. The risk generally starts to increase after age 30. For immunocompromised patients, impaired T cell (i.e., transplant patients, patients receiving chemotherapy, steroids, HIV) had a higher risk and a higher rate of complications than healthy subjects. There is a gender imbalance; the age-specific rates of herpes zoster are greater in women, even when controlling for age. Physical trauma can also be considered a risk factor for zoster (Yawn 2007, Chen 2014, Yun 2016). Previous herpes vaccination may influence the frequency and severity of clinical manifestations of Herpes Zoster reported following COVID 19 vaccination.

1.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTX queried the company global safety database for valid, spontaneous case reports received from HCP, HA, consumers and literature cumulatively since IBD (18 December 2020) to 31 October 2021, worldwide, reported for the SPIKEVAX vaccine, for MedDRA PTs containing the words "Zoster" and/or "Varicella".

1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected

Herpes zoster was reported in 2,786 cases cumulatively (reporting rate 0.15 per 1,000 person-years), which was substantially below the estimated incidence rate of 4.5 cases per 1,000 person-years expected, based on population-based data from the US (81,644 cases expected, rate ratio 0.03, 95% CI 0.03 – 0.04).

Stratified analysis showed a reporting rate that increases with advancing age. No age subgroup showed a reporting rate that was close to or in excess of the expected. Sensitivity analyses assuming that 50% or 25% of exposed cases are captured in the reporting rate with no false positive errors are not consistent with an increased risk in any category. These analyses do not presently suggest a meaningful increased incidence beyond expectation (Table 1-1).

Table 1-1 Observed/Expected Analyses Stratified by Age, Herpes Zoster Expected Rates from the United States

	Person-years	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported RR (95% CI)*	*Assuming 25% of cases were reported RR (95% CI)*
		Cases	Rate	Cases	Rate			
All	18,264,867	2786	0.15	81644	4.5	0.03 (0.03, 0.04)	0.07 (0.07, 0.07)	0.14 (0.13, 0.14)
<18	547,946	6	0.01	471	0.9	0.01 (0.01, 0.03)	*0.03 (0.01, 0.05)*	*0.05 (0.03, 0.08)*
18-64	13,150,704	1,504	0.11	36033	2.7	0.04 (0.04, 0.04)	*0.08 (0.08, 0.09)*	*0.17 (0.16, 0.17)*
≥65	4,566,217	1,067	0.23	16621	3.6	0.06 (0.06, 0.07)	*0.13 (0.12, 0.13)*	*0.26 (0.25, 0.27)*

* Rates presented per 1,000 person-years. Rates from Johnson 2015

Further stratification (gender and age by gender) shows higher reporting rates for females than for males, and an increasing rate with advancing age. No subgroup showed a reporting rate that was close to or in excess of the expected. The same was true in sensitivity analyses where the observed case count was assumed to represent only half or 25% of total herpes zoster cases following SPIKEVAX, where observed rates remained well below the expected incidence. These analyses do not presently suggest a meaningful increased incidence beyond expectation (Table 1-1).

Table 1-2 Observed/Expected Analyses Stratified by Age, Herpes Zoster Expected Rates from the United States

