Appendix 4.2f: Signal Evaluation report: Corneal graft rejection

Signal Evaluation Report

for

mRNA-1273

on

Corneal Graft Rejection

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
CDC	Centers for Disease Control and Prevention
CT	Clinical Trial
DMEK	Descemet Membrane Endothelial Keratoplasty
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
ICSR	Individual Case Safety Report
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RA	Regulatory Authority
SD	Signal Detection
TEAE	Treatment-emergent adverse event
VAERS	Vaccine Adverse Event Reporting System
EVDAS	Eudravigilance Data Analysis System

EXCECUTIVE SUMMARY

This signal evaluation report provides a detailed analysis on the validity of safety topic on Corneal Graft Rejection in association with the administration of mRNA-1273 in adult patients ≥12 yo, based on all information available to the MAH from all sources at the time of document preparation. Having considered the available evidence from case reports in the Eudravigilance database and in the literature, the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should be provided by 29 June 2022 a cumulative review of all cases of corneal graft rejection and related terms (e.g., transplant rejection', 'corneal graft failure') from all available sources (Signal of corneal graft rejection (EPITT ref. No. 19792) triggered by PRAC).

Reports of endothelial corneal transplant rejection following immunization with SARS-CoV-2 messenger RNA vaccine both with Pfizer BNT162b2 messenger RNA Vaccine and Moderna mRNA 1273, (Waller Cornea. 2021) have been reported.[9] The assessment of Corneal Graft Rejection in association with the use of mRNA-1273 in all patients exposed was performed using several data sources which includes Clinical trial data, Non-clinical data, Epidemiological studies, Moderna safety database, Literature review and external databases (VAERS and EVDAS).

Based on the analysis of all the safety data available as of 15 April 2022, the MAH considers that there is no evidence to establish a causal relationship to the administration of Spikevax and corneal graft rejection. The analysis of the safety database, the medical literature information does not support a causal association between Spikevax and the event of acute corneal rejection. Observed to expected analyses do not suggest an increased incidence compared to what is expected among corneal transplant rejection in the general population. Corneal transplant rejection reports were mostly serious, occurred predominantly in the age group 75+ years, mostly within 7 days after the 1st dose of the vaccine.

The MAH considers that review of the safety data conducted during this safety analysis supports the conclusion that the evidence currently does not suggest a causal association between Spikevax, vaccine induced immune activation and corneal graft rejection. Acute corneal transplant rejection in people exposed to mRNA vaccines, does not represent a new safety concern or potential risk hence the signal is refuted and considered closed.

1 INTRODUCTION

This signal evaluation report provides a detailed analysis on the validity of safety topic on Corneal Graft Rejection in association with the administration of mRNA-1273 in adult patients ≥12 yo, based on all information available to the MAH at the time of document preparation.

1.1 SOURCE OF THE SIGNAL

Having considered the available evidence from case reports in the EudraVigilance database and in the literature, the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should provide by 29 June 2022 a cumulative review of all cases of corneal graft rejection and related terms (e.g., transplant rejection', 'corneal graft failure') from all available sources (Signal of corneal graft rejection (EPITT ref. No. 19792) triggered by PRAC).

2. BACKGROUND

2.1 PRODUCT

The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S glycoprotein into a prefusion conformation (S-2P). mRNA-1273 consists of an mRNA that is manufactured with LNPs composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

2.2 EVENT OF INTEREST

Corneal Graft Rejection

For SARS-CoV-2 infection, the major ocular manifestation known to date is viral conjunctivitis. This is potentially due to relatively high conjunctival expression of angiotensin-converting enzyme 2 (ACE2), a functional receptor for COVID-19.[1,2] ACE2 is a part of the renin-angiotensin system, which is a powerful regulator of inflammatory responses. Immune dysregulation induced by SARS-CoV-2 has been found to play an important role in the pathophysiology of organ damage particularly affecting organs with high ACE2 expression.[2–4] Corneal transplantation has a low graft rejection rate because of ocular immune privilege, which can be compromised by increased immune dysregulation. Corneal disease is a common cause of blindness after cataracts, age related macular degeneration, glaucoma, diabetic retinopathy. Common diseases affecting the cornea and often requiring corneal transplant (keratoplasty) are keratoconus, corneal scars, bullous keratopathy, Fuchs endothelial dystrophy and local facial dental and eye infections.

There are 4 types of corneal transplant including Penetrating keratoplasty (PKP) a full thickness--cornea transplant; Endothelial keratoplasty (EK) of which there are two types (DSEK & DMEK): Descemet membrane stripping endothelial keratoplasty (DSEK), which uses donor tissue to replace about one-third of the cornea and Descemet membrane endothelial keratoplasty (DMEK),

which uses a layer of donor tissue that is extremely thin and fragile; Anterior lamellar keratoplasty (ALK) of which there are also 2 types (SALK & DALK)- Superficial anterior lamellar keratoplasty (SALK) replaces the front layers of the cornea, leaving the healthy stroma and endothelium intact, whereas deep anterior lamellar transplant (DALK) procedure is indicated when corneal damage extends deeper into the stroma and is replaced by healthy donor tissue; Artificial cornea transplant (keratoprosthesis) are performed when a donor cornea cannot be used and is replaced by an artificial cornea (keratoprosthesis). DSEK and DMEK have reduced the risk of transplant rejection because less foreign tissue is transplanted.[4]

Graft survival after corneal transplant is largely determined by the risk of immunological graft rejection (allogeneic). Keratoplasty is a long-established procedure, and its success is partially attributed to the presence of immune privilege in the eye; nonetheless, the incidence of rejection is relatively high and 20-30% of patients with corneal transplants experience at least one rejection episode in the first 5 years after transplant. Signs and symptoms of rejection include loss of vision, eye pain, red eyes, and sensitivity to light. Given the high rates of acceptance, corneal grafts in humans are normally performed without tissue matching, and graft acceptance was historically attributed to the absence of passenger leukocytes.[4] Immune privilege appears to facilitate tolerance to allogeneic material in the anterior chamber of the eye and may be associated with absence of vascularity and reduced quantity of corneal lymphatics by preventing delivery of antigens to T cells in lymph nodes behind an efficient blood-retina barrier. Local humoral immunosuppression, low expression of MHC antigens, and anterior chamber-associated immune deviation (ACAID) maintained by antigen specific antigen presenting cells that migrate from the eye and induce specific regulatory T cells that systematically suppress graft rejection by inhibiting T cell and complement activation may all contribute to immune privilege. (Bohringer D et al, 2020, Andersen E et al, 1). The most common cause of graft failure is immunological allograft rejection occurring when immune privilege in the eyes is compromised by trauma, chronic surface inflammation or complexity of the surgical procedure (eg oversized graft). These factors increase the chance of graft rejection in the first 3 years after transplantation. Topical steroids are the usual prophylaxis to aid suppression of graft rejection but may not be successful in cases where non-regenerative graft epithelium is immunologically destroyed. High risk patients may be treated with topical and systemic immunosuppression including cyclosporine A and mycophenolate mofetil (Bohringer D, Aboudou et al, 2015) to avoid repeat keratoplasty which carries an elevated risk of graft rejection, irrespective of the initial indication and increases the risk of subsequent blindness. The SARS Covid 19 pandemic has seen hundreds of millions of people successfully vaccinated against Covid 19 with mRNA vaccines. These mRNA vaccines, Pfizer BNT162b2 (Comirnaty, SmPC), and Moderna mRNA 1273, stimulate a robust immune response against SARS-CoV-2 (SpikeVax SmPC). Reports of endothelial corneal transplant rejection following immunization with SARS-CoV-2 messenger RNA vaccine both with Pfizer BNT162b2 messenger RNA Vaccine and Moderna mRNA 1273, (Waller Cornea. 2021) have been reported.[9]

Vaccination incites immune responses that can induce Class II MHC complex antigens in all layers of the grafted cornea and could trigger allograft rejection as has been described with influenza vaccine.[2,10] Ongoing rampant vaccination against COVID-19 has triggered a review among ophthalmologists regarding rejection of endothelial or full thickness keratoplasty among recipients of corneal grafts in patients exposed to COVID 19 Vaccination.[3] It has become common practice

by ophthalmologists to " hike up" topical steroids prior to any type of COVID19 vaccination in patients with a history of corneal allografts and awaiting corneal transplant surgery (Swetha Ravichandran; Allan B, Lee et al) and according to Lee at al, intensive corticosteroid therapy will enable graft preservation if graft rejection is suspected.[2,11,12] These clinical recommendations are not yet supported by evidence from any randomized trials. Potential risk factors for corneal rejection include the existence of co-morbidities and risk factors such as smoking, diabetes, hypertension, history of local eye and facial infections and previous corneal rejection but only a history of previous corneal transplant rejection is significantly associated with corneal transplant rejection. Graft failure in herpetic keratitis is most commonly due to allograft rejection in 64% and epithelial viral recurrence in (15%) (Cobo et al, 1980). Three cases of corneal allograft rejection have been reported as temporally associated with recombinant herpes zoster subunit vaccine (RZV) (Matoba A). Small case series have been published of rare events of corneal graft rejection approximately 1-2 weeks after vaccination, with other vaccines, most often following the influenza vaccine. Solomon et al reported a case of bilateral corneal graft rejection after influenza vaccination.[13] Case reports of immunization associated corneal transplant rejection have implicated other vaccines including, yellow fever,[14] herpes,[15] and rabies vaccines.[9,12] No specific mechanism has been identified in the corneal rejection events that have been reported after using these other vaccines.

3. REVIEW OF DATA FROM ALL SOURCES

The assessment of Corneal Graft Rejection in association with the use of mRNA-1273 in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below.

3.1 CLINICAL TRIAL DATA

Clinical trial data from mRNA-1273 Study P301 Part A, was searched for MedDRA PT: Corneal graft rejection. No events were identified.

3.2 NON-CLINICAL DATA

No nonclinical data relevant to ECGR are available (IB version 8.0 dated 20 December 2021).

3.3 EXTERNAL DATABASES

VAERS and EVDAS were reviewed for the PTs: Endothelial Corneal Graft Rejection

- VAERS: following are the EB05 observed for the PT. No Disproportionality was observed

  Endothelial Corneal Graft Rejection (EB05: 0.76).

- EVDAS: The PT relevant of Endothelial Corneal Graft Rejection showed disproportionality in North America (ROR: 2.93) and Japan (ROR:9.40).

3.4 EPIDEMIOLOGICAL STUDIES

Corneal transplant is the most commonly performed transplant surgery worldwide.[16,17]Although the success rate of corneal transplant is high as cornea is immune-privileged site, the most common cause of graft failure is allogenic rejection.[18] There are multiple factors associated with risk of rejection such as type of presence of vascularization of the cornea preoperatively, and previous corneal rejection and type of corneal transplant procedure.[19] The graft rejection refers to specific immunologic response of the host to the donor corneal tissue, which progresses to graft failure in 49% of the patients. Graft failure can also be non-immune mediated, such as primary donor failure. Primary donor graft failure is defined as cornea edema that never clears from the immediate postoperative period secondary to inherent deficiencies in the donor graft, surgical trauma, or improperly stored tissue.

Although rare, there have been published cases and case series of corneal graft rejection approximately 1-2 weeks after vaccination, most often following the influenza vaccine. Solomon et al reported a case of bilateral corneal graft rejection after influenza vaccination.[13] In the United Kingdom, there have also now been 2 case reports of patients with DMEK, who experienced episodes of rejection at 1 week and 3 weeks after SARS-CoV-2 Pfizer vaccines [9] and a case report of penetrating keratoplasty rejection post Pfizer vaccine in Israel.[20] Yu et al published case report of penetrating keratoplasty rejection after mRNA-1273 vaccine.[21] All the studies concluded that although the reports point to temporal association between mRNA vaccines and corneal transplant rejection, there lacks direct immunologic evidence of causation by COVID-19 virus or it's mRNA. In the US, from 2005 – 2014, the number of corneal transplants ranged from 42,606 to 51,237 per year.[22] The graft rejection rates are influenced by the method of the corneal transplant, with rates ranging from 1.9% to 41%.[23] In United Kingdom, the reported frequency of rejection of corneal transplantation varies from 8% - 37% (Wertheim MS et al, 2006). The 5-year cumulative occurrence of corneal transplant rejection was reported by Guilbert et al, where the authors retrospectively followed 1438 corneal transplants for 15 years after surgery. The authors reported that the 5-year cumulative occurrence of rejection was 37.5% for 0-10 years; 30.6% for 11-20 years; 23.4% for 21-30 years; 20.6% for 31-40 years; 42.3% for 41-50 years; 22.1% for 51-60 years; 25.1% for 61-70 years; 24.1% for 71-80 years; 20.1% for 81-90 years; and 23.6% ≥ 91 years. However, there was no information regarding age stratified incidence or proportion of corneal transplant rejection. To date, there is no published literature for overall or age and gender stratified incidence for corneal transplant rejection. The overall incidence was estimated using the data for number of corneal transplants per year in 2014 in the US.[22] The population based corneal transplant rate per 100,000 persons was calculated using the mid-year US population (estimates as of July 1st). This population-based rate was multiplied by the proportion of corneal transplant rejection to estimate the incidence of corneal transplant rejection rate per 100,000 persons. Based on this calculation, the estimated incidence ranged between 0.25 to 6.0 per 100,000 persons. Given that incidence estimates stratified by age and gender were not available, the lower bound of this range was used to support observed to expected estimates. As of 15 April 2022, approximately 633 million doses of Spikevax had been administered to 280.9 million individuals globally. In order to estimate the reporting rate of corneal transplant rejection, the MAH assumed a 21-day risk window following each administered dose to calculate exposed person-years. To increase sensitivity, all cases were included regardless of whether they occurred in this window. Stratification by age and gender assumed the demographic distribution of vaccine recipients in the

US as published by the US CDC. Considering all data accrued in the Moderna Inc. Global Safety Database through 15 April 2022, 9 cases (1 duplicate report) of corneal transplant rejection were observed. The resulting reporting rate was 0.003 cases per 100,000 persons, was below the lower bound of estimated reference range (0.25 per 100,000 persons, 702 cases expected rate ratio 0.01, 95% CI 0.02 - 0.04). Stratification of observed to expected analyses by age and gender showed similar results, with reporting rates below the lower bound of estimated reference range. In sensitivity analyses based on assumed poor case capture with no false positive errors, overall reporting rates remained below or consistent with background incidence.

Table 1 Observed-to-Expected Analyses, Corneal Transplant Rejection, Estimated Expected Rates from the United States – Cumulative 15 April 2022

Age/Gender	People	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	280929079	9	0.003	702	0.25	0.01 (0.01, 0.02)	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)
By age								
<18 years	8427872	0	0.000	21	0.25	NA	NA	NA
18-24 years	23598043	0	0.000	59	0.25	NA	NA	NA
25-39 years	57590461	1	0.002	144	0.25	0.01 (0, 0.05)	0.01 (0, 0.06)	0.03 (0.01, 0.08)
40-49 years	40734716	1	0.002	102	0.25	0.01 (0, 0.07)	0.02 (0, 0.08)	0.04 (0.01, 0.11)
50-64 years	73322490	2	0.003	183	0.25	0.01 (0, 0.04)	0.02 (0.01, 0.06)	0.04 (0.02, 0.09)
65-74 years	45791440	2	0.004	114	0.25	0.02 (0, 0.07)	0.03 (0.01, 0.09)	0.07 (0.03, 0.14)
75+ years	31464057	3	0.010	79	0.25	0.04 (0.01, 0.12)	0.08 (0.03, 0.17)	0.15 (0.08, 0.28)
By gender								
Male	131372926	3	0.002	328	0.25	0.01 (0, 0.03)	0.02 (0.01, 0.04)	0.04 (0.02, 0.07)
Female	149556153	6	0.004	374	0.25	0.02 (0.01, 0.04)	0.03 (0.02, 0.06)	0.06 (0.04, 0.1)
By age and gender								
MALE								
<18 years	3941188	0	0.000	10	0.25	NA	NA	NA
18-24 years	11035326	0	0.000	28	0.25	NA	NA	NA
25-39 years	26931450	1	0.004	67	0.25	0.01 (0, 0.11)	0.03 (0.01, 0.12)	0.06 (0.02, 0.16)

40-49 years	19049074	0	0.000	48	0.25	NA	NA	NA
50-64 years	34288334	0	0.000	86	0.25	NA	NA	NA
65-74 years	21413787	1	0.005	54	0.25	0.02 (0, 0.14)	0.04 (0.01, 0.15)	0.07 (0.03, 0.21)
75+ years	14713768	1	0.007	37	0.25	0.03 (0, 0.2)	0.05 (0.01, 0.23)	0.11 (0.04, 0.31)
FEMALE								
<18 years	4486685	0	0.000	11	0.25	NA	NA	NA
18-24 years	12562717	0	0.000	31	0.25	NA	NA	NA
25-39 years	30659011	0	0.000	77	0.25	NA	NA	NA
40-49 years	21685642	1	0.005	54	0.25	0.02 (0, 0.13)	0.04 (0.01, 0.15)	0.07 (0.03, 0.2)
50-64 years	39034156	2	0.005	98	0.25	0.02 (0.01, 0.08)	0.04 (0.02, 0.11)	0.08 (0.04, 0.17)
65-74 years	24377653	1	0.004	61	0.25	0.02 (0, 0.12)	0.03 (0.01, 0.13)	0.07 (0.02, 0.18)
75+ years	16750289	2	0.012	42	0.25	0.05 (0.01, 0.2)	0.1 (0.03, 0.27)	0.19 (0.09, 0.41)

3.5 REVIEW OF PHARMACOVIGILANCE DATABASE

3.5.1 Methodology

The company global safety database was queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 December 2020 to 15 April 2022, worldwide, reported for the mRNA-1273 vaccine (Spikevax) using a combination of two approaches: 1) MedDRA PT "Corneal graft rejection" alone or 2) MedDRA PT "Transplant rejection" and then manually review of the events verbatim for "vision" related terms. This search retrieved a total of a total of 8 cases (1 duplicate report) (9 events) of corneal transplant rejection Table 2 summarizes the PTs of the 9 cases (10 events) received in the global safety database.

3.5.2 Results

Cumulatively, a total of 9 cases (10 events) of corneal transplant rejection were reported, of which all were considered serious and 8 being medically confirmed. There were no cases with fatal outcomes. Four cases ([redacted]) were reported from a single literature source.

Case distribution by country included France and Italy (10.0% each), Switzerland and the United States (40.0% each). Most reports were forwarded from regulators (5 cases; 55.6%) and literature non-study (4; 44.4%).

Table 2 Number and Percentage of Corneal Transplant Rejection Events Reported by Preferred Terms (PTs) - Cumulative to 15 April 2022

PT	Total Number of Events	
	# Events	% Total Events
Corneal graft rejection	8	80.0
Transplant rejection	2	20.0
Grand total	**10**	**100.0**

Cases of corneal transplant rejection were disproportionately reported in females (6 cases) most frequently in the 75+ year age group (33.3%) with the mean age of 65.9 years (SD 17.8) and a median age of 69.0 years (min 33.0 /max 86.0). Age and gender are tabulated below in Table 3. Ethnicity was not provided, and no clustering of cases was observed.

Table 3 Number and Percentage of Corneal Transplant Rejection Cases Reported by Age and Gender - Cumulative to 15 April 2022

Age Group	Female		Male		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
30-39	-	-	1	33.3	1	11.1
40-49	1	16.7	-	-	1	11.1
50-64	2	33.3	-	-	2	22.2
65-74	1	16.7	1	33.3	2	22.2
75+	2	33.3	1	33.3	3	33.3
Grand total	6	100.0	3	100.0	9	100.0

Medical and drug history is summarized below. All cases reported a history of keratoplasty although the date of the procedure was usually not provided, COVID-19 mRNA vaccination was reported using Spikevax but whether corneal rejection occurred after the first or second dose was not always provided. Most common presenting symptoms were a decline in visual acuity in 5 events. Other reported symptoms were blurry vision or photophobia. Other symptoms were generally not provided. When available, TTO after dose 1 represented the highest number of events (5-6 days for 2 events and 14-29 days for 1 event). Duration of events included an average number of days of 7.0 (SD: 9.9) with median number of days of 7.0 (min 0; max 14). Time to onset data was missing for 6 cases (60.0%).

Table 4 Distribution of Reported Events of Corneal Transplant Rejection by Associated Dose Number and Time to Onset (TTO) - Cumulative to 15 April 2022

Dose Number	TTO All Doses (Days)	Total of # Events	Total of % Events
Dose 1	Subtotal	3	30.0
	05-06	2	20.0
	14-29	1	10.0
Dose 2	Subtotal	1	10.0
	03-04	1	10.0
Unknown	Subtotal	6	60.0
	Missing	6	60.0
Grand total	Grand total	10	100.0

3.5.3 Summary

Based on the analysis of all the safety data available as of 15 April 2022, the MAH considers that there is no evidence to establish a causal relationship to the administration of Spikevax and corneal graft rejection. Acute corneal transplant rejection in people exposed to mRNA vaccines, does not represent a new safety concern or potential risk.