	Person-years	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported RR (95% CI)*	*Assuming 25% of cases were reported RR (95% CI)*
		Cases	Rate	Cases	Rate			
All	18,264,867	2786	0.15	81644	4.5	0.03 (0.03, 0.04)	0.07 (0.07, 0.07)	0.14 (0.13, 0.14)
By age								
<18	547,946	6	0.01	471	0.9	0.01 (0.01, 0.03)	*0.03 (0.01, 0.05)*	*0.05 (0.03, 0.08)*
18-24	1,643,838	50	0.03	4504	2.7	0.01 (0.01, 0.01)	*0.02 (0.02, 0.03)*	*0.04 (0.04, 0.05)*
25-39	4,018,271	381	0.09	14627	3.6	0.03 (0.02, 0.03)	*0.05 (0.05, 0.06)*	*0.1 (0.1, 0.11)*
40-49	2,739,730	389	0.14	12384	4.5	0.03 (0.03, 0.03)	*0.06 (0.06, 0.07)*	*0.13 (0.12, 0.13)*
50-64	4,748,865	684	0.14	32007	6.7	0.02 (0.02, 0.02)	*0.04 (0.04, 0.05)*	*0.09 (0.08, 0.09)*
65-74	2,739,730	591	0.22	25534	9.3	0.02 (0.02, 0.03)	*0.05 (0.04, 0.05)*	*0.09 (0.09, 0.1)*
75+	1,826,487	476	0.26	21954	12.0	0.02 (0.02, 0.02)	*0.04 (0.04, 0.05)*	*0.09 (0.08, 0.09)*
By gender								
Male	8,675,812	860	0.10	31753	3.7	0.03 (0.03, 0.03)	*0.05 (0.05, 0.06)*	*0.11 (0.1, 0.11)*
Female	9,589,055	1856	0.19	50343	5.3	0.04 (0.04, 0.04)	*0.07 (0.07, 0.08)*	*0.15 (0.14, 0.15)*
By age and gender								
Male								
<18	260,274	2	0.01	216	0.8	0.01 (0, 0.04)	*0.02 (0.01, 0.05)*	*0.04 (0.02, 0.07)*
18-24	780,823	14	0.02	1890	2.4	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.02, 0.04)*
25-39	1,908,679	123	0.06	6108	3.2	0.02 (0.02, 0.02)	*0.04 (0.04, 0.05)*	*0.08 (0.07, 0.09)*
40-49	1,301,372	127	0.10	5088	3.9	0.02 (0.02, 0.03)	*0.05 (0.04, 0.06)*	*0.1 (0.09, 0.11)*
50-64	2,255,711	184	0.08	11301	5.0	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.07 (0.06, 0.07)*
65-74	1,301,372	204	0.16	9825	7.6	0.02 (0.02, 0.02)	*0.04 (0.04, 0.05)*	*0.08 (0.08, 0.09)*
75+	867,581	170	0.20	9162	10.6	0.02 (0.02, 0.02)	*0.04 (0.03, 0.04)*	*0.07 (0.07, 0.08)*
Female								
<18	287,672	4	0.01	256	0.9	0.02 (0.01, 0.04)	*0.03 (0.02, 0.06)*	*0.06 (0.04, 0.1)*
18-24	863,015	35	0.04	2624	3.0	0.01 (0.01, 0.02)	*0.03 (0.02, 0.03)*	*0.05 (0.05, 0.06)*
25-39	2,109,592	253	0.12	8544	4.1	0.03 (0.03, 0.03)	*0.06 (0.05, 0.06)*	*0.12 (0.11, 0.13)*
40-49	1,438,358	260	0.18	7336	5.1	0.04 (0.03, 0.04)	*0.07 (0.06, 0.08)*	*0.14 (0.13, 0.15)*
50-64	2,493,154	499	0.20	20818	8.4	0.02 (0.02, 0.03)	*0.05 (0.04, 0.05)*	*0.1 (0.09, 0.1)*
65-74	1,438,358	385	0.27	15879	11.0	0.02 (0.02, 0.03)	*0.05 (0.05, 0.05)*	*0.1 (0.09, 0.1)*
75+	958,905	303	0.32	12773	13.3	0.02 (0.02, 0.03)	*0.05 (0.04, 0.05)*	*0.09 (0.09, 0.1)*

* Rates presented per 1,000 person-years. Rates from Johnson 2015

Overview of Cases:

Post authorization data:

Cumulatively, (18 Dec 2020 to 31 Oct 2021) there were 2786 cases (2833 events) of herpes zoster, of which 621 cases were serious, including 9 cases with fatal outcomes. There were 1567 cases that were medically confirmed (56.2%). Reports received from regulatory authorities accounted

for 73.1% of cases while 26.2% were spontaneous reports and 0.7% were literature reports. Case reports originated from the following regions: United States (1454/ 52.2%), EEA (878/ 31.5%), Switzerland (346/ 12.4%), United Kingdom (44/ 1.6%), Asia (43/ 1.5%), Canada (20/ 0.7%) and Middle East (1/ 0.0%) as shown below in Table 1-9.