3.6 LITERATURE REVIEW

3.6.1 Clinical literature search review

A literature search of PUBMED was performed with data cut-off on 01 May 2022 was performed using the following search criteria: (Corneal graft rejection) OR ("transplant rejection") AND ("2019-nCoV Vaccine mRNA-1273"[Mesh] OR "COVID-19 Vaccines/adverse effects"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "mRNA Vaccines"[Mesh] OR mRNA COVID vaccination [tw] OR mRNA-1273 [tw] OR "mRNA 1273" [tw] OR mRNA1273 [tw] OR "modernatx 1273" [tw] OR "Moderna Covid19 Vaccine" [tw] OR "Moderna Covid-19 Vaccine" [tw] OR Spikevax [tw] OR "2019 nCoV Vaccine mRNA 1273" [tw] OR "mRNA-1273, 2019-nCoV Vaccine" [tw] OR "Moderna COVID-19 Vaccine" [tw] OR "COVID-19 Vaccine, Moderna" [tw] OR "Moderna COVID 19 Vaccine" [tw] OR "Moderna COVID 19 Vaccine" [tw] OR "Vaccine, Moderna COVID-19" [tw] OR Elasomeran [tw] OR "Moderna COVID-19 Vaccine RNA" [tw] OR "Moderna COVID 19 Vaccine RNA" [tw] OR "COVID-19 Vaccine Moderna" [tw] OR "COVID 19 Vaccine Moderna" [tw] OR "Moderna, COVID-19 Vaccine" [tw] OR "mRNA-1273" [tw] OR "mRNA 1273" [tw] OR TAK-919 [tw] OR "TAK 919" [tw]

OR TAK919 [tw] OR M-1273 [tw] OR "M 1273" [tw] OR M1273 [tw] OR mRNA-1273.211 [tw] OR "mRNA 1273.211" [tw] OR COVID-19[tw] OR SARS-CoV-2[tw] OR "COVID-19 vaccines"[tw] OR "mRNA Vaccines"[tw])

The search retrieved 40 articles. Seven (7) articles were identified among patients using mRNA vaccines. Remaining articles were on background data on early and late corneal graft rejection (2 relevant articles) with some summarized by cases of acute corneal rejection reported in association with mRNA vaccines, and acute corneal rejection reported with other vaccines, and 22 articles were identified using "transplant" or "corneal graft rejection with vaccines".

1. Corneal graft rejection and vaccines 22 articles identified (19 relevant; 3 other vaccines and includes articles for covid) https://pubmed.ncbi.nlm.nih.gov/?term=corneal+graft+rejection+AND+vaccines&size=100 2. Early corneal graft rejection AND vaccines https://pubmed.ncbi.nlm.nih.gov/?term=early+corneal+graft+rejection+AND+vaccines&size=100 (1 relevant by Phylactou et al). 3. Late corneal graft rejection AND vaccines (1 article identified)

2. Early corneal graft rejection AND vaccines https://pubmed.ncbi.nlm.nih.gov/?term=early+corneal+graft+rejection+AND+vaccines&size=100 (1 relevant by Phylactou et al).

3. Late corneal graft rejection AND vaccines (1 article identified)

A total of 13 cases of acute corneal transplant rejection were identified, with most of the reports referring to the use of other mRNA COVID-19 vaccine, and 9 were reported after the receipt of either dose 1 or dose 2 of Spikevax. The infrequency of the reports and the associated confounders, as well as the lack of clinical, pathological and detailed ophthalmological information do not provide evidence for a causal relationship between Spikevax induced immune activation and corneal graft rejection. Review of retrieved literature articles suggest a speculative immunological hypothesis between possibility of COVID-19. Cases of CGR has been reported with all types of Covid-19 vaccines. Corneal transplantation has a low graft rejection rate because of ocular immune privilege, which can be compromised by increased immune dysregulation. Possible mechanism of action proposed in the literature include immune-mediated mechanisms triggered by immunization could be responsible for these ocular inflammatory reactions. Immune evasion with SARS-CoV-2,-associated with excessive innate immune activation producing; possible consequence of host dysregulation of the immune system. None of the cases reported prior COVID-19 infection, whether because they were negative or because the information was not provided. Although patients are treated empirically with topical and/or oral steroids, there are no randomized control studies that support the recommendation and, in most reports, the events resolved with treatment. The mechanism of corneal graft rejection occurring in close proximity to vaccination, remains unconfirmed for all vaccines including tetanus toxoid, Hepatitis B, Influenza and Covid-19 vaccines

3.6.2 Literature Conclusion

Endothelial corneal transplant rejection following immunization with any COVID-19 vaccines (Waller Cornea. 2021) have been reported (Phylactou M), ECGR is considered possibly related to early and late immune dysregulation with time to onset within 1-3 day and exceeding 7-10 days. Only a history of previous corneal transplant rejection is significantly associated with corneal transplant rejection. Mechanisms of endothelial graft rejection with COVID 19 vaccines have not been elucidated. However, large population-based studies are required to confirm an association between corneal graft rejection and mRNA vaccines. The medical and literature search results information does not support a causal association between Spikevax and the event of corneal transplant rejection hence the signal is refuted and closed.

4. DISCUSSION AND CONCLUSION

The MAH considers that review of the safety data conducted during this safety analysis supports the conclusion that the evidence currently does not suggest a causal association between Spikevax and corneal graft rejection. Observed to expected analyses do not suggest an increased incidence compared to what is expected among corneal transplant rejection in the general population. Corneal transplant rejection reports were mostly serious, occurred predominantly in the age group 75+ years, mostly within 7 days after the 1st dose of the vaccine.

The analysis of the safety database, the medical and literature information does not support a causal association between Spikevax and the event of acute corneal rejection. The MAH reviewed cases of corneal graft rejection using routine surveillance hence the signal is refuted and considered closed.

Based on the analysis of all the safety data available as of 15 April 2022, the MAH considers that there is insufficient evidence to establish a causal relationship to the administration of Spikevax, immune activation and corneal graft rejection. Acute corneal transplant rejection in people exposed to mRNA vaccines, does not represent a new safety concern or potential risk. This data is in keeping with the conclusion of Dudley et al (2020) who performed a systematic review of the state of vaccine safety and concluded vaccines were very safe. [3]

5. REFERENCES

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APPENDIX 1:

Referring to EMA safety update on Corneal graft rejection (CGR), please provide company assessment, action plan on labeling change, etc. by 29th April 2022.

APPENDIX 2:

Overview of Corneal graft rejection (CGR) Company Safety Database Cases

DLP	15-Apr-22
Summary findings	[redacted]/[redacted] **(duplicate case) (WW ID:** [redacted]**):–** 86 years old female with medical history of hypertension and other comorbidities, who 2 days after the 1st dose of Spikevax presented to her pharmacist with reduced visual acuity in the operated eye, and two days later due to suspicion of starting of transplant rejection a pentacam tomography was performed that showed an increase in corneal graft thickness suggesting transplant decompensation. The patient received the 2nd dose of Spikevax 23 days later with no other information. **MAH Comment :** The patient's gender is considered an important risk factor for corneal graft rejection. Age, associated co-morbidities incomplete ophthalmic history are important confounders and lack of information after second dose of vaccine does not support vaccine induced rejection. The short TTO (2 days) for the development of graft thickness suggesting transplant decompensation, suggests an alternative explanation for the occurrence of the reported events. According to the WHO causality assessment this report is considered unlikely. [redacted]**: (WW ID** [redacted]**):** 33-year-old, male patient who 21 days after the 1st dose of Spikevax experienced corneal graft rejection. No other information was provided. Important information is missing in the report including patient's full medical history as well as any diagnostic or laboratory test conducted

	MAH Comment : According to the WHO causality assessment temporality is possible and this report is conditional based on the lack of information; a causal relationship cannot be excluded due to the lack of information. [redacted]**: (WW ID :** [redacted]**:** Consumer report for a 46 year old female with medical history of Keratoconus, who after an unknown TTO after the 2nd dose of Spikevax reported to be experiencing corneal graft rejection. No other information was provided. Important information is missing in the report including patient's full medical and ophthalmic history as well as any diagnostic or laboratory test conducted. **MAH Comment :** Important information is missing in the report including patient's medical history as well as any diagnostic or laboratory test conducted, including testing for SARS-CoV2. According to the WHO causality assessment this report is unassessable based on the lack of information. Temporality could not be established because of the lack of TTO in order to establish a temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of information. [redacted]**: (WW ID:** [redacted]**:** Literature nonstudy case report for a 61-year-old female with medical history of with medical history of keratoplasty with extracapsular cataract extraction and posterior chamber intraocular lens placement 3 years ago, and subsequent keratoplasty wound dehiscence after an accidental blunt trauma with clear compact cornea graft placement a year ago who one week after the 2nd dose of Spikevax complained of declining vision of 2-day duration on the operated eye. On examination, best-corrected visual acuity (BCVA) was reduced to 20/80. Slitlamp examination revealed mild conjunctival inflammation, a corneal endothelial rejection line with fresh KP, and diffuse edema of the inferior third of the corneal graft. Patient was treated and at a 6-week follow-up vision improved to 20/60 with resolution of conjunctival inflammation. **MAH comment :** This report for this 61-year-old-female, as well as the other 3 reports included in the same literature article, according to the authors based solely on clinical observations, "admittedly lack direct immunologic evidence of causation by either the COVID19 virus or its mRNA. In addition, although the details of events in all 4 cases point to a temporal and causal association between the COVID-19 vaccination and rejection, a population based study looking at the increase in rates of incidence of corneal graft rejection after the vaccination is much needed". Important information is missing in the report

	including patient's full medical history as well as any other laboratory test conducted, as well as any concomitant medications. According to the WHO causality assessment this report is possible based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of additional information. **[redacted] : (WW ID [redacted]** **[redacted]:** Literature nonstudy report for a 74-year-old male with unknown medical history and who 6 month before his 1 st dose of Spikevax had received Descemet membrane endothelial keratoplasty (DMEK) for pseudophakic bullous keratopathy. The early postoperative course was uneventful with the BCVA improving to 20/25 within 6 weeks with excellent corneal clarity. At the 3-month postoperative visit (3 months before his 1st dose), he was found to have mild cystoid macular edema (CME) while maintaining a clear cornea. By the 5-month postoperative visit, the CME had fully resolved with treatment. At this time, the visual acuity had returned to 20/25. Three weeks after receiving his 1st dose of Spikevax the patient had a scheduled follow up visit at which he reported having 2 weeks of decreased vision on the operated eye and was found to have BCVA reduced to 20/60, and an increased on the central corneal thickness. Slit-lamp examination revealed an endothelial rejection line in the superior aspect of the DMEK disk accompanied by microcystic epithelial and stromal oedema. Patient denied exposure to SARS-CoV-2 and 3 months previously had a negative test, but it is unknown if additional test was performed at that time. Treatment was initiated at the time and within 2 days the stromal oedema had reduced. Patient received the 2nd dose of Spikevax as planned without any new event. Three weeks after the second vaccine and 5 weeks after initial presentation of rejection, BCVA improved to 20/40, with near resolution of the endothelial rejection line. **MAH comment :** This report for this 74-year-old-male, as well as the other 3 reports included in the same literature article, according to the authors based solely on clinical observations, "admittedly lack direct immunologic evidence of causation by either the COVID19 virus or its mRNA. In addition, although the details of events in all 4 cases point to a temporal and causal association between the COVID-19 vaccination and rejection, a population-based study looking at the increase in rates of incidence of corneal graft rejection after the vaccination is much needed". Important information is missing in this report including patient's full medical history as well as any other laboratory test conducted, including a new test for SARS-CoV-2. Important risk factors are also associated with this patient including his history of very recent eye surgery including oedema in the past two- three months. According to the WHO causality assessment this report is unlikely. The negative rechallenge of receiving the 2nd dose without experiencing any new events is an important determinant in this assessment.

	[redacted] : (WW ID [redacted] – Literature nonstudy case report for a 69-year-old female with medical history of type 2 diabetes mellitus and nonprogressive Salzmann nodular degeneration in the left eye who had received DSAEK in both eyes 6 years ago for Fuchs endothelial corneal dystrophy, and who approximately 2 weeks after the 2nd dose of Spikevax. reported declining vision in the left eye. At presentation, which was 4 weeks after the 2nd dose, BCVA was reduced to 20/50 in the involved eye. Slitlamp examination showed conjunctival injection, trace anterior chamber cells, and corneal stromal edema. Patient was treated and within 3 weeks, BCVA in the left eye recovered to 20/30 with resolution of anterior chamber cells and improvement of stromal edema. No other information was provided. **MAH Comment :** This report for this 69-year-old-female, as well as the other 3 reports included in the same literature article, according to the authors based solely on clinical observations, "admittedly lack direct immunologic evidence of causation by either the COVID19 virus or its mRNA. In addition, although the details of events in all 4 cases point to a temporal and causal association between the COVID-19 vaccination and rejection, a population-based study looking at the increase in rates of incidence of corneal graft rejection after the vaccination is much needed". Important information is missing in the report including patient's full medical history as well as any other laboratory test conducted, including a test for SARSCoV-2. Important risk factors are also associated with this patient including her history of type 2 diabetes as well as any other laboratory test conducted, including testing for SARS-CoV-2. According to the WHO causality assessment this report is possible based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of information. [redacted] : (WW ID : [redacted]) : Literature report for a 77-year-old male with medical history of corneal edema secondary to amantadine usage for mild relapsing-remitting multiple sclerosis.Twenty-two years previously patient had received PKP with cataract extraction in the left eye. The patient 1 week after 2nd dose of Spikevax reported experiencing increasing photophobia, brow ache, and decreased vision in the left eye, and one week later was found that BCVA had declined to 20/60. Slitlamp examination showed mild conjunctival hyperemia and injection, mild corneal edema, anterior chamber flare and cell, as well as numerous mixed KP. One week thereafter, the patient's symptoms had resolved and BCVA improved to 20/40. Slitlamp examination demonstrated reduced KPs and complete resolution of corneal edema as well as the anterior chamber cells and flare.

MAH Comment : This report for this 77-year-old-female, as well as the other 3 reports included in the same literature article, according to the authors based solely on clinical observations, "admittedly lack direct immunologic evidence of causation by either the COVID19 virus or its mRNA. In addition, although the details of events in all 4 cases point to a temporal and causal association between the COVID-19 vaccination and rejection, a population based study looking at the increase in rates of incidence of corneal graft rejection after the vaccination is much needed". Important information is missing in the report including patient's full medical history and current medical history of his multiple sclerosis, as well as any other laboratory test conducted, including a test for SARS-CoV-2. Important risk factors are also associated with this patient including his history of MS, as well as any other laboratory test conducted, including testing for SARS-CoV-2. According to the WHO causality assessment this report is possible based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of information.

[redacted]**: (WW ID :** [redacted]: 61year-old female with unknown medical history and history of Corneal transplant on 01-Jan-1991 who 114 days after receiving and unknown dose of Spikevax experienced corneal graft rejection in the right eye. No other information was provided.

MAH Comment : Important information is missing in the report including patient's medical history as well as any other laboratory test conducted, including testing for SARS-CoV-2. According to the WHO causality assessment this report is unassessable based on the lack of information including the dose information in order to establish a temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of other information. The very prolonged TTO is an important confounder in this report.

[redacted] **: (WW ID :** [redacted] Literature non study case in a 51-year-old male patient with medical history of Keratoplasty with chronic graft failure and glaucoma undergoing treatment with 3 intraocular pressure-lowering agents. The patient had undergone corneal transplantation 3 weeks before his 1st dose of Spikevax. Three days after receiving his 1st dose, the patient began developing eye pain, photophobia, and blurred vision. He was examined shortly after the onset of symptoms and was found to have new graft edema with fine endothelial keratic precipitates indicative of early rejection. Despite treatment with topical steroids, graft failure developed. According to the authors the patient had limited visual prognosis because of his advanced glaucoma.

	MAH Comment : Important information is missing in the report including patient clinical course of the current conditions, as well as any laboratory test conducted. The patient's history of chronic graft failures and other ophthalmic conditions as well as advance glaucoma are important risk factors that provide a more plausible explanation for the occurrence of the reported event of corneal graft rejection. According to the WHO causality assessment this report is considered unlikely. [redacted] **: (WW ID :** [redacted]: Literature non study case in a 51-year-old male patient with medical history of Keratoplasty with chronic graft failure and glaucoma undergoing treatment with 3 intraocular pressure-lowering agents. The patient had undergone corneal transplantation 3 weeks before his 1st dose of Spikevax. Three days after receiving his 1st dose, the patient began developing eye pain, photophobia, and blurred vision. He was examined shortly after the onset of symptoms and was found to have new graft edema with fine endothelial keratic precipitates indicative of early rejection. Despite treatment with topical steroids, graft failure developed. According to the authors the patient had limited visual prognosis because of his advanced glaucoma. **MAH Comment :** Important information is missing in the report including patient clinical course of the current conditions, as well as any laboratory test conducted. The patient's history of chronic graft failures and other ophthalmic conditions as well as advance glaucoma are important risk factors that provide a more plausible explanation for the occurrence of the reported event of corneal graft rejection. According to the WHO causality assessment this report is considered unlikely.

Appendix 4.2g: Signal Evaluation report: IgA Nephropathy

Signal Evaluation Report

for

mRNA-1273

on

IgA Nephropathy

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List of Abbreviations

ADR	Adverse Drug Reaction
CDC	Centers for Disease Control and Prevention
CT	Clinical Trial
DLP	Data Lock Point
CMQ	Customized MedDRA query
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HLT	Higher Level Term
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RA	Regulatory Authority
SD	Signal Detection
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VAERS	Vaccine Adverse Event Reporting System

1 Introduction

This signal evaluation report provides a detailed analysis on the validity of safety topic on IgA nephropathy in association with the administration of mRNA-1273 in patients of all age groups, based on all the information available to the MAH at the time of document preparation.

1.1 Source of the Signal

The PRAC (*Procedure no.: EMEA/H/C/PSUSA/00010897/202112*) requested a "The MAH is requested to add IgA nephropathy to the list of safety concerns as an important potential risk in the PSUR. As a consequence, a risk characterisation and an evaluation of new information for the risk is expected in the next PSUR. The MAH is also requested to discuss in the next PSUR whether IgA nephropathy needs to be added to the list of safety concerns in the RMP."

Also: "It is the PRAC Rapporteur's opinion that the cumulative evidence is not sufficient to warrant amendment of the product information regarding IgA nephropathy at present."

2 Background

Product: The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S glycoprotein into a prefusion conformation (S-2P). mRNA-1273 consists of an mRNA that is manufactured with LNPs composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

Potential signal: IgA nephropathy

IGA nephropathy (IgAN) is estimated to be the most common type of primary glomerulonephritis identified only by kidney biopsy with a global prevalence of 2.5/100,000 adults per year. It is most common in Asian populations followed by European with the least in African populations. The most common symptom of IgA nephropathy is blood in the urine followed by albuminuria. Since the disease is typically asymptomatic in the absence of hematuria, it is very likely underdiagnosed, and the true incidence of early stages of IgA nephropathy is poorly understood. This glomerular disease results from deposits of immunoglobulin A (IgA) in the glomeruli. IgAN can progress for years with no noticeable clinical symptoms or findings on routine tests. Up to 40% of native kidney biopsies from eastern Asia demonstrate IgA nephropathy. In some cases, IgA nephropathy runs in families. Studies have recently found several genetic markers are risk factors for IgAN. In some situations, IgA nephropathy may be related to respiratory or intestinal infections and the immune activity associated with them. Studies have found that serum in patients with IgA nephropathy contain elevated levels of galactose-deficient IgA1 . which initiates an immune response and immune complexes. Diagnosis requires renal biopsy demonstrating IgA complexes in the glomeruli. IgA nephropathy is more common in men than women and can be diagnosed in all ages; however, diagnosis is most common in the second and third decades of life, with 80% of patients between the ages 16-35 years at time of diagnosis. The exact etiology and pathophysiology are presently not known.

3 Review of Data from All Sources

The assessment of IgA nephropathy in association with the use of mRNA-1273 in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below.

3.1 Clinical Trial Data

The topic of IgA nephropathy was cumulatively reviewed in the clinical trial datasets, within the following studies of P301 study (ages ≥18 years; DLP: 04 May 2021), P203 study (ages 12-17 Years; 27 Jan 2022) and P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022), for any PTs including in the HLT Glomerulonephritis and Nephrotic Syndrome. Review of these studies observed Zero cases.