Cases were disproportionately reported for females compared to males [1856 cases (66.6%) vs. 860 cases (30.9%), respectively]; gender was not reported or was unknown for 70 cases (2.5%). The mean age was 58.3 years (SD: 17.1) and the median age was 60.0 years (min 12.0 /max 113.0).

The majority of events (62.9%) were reported in individuals ≥50 years of age (50-64 years (24.6%), 65-74 years (21.2%), and 75+ years (17.1%)). Age classification was missing or unknown in 7.5% of the reports. Less than 5% of reports were in individuals <30 years of age, which is consistent with background epidemiology of reports of herpes zoster. There were more female case reports than male in every age group. (Table 1-3).

Table 1-3 Case Distribution by Gender and Age Group

Age Group (years)	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Events
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	2	0.1%	1	0.0%	-	-	3	0.1%
16-17	2	0.1%	1	0.0%	-	-	3	0.1%
18-29	88	3.2%	40	1.4%	2	0.1%	130	4.7%
30-39	200	7.2%	97	3.5%	4	0.1%	301	10.8%
40-49	260	9.3%	127	4.6%	2	0.1%	389	14.0%
50-64	499	17.9%	184	6.6%	1	0.0%	684	24.6%
65-74	385	13.8%	204	7.3%	2	0.1%	591	21.2%
75+	303	10.9%	170	6.1%	3	0.1%	476	17.1%
Missing	117	4.2%	36	1.3%	56	2.0%	209	7.5%
Grand total	1856	66.6%	860	30.9%	70	2.5%	2786	100.0%

Of the 2833 events, 546 (19.3%) were serious and 2287 (80.7%) were non-serious. The most frequently reported PT was Herpes zoster for both non-serious events (97.9%) and serious events (74.0%) and overall accounted for 93.3% of events (Table 1-4). Ophthalmic herpes zoster was the second most frequently reported event by PT (78 events, 2.8%) followed by herpes zoster oticus (30 events, 1.1%).

Table 1-4 Event Distribution by MedDRA Preferred Term (PT) and Seriousness

PT	Non Serious		Serious		Grand total of # Events	Grand total of % of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Herpes zoster	2,238	97.9%	404	74.0%	2,642	93.3%
Ophthalmic herpes zoster	2	0.1%	76	13.9%	78	2.8%
Herpes zoster oticus	1	0.0%	29	5.3%	30	1.1%
Varicella	23	1.0%	3	0.5%	26	0.9%
Herpes zoster reactivation	14	0.6%	5	0.9%	19	0.7%
Varicella zoster virus infection	5	0.2%	4	0.7%	9	0.3%
Herpes zoster meningitis	-	-	7	1.3%	7	0.2%
Herpes zoster cutaneous disseminated	-	-	6	1.1%	6	0.2%
Herpes zoster meningoencephalitis	-	-	4	0.7%	4	0.1%
Disseminated varicella zoster virus infection	-	-	3	0.5%	3	0.1%
Genital herpes zoster	1	0.0%	2	0.4%	3	0.1%
Varicella post vaccine	2	0.1%	-	-	2	0.1%
Herpes zoster disseminated	-	-	1	0.2%	1	0.0%
Herpes zoster infection neurological	-	-	1	0.2%	1	0.0%
Herpes zoster meningoradiculitis	-	-	1	0.2%	1	0.0%
Varicella virus test positive	1	0.0%	-	-	1	0.0%
Grand total	2,287	100.0%	546	100.0%	2,833	100.0%

The majority of events occurred after the 1st dose (43.9%) with 19.3% of all events occurring <7 days after the first dose. Events occurring after the 2nd dose accounted for 26.5% of all events with 10.5% of all events occurring <7 days after the second dose. Events occurring after the 3rd dose accounted for 0.2% of all events with 0.2% of all events occurring <7 days after the third dose. Dosing information was missing for 29.3% of the events (Table 1-5). The average TTO for all doses was 15.1 days (SD 22.5) and the median TTO for all doses was 8.0 days (min 0/max 242).

Table 1-5 Event Distribution by Dose Number, Time-To-Onset (TTO) and Seriousness

Dose Number	TTO (Days)	Non Serious		Serious		Grand total of # Events	Grand total of % Events
		# Events	% Events	# Events	% Events		
Dose 1	Subtotal	1,008	44.1%	236	43.2%	1,244	43.9%
	0 days	52	2.3%	11	2.0%	63	2.2%
	01-02	191	8.4%	38	7.0%	229	8.1%
	03-04	124	5.4%	33	6.0%	157	5.5%
	05-06	83	3.6%	16	2.9%	99	3.5%
	07-13	228	10.0%	57	10.4%	285	10.1%
	14-29	279	12.2%	53	9.7%	332	11.7%
	30+	51	2.2%	28	5.1%	79	2.8%
Dose 2	Subtotal	568	24.8%	184	33.7%	752	26.5%
	0 days	35	1.5%	7	1.3%	42	1.5%
	01-02	93	4.1%	24	4.4%	117	4.1%
	03-04	75	3.3%	15	2.7%	90	3.2%
	05-06	38	1.7%	11	2.0%	49	1.7%
	07-13	114	5.0%	42	7.7%	156	5.5%
	14-29	110	4.8%	43	7.9%	153	5.4%
	30+	103	4.5%	42	7.7%	145	5.1%
Dose 3	Subtotal	6	0.3%	1	0.2%	7	0.2%
	01-02	2	0.1%	1	0.2%	3	0.1%
	05-06	2	0.1%	-	-	2	0.1%
	30+	2	0.1%	-	-	2	0.1%
Unknown	Subtotal	705	30.8%	125	22.9%	830	29.3%
	Missing	705	30.8%	125	22.9%	830	29.3%
Grand total	Grand total	2,287	100.0%	546	100.0%	2,833	100.0%

Duration data is often not reported for spontaneous cases. For the 2833 events reported in the herpes zoster dataset, Table 1-6 presents events for which we have duration.

For the majority of events, duration was not reported (2612 events, 92.2%). A meaningful pattern of duration cannot be deduced from the minimal data on duration of reported events. The minimal duration data does not support detailed, meaningful analysis.

Table 1-6 Event Counts and Percentages by Duration

Duration Group	Grand total of # Events	Grand total of % of Total Events
<=01 days	10	0.4%
02-03 days	12	0.4%
04-07 days	43	1.5%
07-29 days	117	4.1%
30+ days	39	1.4%
(Empty)	2,612	92.2%
Grand total	2,833	100.0%

The outcome was not reported or unknown for 28.5% of the events. Of the events with a reported outcome, 39.4% were not resolved, 30.9% were either resolved or resolving, 1.0% resolved with sequalae, and 10 events (9 cases) had a fatal outcome (Table 1-7) All fatal cases occurred in individuals > 80 years old. Fatal cases are detailed in Table 1-8.

Table 1-7 Event Outcome

Event Outcome	Grand total of # Events	Grand total of % of Total Events
Fatal	10	0.4%
Not Recovered/Not Resolved	1,115	39.4%
Recovered/Resolved	438	15.5%
Recovered/Resolved with Sequelae	27	1.0%
Recovering/Resolving	436	15.4%
Unknown	807	28.5%
Grand total	2,833	100.0%

Table 1-8 Fatal Case Reports (n=9)