List of PTs in MedDRA HLT of Glomerulonephritis and Nephrotic Syndrome:

Alagille syndrome, Alport's syndrome, Anti-LRP2 nephropathy, Anti-glomerular basement membrane disease, Benign familial haematuria, C1q nephropathy, C3 glomerulopathy, Chronic autoimmune glomerulonephritis, Congenital nephrotic syndrome, Denys-Drash syndrome, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Frasier syndrome, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Goodpasture's syndrome, Granulomatosis with polyangiitis, HIV associated nephropathy, Henoch-Schonlein purpura nephritis, Hepatitis virus-associated nephropathy, IgA nephropathy, IgM nephropathy, Immunotactoid glomerulonephritis, Membranous-like glomerulopathy with masked IgG-kappa deposits, Mesangiolipidosis, Mesangioproliferative glomerulonephritis, Microscopic polyangiitis, Nephritic syndrome, Nephritis allergic, Nephrotic syndrome, Paraneoplastic glomerulonephritis, Paraneoplastic nephrotic syndrome, Post infection glomerulonephritis, Post streptococcal glomerulonephritis, Primary coenzyme Q10 deficiency and Pulmonary renal syndrome

3.2 External Databases

- **VAERS:** No Disproportionate Reporting of Events using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS as of 10 Jun 2022; PT IgA nephropathy (EB05: 1.113; N=53)
- **EVDAS**: PT IgA nephropathy shows Disproportionality as the ROR was >1. The observed ROR for IgA nephropathy was (1.88; N=58). This small disproportionality is not uncommon in EVDAS.

3.3 Non-clinical Data

Not applicable

3.4 Possible Mechanisms of Action

There is no known mechanism of action to account for an association of mRNA-1273 vaccination and IgA nephropathy. IgAN has been observed following infection with any of several viral pathogens, including SARS-CoV-2. It has been proposed that shared epitopes in the SARS-CoV-2 spike proteins and human proteins resulting in cross-reactive antibodies. There are no pathognomonic signs or symptoms that link IgA nephropathy to vaccination.

IgA nephropathy is the most common cause of primary (idiopathic) glomerulonephritis in resource-abundant settings; similarly, it is the most common type of glomerulonephritis in the adverse event reports received by the MAH for Spikevax. With regard to IgA nephropathy and subclinical IgA deposits in kidneys, the scientific literature has found that there is a clinically significant cohort of undiagnosed "latent" IgA nephropathy in the general population as seen in native kidney biopsies. It is also noted that the process of mesangial IgA deposition may be separate from the induction of glomerular injury, and IgA deposition does not necessarily result in subsequent nephritis. Identifying the independent factors that may be critical to each of these processes may improve our overall understanding of the pathogenesis of IgA nephropathy.

3.5 Epidemiological studies

The observed reporting rates for overall and dose specific (3-day risk window and 7-day risk window) were lower than the expected reporting rates (Limited interpretability of numerical increases in some subgroups given poor precision and small numbers). The observed reporting rate of IgA nephropathy with Spikevax considering a 3-day risk window (0.7 cases per 100,000 persons), was below the expected estimated reference rate (0.75 per 100,000 persons). Stratification of observed to expected analyses by age and gender showed similar results. However, under the assumption of under-reporting by 50%, the O/E analysis was greater than 1 (1.96, IC95% 1.34,2.85) considering the 3-day, but not the 7-day risk window (0.92, IC95% 0.69,1.23). see **Appendix 1A**: O/E Analysis Tables for O/E Analysis tables.

3.6 Review of the Pharmacovigilance Database

A cumulative search in Global safety database (GSDB), through 18 Jun 2022 using the search terms from MedDRA HLT glomerulonephritis and nephrotic syndrome was performed. All case reports identified from the above search (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy.

3.7 Results

All case reports As of the DLP (18 Jun 2022), there were 186 cases (176 events) were retrieved. These 186 cases (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy, see the following (**Appendix-2A: Individual Cases Assessment to Identify Case of IgA Nephropathy**) for line listings and MAH review comments of these 186 cases.

Medical review identified 54 cases of IgA nephropathy. Those cases considered IgA flares or relapses were those in which a diagnosis of IgA nephropathy had been made prior to Spikevax vaccination, where an additional diagnosis was made subsequent to the date of vaccination, 20 such cases were identified, of which 19 were serious. Incident (de novo) cases of IgA Nephropathy are those for which the event of IgA Nephropathy occurred after the administration of Spikevax. These reports were identified using renal biopsy, medical diagnosis and reported diagnosis of IgA nephropathy, 34 such cases were identified.

Of these 54 cases, most of the cases were reported from United States (18; 33.3%), France 2, followed by European Economic Area (17; 31.5%) and Asia (11; 20.4%) (Table-1).

Table-1: Summary of Cases Reported for Region stratified by IgA DeNovo and IgA Flare

Region	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
United States	10	18.5	8	14.8	18	33.3
European Economic Area	12	22.2	5	9.3	17	31.5
Asia	8	14.8	3	5.6	11	20.4
Switzerland	3	5.6	2	3.7	5	9.3
United Kingdom		0	2	3.7	2	3.7
Middle East	1	1.9		0	1	1.9
Total Cases	**34**	**63.0**	**20**	**37.0**	**54**	**100.0**

There were no reports of fatal cases. There were no important differences between the number of IgA Nephropathy reports for females (29; 53.7%) compared to males (25; 46.3%), which is different from general data shows that IgA Nephropathy was more common in Men than Women. UpToDate states: "Patients with IgAN may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations in both adults and children." An Overview of 54 Cases is presented in Table-2

Table-2: Summary of Cases Reported for IgA Nephropathy by Age and Gender

Age Group	Female		Male		Total # of Cases	Total % of Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
12 -15	2	3.7	1	1.9	3	5.6
18 -29	6	11.1	7	13.0	13	24.1
30 - 39	6	11.1	5	9.3	11	20.4
40 -49	7	13.0	4	7.4	11	20.4
50 -64	4	7.4	5	9.3	9	16.7
65 - 74	2	3.7	3	5.6	5	9.3
Missing	2	3.7		0.0	2	3.7
Grand Total	**29**	**53.7**	**25**	**46.3**	**54**	**100.0**

The graph below indicates the time from vaccination with Spikevax to onset of IgA nephropathy, where this information was available, and is based on medical review of the cases. Most of the cases reported onset of IgA nephropathy within two days following vaccination with the greatest number of reports occurring after the second dose of Spikevax. This coincides with the known enhanced immune response seen with boosted vaccinations. This pattern is generally similar to that of all adverse events reported following Spikevax immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with this limited number of reports, the finding is simply an observation; there is no clear biological explanation.

Figure-1: Reported IgA Nephropathy DeNovo Events by Dose & Time to Onset Cumulative thru 18 Jun 2022

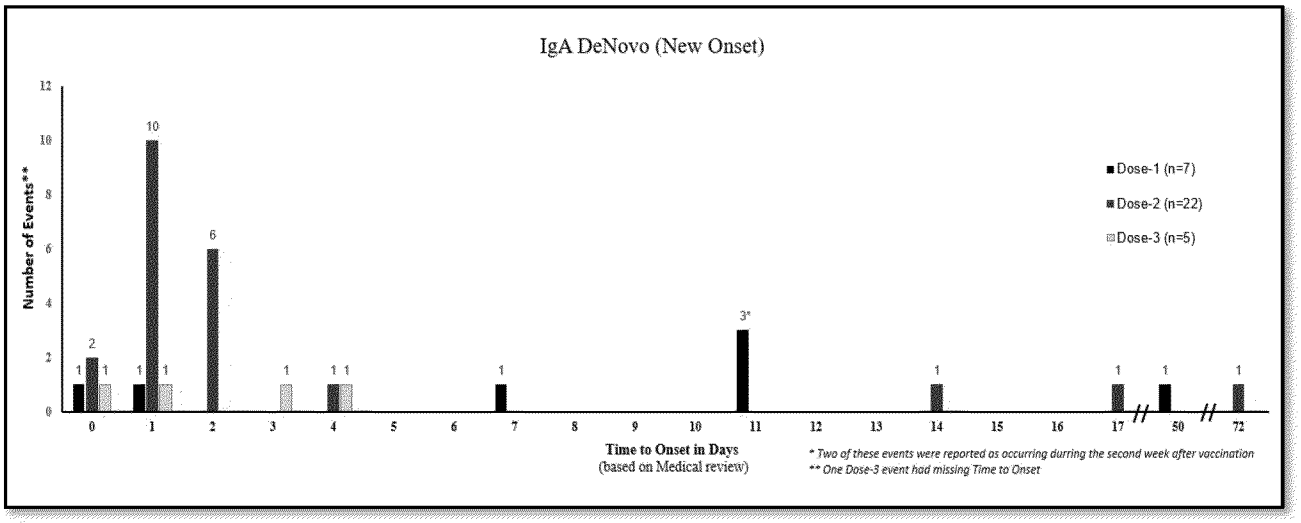
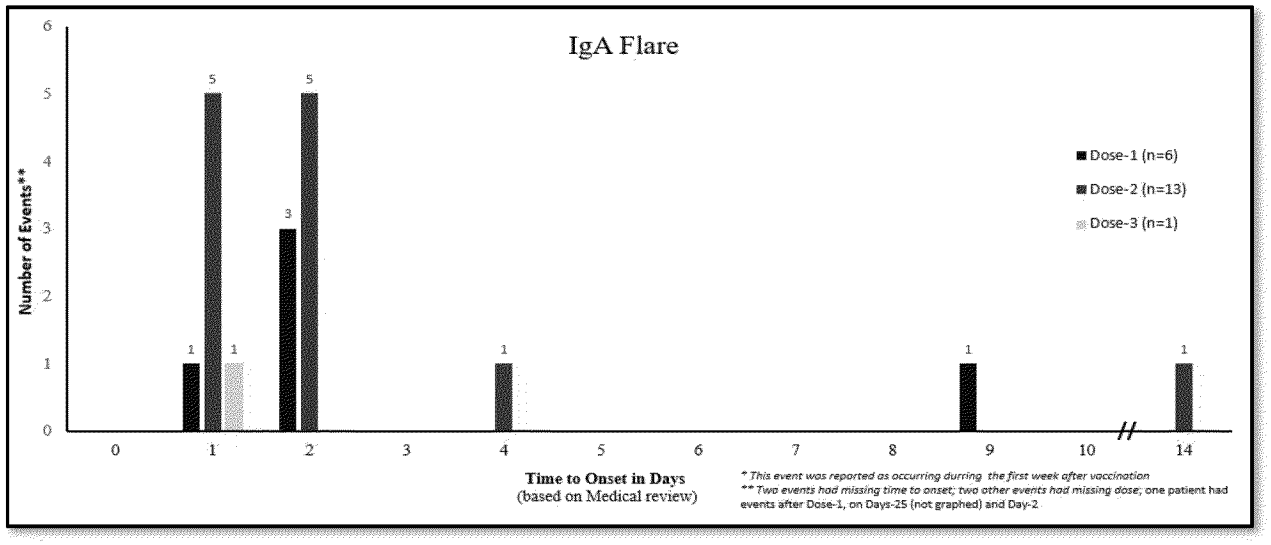


Figure-2: Reported IgA Flare Events by Dose and Time to Onset Cumulative thru 18 Jun 2022



The MAH has re-evaluated cumulatively all cases with IgA nephropathy and flare-up of IgA nephropathy temporally associated with Spikevax according to the WHO-UMC causality assessment. Most of the cases (29; 53.7%) were considered possible based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of important information in the majority of the cases. A summary of WHO causality assessment is presented in Table-3. Additional information on individual cases assessment appears in the **Appendix 3A: WHO Causality Assessment for IgA Nephropathy (54 Cases)**.

Table-3: WHO-UMC Causality Classification for IgA Nephropathy Cases As of 18 Jun 2022

WHO Causality	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Conditional	5	9.3	3	5.6	8	14.8
Possible	20	37.0	9	16.7	29	53.7
Probable		0.0	5	9.3	5	9.3
Unassessable	8	14.8	3	5.6	11	20.4
Unlikely	1	1.9		0.0	1	1.9
Grand Total	**34**	**63.0**	**20**	**37.0**	**54**	**100.0**

Review of monthly counts of cases by initial receipt date did not show any specific pattern as reports were distributed similarly all over the period since 2021 to 2022. The following Table-4 shows the counts of reports by month and year.

Table-4: Distribution of IgA Nephropathy Cases by Year and Month

Initial Receipt date (Year and Month)	IgA Nephropathy				Total # of Cases	Total % of Cases
	DeNovo		Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
2021						
Mar	1	1.9	0	0.0	1	1.9
Apr	0	0.0	0	0.0	0	0.0
May	1	1.9	1	1.9	2	3.7
Jun	4	7.4	1	1.9	5	9.3
Jul	2	3.7	3	5.6	5	9.3
Aug	2	3.7	2	3.7	4	7.4
Sep	1	1.9	2	3.7	3	5.6
Oct	3	5.6	1	1.9	4	7.4
Nov	2	3.7	3	5.6	5	9.3
Dec	2	3.7	0	0.0	2	3.7
2022						
Jan	1	1.9	2	3.7	3	5.6
Feb	2	3.7	2	3.7	4	7.4
Mar	1	1.9	0	0.0	1	1.9
Apr	7	13.0	0	0.0	7	13.0
May	4	7.4	3	5.6	7	13.0
Jun	1	1.9	0	0.0	1	1.9
Grand Total	**34**	**63.0**	**20**	**37.0**	**54**	**100.0**

4 Literature Review

A targeted literature search was performed as of 18 Jun 2022 using PubMed, with the following search string

Search String (PubMed):

((((((((((((((((((((((((((((Glomerulonephritis[MeSH Terms]) OR (Nephrotic syndrome[MeSH Terms])) OR (Haematuria[MeSH Terms])) OR (Glomerulonephritis rapidly progressive[Text Word])) OR (Nephritic syndrome[Text Word])) OR (Glomerulonephritis minimal lesion[Text Word])) OR (Glomerulonephritis acute[Text Word])) OR (Antiglomerular basement membrane disease[Text Word]))) OR (Nephrosis[MeSH Terms])) OR (Hematuria[MeSH Terms])) OR (Glomerulonephritis, IGA[MeSH Terms])) OR (Nephrosis, Lipoid[MeSH Terms])) OR (Nephritis[MeSH Terms])) OR (membranous glomerulonephritis[Text Word])) OR (Glomerular Mesangium[MeSH Terms])) OR (anti-neutrophil cytoplasmic antibody[MeSH Terms])) OR (Vasculitis[MeSH Terms])) OR (Glomerulonephritis, Membranous[MeSH Terms])) OR (macrohaematuria[Text Word])) OR (minimal change disease[Text Word])) OR (pr3-anca[Text Word])) OR (IgA Nephropathy)) OR (minimal change disease)) OR (glomerulonephritis)) OR (glomerulonephritides) NOT (adult multisystem inflammatory disease, COVID-19 [MeSH Terms])) NOT (pediatric multisystem inflammatory disease, COVID-19 [MeSH Terms])) NOT (MIS-A)) NOT (Multisystem Inflammatory Syndrome[Title/Abstract])) NOT (case report[Title/Abstract])) NOT (A case[Title])) NOT (case reports[Title/Abstract]) AND ("mrna vaccines"[MeSH Terms] OR "2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mRNA 1273"[All Fields] OR "mRNA 1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mrna1273"[All Fields]) OR ("modernatx"[All Fields] OR "1273"[All Fields]) OR "1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "m 1273"[All Fields]) OR "m 1273"[All Fields] OR ("moderna"[All Fields] OR ("covid 19 vaccines"[MeSH Terms] OR ("covid 19"[All Fields] OR "vaccines"[All Fields]) OR "covid 19 vaccines"[All Fields] OR ("covid19"[All Fields] OR "vaccine"[All Fields]) OR "covid19 vaccine"[All Fields])) OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "SPIKEVAX"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "elasomeran"[All Fields]) OR "CX-024414"[All Fields] OR "tak 919"[All Fields] OR "tak 919"[All Fields] OR ("2019 ncov

vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields]) OR (SARS-CoV-2 vaccination) OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields])) AND (2020/01/01:2022/06/18[Date - Publication] OR 2020/01/01:2022/06/18[Date - Create] OR 2020/01/01:2022/06/18[Date - Entry])

Summary of the Results:

- The search retrieved 769 articles, review of these titles and abstracts showed a number of literature articles that reported case series or case reports of IgA Nephropathy following vaccination with SPIKEVAX resulted in individual review of the cases. All such cases are described in the tabulation in the Appendix A2, including causality assessment and its justification.
- The European Renal Association and the European Vasculitis Society stated in March 2022: "COVID-19 vaccines are safe, exhibiting a very low risk of de novo or relapsing immune-mediated kidney disease. Population-based studies will determine whether this is causal or coincidental. Such cases respond to standard management, including the use of immunosuppression. [We] recommend that patients with immune-mediated kidney diseases follow national guidance on vaccination."
- Overall, review of retrieved literature did not identify any pathognomonic sign that would causally link vaccination against SARS-Covid-19 with any type of glomerulonephritis or nephrotic syndrome and that would distinguish such potential vaccine adverse reactions from background events that occur in the absence of vaccination. In addition, there is heterogeneity in the types of glomerulonephritis reported, rather than one predominant type, which does not support causality with regard to Spikevax. Moreover, multiple and widely varying potential mechanisms have been suggested to explain such a potential link, some of which have already been summarized and reviewed in the initial signal evaluation on this topic, previously submitted. However, to date, there has not been consensus or strong evidence with regard to any of these potential mechanisms.

Conclusion: Literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and IgA Nephropathy

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

The MAH conducted an extensive evaluation of the potential signal of IgA nephropathy as signal trigger based on PRAC PSUR assessment report received on 07 July 2022. The signal evaluation included a cumulative review of clinical trial data for any terms from HLT of Glomerulonephritis and nephrotic syndrome from mRNA-1273 studies (P301, P203 and P204), review in the MAH global safety database with a data-lock point (DLP) of 18 Jun 2022, along with review of the literature.

IgA nephropathy is the most common form of primary glomerulopathy, the extent of which is unknown given the predominantly latent nature of the disease. It may remain silent for years without clinical signs or symptoms. IgA nephropathy has been found in families and recent data has demonstrated various genetic markers. Potential triggers include respiratory and gastrointestinal illnesses as well as other immune activation events. The exact etiologies and pathophysiology of IgA nephropathy remain unknown.

There were no reports from clinical trials for either the placebo and mRNA-1273 arms, for events within the terms including MedDRA HLT of Glomerulonephritis and nephrotic syndrome. Post marketing data had identified 54 cases as IgA nephropathy, review of these cases did not show any prominent clinical pattern of occurrence of IgA Nephropathy outside of what would be expected in a large, vaccinated population. Many of the reports were medically confirmed. The observed reporting rates of IgA Nephropathy are well below background incidence rates.

Overall, 54 IgA nephropathy reports in 662,871,167 doses administered, shows an approximate reporting rate < 1 case per 10 million doses. Of these, 34 cases were DeNovo and 20 cases were flares/relapses. The number of vaccinees with IgA nephropathy is unknown, and therefore an observed rate of IgA flares cannot be estimated; in addition, there is no established background rate of IgA flares which also precludes an O/E analysis. Persons with IgA nephropathy are already likely to seek medical attention when they have gross haematuria or other signs and symptoms of renal dysfunction. No data have indicated the value of active screening or additional education of IgA nephropathy patients' post-vaccination. Time to onset data suggest that patients with flares are mostly diagnosed within 2 days of vaccination. Renal patients are at increased risk of serious illness and death due to Covid-19 disease, thus vaccination is of great benefit to them, as suggested by The European Renal Association and the European Vasculitis Society, which stated (March 2022): "*COVID-19 vaccines are safe, exhibiting a very low risk of de novo or relapsing immune-mediated kidney disease. Population-based studies will determine whether this is causal or coincidental. Such cases respond to standard management, including the use of immunosuppression. [We] recommend that patients with immune-mediated kidney diseases follow national guidance on vaccination.*"

The available data are limited by frequent missing data elements to facilitate full medical review and absence of clear negative and positive rechallenge information (which is common with vaccine products). There were no trends regarding age and other factors. There was no clear association with mRNA-1273 administration and the events of IgA Nephropathy.