Case ID	Country	Report Type	Age (yr) / Gender	PT	Medical History	Concomitant Medications	Dose #; TTO	Summary
(b) (6)	NETHERLANDS	Regulatory Authority	101 / Female	Herpes zoster	No adverse event(H)		Dose 1; 3 days	A 101-year-old, female experienced drowsiness, decreased appetite, malaise and herpes zoster 3 days post dose 1. The patient died 10 days post dose 1 due to drowsiness, decreased appetite, malaise and herpes zoster. Medical history and concomitant medications were not reported. Autopsy information was not provided. Causality was not provided for the events.
(b) (6)	UNITED STATES	Regulatory Authority	81 / Female	Herpes zoster	Dust allergy; Drug hypersensitivity; Chronic lymphocytic leukaemia(C); Essential hypertension(C); Type 2 diabetes mellitus(C); Hyperlipidaemia(C); Diverticulum(C)	ACETAMINOPHEN ; ALLOPURINOL; AMLODIPINE; EZETIMIBE; FUROSEMIDE; LATANOPROST; LISINOPRIL; LORATADINE; MESALAMINE; METFORMIN; METOPROLOL; MOMETASONE; MULTIVITAMIN [VITAMINS NOS]; OMEPRAZOLE	Dose 1; 8 days	An 81-year-old female experienced cardio-respiratory arrest, loss of consciousness, burning sensation, rash pruritic, fatigue, pyrexia, and myalgia 1-day post dose 1. Diagnostic testing at that time included blood lactic acid: 1.43 (Low); C-reactive protein: 0.9 (normal); computerized tomogram head: negative/normal; metabolic function test: normal; white blood cell count: 24.8 (High)(consistent with CLL CMP - WNL). 8 days post dose 1, she developed herpes zoster. 12 days post dose 1, she experienced hypoaesthesia, neck pain and pain in extremity, and subsequently died that day. The cause of death was not reported. It is unknown if an autopsy was performed. Medical history was significant for Chronic lymphocytic leukemia, Essential hypertension, Non-insulin-dependent diabetes mellitus, Hyperlipidemia and Diverticulosis. The reporter did not allow further contact. Causality was not provided for the events.
(b) (6)	UNITED STATES	Regulatory Authority	89 / Female	Herpes zoster oticus	Drug hypersensitivity; Atrial fibrillation(H); Osteoarthritis(H)	AMIODARONE; ELIQUIS	Dose 2; 1 day	An 89 year-old female experienced Aphasia, Dysphagia, Condition aggravated, Feeding tube user, Facial paralysis, Herpes zoster oticus, Tongue paralysis, Shock, Pain, Rash, and Ear pain 1 day post dose 2 (28 days post dose 1)

Case ID	Country	Report Type	Age (yr) / Gender	PT	Medical History	Concomitant Medications	Dose #; TTO	Summary
								and subsequently died 51 days post dose 2 (78 days post dose 1). The cause of death was not reported. The patient had an extensive 6-week hospital stay with feeding tubes and multiple diagnostic tests (tests and results not reported). It was reported that the main issue was pain control, and that the patient was unable to speak well and lost the ability to swallow. No available treatment information. The patient's past medical history included Atrial fibrillation and Osteoarthritis. It is unknown if an autopsy was performed. Causality was not provided for the events.
(b) (6)	FRANCE	Regulatory Authority	88 / Male	Herpes zoster, Herpes zoster disseminated	Type 2 diabetes mellitus(C); Cardiac pacemaker insertion; Arterial disorder(C); Myocardial ischaemia(H); Epilepsy(C); Ex-tobacco user(H); Cardiac failure(C)		Dose 2; 27 days	An 88-year-old male patient experienced Herpes zoster and Disseminated varicella zoster 27 days post dose 2 (date not provided for dose 1). The patient died on 23-May-2021, 41 days post dose 2 (date not provided for dose 1). The reported cause of death was Herpes zoster and Herpes zoster disseminated. An autopsy was not performed. Medical history included Type 2 diabetes mellitus, Cardiac pacemaker insertion, Arterial disorder, Myocardial ischaemia, Epilepsy, Ex-tobacco user, and Cardiac failure. Causality was not provided for the events.
(b) (6)	UNITED STATES	Regulatory Authority	86 / Female	Varicella zoster virus infection	Femur fracture(C); Chronic kidney disease(C)	HYDRALAZINE; PRAVASTATIN; PLAVIX; IMDUR; TRIAMTERENE	Unknown; 26 days	An 86-year-old female experienced Meningitis, Anaemia, Asthenia, Confusional state, Tremor, and Varicella zoster virus infection 26 days after receiving a dose of mRNA-1273 (unknown if dose 1 or dose 2). Diagnostic testing included Blood test: abnormal, Body temperature: low, and Hemoglobin: low. The patient died on 13 Jun 2021, 3 months and 18 days after receiving a dose of mRNA-1273

Case ID	Country	Report Type	Age (yr) / Gender	PT	Medical History	Concomitant Medications	Dose #; TTO	Summary
								(unknown if dose 1 or dose 2). The cause of death was not reported and is unknown if an autopsy was performed. Concurrent medical conditions included Femur fracture and Chronic kidney disease stage 3. Causality for the events was not provided. No further information is expected.
(b) (6)	UNITED STATES	Spontaneous	88 / Female	Herpes zoster	Dementia Alzheimer's type(C); Thyroid disorder(C); Incontinence(C); Glaucoma(C); Chronic kidney disease(C)	LEVOTHYROXINE; HYDROXYZINE; DONEPEZIL; LISINOPRIL; MYRBETRIQ; TIMOLOL; LATANAPROST/TIMOLOL; VITAMIN D3	Dose 2; 6 days	A 88-year-old female patient experienced Pruritus, Erythema, and Hypersensitivity reaction, Herpes zoster, and Rash 6 days post dose 2 (34 days post dose 1), which was described as bumps on left leg that spread to groin region and all over thighs, which were painless but itchy. Pictures were sent by the home health nurse to the managing physician who prescribed medications for treatment (specific medication not provided). The patient experienced a Stroke and subsequently died due to the stroke, 28 days post dose 2. It is unknown if an autopsy was performed. Testing in 2021 (specific date not reported) included Blood pressure, Body temperature and Heart rate which were normal. Medical history was significant for Alzheimer's disease, Thyroid Disorder, Incontinence, Glaucoma and Chronic kidney disease stage 3. Causality was not provided for the events. Reporter did not allow further contact.
(b) (6)	UNITED STATES	Regulatory Authority	84 / Male	Herpes zoster	Type 2 diabetes mellitus(C); Blood cholesterol(C)Hypertension		Unknown	On 01 Apr 2021, an 84-year-old male patient experienced Herpes zoster (22 days prior to dose 2; date of dose 1 unknown). Diagnostic testing at that time included MRI, CT, and X-ray; results not provided. Treatment included anti-viral medication, 400 mg. The patient did not improve and was taken to the hospital on 17 May 2021. The patient was transferred to the hospital on 26 May 2021 and subsequently died

Case ID	Country	Report Type	Age (yr) / Gender	PT	Medical History	Concomitant Medications	Dose #; TTO	Summary
								on 04 Jun 2021 (1 month 13 days post dose 2; date of dose 1 unknown). Cause of death not reported. Causality was not provided for the events and it is unknown if an autopsy was performed. Medical history included Type 2 diabetes mellitus, Cholesterol and Hypertension. Concomitant medication was reported as medication for high blood pressure, cholesterol, and diabetes (specific medication not reported), as well as anti-depressants (not specified). Source document received by Regulatory Authority (RA) also stated two doses given on same date (providing different lot numbers). No further information is expected.
(b) (6)	ITALY	Regulatory Authority	89 / Female	Herpes zoster	Chronic COPD and Senile degenerative hemiocardioscierosis due to COPD		Dose 2; 2 days	An 89-year-old female experienced Herpes zoster 2 days post dose 2 (30 days post dose 1) located on her right hip front-back and thigh, vast in size. She was confined to bed for frequent dressings and had stopped eating and drinking. The patient subsequently died on 08 Jun 2021, 35 days post dose 2 (63 days post dose 1). The reported cause of death was ”shingles”. An autopsy was not performed. Medical history included Chronic COPD and Senile degenerative hemiocardioscierosis due to COPD. Causality was not provided for the event.
(b) (6)	UNITED STATES	Regulatory Authority	82 / Male	Herpes zoster	Drug hypersensitivity; Drug hypersensitivity; Atrial fibrillation(H); Hypothyroidism(C); Hypertension(C); Hyperlipidaemia(C); Sleep apnoea syndrome(C);	KEPPRA [LEVETIRACETAM]; TRIAMTERENE HCTZ; STIOLTO RESPIMAT; CARVEDILOL; TESTOSTERONE; XARELTO;	Dose 1; 37 days	An 82-year-old male patient experienced Herpes zoster 37 days post dose 1 (latency unknown for dose 2). The patient also experienced Arthralgia, Axillary pain, Bladder hypertrophy, Condition aggravated, Confusional state, Dizziness, Hypotension, Lung disorder, Lymphadenectomy, Mental status changes, Oedema), Pain in extremity,