6 Conclusion

IgA nephropathy is the most common primary glomerulonephritis in the world estimated at 2.5/100,000 per year with higher reported rates in Asian populations and potential genetic links. It is known to remain latent, undiagnosed for years with no clinical signs or symptoms and is seen >5% of native kidney biopsies. Additionally, it is associated with IgA immune complexes in the serum and glomeruli of patients. The MAH findings reviewed with respect to Spikevax did not show convincing evidence of a link to IgA nephropathy as there is no clear pattern with respect to temporal relationships, or underlying demographics or comorbidities that suggests an predisposition to association of Spikevax with IgA nephropathy, also lack of evidence across data sources reviewed, with extremely low reporting rate (*< 1 case per 10 million doses administered*), most importantly, there is no biological basis and pathophysiological mechanism for this finding. Therefore, the MAH refutes the signal of IgA nephropathy. The MAH does not plan to update the product information and/or risk management plan, including relevant risk minimization measures.

Overall, based on the analysis of all available safety data as of 18 Jun 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and the development of IgA nephropathy. No new or emerging safety issues of concern were identified. The MAH will continue to monitor events for IgA Nephropathy using routine pharmacovigilance surveillance.

The MAH considers, in agreement with the PRAC's Rapporteur's opinion, that the cumulative evidence is not sufficient to warrant amendment of the product information regarding IgA nephropathy at present, nor to include IgA Nephropathy to the list of safety concerns in the Spikevax's risk management plan.

7 References

Allyson C. Egan, Andreas Kronbichler, Irmgard Neumann, Kerstin Westman, Ingeborg M. Bajema, David R.W. Jayne, The Sound of Interconnectivity; The European Vasculitis Society 2022 Report. Open Access Published: May 26, 2022DOI:https://doi.org/10.1016/j.ekir.2022.05.01

UPtoDate:https://www.uptodate.com/contents/search?search=iga%20nephropathy&sp=0&searchType=PLAIN_TEXT&source=USER_INPUT&searchControl=TOP_PULLDOWN&searchOffset=1&autoComplete=true&language=&max=0&index=0~10&autoCompleteTerm=iga&rawSentence=

1 Appendix 1A: O/E Analysis Tables

Evaluation Results– O/E Analysis, 0-3 days

Outcome	People	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			
IgA Nephropathy 0-3 days								
All	5444527	40	0.7	41	0.75	0.98 (0.63, 1.51)	1.96 (1.34, 2.85)	3.92 (2.78, 5.52)
By age								
<12	7873	0	0.0	0	0.5	NA	NA	NA
12-17	149580	3	2.0	1	0.5	4.01 (0.42, 38.56)	8.02 (0.97, 66.64)	16.04 (2.09, 123.4)
18-24	636660	9	1.4	6	1	1.41 (0.5, 3.97)	2.83 (1.12, 7.12)	5.65 (2.38, 13.42)
25-39	1043425	14	1.3	10	1	1.34 (0.6, 3.02)	2.68 (1.3, 5.52)	5.37 (2.74, 10.52)
40-49	1026927	5	0.5	10	1	0.49 (0.17, 1.42)	0.97 (0.41, 2.34)	1.95 (0.91, 4.16)
50-64	1316727	7	0.5	13	1	0.53 (0.21, 1.33)	1.06 (0.5, 2.26)	2.13 (1.1, 4.11)
65-74	851924	2	0.2	9	1	0.23 (0.05, 1.09)	0.47 (0.14, 1.52)	0.94 (0.36, 2.43)
75+	411408	0	0.0	4	1	NA	NA	NA
By gender								
Male	2549371	17	0.7	19	0.75	0.89 (0.46, 1.71)	1.78 (1.01, 3.12)	3.56 (2.14, 5.91)
Female	2895153	23	0.8	22	0.75	1.06 (0.59, 1.9)	2.12 (1.27, 3.52)	4.24 (2.66, 6.75)
IgA Nephropathy 0-3 days								
Male								
<12	3686	0	0.0	0	0.5	NA	NA	NA
12-17	70040	1	1.4	0	0.5	NA	NA	NA
18-24	298113	5	1.7	3	1	1.68 (0.4, 7.02)	3.35 (0.92, 12.19)	6.71 (1.99, 22.58)
25-39	488579	6	1.2	5	1	1.23 (0.37, 4.02)	2.46 (0.87, 6.97)	4.91 (1.87, 12.87)
40-49	480853	1	0.2	5	1	0.21 (0.02, 1.78)	0.42 (0.08, 2.14)	0.83 (0.22, 3.1)

50-64	616551	3	0.5	6	1	0.49 (0.12, 1.95)	0.97 (0.31, 3.02)	1.95 (0.73, 5.19)
65-74	398909	1	0.3	4	1	0.25 (0.03, 2.24)	0.5 (0.09, 2.74)	1 (0.25, 4.01)
75+	192640	0	0.0	2	1	NA	NA	NA
Female	0							
<12	4186	0	0.0	0	0.5	NA	NA	NA
12-17	79540	2	2.5	0	0.5	NA	NA	NA
18-24	338547	4	1.2	3	1	1.18 (0.26, 5.28)	2.36 (0.63, 8.91)	4.73 (1.38, 16.22)
25-39	554847	8	1.4	6	1	1.44 (0.5, 4.16)	2.88 (1.13, 7.37)	5.77 (2.41, 13.79)
40-49	546074	4	0.7	5	1	0.73 (0.2, 2.73)	1.47 (0.48, 4.48)	2.93 (1.07, 8)
50-64	700176	4	0.6	7	1	0.57 (0.17, 1.95)	1.14 (0.41, 3.15)	2.29 (0.94, 5.55)
65-74	453015	1	0.2	5	1	0.22 (0.03, 1.89)	0.44 (0.09, 2.28)	0.88 (0.24, 3.29)
75+	218768	0	0.0	2	1	NA	NA	NA

Evaluation Results– O/E Analysis, 0-7 days

Outcome	People	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			
IgA Nephropathy 0-7 days								
All	12703896	44	0.3	95	0.75	0.46 (0.32, 0.66)	0.92 (0.69, 1.23)	1.85 (1.44, 2.37)
By age								
<12	18370	0	0.0	0	0.5	NA	NA	NA
12-17	349021	3	0.9	1	0.5	1.72 (0.18, 16.53)	3.44 (0.41, 28.56)	6.88 (0.89, 52.89)
18-24	1485541	10	0.7	1	1	0.67 (0.09, 5.26)	1.35 (0.18, 10.03)	2.69 (0.37, 19.59)
25-39	2434659	14	0.6	8	1	0.58 (0.24, 1.37)	1.15 (0.52, 2.52)	2.3 (1.1, 4.82)

40-49	2396163	8	0.3	13	1	0.33 (0.14, 0.81)	0.67 (0.32, 1.39)	1.34 (0.7, 2.54)
50-64	3072362	7	0.2	36	1	0.23 (0.1, 0.51)	0.46 (0.25, 0.84)	0.91 (0.56, 1.49)
65-74	1987823	2	0.1	49	1	0.1 (0.02, 0.41)	0.2 (0.07, 0.56)	0.4 (0.19, 0.85)
75+	959952	0	0.0	35	1	NA	NA	NA
By gender								
Male	5948532	19	0.3	45	0.75	0.43 (0.25, 0.73)	0.85 (0.55, 1.31)	1.7 (1.18, 2.46)
Female	6755357	25	0.4	51	0.75	0.49 (0.31, 0.8)	0.99 (0.67, 1.46)	1.97 (1.41, 2.77)
IgA Nephropathy 0-7 days								
Male								
<12	8601	0	0.0	0	0.5	NA	NA	NA
12-17	163427	1	0.6	1	0.5	1.22 (0.08, 19.57)	2.45 (0.22, 26.99)	4.9 (0.55, 43.8)
18-24	695597	6	0.9	7	1	0.86 (0.29, 2.57)	1.73 (0.68, 4.38)	3.45 (1.49, 8.01)
25-39	1140017	6	0.5	11	1	0.53 (0.19, 1.42)	1.05 (0.46, 2.39)	2.11 (1.03, 4.3)
40-49	1121991	2	0.2	11	1	0.18 (0.04, 0.8)	0.36 (0.11, 1.12)	0.71 (0.29, 1.77)
50-64	1438618	3	0.2	14	1	0.21 (0.06, 0.73)	0.42 (0.16, 1.09)	0.83 (0.39, 1.8)
65-74	930788	1	0.1	9	1	0.11 (0.01, 0.85)	0.21 (0.05, 0.99)	0.43 (0.13, 1.4)
75+	449492	0	0.0	4	1	NA	NA	NA
Female								
<12	9768	0	0.0	0	0.5	NA	NA	NA
12-17	185594	2	1.1	1	0.5	2.16 (0.2, 23.77)	4.31 (0.48, 38.57)	8.62 (1.08, 68.93)
18-24	789944	4	0.5	1	1	0.51 (0.06, 4.53)	1.01 (0.13, 8.1)	2.03 (0.27, 15.27)
25-39	1294642	8	0.6	6	1	0.62 (0.21, 1.78)	1.24 (0.48, 3.16)	2.47 (1.03, 5.91)
40-49	1274172	6	0.5	11	1	0.47 (0.17, 1.27)	0.94 (0.42, 2.13)	1.88 (0.92, 3.85)
50-64	1633744	4	0.2	12	1	0.24 (0.08, 0.76)	0.49 (0.2, 1.2)	0.98 (0.46, 2.07)

65-74	1057035	1	0.1	21	1	0.09 (0.01, 0.7)	0.19 (0.04, 0.81)	0.38 (0.13, 1.1)
75+	510459	0	0.0	12	1	NA	NA	NA

2 Appendix-2A: Individual Cases Assessment to Identify Case of IgA Nephropathy

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	13	Female	0	0	Dysuria, Haematuria, Headache, IgA nephropathy, Myalgia, Pollakiuria, Post infection glomerulonephritis, Proteinuria, Pyrexia	Serious				yes, but no biopsy	no	no	1	0	[redacted]	0
		Regulatory Authority	13	Female	Nephrotic syndrome(H)	0	Fatigue, Nephrotic syndrome	Non Serious				no	no	no		6		0
		Spontaneous	14	Female	0	0	Back pain, Haematuria, IgA nephropathy, Pyrexia, Sinus arrhythmia	Serious				yes	no	no	2	1		3006277; 3006277
		Regulatory Authority	14	Male	SPIKEVAX	0	Glomerulonephritis, Haematuria, Proteinuria	Serious				yes	yes	no	?	1		214024
		Regulatory Authority	14	Male	0	0	Glomerulonephritis, Haematoma	Serious				no	no	no		0		0
		Literature-Non-Study	16	Female	Nephrotic syndrome(H); MYCOPHENOLATE MOFETIL(H); RITUXIMAB(H)	0	Nephrotic syndrome	Serious				no	no	no		1		0
		Regulatory Authority	19	Male	0	0	Glomerulonephritis, Haematuria	Serious	Not reported	On 16-Mar-2021, Antinucle		no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										ar antibody: high (High) High. On 16-Mar-2021, Blood pressure measurement: normal (normal) normal. On 16-Mar-2021, C-reactive protein: 11.5 (Inconclusive) Inconclusive. On 16-Mar-2021, Full blood count: normal (normal) Normal. On 16-Mar-2021, Metabolic function test: normal (normal) Normal. On 16-Mar-2021, Streptococcus test: inconclusive (Inconclusive) Not recovered /not resolved.. On 16-Mar-2021, Total complement activity test: high (High)							[redacted]	

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										High. On 16-Mar-2021, Ultrasound scan: normal (normal) Renal sonogram was done. On 16-Mar-2021, Vital signs measurement: normal (normal) normal. Hematuria.								
[redacted]		Literature-Non-Study	19	Male	Haematuria(H); IgA nephropathy(C)	0	Haematuria, IgA nephropathy	Serious				yes, by kidney biopsy	yes, history of IgA N	no	2	2	[redacted]	0
		Literature-Non-Study	19	Male	Haematuria(H)	0	Haematuria, IgA nephropathy	Serious				yes, but no biopsy	yes, history of IgAN	no	2	4		0
		Regulatory Authority	19	Male	0	0	Nephrotic syndrome	Serious			Nephrotic syndrome	no	no	no		21		0
		Regulatory Authority	19	Male	0	0	Generalised oedema,	Serious				no	no	no		1		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
							Nephrotic syndrome											
[redacted]		Regulatory Authority	19	Male	COVID-19(C)	ENANTYUM	Glomerulonephritis minimal lesion, Nephrotic syndrome	Serious				no	no	no		0		216039
		Regulatory Authority	20	Unknown	0	0	Chills, Decreased appetite, Erythema, Flank pain, Glomerulonephritis, Haematuria, Headache, Pyrexia	Serious			Kidney injury	no	no	no		2		3002912; 3002186
		Literature-Non-Study	20	Male	Conjunctivitis(C); Glomerulonephritis(C)	0	Acute kidney injury, IgA nephropathy	Serious				yes	no	no	2	1		0
		Spontaneous	20	Female	0	0	Glomerulonephritis rapidly progressive, IgA nephropathy	Serious				yes	no	no	3	1		3006277
		Regulatory Authority	21	Female	0	0	IgA nephropathy	Serious			IgA nephropathy	yes, hut no hiopsy	no	no	2	0		3002181; 3002181
		Literature-Non-Study	21	Male	Focal segmental glomerulosclerosis(C); Renal transplant; RITUXI	0	Focal segmental glomerulosclerosis	Serious			Focal segmental glomerulosclerosis	no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					MAB(H); LOSARTAN(H)												[redacted]	
[redacted]		Literature-Non-Study	21	Female	Nephritis(H)	0	Glomerulonephritis rapidly progressive	Serious				yes	no	no	2	1		0
		Regulatory Authority	22	Female	0	0	Abdominal pain upper, Acute kidney injury, Blood creatinine increased, Haematuria, IgA nephropathy, Proteinuria	Non Serious				yes, by kidney biopsy	no	possible	2	2		3002188; 3002188
		Literature-Non-Study	22	Male	Henocb-Scbonlein purpura(C); Haematuria(C); IgA nephropathy(C)	PERINDOPRIL	Arthralgia, Haematuria, IgA nephropathy, Proteinuria	Serious	Steroids for 6 mo followed by RAASi	laboratory studies for current analysis		yes, by kidney biopsy	yes, history of IgA N	Possible	1,2	2,25(D1); 2(D2)		0
		Literature-Non-Study	22	Male	IgA nephropathy(C); Hypertension(C); Henocb-Scbonlein purpura(C)	PERINDOPRIL	Arthralgia, Haematuria, IgA nephropathy, Inappropriate scbedule of product administration, Proteinuria	Non Serious				duplicate (yes, by kidney biopsy)	duplicate (yes, history of IgA N)	Possible		2		300042722
		Regulatory Authority	22	Female	Nephrotic syndrome(C)	0	Condition aggravated, Glomerulonephritis, Nephrotic syndrome	Serious				no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	23	Male	IgA nephropathy(C); Spondylitis(C)	0	Albuminuria, Condition aggravated, Haematuria, IgA nephropathy	Serious	Not reported	Not reported		yes, hut no hiopsy	yes, history of IgA N	no	1	2	[redacted]	300042722
		Literature-Non-Study	23	Male	Fragile X syndrome(C); Interstitial lung disease(C)	0	Glomerulonephritis rapidly progressive	Serious			ANCA-associated and antiglomerular basement membrance glomerulonephritis	no	no	no		0		0
		Spontaneous	24	Male	Colitis ulcerative(C); Eosinophilic oesophagitis(C); Asthma(C); Cholangitis sclerosing(C); Mycotic allergy; Seasonal allergy	ENTYVIO	Hypervolaemia, Nephrotic syndrome, Weight increased	Serious				no	no	no		4		032B21A
		Regulatory Authority	24	Male	Mycotic allergy; Colitis ulcerative(H); Cholangitis sclerosing(H); Eosinophilic oesophagitis(H)	0	Feeling abnormal, Nephrotic syndrome, Peripheral swelling, Swelling face, Weight increased	Serious				no	no	no		1		032B121A
		Regulatory Authority	24	Female	0	ARANKELLE	Glomerulonephritis	Serious				no	no	no		?		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]																[redacted]	
		Regulatory Authority	25	Female	0	0	Haematuria, Nephritic syndrome	Serious	Not reported	Not reported		no	no	no		4		300042698
		Literature-Non-Study	25	Female	0	0	Glomerulonephritis minimal lesion	Serious				no	no	negative rechallenge		26		0
		Regulatory Authority	26	Female	Food allergy; Systemic lupus erythematosus(H)	0	Lupus nephritis, Myalgia, Nephrotic syndrome, Periorbital swelling, Proteinuria, Pyrexia, Systemic lupus erythematosus	Serious	Not reported	Not reported		no	no	no		3		0
		Regulatory Authority	26	Male	0	0	Joint swelling, Nephrotic syndrome, Swelling, Swelling face	Serious			Nephrotic syndrome	no	no	no		8		047B21A; 038B21A
		Regulatory Authority	26	Female	0	0	Flank pain, Haematuria, IgA nephropathy, Proteinuria	Serious			IgA nephropathy	yes, but no biopsy	no	no	2	2		3002620
		Literature-Non-Study	26	Female	Dialysis	0	Glomerulonephritis membranous, Glomerulonephropathy	Serious				no	no	no		4		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]																[redacted]	
		Literature-Non-Study	26	Male	Tobacco user(H)	0	Focal segmental glomerulosclerosis	Non Serious				no	no	no		?		0
		Regulatory Authority	27	Male	Crohn's disease(C)	0	Acute kidney injury, Condition aggravated, Crohn's disease, Decreased appetite, Diarrhoea, Nephrotic syndrome, Oedema, Weight decreased	Serious			Acute kidney injury, nephrotic syndrome	no	no	no		0		0
		Regulatory Authority	27	Female	Hypothyroidism(C)	0	IgA nephropathy	Serious				yes	no	no	2	2		3002620
		Literature-Non-Study	28	Male	0	0	Chills, Condition aggravated, IgA nephropathy, Pyrexia	Serious			Ig A nephropathy	yes, by kidney biopsy	yes, history of IgA N	no	2	1		0
		Regulatory Authority	29	Male	Animal hite	ZINC; VITAMIN C ACID; MULTIVITAMINS;MINERALS	Nephrotic syndrome	Serious	Not reported	kidney biopsy, results not reported		no	no	no		16		0
		Regulatory Authority	29	Female	0	0	Blood creatinine increased, Glomerulonephritis, Hypertension	Serious			Rapidly progressive glomerulonephr	no	no	no		11		006d21a

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
											itis, Hypertension						[redacted]	
[redacted]		Spontaneous	29	Male	0	0	IgA nephropathy, Pyrexia	Serious				yes	no	no	2	2		3004497; 3002618
		Regulatory Authority	30	Female	Drug hypersensitivity; IgA nephropathy(H)	IRBESARTAN; HCTZ	Abdominal pain, Chills, Haematuria, IgA nephropathy, Myalgia, Pyrexia	Serious	Not reported	Not reported		yes, hut no hiopsy	yes, history of IgA N	no	1	1		0
		Literature-Non-Study	30	Male	INFLUENZA VACCINE	0	Chills, Chromaturia, Diarrhoea, Headache, IgA nephropathy, Proteinuria, Pyrexia	Serious	angiotensin receptor blocker losartan	In 2021, Biopsy kidney: ahnormal (abnormal) light microscopy revealed nine glomeruli with mild mesangial expansion and hyper cellularity without endocapillary hyper cellularity, one of which showed segmental adhesion of a capillary loop to the Bowman capsule.. In 2021, Blood creatine phosphokinase (49-439): 254 (normal) U/L. In 2021, Blood creatinine (0.76-		yes, by kidney biopsy	no	no	2	1		012M20A; 012L20A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Caseseriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										1.27): 1.03 (normal) remained stable after six weeks of therapy and 1.02 (normal) mg/dL. In 2021, Blood immunoglobulin A (90-386): 444 (High) mg/dL. In 2021, Blood pressure measurement: 125/73 (normal) mmHg. In 2021, C-reactive protein: normal (normal) normal. In 2021, Complement factor C3 (82-167): 105 (normal) mg/dL. In 2021, Complement factor C4 (12-38): 19 (normal) mg/dL. In 2021, Glomerular filtration rate: 98 (normal) cc/min/1.73m2. In 2021, Immunology test: abnormal (abnormal) 3+ diffuse								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										granular mesangial staining for IgA. Staining was weekly positive for C3 and negative for IgG and other immunoglobulins/complement antibodies. ultrastructural examination revealed scattered immune-type electron-dense deposits in the mesangium and mild podocyte foot process effacement.. In 2021, Physical examination: normal (normal) normal, lack of lower extremity edema, rash, lymphadenopathy and throat erythema. In 2021, Protein urine: 800 (normal) mg. In 2021, Red blood cell								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										sedimentation rate: normal (normal) normal. In 2021, Serology test: negative (Negative) negative for glomerulonephritis, Hepatitis B, C, HIV, anti-nuclear and anti-neutrophil cytoplasmic antibo							
[redacted]		Spontaneous	30	Male	0	0	IgA nephropathy, Pyrexia	Serious				-	-	duplicate		0	[redacted]	3002618; 3004497
		Regulatory Authority	31	Male	0	0	Glomerulonephritis, Nephropathy	Serious			IgA nepbropathy	yes, but no biopsy	no	no	2	72		300042721; 300042721
		Spontaneous	32	Female	0	0	Haematuria, IgA nephropathy	Serious	Not reported	kidney biopsy, three computerized tomography scans preformed, blood work and a Cystoscopy done. Results not reported.		yes, by kidney biopsy	no	no	2	0		026C21A
		Regulatory Authority	32	Male	Gastritis (C)	0	Abdominal distension, Ascites, Glomerulonephritis minimal lesion, Nephrotic syndrome, Oliguria,	Serious	Not reported	Not reported		no	no	no		22		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
							Peripheral swelling, Proteinuria, Weight increased											
[redacted]	[redacted]	Regulatory Authority	32	Female	0	0	Chills, Decreased appetite, IgA nephropathy, Pyrexia, Vomiting	Non Serious				yes	yes	no	3	1	[redacted]	0
		Regulatory Authority	32	Male	0	0	Focal segmental glomerulosclerosis, Hypertension, Oedema, Proteinuria	Serious				no	no	no		68		LOT 214007
		Regulatory Authority	32	Male	0	0	Focal segmental glomerulosclerosis, Nephrotic syndrome	Serious				no	no	no		37		214007
		Regulatory Authority	32	Male	Multiple allergies; Seasonal allergy; Seasonal allergy; Seasonal allergy; Seasonal allergy; Seasonal allergy; Mite allergy; Seasonal allergy; Asthma(H); Lower limb fracture(H); Exostosis(H); Exostosis(H); Perthes disease(	0	Blood pressure increased, Eyelid oedema, Focal segmental glomerulosclerosis, Influenza like illness, Oedema peripheral	Serious				no	no	no		68		214007

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					H); SPIKE VAX													
[redacted]		Spontaneous	32	Male	Seasonal allergy; Perthes disease(H); Exostosis(C); Mite allergy; Seasonal allergy; Asthma(C); Seasonal allergy; Seasonal allergy; Back pain(H); Fracture (H); Biopsy kidney	0	Blepharitis, Cushing's syndrome, Focal segmental glomerulosclerosis, Hypoaesthesia, Impaired quality of life, Inappropriate schedule of product administration, Pancreatitis acute	Serious				no	no	no		103	[redacted]	0
		Literature-Non-Study	33	Female	Glomerulonephritis minimal lesion(H)	0	Glomerulonephritis minimal lesion	Serious			Minimal Change Disease Relapse	no	no	no		0		0
		Regulatory Authority	33	Female	Renal artery stenosis (H)	0	IgA nephropathy	Serious				yes	no	no	2	1		0
		Regulatory Authority	34	Male	0	0	Nephrotic syndrome	Non Serious			Nephrotic syndrome	no	no	no		25		0
		Regulatory Authority	34	Female	0	0	Glomerulonephritis, Renal haemorrhage	Serious				no	no	no		1		214012

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
																	[redacted]	
[redacted]		Literature-Non-Study	34	Male	0	0	Glomerulonephritis minimal lesion, Nephrotic syndrome	Serious				no	no	no		0		0
		Regulatory Authority	35	Female	Drug hypersensitivity; Breast cancer(C); Renal transplant	0	Biopsy kidney abnormal, Complications of transplanted kidney, Computerised tomogram, Cystoscopy, Glomerulonephritis, Haematuria, Immunoglobulin therapy	Serious			IgA nephropathy	no	no	no		1		0
		Literature-Non-Study	35	Male	Nephrolithiasis(H); Colitis ulcerative(H)	0	IgA nephropathy	Serious				yes	no	no	2	2		0
		Regulatory Authority	35	Male	0	COVALSACOR	Chromaturia, IgA nephropathy, Renal pain	Serious				yes	yes	no	?	1		3004953
		Regulatory Authority	36	Female	0	0	Cough, Cystitis, Ear pain, Glomerulonephritis, Haematuria, Proteinuria, Pyrexia	Serious				no	no	no		1		3005244

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Literature-Non-Study	37	Female	Pneumonia(H); Glomerulonephritis(C)	0	IgA nephropathy	Serious				yes	no	no	2	1	[redacted]	0
		Literature-Non-Study	38	Female	IgA nephropathy(C); INFLUENZA VACCINE; Gastroenteritis(H)	0	Chills, Condition aggravated, Fatigue, Headache, IgA nephropathy, Myalgia, Pyrexia	Serious	RAASi (renin-angiotensin-aldosterone system inhibitor)		IgA nephropathy	yes, by kidney biopsy	yes, history of IgA N	no	2	1		0
		Regulatory Authority	39	Male	Hypertension(H); Pulmonary embolism(H); Urine analysis abnormal(H)	[redacted] XARELTO; CANDESARTAN	Acute kidney injury, Haematuria, IgA nephropathy, Influenza like illness, Pyrexia	Serious	(Solu-Medrol (methylprednisolone) 500 mg iv. for 3 days with steroid tapering) as well as Endoxan(cyclophosphamide) (1000 mg monthly for 6 months			no	no	no		7		0
		Literature-Non-Study	39	Male	Hypertension(H)	0	Acute kidney injury, Haematuria, IgA nephropathy, Influenza like illness, Nephritic syndrome, Pyrexia, Vasculitis	Serious	Not reported	In 2021, Biopsy kidney: iga nephritis (abnormal) revealed severe crescentic IgA nephritis. In 2021,		yes, by kidney hiopsy	no	no	2	1		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										Blood creatinine: normal (normal) normalized. In 2021, Haematuria: persisted (Inconclusive) persisted. In 2021, Immunohistochemistry: negative (Negative) Negative. In 2021, Proteinuria: decreased (Inconclusive) significantly decreased. In 2021, SARS-CoV-2 test: negative (Negative) Negative.							[redacted]	
[redacted]		Literature-Non-Study	39	Female	Systemic lupus erythematosus(C); Lupus nephritis(C); Autoimmune thyroiditis(C); Renal tubular atrophy(C); Kidney fibrosis(C); Proteinuria(C)	MYCOPHENOLATE MOFETIL	Acute kidney injury, Cellulitis, Deep vein thrombosis, Glomerulonephritis, Inappropriate schedule of product administration, Lupus nephritis, Tubulointerstitial nephritis	Serious				no	no	yes		17, 25		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	40	Male	Thalassaemia beta(C); Cardiac disorder FH; HypertensionFH; SPIKEVAX(H)	Protein powder	Headache, Hypertension, IgA nephropathy	Serious			IgA nephropathy	yes, by kidney biopsy	no	no	2	I7	[redacted]	3005697
		Literature-Non-Study	40	Female	0	0	IgA nephropathy	Serious				yes	no	no	2	4		0
		Regulatory Authority	41	Female	Obesity(H); Disease risk factor(H)	DESLORATADINE	Chromaturia, Haematuria, IgA nephropathy, Skin haemorrhage	Serious				yes, but no biopsy	no	no	2	2		3001635
		Spontaneous	41	Female	Anxiety (C)	LEXAPRO; BACITRACYCIN PLUS	Abdominal distension, Focal segmental glomerulosclerosis, Nephrotic syndrome, Peripheral swelling, Renal disorder	Serious				no	no	no		7		014C21A; 036B21A
		Regulatory Authority	41	Female	0	LEXAPRO	Fatigue, Focal segmental glomerulosclerosis, Nephrotic syndrome, Swelling	Serious		Nephrotic syndrome, focal segmental glomerulosclerosis		no	no	no		37		014c21a; 036b21a
		Literature-Non-Study	41	Female	Haematuria(H); IgA nephropathy(C)	0	IgA nephropathy	Serious				yes	yes	no	2	2		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]		Literature-Non-Study	42	Female	0	0	Haematuria, IgA nephropathy	Serious				yes	no	no	2	1		0
		Regulatory Authority	42	Female	Mite allergy; Drug hypersensitivity; Allergy to animal; Lactose intolerance	0	Nephrotic syndrome	Serious				no	no	no		10		LOT000073A
		Literature-Non-Study	43	Male	0	0	Glomerulonephritis minimal lesion, IgA nephropathy, Nephrotic syndrome	Serious			Minimal Change Disease, Nephrotic Syndrome, IgA nephropathy			[redacted] has F/U		0		0
		Literature-Non-Study	43	Male	COVID-19(H)	0	IgA nephropathy	Serious			IgA nephropathy	(Dup of [redacted] yes, hy kidney biopsy	no	possible	dup of [redacted]	dup		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Literature-Non-Study	43	Male	0	0	Glomerulonephritis minimal lesion, IgA nephropathy	Serious			IgA nephropathy, minimal change disease	yes, by kidney biopsy	no	no	1	7	[redacted]	0
		Literature-Non-Study	44	Male	0	0	Acute kidney injury, IgA nephropathy, Tubulointerstitial nephritis	Serious			IgA nephropathy, acute interstitial nephritis	yes, by kidney biopsy	no	no	1	11		0
		Literature-Non-Study	44	Male	Nephrotic syndrome(H)	0	Injection site erythema, Lymphadenopathy, Nephrotic syndrome	Serious				no	no	no		1		0
		Regulatory Authority	44	Female	Hypersensitivity; Multiple sclerosis (H); Alcohol use(C)	COVID-19 Vaccine Moderna; COVID-19 Vaccine Moderna	Glomerulonephritis minimal lesion, Pyrexia, Vaccination site reaction	Serious				no	no	no		10		0
		Regulatory Authority	45	Female	Ex-tobacco user(H); Cholestasis of pregnancy(H); Toxic skin eruption (H); Sciatica (H)	0	Glomerulonephritis acute	Serious	Not reported	Not reported		no	no	no		1		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifie	Batch/Lot Number
[redacted]	[redacted]	Literature-Non-Study	45	Female	End stage renal disease(C); Renal transplant; COVID-19 pneumonia(H); Delayed graft function (H); Lupus nephritis(H)	TACROLIMUS; MYCOPHENOLIC ACID	Glomerulonephritis minimal lesion	Serious			Minimal change disease	no	no	no		0	[redacted]	0
		Regulatory Authority	45	Male	Glomerulonephritis minimal lesion(H)	CELLCEPT [MYCOPHENOLATE MOFETIL]	Nephrotic syndrome	Serious				no	no	no		0		3005790
		Literature-Non-Study	45	Female	0	0	Glomerulonephritis minimal lesion	Serious				no	no	no		11		0
		Regulatory Authority	46	Female	0	0	Dizziness, Haematuria, Headache, IgA nephropathy, Influenza, Proteinuria, Renal pain	Serious				yes	no	no	3	4		3003609
		Regulatory Authority	47	Male	0	HYDROCHLOROTHIAZIDE	Nephrotic syndrome	Serious			Nephrotic Syndrome	no	no	no		85		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifie	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	47	Female	Glomerulonepbritis(H); COVID-19 VACCINE MODERNA	0	Disease recurrence, Glomerulonephritis	Non Serious				no	no	no		5	[redacted]	3001657
		Literature-Non-Study	47	Male	0	0	Glomerulonephritis membranous	Serious				no	no	no		6		0
		Regulatory Authority	47	Female	COMIRNATY(H); VAXZEVRIA(H)	0	Biopsy kidney, IgA nephropathy, Mesangioproliferative glomerulonephritis	Serious				yes	no	no	3	?		000106A
		Regulatory Authority	48	Female	0	0	Glomerulonephritis	Serious	Not reported	Not reported		no	no	no		2		3001177; 3000493
		Regulatory Authority	48	Male	IgA nephropathy(C); Renal impairment(C); Anxiety(C); Reflux laryngitis(C)	CITALOPRAM; OMEPRAZOLE	Amnesia, Blood urine present, Dyspnoea, Fluid retention, Hypophagia, IgA nephropathy, Nausea, Tinnitus	Serious	The patient was prescribed antibiotics for a suspected UTI	On 02-Jul-2021, EGFR status assay: 45 (Low) eGFR bad fallen from 56 (measured with a blood test in March 2021) to 45.. On 02-Jul-2021, SARS-CoV-2 test: negative covid-19 test (Negative) Negative COVID-		yes, but no biopsy	yes, history of IgA N	no	2	1		3002621

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]									19 test. On 09-Jul-2021, EGFR status assay: 48 (Inconclusive) eGFR bad partially recovered to 48..							[redacted]	
		Literature-Non-Study	48	Unknown	Nephrotic syndrome(H)	0	Nephrotic syndrome	Serious				no	no	no		7		0
		Regulatory Authority	49	Female	Pulmonary tuberculosis(H); Pulmonary bypoplasia(C); Skin bypopigmentation(C); Food allergy; Seasonal allergy; Hysterectomy; Retinitis pigmentosa(C); Microalbuminuria(C); Haematuria(C); Haemoptysis(H)	SYMBICORT	Condition aggravated, Goodpasture's syndrome, Haematuria, Haemoptysis, Microalbuminuria	Serious	Not reported	HAEMATURIA (showed glomerular baematuria in the urine sediments associated with microalbuminuria) outcome was unknown. DIAGNOSTIC RESULTS (normal ranges are provided in parenthesis if available): On 04-Feb-2021, Computerised tomogram: appearanc		no	no	no		0		3001530