Case ID	Country	Report Type	Age (yr) / Gender	PT	Medical History	Concomitant Medications	Dose #; TTO	Summary
					Seizure(C); Oedema(C); Coronary artery disease(C); Squamous cell carcinoma(C)	LEVOTHYROXINE; DICLOFENAC; CELECOXIB		Pulmonary artery dilatation, Pulmonary hypertension, Pulmonary mass, Retroperitoneal lymphadenopathy, Splenic lesion, Tenderness, and Urinary tract infection. Testing included Blood pressure measurement and Heart rate, both of which were increased (High) (NOS). Additional numerous tests (NOS) and labs (NOS) were performed during course of complaints from March to July; results included increased conspicuity of pulmonary nodules, bibasilar interlobular septal thickening, dilated pulmonary artery, new splenic lesions and hypodensity, new bilateral inguinal, iliac chanin and retroperitoneal lymphadenopathy, urinary bladder wall thickening. The patient died on 07 Jul 2021 (4 months and 15 days post dose 1; latency unknown for dose 2). The cause of death was not reported, and it was unknown if an autopsy was performed. Medical history included allergies to aspirin and Valacyclovir, Atrial fibrillation, Hypothyroidism, Hypertension, Hyperlipidemia, Sleep apnea, Seizure, Edema, Coronary artery disease and Squamous cell carcinoma. Causality was not provided for the events.

The majority of cases were reported from the United States (52.2%) followed by the European Economic Area (31.5%), which is consistent with the distribution patterns of SPIKEVAX globally.

Table 1-9 Case Counts by Region

Region	Grand total of # Cases	Grand total of % of Total Cases
Asia	43	1.5%
Canada	20	0.7%
European Economic Area	878	31.5%
Middle East	1	0.0%
Switzerland	346	12.4%
United Kingdom	44	1.6%
United States	1,454	52.2%
Grand total	2,786	100.0%

Patients with History of Herpes Zoster/Shingles Vaccination

Cumulatively, 142 cases were in subjects with a medical history of herpes zoster or a related event (ex: ophthalmic herpes zoster).

All reports of herpes zosters were reviewed for any mention of “Shingrix”, “Zostavax”, “shingles vaccine”, “herpes zoster vaccine”, “zoster vaccine” and “herpes vaccine. Cumulatively, 39 cases were in individuals who received Shingrix (unknown number of doses or temporal relationship to herpes zoster event onset), 6 cases were in individuals who received Zostavax, and 10 cases were in individuals who received an unnamed “shingles vaccine”. In one case, the individual reportedly received Shingrix and Zostavax. In total, 56 cases (57 events), were in individuals who reported receiving at least one shingles vaccine. Of these, 39 were female, 14 were male and 3 had an unknown gender. The age range of these individuals was 30-85 years old with a median age of 67 years. The time to onset for events of herpes zoster after Dose 1 of SPIKEVAX was a median of 10 days in these individuals and the time to onset for events of herpes zoster after Dose 2 of SPIKEVAX was a median of 16 days in these individuals. The most frequently reported event in these individuals was herpes zoster as shown in Table 1-10 below.