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										e of very discreet centrilobular groundglass opacities of nonspecific appearance located at the posterior segment of the upper right lobe, wbich may correspond to a focus of alveolar bemorrhage in the context, as well as the absence of detectable significant pulmonary systemic arterial malformation, and absence of suspicious mass.. On 04-Feb-2021, Laboratory test: stable baemoglobin an the absence of coagulation disorder. On 04-Feb-2021, Mycobacterium test: PCR negative.								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										On 04-Mar-2021, Anti-glomerular basement membrane antibody: unknown detection of lupus, anti-glomerular antibodies, complement abnormalities etc, in the norm. On 04-Mar-2021, Antinuclear antibody: 80 except for speckled ANA at the limit of the norm at 80. On 04-Mar-2021, Complement factor: unknown detection of lupus, antiglomerular antibodies, complement abnormalities, etc. On 04-Mar-2021, Laboratory test: glomerular haematuria in the								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										urine sediments associated with microalbuminuria. The action taken with mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) was unknown. For mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular), the reporter considered HAEMOPTYSIS [redacted] to be possibly related. No further causality assessments were provided for MICROALBUMINURIA (showed glomerular baematuria in the urine sediments associated with microalbuminuria), GOODPASTURE'S								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										SYNDROME (differential diagnosis includes an autimmune disorde like Goopasture's syndrome), CONDITION AGGRAVATED (a (re)activation of autoimmune diseases, taking into account the evoked differential diagnosis) and HAEMATURIA (showed glomerular haematuria in the urine sediments associated with microalbuminuria). Treatment information was not provided. On an unknown date, laboratory work-up was done. It showed stable haemoglobin and								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										the absence of coagulation disorder. On an unknown date, mycobacterium PCR and urinary toxicology. The results were negative. The patient had a history of hospitalization in October 2019 following an episode of hemoptysis attributed to alveolar haemorrhage on the aforementioned vascular abnormality, with negative tuberculosis tests. There was no indication for embolization and there was no recurrence to date. On the evening of 02-Apr-2021 at 8:30 p.m., the patient presented								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										with an episode of hemoptysis (estimated at 50 ml) without associated symptoms (absence of cough and chest pain). Recurrence of hemoptysis a few hours later, on 03-Apr-2021 at 4 am. The differential diagnosis includes an autoimmune disorder like Goodpasture syndrome, the autoimmune workup being nonetheless non worrisome (detection of lupus, anti-glomerular antibodies, complement abnormalities etc. in the norm								
[redacted]	[redacted]	Regulatory Authority	49	Male	0	0	Glomerulonephritis acute	Serious				no	no	no		15	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
																	[redacted]	
[redacted]		Regulatory Authority	49	Female	0	0	Axillary pain, Fatigue, Haematuria, Headache, IgA nephropathy, Injection site pain, Pain in extremity, Vaccination site pain	Serious				yes	yes	no	1	2		000133A
		Literature-Non-Study	50	Female	Hypertension(C); Antiphospholipid syndrome(C); Obesity(C); Transient ischaemic attack(H); IgA nephropathy(C)	AMLODIPINE; FUROSEMIDE; OLMESARTAN; WARFARIN; ENOXAPARIN	Haematuria, IgA nephropathy, Myalgia, Pyrexia	Serious	Not reported	serum creatinine of 1.7 mg/dl and a urine protein-creatinine ratio of 2 g/g (increased from baseline values of 1.3 mg/dl and 1.3 g/g, respectively, 7 months prior to presentation). Urinalysis demoustrated >50 red blood cells per high-power field (increased from haseline 10–20 red blood cells 7 months prior to presentation). Serologies included negative or normal		yes, by kidney biopsy	yes, history of IgA N	no	2	2		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										anti-nuclear antibody, anti-neutrophil cytoplasmic autoantibody, hepatitis B surface antigen, hepatitis C virus antibody, PLA2R antibody, C3, and C4. The biopsy, performed 19 days after the onset of macrohematuria, demonstrated IgA nephropathy (Figure 1 a and b). Among 12 glomeruli sampled, 3 were globally sclerotic and 1 contained a segmental scar. The remainder had mild diffuse mesangial hypercellularity, and 1 glomerulus displayed active segmental fibrinoid necrosis with mild leukocyte infiltration, rupture								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										of glomerular basement membrane, and an overlying segmental cellular crescent. There was 30% tubulointerstitial scarring and moderate arterio- and arteriolosclerosis. Immunofluorescence revealed global granular mesangial staining for IgA (3+), C3 (1+), kappa (2-3+), and lambda (3+). The Oxford MEST-C score (where M is mesangial hypercellularity; E is endocapillary hypercellularity; S is segmental sclerosis; T is tubular atrophy and interstitial fibrosis >25%; C is active cellular or fibrocellular								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										crescent) was M1E0S1T1C1.								
[redacted]	[redacted]	Regulatory Authority	50	Male	Arthropod sting; Arthritis (C)	NAPROXEN; MULTIVITAMIN [VITAMINS NOS]; TESTOSTERONE; BOOSTER C	Deep vein thrombosis, Generalised oedema, Nephrotic syndrome, Pulmonary embolism	Serious			Nephrotic syndrome	no	no	no		19	[redacted]	d42120a; 025j20-21
		Literature-Non-Study	50	Male	Hypertension(C); Renal impairment(C); Proteinuria(H)	0	Haematuria, IgA nephropathy, Proteinuria	Serious			IgA nephropathy	yes, by kidney biopsy	yes, history of IgA N	no	2	1		0
		Regulatory Authority	52	Female	Type IIa hyperlipidaemia (C); Hypersensitivity (C)	0	Acute kidney injury, Chromaturia, Gaze palsy, Headache, IgA nephropathy, Myalgia, Pyrexia	Serious	Not reported	Kidney Biopsy 46 days post dose 1: IgA nephropathy. Creatine 1.7 unknown date.		yes, hy kidney hiopsy	no	no	1	1		0
		Literature-Non-Study	52	Male	Hypertension(C)	AMLODIPINE	Asthenia, Glomerulonephritis rapidly progressive, Headache	Serious			Rapidly progressive ANCA glomerulonephritis	no	no	no		11		0
		Regulatory Authority	53	Female	0	0	Glomerulonephritis	Serious				no	no	no		24		3002542; 000106A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
							membranoproliferative, Lympbadenopathy, Normochromic anaemia, Normocytic anaemia, Splenomegaly											
[redacted]		Literature-Non-Study	53	Female	Gluten sensitivity(C); Fructose intolerance(C); Histamine intolerance(C); Restless legs syndrome(C)	0	IgA nephropathy	Serious				yes	yes	no	2	1		0
		Literature-Non-Study	54	Female	Pbaryngitis streptococcal(H); Obesity(C); Hypertension(C); Gastrooesophageal reflux disease(C); IgA nephropathy(C)	ENALAPRIL; HYDROCHLOROTHIAZIDE; PROPRANOLOL	Acute kidney injury, IgA nephropathy	Serious			Ig A nephropathy	yes, by kidney biopsy	yes, history of IgA N	no	2	2		0
		Regulatory Authority	54	Female	SPIKEVAX	0	Glomerulonephritis, Glomerulonephritis minimal lesion	Serious			Glomerulonephritis	no	no	no		0		3003655
		Regulatory Authority	54	Male	0	0	Nephrotic syndrome	Serious				no	no	no		1		3005290
		Literature-Non-Study	54	Male	Myocardial infarction(H)	0	Focal segmental glomerulosclerosis, Tubulointerstitial nephritis	Serious								0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]		Literature-Non-Study	54	Male	Glomerulosclerosis(C)	0	Glomerulonephritis membranous	Serious				no	no	no		1		0
		Literature-Non-Study	54	Female	0	0	Glomerulonephritis minimal lesion	Serious				no	no	no		62		0
		Regulatory Authority	55	Male	Chronic hepatitis B(C); Hyperlipidaemia(C); Hyperuricaemia(C); Polycythaemia(C)	BARACLUDE	Altered state of consciousness, Atrial fibrillation, Diarrhoea, Disturbance in attention, IgA nephropathy, Nausea, Oliguria, Renal failure, Renal tubular necrosis, Seizure, Vomiting	Serious			Ig A nephropathy	yes, hy kidney hiopsy	no	no	1	50		0
		Regulatory Authority	55	Female	Suspected COVID-19(H); COMIRNATY; COMIRNATY	PARACETAMOLO	Focal segmeotal glomerulosclerosis	Serious								0		LOT 216036
		Regulatory Authority	55	Male	Diverticular perforation(H); COVID-19(H); Vitreous floaters(	0	Glomerulonephritis minimal lesion	Serious				no	no	no		7		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					H); SPIKEVAX													
[redacted]		Regulatory Authority	55	Male	0	0	Hypertension, Nephrotic syndrome	Serious				no	no	no		15	[redacted]	3004498
		Regulatory Authority	56	Male	0	DIOVAN; BISOPROLOL KRKA; ATORVASTATIN; [redacted] SPIRONOLACTONE; PANADOL	Amyloidosis, Myocardial ischaemia, Nephrotic syndrome, Pulmonary oedema, Renal failure	Serious				no	no	no		0		3001650; 3002546
		Literature-Non-Study	56	Male	Essential hypertension(C); COVID-19(H); ASPIRIN [ACETYLSALICYLIC ACID](H); Occupational exposure to product(C)	LISINOPRIL/HYDROCHLOORTHIAZIDE; AMLODIPINE; CLONIDINE; LABETALOL	Glomerulonephritis membranous	Serious				no	no	no		?		0
		Regulatory Authority	57	Female	Neutropenia(C); Nephrot	0	Abdominal distension, Biopsy kidney,	Serious			Nephrotic	no	no	no		43		017C21A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					ic syndrome(H); Ruhber sensitivity; Drug hypersensitivity; MODERNA COVID-19 VACCINE; MODERNA COVID-19 VACCINE		Condition aggravated, Fluid retention, Full blood count, Laboratory test abnormal, Magnetic resonance imaging, Nephrotic syndrome, Oedema peripheral, Protein urine present, Urine abnormality, Urine analysis abnormal, Weight increased				syndrome						[redacted]	
[redacted]		Regulatory Authority	57	Female	0	0	Fatigue, Glomerulonephritis	Non Serious				no	no	no		20		3001651
		Literature-Non-Study	57	Male	Chronic kidney disease(H)	0	IgA nephropathy	Serious				yes	no	no	2	1		0
		Regulatory Authority	58	Male	Gout(C); Hypertension(C); Psoriasis(C)	ALLOPURINOL; AMLODIPINE; ASA; LISINOPRIL; METOPROLOL XL	Acute kidney injury, Cutaneous vasculitis, Glomerulonephritis, Haematuria, Henoch-Schonlein purpura, IgA nephropathy, Proteinuria, Purpura	Serious	PREDNISONE at a dnse of 80 mg once a day	On 06-Apr-2021, Biopsy skin: ahnormal (abnormal) abnormal. On 23-Apr-2021, Blood creatinine: 0.9 mg/dl (Inconclusive) serum creatinine 0.9 mg/dL.		yes, by kidney hiopsy	no	no	1	I1		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										On 23-Apr-2021, Urine analysis: abnormal (abnormal) abnormal. On 10-May-2021, Blood creatinine: 3.67 mg/dl (Inconclusive) 3.67 mg/dL. On 12-May-2021, Blood creatinine: 3.98 mg/dl (Inconclusive) 3.98 mg/dL. On 27-May-2021, Biopsy kidney: ahnormal (abnormal) Abnormal.								
[redacted]		Regulatory Authority	58	Male	0	0	Nephrotic syndrome, Renal failure	Serious			Nephrotic syndrome	no	no	no		0	[redacted]	0
		Regulatory Authority	58	Male	0	0	Nephrotic syndrome	Serious			Minimal Change Disease, Nephrotic Syndrome	no	no	no		6		3004666; 3003656
		Regulatory Authority	58	Male	SPIKEVAX	JAMPDORZOLAMIDE-	Glomerulonephritis membranous, Oedema peripheral, Proteinuria	Non Serious			Membranous neph	no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
						TIMOLOL					ropathy							
[redacted]	[redacted]	Literature-Non-Study	58	Male	0	0	Glomerulonephritis rapidly progressive	Serious				no	no	no		4	[redacted]	0
		Regulatory Authority	58	Female	0	0	Glomerulonephritis, Oedema, Pericarditis	Serious				no	no	no		9		017G21A
		Spontaneous	59	Male	Glomerulonephritis membranous(H)	0	Arthralgia, Fatigue, Glomerulonephritis membranous, Hypokinesia, Insomnia, Pain, Pain in extremity	Serious	Not reported	C-reactive protein "very high"		no	no	no		0		031A21A; 040A21A
		Spontaneous	59	Male	0	METOPROLOL; OMEPRAZOLE	Nephrotic syndrome, Peripheral swelling, Swelling, Swelling face	Serious	prednisone, "diuretics"	Not reported		no	no	no		0		016B21A; 025A21A
		Literature-Non-Study	60	Female	0	0	Anti-glomerular basement membrane disease	Serious			Anti-GBM disease	no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Literature-Non-Study	60	Female	0	0	Anti-glomerular basement membrane disease	Serious				no	no	no		0	[redacted]	0
		Literature-Non-Study	60	Female	Hypertension(C); Hypothyroidism(C); Diffuse large B-cell lymphoma(C)	0	Acute kidney injury, Cough, Dyspnoea, Exercise tolerance decreased, Fatigue, Glomerulonephritis, Tubulointerstitial nephritis	Serious				no	no	no		28		0
		Literature-Non-Study	60	Male	0	0	Glomerulonephritis minimal lesion	Serious				no	no	no		5		0
		Literature-Non-Study	60	Female	0	0	Glomerulonephritis membranoproliferative	Serious				no	no	no		84		0
		Regulatory Authority	62	Male	Sinusitis (C)	LISINOPRIL; ATO	Abnormal loss of weight, Acute kidney injury, Arthralgia,	Serious		On 31-Jan-2021, Biopsy: negative		no	no	no		2		041L20A; 010A21A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
						RVASTATIN; CETRIZINE	Arthritis, Arthropathy, Asthenia, Dysarthria, Dyspnoea, Fatigue, Glomerulonephritis, Glomerulonephritis rapidly progressive, Helicobacter infection, Joint swelling, Microcytic anaemia, Movement disorder, Nephropathy, Ocular hyperaemia, Pain, Pain in extremity, Pallor, Renal atrophy, Renal necrosis, Tendonitis, Tremor, Yellow skin			(Negative) Negative. On 31-Jan-2021, Blood folate: inconclusive (Inconclusive) Inconclusive. On 31-Jan-2021, Blood iron: ahnormal (abnormal) Abnormal. On 31-Jan-2021, Blood test: inconclusive (In							[redacted]	
[redacted]		Literature-Non-Study	62	Female	Modified radical mastectomy; Hypertension(C); Hyperlipidaemia(C); ANASTROZOL(H); Proteinuria(H); Chemotherapy; Glomerulonephritis membranous(C); Invasive ductal hreast carcinoma(C)	0	Glomerulonephritis membranous	Serious			Membranous nephropathy	no	no	no		0	[redacted]	0
		Literature-Non-Study	62	Male	0	0	Glomerulonephritis rapidly progressive, Microscopic polyangiitis	Serious				no	no	no		?		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
																	[redacted]	
[redacted]	[redacted]	Literature-Non-Study	63	Female	Hypertension(C); Tobacco abuse(C)	0	Dyspnoea, Fatigue, Generalised oedema, Glomerulonephritis minimal lesion, Hyperlipidaemia, Hypertension, Hypoalhuminaemia, Nephrotic syndrome, Periorhital oedema, Product dose omission issue, Proteinuria, Renal tubular injury, Tubulointerstitial nephritis, Urine abnormality	Serious	The patient was treated with VALSARTAN (oral) for Renin-angiotensin system inhibition, at a dose of 80 mg twice a day; DIURETICS for Adverse event, at an unspecified dose and frequency; METHYLPREDNISOLONE (METHYLPREDNISOLON [METHYLPREDNISOLONE]) (intravenous) for Adverse event, at a dose of 500 mg, pulse, for 3 days and PREDNISONE (oral) for	uncontrolled hypertension (181/82 mm Hg) as well as mildacute kidney injury (serum creatinine 1.48 mg/dl; haselinew as 0.7 mg/dl). Hypoalbuminemia (0.7 g/dl), urinalysis with 3þproteinuria (without microscopic hematuria), andhyperlipidemia (triglycerides, 221 mg/dl; total cholesterol,450 mg/dl) were noted. Nephrotic syndrome wasconfirmed as the 24-hour urine collection revealed 13.4 gproteinuria. Renal biopsy was promptly performed. Pathology confirmed		no	no	no		4	[redacted]	006B21A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
									Adverse event, at a dose of 1 mg/kg	MCD, with mild acute tubular injury,although a focal acute interstitial nephritis was also pre-sent. Four of 69 sampled glomeruli were globally sclerosed. There was 10% tubulointerstitialfibrosis. The sampledglomeruli were found to bave 100% foot process efface-ment								
[redacted]	[redacted]	Literature-Non-Study	63	Male	Hypertension(C); Chronic obstructive pulmonary disease(C); Latent tuberculosis(H); Giant cell arteritis(C)	0	Glomerulonephritis rapidly progressive, Headache, Microscopic polyangiitis, Pyrexia	Serious			ANCA and MPO-associated glomerulonephritis, microscopic polyangiitis	no	no	no		0	[redacted]	0
[redacted]	[redacted]	Regulatory Authority	64	Male	COVID-19 immunisation(H); Toxic nodular goitre(H); Hypertension(C	LOSARTAN	Blood urine present, Chills, COVID-19 immunisation, IgA nephropathy, Myalgia, Pyrexia	Serious				yes	no	no	3	0	[redacted]	3006273

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					); COVID-19 immunisation(H)													
[redacted]		Regulatory Authority	64	Male	COVID-19(H); Raynaud's phenomenon(C)	VAXZEVRIA	COVID-19 immunisation, Glomerulonephritis rapidly progressive, Granulomatosis with polyangiitis, Pneumonitis, Polyneuropathy	Serious				no	no	no		7	[redacted]	216001
		Regulatory Authority	65	Male	Colitis microscopic(C); Ex-tobacco user(C); Alcohol use(C)	BUDENOFALK	Acute kidney injury, Nephrotic syndrome	Serious			Minimal Change Disease, Nephrotic Syndrome	no	no	no		8		3001530
		Literature-Non-Study	65	Male	Colitis microscopic(C)	BUDENOFALK	Glomerulonephritis minimal lesion	Serious				no	no	rechallenge was negative		8		0
		Regulatory Authority	66	Male	IgA nephropathy(C); Diabetes mellitus(C); Nephritis(H)	0	Decreased appetite, Discomfort, Fatigue, Generalised oedema, Hypoalbuminaemia, IgA nephropathy, Proteinuria	Serious			IgA nephropathy	yes, but no biopsy	yes, history of IgA N	no	2	14		0
		Literature-Non-Study	66	Male	0	0	IgA nephropathy, Pericarditis	Serious			IgA nephropathy	yes, but no biopsy	no	no	1	11		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
																	[redacted]	
[redacted]		Literature-Non-Study	66	Male	Atrial fibrillation(C)	0	Blood creatinine increased, IgA nephropathy, Renal tubular injury	Serious			IgA nephropathy	(Dup of [redacted] yes, hy kidney hiopsy	no	no	dup of [redacted]	dup		0
		Regulatory Authority	66	Male	0	0	Glomerulonephritis membranous	Serious			membranous nephropathy, PLA2R positive	no	no	no		33		0
		Regulatory Authority	66	Female	Nephrotic syndrome(C); Dyslipidaemia(C); Goitre(H); Uterine leiomyoma(C)	0	IgA nephropathy, Nephrotic syndrome	Serious				yes	yes	no	1	9		0
		Regulatory Authority	66	Male	0	0	IgA nephropathy	Serious				yes	no	no	3	3		216001
		Literature-Non-Study	67	Female	Glomerulonephritis minimal lesion(C)	0	Glomerulonephritis minimal lesion	Serious			Minimal change disease	no	no	no		18		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
[redacted]		Regulatory Authority	67	Female	Hypertension(C)	0	Nephrotic syndrome	Serious			Nephrotic syndrome	no	no	no		2		019G21A
		Regulatory Authority	67	Male	Hypertension(C); Type 2 diabetes mellitus (C)	0	Abdominal pain, Acute kidney injury, Blood creatinine increased, Blood pressure increased, Cough, Diarrhoea, Dizziness, Electrolyte imbalance, Gingivitis, Hyperglycaemia, Hypocalcaemia, Myalgia, Nephrotic syndrome, Neutropenia, Oropharyngeal pain, Pyrexia, Rhinorrhoea, White blood cell count normal	Serious			Nephrotic syndrome	no	no	no		202		0
		Regulatory Authority	67	Male	COMIRNATY; COMIRNATY; Nephrectomy; Appendicectomy (H); Spinal fracture(H); Fall(H); Spinal fusion surgery; Arthros	LIPITOR; CARDIOASPIRINE; COVERSYL [PERINDOPRIL ARGININE]; BISO	COVID-19 immunisation, Haematuria, Nephrotic syndrome, Renal disorder, Type III immune complex mediated reaction	Serious				no	no	no		>30		3004955

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					copy; Acute myocardial infarction(H); Percutaneous coronary intervention; Stent placement; Cardiomyopathy(C); Hypokinesia(H)	PROLOL											[redacted]	
[redacted]		Regulatory Authority	68	Male	0	0	Glomerulonephritis	Non Serious				no	no	no		29		0
		Regulatory Authority	68	Male	Myocardial infarction(H); Drug hypersensitivity; Type 2 diabetes mellitus (C); Inguinal hernia(H); COMIRNATY; COMIRNATY	[redacted] OMEPRAZOLCT; ATORVASTATINEG; [redacted] LOSARTAN VIR; FUROSEMIDEEMEC; INSULINE NOVO; [redacted]	Arthralgia, IgM nephropathy, Nephrotic syndrome	Serious				no	no	no		96		094F21ABS

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
						[redacted] GLICLAZIDE DOC; METOPROLOL-B; AMLODIPINE; CALCIUMCARBONAAT; COTRIMOXAZOL; [redacted] METFORMINE RPG													
[redacted]		Literature-Non-Study	68	Male	0	0	Episcleritis, Glomerulonephritis rapidly progressive, Interstitial lung disease, Microscopic polyangiitis, Neuropathy peripheral	Serious				no	no	no		0	[redacted]	0
		Regulatory Authority	69	Female	Hypertension(C); Hypercholesterolaemia(C); Tobacco user(C)	0	Glomerulonephritis minimal lesion, Nephrotic syndrome, Oedema peripheral, Proteinuria	Serious				no	no	no		7 to 38		3001531; 3002336
		Literature-Non-Study	69	Male	Diahetes mellitus (C)	0	Glomerulonephritis membranous, Inappropriate schedule of product administration, Nephrotic syndrome	Serious				no	no	no		1		0
		Spontaneous	70	Male	Sudden hearing loss(C);	MET OPRO LOL;	Cerebrovascular accident, Glomerulonephrit	Serious				no	no	no		0		011A21A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					Bell's palsy(C); Drug hypersensitivity; Drug hypersensitivity; Hyperlipidaemia(C); Hypertension(C); Hypersensitivity; Otitis media(C); Anaemia(C); Chronic kidney disease(C); Plasmapheresis	ATORVASTATIN	is, Granulomatosis with polyangiitis, Immunisation reaction, Inappropriate schedule of product administration, Off label use, Pain, Pain in extremity, Pallor, Pleural effusion, Pulmonary mass, Renal failure										[redacted]	
[redacted]	[redacted]	Literature-Non-Study	70	Male	Glomerulonephritis membranous(H)	0	Glomerulonephritis membranous	Serious			Phospholipase A2 receptor membranous nephropathy	no	no	no		25		0
		Literature-Non-Study	70	Female	Urinary tract infection(H)	0	Acute kidney injury, Anti-neutrophil cytoplasmic antibody positive vasculitis, Dizziness, Glomerulonephritis rapidly progressive, Headache, Pulmonary haemorrhage, Pulmonary renal syndrome, Pulmonary vasculitis	Serious			ANCA-associated glomerulonephritis, rapidly progressive glomerulonephritis,	no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
											pulmonary vasculitis							
[redacted]		Regulatory Authority	71	Female	Hypertension(C); Hepatic steatosis (C); Pain(H); Pyrexia(H); Peripheral swelling (H)	0	Acute kidney injury, IgA nephropathy, Malaise	Serious			IgA nephropathy	yes, hy kidney hiopsy	no	no	2	1	[redacted]	3003657
		Literature-Non-Study	71	Female	0	0	Glomerulonephritis rapidly progressive	Serious				no	no	no		14		0
		Spontaneous	71	Female	Sjogren's syndrome(C); Aortic aneurysm(C); Uterine prolapse (C); Duodenal ulcer(H); Dizziness(H); Dermal cyst(H); Colorectal adenoma(H); Spinal cord injury cervical (H); Dropped head	CROTAMITON; MIROGABALIN BESILATE; LOXOPROFEN; PAROXETINE; OMEGA-3-ACID ETHYL ESTER; ELDECALCITOL; TORASEMIDE;	Cognitive disorder, Encephalitis, Encephalopathy, Fall, Nephrotic syndrome, Road traffic accident, Systemic lupus erythematosus	Serious				no	no	no		?		000001A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
					syndrome(C); COMIRNATY; COMIRNATY; COMIRNATY	CLOSTRIDIUM BUTYRICUM; LUBIPROSTONE; METHYLPREDNISOLONE; LIMAPROST ALFADEX; FAMOTIDINE; ROSUVASTATIN; SENNA SPP. LEAF; MONTELUKAST; RUPATADINE FUMARATE; CICLESONIDE; FLUTICASONE													
[redacted]	UNITED STATES	Literature-Non-Study	72	Male	Glomerulosclerosis(C)	0	Glomerulonephritis minimal lesion	Serious				no	no	no		7	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifie	Batch/Lot Number
[redacted]		Regulatory Authority	74	Male	0	0	Glomerulonephritis minimal lesion, Peripheral swelling	Serious				no	no	no		9		023F21A
		Regulatory Authority	75	Female	Seasonal allergy; Galactose intolerance(C); Alcoholic(C); Tobacco user(C); Renal impairment(C); Liver disorder (C)	RALOXIFENE	Deafness, Diarrhoea, Glomerulonephritis rapidly progressive, Inflammatory marker increased	Serious			Rapidly progressive glomerulonephritis	no	no	no		74		0
		Regulatory Authority	76	Male	Gluten sensitivity; Coeliac disease(C)	0	Chronic kidney disease, Cognitive disorder, Confusional state, Fall, Glomerulonephritis, Mobility decreased, Monoplegia, Renal failure, Sensory loss, Vasculitis	Serious	Not reported	On 21-Feb-2021, Antineutrophil cytoplasmic antibody: positive (Positive) positive. On 21-Feb-2021, Antinuclear antibody: positive (Positive) positive. On 21-Feb-2021, Biopsy kidney: abnormal (abnormal) abnormal. On 21-Feb-2021, Blood creatine phosphokinase: normal (normal) normal. On 21-Feb-2021, Blood lactate		no	no	no		4		024M20A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										dehydrogenase: increase (High) increase.							
[redacted]		Regulatory Authority	76	Male	Cutaneous T-cell lymphoma(C); Hypertension(C); Glomerulonephritis membranous(C)	0	Glomerulonephritis membranous, Interchange of vaccine products, Off label use	Serious			Membranous nephropathy	no	no	no		0	[redacted]	0
		Literature-Non-Study	76	Female	0	0	Glomerulonephritis rapidly progressive	Serious				no	no	no		5		0
		Regulatory Authority	77	Male	Ischaemic stroke(H); Glomerulonephritis memhranous(H); Hypertension(C)	0	Disease recurrence, Glomerulonephritis membranous	Serious	Not reported	Not reported		no	no	no		0		0
		Regulatory Authority	77	Female	Aplasia pure red cellFH; Fond allergy; Hypertension(C); Osteoporosis(C); Appendicitis(H); Erysipelas(H)	[redacted] FAMOTIDINE; EPERISONE HYDROCHLORIDE; LISINOPRIL; RAL	Nephrotic syndrome	Serious			Nephrotic syndrome	no	no	no		9		3003189; 3002180

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
						OXIFENE HYDROCHLORIDE; AMLODIPINE;												
		Literature-Non-Study	77	Female	Hypergammaglobulinaemia benign monoclonal(C); Atrial fibrillation(C); Hypertension(C)	0	Glomerulonephritis rapidly progressive	Serious				no	no	no		58		0
		Literature-Non-Study	79	Female	Glomerulonephritis rapidly progressive(C)	0	Glomerulonephritis rapidly progressive	Serious				no	no	no		21		0
		Regulatory Authority	80	Male	Hypertension(C); Diahetes mellitus(C); Gout(H)	0	Acute kidney injury, Cold sweat, Dizziness, Glomerulonephritis, Pyrexia	Serious			Pauci immune glomerulonephritis	no	no	no		5		0
		Literature-Non-Study	80	Female	0	0	Anti-neutrophil cytoplasmic antibody positive vasculitis, Diarrhoea, Fall, Gait disturbance, Glomerulonephritis rapidly	Serious				no	no	no		25		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
							progressive, Humerus fracture, Malaise										[redacted]	
[redacted]	[redacted]	Regulatory Authority	81	Male	Tobacco user(H); Renal disorder (H); Liver disorder (H); Adenocarcinoma(H); Radiotherapy; Transurethral prostatectomy	0	Glomerulonephritis rapidly progressive, Pulmonary mass, Pyrexia, Renal failure, Vasculitis	Serious	Not reported	On 25-Feb-2021, Computerised tomogram: parenchymal lung masses (abnormal) Several hilateral parenchymal lung masses (foci) (size 5.5 cm and 5.7 cm for the largest) containing possibly necrotic areas and small calcifications, as well as an acute inflammatory reaction.. On 01-Mar-2021, Biopsy lung: foriegn-body multinucleated macrophages (abnormal) Few foreign-body multinucleated macrophages of a chronic and active inflammation, partly necrotic in stromal collagen,		no	no	no		17	[redacted]	300042723; 300042460

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										without visible flora, without granuloma sui generis, without eosinophilia, without acute vascularity, without dysplastic or neoplastic tissue..								
[redacted]	[redacted]	Literature-Non-Study	81	Male	0	0	Acute kidney injury, Condition aggravated, Glomerulonephritis, Influenza like illness, Necrosis, Pleural effusion, Proteinuria, Vasculitis	Serious	"high-dose glucocorticoids, cyclophosphamide,and plasmapheresis"	laboratory workup showed AKI,proteinuria in the nonnephrotic range, and an elevatedproteinase 3 (PR3) anti–neutrophil cytoplasmic antibody(ANCA) titer. A pulmonary computed tomography scandemonstrated hilateral necrotic masses of the lung parenchyma and slight pleural effusion, without evidenceof tumor or lymphadenopathy. kidneybiopsy performed		no	no	no		0	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										at day 22 after the second vaccine doseshowed severe pauci-immune crescentic glomerulone-phritis with capillary necrosis and vasculitis present inthe renal vessel wall								
[redacted]	[redacted]	Regulatory Authority	82	Male	Myocardial ischaemia(C); Atrial fibrillation(C); Cognitive disorder(C); Benign prostatic hyperplasia(C); Lumbar puncture	FINASTERID STREULI; ASPIRIN CARDIO; ELIQUIS; NITRODERM; BELOC ZOK; TRIATEC [LOSARTAN POTASSIUM]; SIMCORA	Arthralgia, Asthenia, Confusional state, Consciousness fluctuating, IgA nephropathy, Oedema, Petechiae, Rash, Somnolence, Vasculitis	Serious		On 24-Feb-2021, Antineutrophil cytoplasmic antibody: negative (Negative) negative. On 24-Feb-2021, Antinuclear antibody: negative (Negative) negative. On 24-Feb-2021, Biopsy skin: minimal perivascular dermatitis (Inconclusive) skin punch biopsy from the left thigh was performed on 26-Feb-21.Possible urticarial		no	no	no		25	[redacted]	300042460

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										dermatitis .. On 24-Feb-2021, Blood culture: contaminated (Inconclusive) contamination with Staphylococcus hominis and Staphyloco								
[redacted]		Literature-Non-Study	82	Female	0	0	Anti-neutrophil cytoplasmic antibody positive vasculitis, Glomerulonephritis rapidly progressive	Serious			Pauci immune crescentic glomerulonephritis, MPO-ANCA associated vasculitis	no	no	no		25	[redacted]	0
		Regulatory Authority	82	Female	0	SPIKEVAX	Goodpasture's syndrome, Haemoptysis	Serious				no	no	no		?		007G21/7
		Literature-Non-Study	82	Male	0	0	Glomerulonephritis minimal lesion	Serious				no	no	no		79		0
		Literature-Non-Study	83	Male	0	0	Glomerulonephritis minimal lesion,	Serious			Minimal	no	no	no		25		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
							Renal tubular necrosis				change disease, acute tubular necrosis						[redacted]	
[redacted]	[redacted]	Regulatory Authority	100	Female	0	0	Abdominal distension, Abdominal pain, Bladder catheterisation, Bladder dilatation, Bladder hypertrophy, Bladder scan, Chest X-ray normal, Computerised tomogram abdomen abnormal, Constipation, COVID-19, Electrocardiogram abnormal, Hypoacusis, Laboratory test abnormal, Leukocytosis, Nephrotic syndrome, Pyrexia, SARS-CoV-2 test positive, Sinus tachycardia, Tachycardia, Urinary retention, Urinary tract infection, Urine analysis abnormal	Serious			Nephrotic syndrome	no	no	no		243		01M20A
[redacted]	[redacted]	Literature-Non-Study	0.00	Female	0	0	Acute kidney injury, Anti-glomerular basement membrane disease, Decreased appetite, Haematuria, Nausea, Pyrexia	Serious	methylprednisolone, Cytoxan, plasmapheresis, and hemodialysis, and she remains dialysis-	On an unknown date, Biopsy kidney: crescentic glomerulonephritis (abnormal) a diffusely crescentic glomerulonephritis,		yes, by kidney biopsy	no	no	2	14		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
									dependent	with 100% active cellular crescents and no significant chronic injury. On an unknown date, Blood creatinine: 7.8 mg/dl (High) 7.8 mg/dl. On an unknown date, HIV test: negative (Negative) Negative. On an unknown date, Hepatitis B virus test: negative (Negative) negative. On an unknown date, Hepatitis C virus test: negative (Negative) negative. On an unknown date, Immunology test: linear staining of gbms for igg (3+) (abnormal) linear staining of GBMs for IgG (3+), and								

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
										granular mesangial staining for IgA (2–3+), with associated rare mesangial deposits by electron microscopy.								
[redacted]	[redacted]	Spontaneous	0.00	Unknown	0	0	Erythema multiforme, Glomerulonephritis, Nephrotic syndrome	Serious			"Invalid" case	no	no	no		0	[redacted]	0
[redacted]		Regulatory Authority	0.00	Female	IgA nephropathy(C); Blood urine present(H)	0	Blood urine present, IgA nephropathy	Serious			Ig A nepbropathy	yes, but no biopsy	yes, history of IgA N	no	1,2	?		0
[redacted]		Literature-Non-Study	0.00	Unknown	0	0	Glomerulonephritis membranous, Glomerulonephritis minimal lesion	Serious				no	no	no		0		0
[redacted]		Literature-Non-Study	0.00	Unknown	0	0	Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Proteinuria	Serious				no	no	no		0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	Case Seriousness	Therapy	Diagnostic Workup	Main Diagnosis	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	WW Identifier	Batch/Lot Number
																	[redacted]	
[redacted]		Literature-Non-Study	0.00	Unknown	0	0	Blood creatinine increased, Haematuria, IgA nephropathy, Proteinuria	Serious				(Invalid due to no Moderna vaccine) yes	no	no	?invalid case	?invalid case		0
		Regulatory Authority	0.00	Female	HER2 negative breast cancer(H)	0	Glomerulonephritis minimal lesion, Nephrotic syndrome	Serious				no	no	no		73		0

3 Appendix 3A: WHO Causality Assessment for IgA Nephropathy (54 Cases)

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	13	Female	0	0	Dysuria, Haematuria, Headache, IgA nephropathy, Myalgia, Pollakiuria, Post infection glomerulonephritis, Proteinuria, Pyrexia	Conditional	This case of IgA nephropathy with hematuria and proteinuria on the day of vaccination with the first dose represents a short time to onset, and more specificity with respect to the timing is needed. Similarly the symptom of dysuria needs further explanation and is atypical at diagnosis of IgAN. Moreover, the diagnosis of post-infection glomerulonephritis is not typical, and more information would be required to understand it. Biopsy results would also be very useful. WHO Causality: Conditional.	yes, but no biopsy	no	no	1	0	0	[redacted]	0
		Spontaneous	14	Female	0	0	Back pain, Haematuria, IgA nephropathy, Pyrexia, Sinus arrhythmia	Unassessable	Onset of renal symptoms three days after dose 2 represents a clear temporal association. It is notable that a biopsy was not performed, and thus the case was reported as suspected IgA nephropathy. Although the presence of hematuria and proteinuria are consistent with this diagnosis, the finding of normal "blood IgA" does not support this diagnosis. In addition, measurement of serum C3 was not reported and could have helped support a diagnosis in the absence of a biopsy. (Maeda et al. Significance of serum IgA levels and serum IgA/C3 ratio in diagnostic analysis of patients with IgA nephropathy. J Clin Lab Anal 2003;17(3):73-6. doi: 10.1002/jcla.10071. PMID: 12696075 PMCID: PMC6808150 DOI: 10.1002/jcla.10071). Although given the temporal association it is possible that this patient's renal illness was caused by vaccination, the illness itself was not definitively diagnosed, nor was any treatment (apart from an antibiotic) reported. Therefore, this case is assessed for WHO Causality as Possible.	yes	no	no	2	1	0		3006277; 3006277
		Regulatory Authority	14	Male	SPIKEVAX	0	Glomerulonephritis, Haematuria, Proteinuria	Unassessable	In IgA vasculitis, kidney involvement has been reported in 20 to 54 percent of children; kidney involvement is more prevalent in older children and adults (UpToDate). Therefore, the occurrence of kidney involvement in this patient is not unexpected. Spikevax may have led to a flare of IgA vasculitis (this time involving the kidney) in this patient; however, the absence of detail on the patients previous	yes	yes	no	?	1	0		214024

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									pattern of episodes of IgA vasculitis, including their frequency and anatomic location, provides sub-optimal data for WHO Causality for this patient and thus the assessment is Possible.								
[redacted]	[redacted]	Literature - Non-Study	19	Male	Haematuria(H); IgA nephropathy(C)	0	Haematuria, IgA nephropathy	Possible	This 19 year old man was around the peak age of incidence of IgA nephropathy. He had a 6 month history of microhematuria before Spikevax. The circumstances and possible symptoms that led to the detection of his microhematuria were not described. It was only stated the there was no prior history of macrohematuria. Kidney biopsy about 3 weeks after second dose of Spikevax demonstrated IgA nephropathy, with evidence of some non-acute pathological changes. WHO Causality is Possible, as it is not clear how his IgAN would have evolved in the absence of vaccination, and additional historical information was not provided.	yes, by kidney biopsy	yes, history of IgAN	no	2	2	0	[redacted]	0
		Literature - Non-Study	19	Male	Haematuria(H)	0	Haematuria, IgA nephropathy	Probable	A 19 year old male with prior diagnosis of IgAN that had been in remission for six months before relapse which was this adverse event. It involved gross hematuria and proteinuria, with normal serum albumin and creatinine. The onset was two days after dose 2. Treatment was conservative, and the gross hematuria resolved in two days. No other precipitant for the adverse events was reported in this literature case, and so WHO Causality is Probable.	yes, but no biopsy	yes, history of IgAN	no	2	4	0		0
		Literature - Non-Study	20	Male	Conjunctivitis(C); Glomerulonephritis(C)	0	Acute kidney injury, IgA nephropathy	Possible	Male patient age 20 years developed de novo IgA nephropathy 1 day after the second dose. This is around the peak age of background incidence of this condition, which has a male predominance. The patient presented with fever, chills, body aches and dizziness. Patient also had rhinoconjunctivitis which was described as allergic. Diagnosis was by renal biopsy. Duration of hematuria was three days. Normalization of serum creatine and significant decrease in proteinuria was noted. However, microhaematuria persisted. Follow-up was scheduled after 7 weeks. WHO Causality is Possible due to temporal associatoin and cannot be ruled out, although demographics and rhinoconjunctivitis are possible confounders.	yes	no	no	2	1	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Spontaneous	20	Female	0	0	Glomerulonephritis rapidly progressive, IgA nephropathy	Possible	This patient had haematuria the day following dose 3 of Spikevax. Patient also had signs, symptoms and laboratory findings of nephrotic syndrome. Renal biopsy specimen indicated IgA nephropathy. Past medical history and absence of exposures or other clinical information that would suggest the presence of confounders was not mentioned or reported. This case is WHO Causality - Possible - due to temporal association, and causality cannot be ruled out due to limited information.	yes	no	no	3	1	The events developed after the administration of ELASOMERAN and there is temporal relationship.	[redacted]	3006277
		Regulatory Authority	21	Female	0	0	IgA nephropathy	Unassessable	This report contains insufficient information to make a causality assessment.	yes, but no biopsy	no	no	2	0	The event developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.		3002181; 3002181
		Literature - Non-Study	21	Female	Nephritis(H)	0	Glomerulonephritis rapidly progressive	Possible	A 21-year-old female patient with a history of Nephritis, type not specified, developed Rapidly progressive glomerulonephritis and was hospitalized. Onset was one day after dose 2. At the time of the report, Rapidly progressive glomerulonephritis was resolving. Kidney biopsy found IgA dominance in mesangium. There was also hematuria and proteinuria. IgA nephropathy flare cannot be determined because the report does not describe the type of nephritis that was previously diagnosed, nor does the report describe the past clinical experience of the patient with nephritis. Therefore, WHO Causality is Possible.	yes	no	no	2	1	0		0
		Regulatory Authority	22	Female	0	0	Abdominal pain upper, Acute kidney injury, Blood creatinine increased, Haematuria, IgA nephropathy, Proteinuria	Possible	This age of the patient, 22 years, in this case is at the peak age of the background occurrence of IgA nephropathy in the second and third decades of life (UpToDate). The onset of the first episode on the day following dose 1 is a very short interval and raises the issue of pre-existing pathology. Indeed it is known that IgA	yes, by kidney biopsy	no	possible	2	2	.		3002188; 3002188

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									nephropathy often occurs following prior chronic deposition of IgA in the glomerulus. Although the report says that symptoms slowly faded after dose 1, laboratory evidence consistent with this was not provided. The time to onset for dose 2 was not clearly specified. Medical history was not reported and may have provided other possible explanations. Although this case has elements consistent with positive rechallenge, this is not a clear case of it. WHO Causality is Possible.								
[redacted]		Literature - Non-Study	22	Male	Henoch-Schonlein purpura(C); Haematuria(C); IgA nephropathy(C)	PERINDOPRIL	Arthralgia, Haematuria, IgA nephropathy, Proteinuria	Possible	This 22 year old man had pre-existing IgA nephropathy, so clearly Spikevax did not cause the onset of this illness. Thus the question here is to assess the occurrence of relapse after each of two doses of Spikevax. The occurrence of gross hematuria two days after both dose 1 and 2 is consistent with positive rechallenge; however, the occurrence of gross hematuria 25 days after dose 1 (and before dose 2) is not, and this may suggest an element of naturally relapsing-remitting disease in this patient. It is notable also that the GFR, a global measure of kidney function, actually was improved one month after dose 2 compared to before Spikevax and that the patient's symptoms spontaneously regressed. WHO Causality is Possible.	yes, by kidney biopsy	yes, history of IgAN	Possible	1,2	2,25(D1); 2(D2)	0	[redacted]	0
		Regulatory Authority	23	Male	IgA nephropathy(C); Spondylitis(C)	0	Albuminuria, Condition aggravated, Haematuria, IgA nephropathy	Conditional	This 23 year old male had, at the time of vaccination, concurrent IgA nephropathy (Rheumatoid purpura/IgA nephropathy) and Spondylarthritis. Two days following vaccination with dose 1, this patient's IgA Nephropathy was reported as aggravated with macroscopic hematuria. Alhuminuria was reported 31 days post Spikevax dose 1. No other details were provided. It is unclear what had been the pattern of clinical exacerbations for this patient prior to vaccination. Medical history is lacking. WHO Causality is Conditional due to important missing information.	yes, but no biopsy	yes, history of IgAN	no	1	2	Melders kvalifikasjon: Hjelpepleier.		300042722
		Regulatory Authority	26	Female	0	0	Flank pain, Haematuria, IgA nephropathy, Proteinuria	Conditional	This cousumer report reports the onset of IgAN two days after dose 2, with haematuria, proteinuria and flank pain. The report lacks the biopsy results necessary to make the diagnosis. It also notes that the patient had an elevated WBC level and was treated with Cefotaxim [sic.] so that it appears that infection was also possible.	yes, but no biopsy	no	no	2	2	0		3002620

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									More information is needed to evaluate this adverse event. WHO Causality is Conditional.								
[redacted]	[redacted]	Regulatory Authority	27	Female	Hypothyroidism(C)	0	IgA nephropathy	Possible	This is a report from a consumer concerning a 27 year old female, with a history of hypothyroidism, who experienced IgA nephropathy 2 days after dose 2 of Spikevax and was hospitalized. She had gross hematuria and severe proteinuria, flank pain and nausea. Approximately 2 weeks after the vaccination, laboratory values had improved again (microhematuria, lighter proteinuria) without medication. Patient followed up with a nephrologist every 3 months after vaccination. After being diagnosed with COVID-19, gross hematuria and proteinuria again occurred. Prior to vaccination patient never had blood in urine and never had any kidney problems. The outcome of the event was reported as resolved with sequelae. Underlying history of hypothyroidism could be a confounder for the event. The mode of diagnosis of IgA nephropathy (biopsy?) was not specified, nor were laboratory values. This is not a case of positive rechallenge because the IgA nephropathy occurred only once after vaccination. Also there was not full remission of the first episode. This case is WHO Causality Possible for the above reasons.	yes	no	no	2	2	0	[redacted]	3002620
		Literature - Non-Study	28	Male	0	0	Chills, Condition aggravated, IgA nephropathy, Pyrexia	Probable	Literature report describing a 28 year old male with prior IgAN diagnosis who was treated with Losartan 100mg daily. The day of second dose of Spikevax, he developed fever to 39 degrees and chills. The next day fever continued and the patient had gross hematuria. On subsequent exam the patient's urine protein excretion had risen to 925mg/24 hr, above the usual <500mg/24h. Urinalysis revealed hemoglobin and and 10-20 RBCs per high power field, with no RBCs. Since other potential precipitants of relapse were not described and the patient clearly had reactogenicity to Spikevax at the time of hematuria, WHO Causality is Probable.	yes, by kidney biopsy	yes, history of IgAN	no	2	I	0		0
		Spontaneous	29	Male	0	0	IgA nephropathy, Pyrexia	Possible	Gross hematuria noticed two days after dose 2 of Spikevax that was noted to continue 2 days later. The patient took an over-the-counter drug [redacted] 3 times.	yes	no	no	2	2	The possibility of IgA nephropat		3004497; 3002618