Table 1-10 Events of Herpes zoster by Seriousness in Individuals that Received at Least One Shingles Vaccine

Preferred Term	Non Serious	Serious	Grand Total
Disseminated varicella zoster virus infection	0	1	1
Herpes zoster	49	2	51
Herpes zoster oticus	0	2	2
Herpes zoster reactivation	1	0	1
Ophthalmic herpes zoster	0	1	1
Varicella	1	0	1
Grand Total	51	6	57

Immunocompromised Patients

Medical history and reported concomitant medications were reviewed to identify individuals that had at least one immunocompromising condition by medical history, were receiving at least one potentially immunocompromising concomitant medication or could be considered immunocompromised by either medical history or concomitant medications. Overall, medical history was not reported in almost half (48.28%) of the cases of herpes zoster and no concomitant medications were reported for 65.1% of cases of herpes zoster. Cumulatively, 2.12% of cases had a medical history of a potentially immunocompromising condition or reported use of a potentially immunocompromising concomitant medication. However, incomplete or missing medical history and concomitant medication data makes it difficult to fully assess for potential risk factors for zoster reactivation.

Table 1-11 Cases of Zoster by Reports of Immunocompromising Medical History Conditions or Potentially Immunocompromising Concomitant Medications

	N (cases)	%
MI-IMMUN-SUP (MHX or CM)		
NO	2,727	97.88%
YES	59	2.12%
MI-MHX-IMMUN-SUP		
MISSING	1,345	48.28%
NO	1,407	50.5%
YES	34	1.22%
MI-CM-IMMUN-SUP		
MISSING	1,813	65.08%
NO	948	34.03%
YES	25	0.9%

1.5 Discussion

Cumulatively, there were 2786 cases (2833 events) reported, with 860 reports in males (30.9%) and 1856 reports in females (66.6%), with the majority of the reports in patients ≥ 50 years of age (62.9%) (mean 60.0 years). Cumulatively, there were 1244 (43.9%) reports occurring after the 1st dose, 752 (26.5%) after the 2nd dose, and 7 (0.2%) after the 3rd dose with 830 (29.3%) missing dose number.

The MAH review of available data does not suggest a causal association between receipt of Spikevax and occurrence of zoster; however, the MAH recognizes that the limitation of evaluating the available information included the probable under-reporting of medical history/concomitant medications to accurately assess risk factors for zoster reactivation or prior receipt of a zoster vaccine. While immunosuppression and age are the primary risk factors for zoster reactivations, other triggers include radiation, physical trauma, stress, or other infections. Although a temporal association may exist between SPIKEVAX administration and this small number of Herpes Zoster cases, information is inadequate to assess a causal association between SPIKEVAX administration and the risk of primary Herpes Zoster infection or Herpes zoster reactivation. The observed reporting rate for post-marketing reports of herpes zoster is well below the expected background incidence rate overall and for all age and gender-specific subgroups.

Despite the lack of available data on a causal association between receipt of Spikevax, investigators have hypothesized that mechanisms for reactivation of VZV with manifestation of shingles. Suggested pathogenic mechanisms for reactivation of the varicella zoster virus after vaccination for SARS-CoV-2 COVID-19 include vaccine-associated lymphopenia or lymphocyte impairment, especially CD3+CD8+ lymphocytes and functional impairment of CD4+ T cells, as well as natural killer cells. Other theories have postulated a role of abrogations

in toll-like receptor signaling and expression in vaccinated individuals, which may also potentially contribute to zoster reactivation (Katsikas-Triantafyllidis 2021).

1.6 Conclusion

Based on the analysis of all the safety data presented in this analysis available as of 31 October 2021, the MAH considers that there is insufficient information to support a potential causal association between SPIKEVAX and herpes zoster reactivation. These data do not represent a new safety issue of concern. The MAH will continue to monitor events for events of herpes zoster through routine surveillance.

1.7 References

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