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									Kidney biopsy 6 months later showed IgA nephropathy. No other relevant clinical details noted. Because of the temporal association WHO Causality is Possible and cannot be ruled out due to limited clinical descriptions and absent medical history.						hy due to this drug cannot be denied. senders comment : The events developed after the administration of ELASOMERAN and there is temporal relationship.	[redacted]	
[redacted]		Regulatory Authority	30	Female	Drug hypersensitivity; IgA nephropathy(H)	IRBESARTAN; HCTZ	Abdominal pain, Chills, Haematuria, IgA nephropathy, Myalgia, Pyrexia	Possible	This case involves a patient previously diagnosed with IgA nephropathy who experienced 5 days of gross hematuria beginning one day after the first dose of Spikevax. Abdominal pain, fever and myalgia lasted 8 hours. Basic metabolic panel results were normal. At 33 days after vaccination it was reported the symptoms had resolved. Given no history of the course of the patient's disease prior to vaccination and the frequency of flares of this relapsing-remitting disease, it is not possible to assess with precision the likelihood that vaccination caused the flare in question. Therefore, WHO Causality assessed as Possible.	yes, but no biopsy	yes, history of IgAN	no	1	1	0		0
		Literature - Non-Study	30	Male	INFLUENZA VACCINE	0	Chills, Chromaturia, Diarrhoea, Headache, IgA nephropathy, Proteinuria, Pyrexia	Possible	This detailed literature report involves a 30 year old man who, on the day following the second dose, developed fever, chills and headache, as well as brown-colored urine--a finding consistent with IgA Nephropathy. Kidney biopsy confirmed IgA nephropathy one month later. The authors of the reported stated that IgA nephropathy is proposed to be a multi-hit disease; such hits can include aberrant galactosylation of IgA, formation of immune complexes including such aberrant IgA, deposition of the complexes in the kidneys and finally an immunological/inflammatory response to such complexes in the glomeruli. Although, as the authors stated, "correlation	yes, by kidney biopsy	no	no	2	1	0		012M20A; 012L20A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									does not inherently imply causation", it is possible that the vaccine caused such an immunological/inflammatory response. Therefore WHO Causality is Possible. One cannot infer probable causality for disease causation because, as the authors state, multiple hits are involved. Those hits likely preceded vaccination. On the other hand, one cannot infer that vaccination probably caused a relapse because the condition of IgA nephropathy had not been diagnosed prior to vaccination.								
[redacted]	[redacted]	Regulatory Authority	31	Male	0	0	Glomerulonephritis, Nephropathy	Unassessable	This consumer report lacks basic details, and in addition the timeline reported includes only 3 days between dose 1 and dose 2 and then 42 days to development of IgA nephropathy. WHO Causality is Unassessable.	yes, but no biopsy	no	no	2	72	0	[redacted]	300042721; 300042721
		Spontaneous	32	Female	0	0	Haematuria, IgA nephropathy	Unassessable	This report from a consumer contains insufficient information to make a causality assessment.	yes, by kidney biopsy	no	no	2	0	0		026C21A
		Regulatory Authority	32	Female	0	0	Chills, Decreased appetite, IgA nephropathy, Pyrexia, Vomiting	Possible	Theis 32 year old female patient had a prior history of IgA nephropathy and experienced fever and gross hematuria on the day after the third dose. Other relevant details are limited, such as prior history of disease relapses (after prior vaccine doses and also at other times), treatments and laboratory findings from the current adverse event. WHO Causality is Possible.	yes	yes	no	3	1	0		0
		Regulatory Authority	33	Female	Renal artery stenosis(H)	0	IgA nephropathy	Possible	This report by a consumer describes the occurrence of IgA nephropathy in a 33-year-old female patient who received mRNA-1273 (Spikevax) for COVID-19 vaccination. The patient's past medical history included Renal artery stenosis (RAS). On 24-Jun-2021, the patient received second dose of Spikevax. On 25-Jun-2021, the patient experienced IGA NEPHROPATHY. At the time of the report, IGA NEPHROPATHY (IgA nephropathy) was resolving. No concomitant medication was reported. No treatment medication was reported. The medical history of Renal artery stenosis	yes	no	no	2	1	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									remains a confounder , and there has been a literature report and reviewo f the coexistence of IgA nepropathy and renal artery stenosis in Takayasu arteritis (Ito, N., Shirai, T., Toyohara, T. et al. "Coexistence of IgA nephropathy and renal artery stenosis in Takayasu arteritis: case report and literature review". Rheumatol Int (2022). https://doi.org/10.1007/s00296-021-05066-0). WHO Causality possible based on temporal association, with the potential for confounding by renal artery stenosis; also the absence of prodromal symptoms prior to vaccination and the absence of potential precipitants of IgA nephropathy such as infections were not reported.								
[redacted]		Literature - Non-Study	35	Male	Nephrolithiasis(H); Colitis ulcerative(H)	0	IgA nephropathy	Possible	This patient developed gross hematuria and sub-nephrotic proteinuria 2 days after dose 2 of Spikevax. Kidney biopsy showed IgA nephropathy. The patients medical history of nephrolithiasis and ulcerative colitis are confounders.	yes	no	no	2	2	0	[redacted]	0
		Regulatory Authority	35	Male	0	CO VALS ACOR	Chromaturia, IgA nephropathy, Renal pain	Unassessable	This report is WHO Causality Unassessable because it reports very limited information: Darker color of urine and Pain in the kidney area, along with Increase in IgA nephropathy. This occurred 15 hours after an unknown dose number of Spikevax. Clinical details, medical history and mode of diagnosis of IgA nephropathy (biopsy?) are not reported. In addition, the indications for HYDROCHLOROTHIAZIDE and VALSARTAN were not stated.	yes	yes	no	?	1	0		3004953
		Literature - Non-Study	37	Female	Pneumonia(H); Glomerulonephritis(C)	0	IgA nephropathy	Possible	This case of de novo IgA nephropathy had onset with hematuria the day following the second dose. Diagnosis was by renal biopsy. The duration of the episode was one day. There was also fever, difficulties breathing, myalgia, arthralgia and proteinuria at presentation. Other clinical details of the current illness relevant to causality assessment were not provided. WHO Causality assessment is Possible because of temporal association and cannot be ruled out with the limited information available.	yes	no	no	2	1	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Literature - Non-Study	38	Female	IgA nephropathy(C); INFLUENZA VACCINE; Gastroenteritis(H)	0	Chills, Condition aggravated, Fatigue, Headache, IgA nephropathy, Myalgia, Pyrexia	Probable	This 38 year old woman diagnosed with IgAN in 2005 had experienced macroscopic hematuria occasionally following influenza vaccine and during one episode of gastroenteritis. Within a day after dose 2 of Spikevax, she experienced systemic symptoms, ranging from body aches, headache, and fatigue to fever and chills. Hematuria indicating exacerbated IgAN was also observed for 3 days, as well as an increase in proteinuria. This patient's tendency for, and history of, IgAN exacerbation following immunologic stimulation makes it probable that Spikevax also precipated such an event. WHO Causality is Probable.	yes, by kidney biopsy	yes, history of IgAN	no	2	1	0	[redacted]	0
		Literature - Non-Study	39	Male	Hypertension(H)	0	Acute kidney injury, Haematuria, IgA nephropathy, Influenza like illness, Nephritic syndrome, Pyrexia, Vasculitis	Possible	In this case from a literature report, the onset of severe fever (temperature not reported), flu-like symptoms and macrohematuria were noted "immediately" (TTO not specified) after the second dose. AKI (acute kidney injury) with nephritic syndrome was diagnosed. Kidney biopsy revealed severe crescentic IgA nephritis; presence of active versus chronic crescents was not described. Treatment with high dose corticosteroids and cyclophosphamide was followed by normalization of creatine (no levels reported) and significant decrease in proteinuria (no levels reported), but microhematuria persisted. Detailed medical history was not provided and concomitant medication were not provided. This case is essentially reports a temporal association with Spikevax, without other explanatory factors; thus, given this and the lack of detail provided for this case, WHO Causality is Possible.	yes, by kidney biopsy	no	no	2	1	0		0
		Regulatory Authority	40	Male	Thalassaemia beta(C); Cardiac disorder FH; HypertensionFH; SPIKEVAX(H)	Protein powder	Headache, Hypertension, IgA nephropathy	Possible	This regulatory authority case was in a 40-year-old male patient who received mRNA-1273 (Spikevax.) Family history included Cardiac disorder NOS (both mother's and father's side) and Hypertension (Mother). Concurrent medical conditions included Beta thalassemia minor. On 23-Aug-2021, the patient received second dose of mRNA-1273 (Spikevax). The patient experienced hypertension with presumed onset shortly after vaccination. On 09-Sep-2021, the patient experienced Headache, IgA nephritis and hypertension	yes, by kidney biopsy	no	no	2	17	Thank you for reporting your suspected adverse event following a vaccination. Since the vaccine is new, it is		3005697

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									and was hospitalized. Biopsy: abnormal (abnormal) IgA nephropathy. On 09-Sep-2021, Blood creatinine: high (High) 200. On 14-Oct-2021, Blood creatinine: high (High) 189. On 14-Oct-2021, Blood pressure measurement: high (High) 166/91-147/101-167/100. On 14-Oct-2021, Glomerular filtration rate: high (High) 37. Hypertension and beta thalassemia minor might have contributed to the detection of IgAN through hematuria. More information on biopsy resuls would allow the possibility to determine the acuteness and /or chronicity of the pathological changes in the kidney that led to detection of this adverse event. WHO Causality: Possible.						subject to special monitoring to detect new safety information as quickly as possible. It is particularly important that serious and/or unusual adverse events be reported. Your report is therefore important for increasing knowledge about side effects that have not been discovered in studies, and is an important contribution to the international cooperation to maintain safe vaccination worldwide. Reports after coronavir		

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															us vaccination in the Adverse Effects Register are processed by the [redacted] Institute of Public Health in cooperation with the Regional Medicines Information Centers [redacted] [Regional Medicines Information Centers])). We do not have the capacity to send individual assessments of adverse event reports at this time. The [redacted] Medicines Agency publishes weekly summaries of		

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															reports of suspected adverse reactions following [redacted] Causality is assessed according to international criteria (1). If you have further information related to the event, such as information about the outcome, a copy from the medical record/discharge summary/ laboratory results and/or other investigations, this can be sent in response to this		

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															message. The information is treated securely, and this dialogue will be deleted automatically after 4 months. The processing and storage of personal data is done in accordance with the Personal Health Data Filing System Act. For updated information and advice on the use of vaccines and precautions, please refer to the Vaccination Guide (2): [redacted]		

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															[redacted] Questions about corona vaccines which cannot be answered by a local professional can be directed to [redacted] We request that certain categories of personal data (health information) not be sent by email. If it is impossible to ask a question without including such information, we recommend calling the vaccine line (tel.: [redacted] –open every weekday from 01:00		

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															p.m.-02:30 p.m.). References: 1) Edwards IR, Aronsen, JK. Adverse reactions: definitions, diagnosis and management. Lancet 2000; 356:1255-1259. 2) [redacted] The Vaccination Guide: Coronavirus vaccine. [redacted]		
[redacted]		Literature - Non-Study	40	Female	0	0	IgA nephropathy	Possible	In this multi-patient case series of 29 cases from a convenience sample of a widely dispersed [redacted] geographic distribution, there were not numerous details on each case. The onset of symptoms was less than one week after dose 2, and IgA nephropathy was subsequently diagnosed by biopsy. No information about medical history or	yes	no	no	2	4	0	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									possible confounders was reported. WHO Causality is Possible, and a causal association cannot be ruled out because of lack of clinical information.								
[redacted]		Regulatory Authority	41	Female	Obesity(H); Disease risk factor(H)	DESLORATADINE	Chromaturia, Haematuria, IgA nephropathy, Skin haemorrhage	Unassessable	This case reported by a consumer involves a patient with 3 days of hematuria beginning two days after the first Spikevax dose. The reason for the low Hb of 8.8 is not specifically reported, and there are multiple possibilities depending on the duration, severity and pathology of the renal disease, as well as other possible medical issues in this patient with high BMI of 30.4. We do not know whether there was a renal biopsy or the results, if any. The nature of skin hemorrhage is not reported. We do not know if this is de novo or flare of IgA nephropathy. Due to missing information, this report is Unassessable for causality.	yes, but no biopsy	no	no	2	2	0	[redacted]	3001635
		Literature - Non-Study	41	Female	Haematuria(H); IgA nephropathy(C)	0	IgA nephropathy	Probable	This patient had been diagnosed with suspected IgA nephropathy in 2013, but there was no biopsy to confirm the diagnosis. There had previously been haematuria. She developed hematuria two days after dose 2 of Spikevax that lasted two days and resolved spontaneously. It is possible that Spikevax caused a relapse of IgA nephropathy, but this diagnosis was not confirmed so we should not infer greater probability.	yes	yes	no	2	2	0		0
		Literature - Non-Study	42	Female	0	0	Haematuria, IgA nephropathy	Possible	A 42 year old woman developed dark reddish urine the day following the second dose of Spikevax. Gross hematuria disappeared within several days. Follow up showed persistent microscopic hematuria and proteinuria. Kidney biopsy 8 weeks after vaccination showed IgA nephropathy. No risk factors or past history for IgA nephropathy were noted in this literature report; presence of unspecified viral markers and autoantibodies were checked by testing. Due to the temporal association, this case is considered WHO Causality Possible. This is new onset disease, and there is a background rate of these occurrences in the absence of vaccination.	yes	no	no	2	1	0		0
		Literature - Non-	43	Male	0	0	Glomerulonephritis minimal lesion, IgA nephropathy	Conditional	This literature case entitled "Minimal change disease following the Moderna COVID-19 vaccine: first case report" involves a 43 year old man who began to experience edema in the lower extremities 7	yes, by kidney biopsy	no	no	1	7	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
		Study							days after dose 1 of Spikevax that progressed for about 2 more weeks to become extensive edema at presentation. He only had 4 red blood cells per high power field on urine microscopy, while his 24-h urine protein was 15 g. Renal biopsy showed concomitant Minimal Change Disease and IgA nephropathy with 2+ mesangial deposition of immunoglobulin A (IgA.) IgA deposition can sometimes occur as an incidental finding--the prevalence of clinically silent IgA nephropathy may be surprisingly high; in a Japanese study, 16% of donor kidneys had glomerular IgA deposits and nearly 2% exhibited mesangioproliferative changes with C3 deposits characteristic of IgA nephropathy. With respect to the literature case in question, the clinical picture was most compatible with minimal change disease (consistent with the article's title), but electron microscopy, as noted by the authors, was not performed to further elucidate. WHO Causality with regard to causation of IgA nephropathy is Conditional due to the lack of electron microscopy needed to confirm etiological pathophysiology, especially for minimal change disease.							[redacted]	
[redacted]		Literature - Non-Study	44	Male	0	0	Acute kidney injury, IgA nephropathy, Tubulointerstitial nephritis	Possible	This literature report is part of a case series and provides limited details and no medical history but does describe onset of biopsy-proven IgA nephropathy two weeks after dose 1. This is classified as WHO Causality Possible.	yes, by kidney biopsy	no	no	I	11	0		0
		Regulatory Authority	46	Female	0	0	Dizziness, Haematuria, Headache, IgA nephropathy, Influenza, Proteinuria, Renal pain	Conditional	A consumer reported Gross hematuria, proteinuria, kidney pain and "Suspected boost of IgA nephropathy" that began four days after the second dose of Spikevax. It is not clear what "suspected boost of IgA nephropathy means." A biopsy diagnosis was not described. More clinical information is needed, thus WHO Causality is Conditional.	yes	no	no	3	4	0		3003609
		Regulatory Authority	47	Female	COMIRNATY(H); VAXZE	0	Biopsy kidney, IgA nephropathy, Mesangioproliferative	Unassessable	Extremely limited clinical information provided.	yes	no	no	3	?	0		000106A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
					VRIA(H)		glomerulonephritis										
[redacted]	[redacted]	Regulatory Authority	48	Male	IgA nephropathy(C); Renal impairment(C); Anxiety(C); Reflux laryngitis(C)	CITALOPRAM; OMEPRAZOLE	Amnesia, Blood urine present, Dyspnoea, Fluid retention, Hypophagia, IgA nephropathy, Nausea, Tinnitus	Conditional	This consumer with previously diagnosed IgA nephropathy reported that he developed hematuria the day following his second dose of Spikevax and that his EGFR decreased from 56 to 45. He also reported that he was prescribed antibiotics to treat a suspected urinary tract infection, and this provides an alternative explanation for the hematuria. The drop in EGFR might alternatively be explained by natural history of disease, measurement imprecision, or day-to-day biological variation. This case is WHO Causality Conditional due to missing urine culture results.	yes, but no biopsy	yes, history of IgAN	no	2	I	0	[redacted]	300262I
		Regulatory Authority	49	Female	0	0	Axillary pain, Fatigue, Haematuria, Headache, IgA nephropathy, Injection site pain, Pain in extremity, Vaccination site pain	Possible	This adverse event was reported by a consumer. A 49 year old female experienced gross hematuria 2 days after dose 1 of Spikevax. The prior day she experienced injection site pain, arm pain, headache and fatigue. Laboratory abnormalities were not reported. The patient was admitted to hospital and treated with corticosteroids. The patient had a history of IgA nephropathy that was not in need of treatment. This is a WHO Causality Possible case of relapse of IgA nephropathy, but better documentation of the relapse would be needed for a Probable assessment.	yes	yes	no	1	2	Are you or the person concerned aware of allergies? If yes, which one? No Information on on risk factors or pre-existing conditions IGA nephropathy that was not in need of treatment. /On 13.01.2022, I noticed for the first time that my urine was blood red. Since the urine had not improved until the next day,		000133A

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
															I went to the family doctor on 14.01.2022. Due to severe macrobematuria, I was admitted to hospital by the family doctor. I received a bubble level there. It turned out that bloody urine was emptied from both ureter ostia. I was then given a continuous bubble flush from 14.01.-15.01.2022. I also received cortisone boosting 2x with dexamethasone 4 mg i.V., there were none abnormalities in laboratory chemistry. On 17.01.2022, I went to a settled		

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															nephrologist. He confirmed that it was a reaction to vaccination. I received another date for review.		
[redacted]		Literature - Non-Study	50	Female	Hypertension(C); Antiphospholipid syndrome(C); Obesity(C); Transient ischaemic attack(H); IgA nephropathy(C)	AMLODIPINE; FUROSEMIDE; OLMESARTAN; WARFARIN; ENOXAPARIN	Haematuria, IgA nephropathy, Myalgia, Pyrexia	Possible	This 50 year old woman had previously been diagnosed with antiphospholipid syndrome, which is a vascular disease that can affect the glomerular tuft, interstitial vessels, and peritubular vessels. In addition, this patient has pre-existing renal abnormalities, with baseline values of serum creatine 1.3 mg/dl and urine protein;creatinine ratio 1.3 g/g, respectively, 7 months prior to presentation, along with 10-20 rbcs in urine per high power field. Gross hematuria resolved within 5 days. The presence of focal glomerular and tubulointerstitial scarring suports the possibility that immune response to vaccination exacerbated a preexisting IgA nephropathy. Anticoagulation with warfarin, started three months prior to presentation, may have potentiated the development of gross hematuria and is a confounder. WHO Causality is Possible.	yes, by kidney biopsy	yes, history of IgAN	no	2	2	0	[redacted]	0
		Literature - Non-Study	50	Male	Hypertension(C); Renal impairment(C); Proteinuria(H)	0	Haematuria, IgA nephropathy, Proteinuria	Possible	Literature case of 50 year old man with exacerbation of IgA nephropathy with hematuria within 24 hours after second dose Spikevax. RBCs per HPF increased from 11-25 prior to 50+, UCPR from 2.4 to 3.56 and serum Cr from 1.17 to 1.54. One month post second dose, hematuria and proteinuria returned to baseline with renin-angiotensin-aldosterone system inhibition, serum Cr was improving, all without immunosuppressive therapy. Patient underwent a kidney biopsy, showing an active and chronic IgA nephropathy with 13% active crescents. Given the chronic nature of this patient's IgAN and the lack of history about the natural course of his disease, this case is assessed as WHO Causality: Possible.	yes, by kidney biopsy	yes, history of IgAN	no	2	1	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	Regulatory Authority	52	Female	Type IIa hyperlipidaemia(C); Hypersensitivity (C)	0	Acute kidney injury, Chromaturia, Gaze palsy, Headache, IgA nephropathy, Myalgia, Pyrexia	Possible	There is a temporal association with an extremely rapid time to onset, one day. All symptoms resolved in 72 hours. The biopsy diagnosing IgA nephropathy was performed 44 days after the onset, and 41 days after the resolution, of symptoms. So it is hard to determine if this is new onset IgA nephropathy or a flare of pre-existing disease; moreover, the histopathology is not reported beyond the diagnosis. In addition, medical history and the timing of the laboratory testing of creatine level were not specified. Given the lack of details, causality is considered possible.	yes, by kidney biopsy	no	no	1	1	This case concerns a 52-year-old, female patient, who experienced acute kidney injury, chromaturia, gaze palsy, headache, IgA nephropathy, myalgia, low grade fever. Based on the current available information and temporal association between the use of the product and the start date of the event, a causal relationship cannot he excluded.	[redacted]	0
[redacted]	[redacted]	Literature - Non-Study	53	Female	Gluten sensitivity(C); Fructose intolerance(C); Histamine intolerance(C);	0	IgA nephropathy	Probable	This patient had been diagnosed with IgA nephropathy by renal biopsy in 2016. Concurrent medical conditions included Gluten intolerance, Fructose intolerance, Histamine intolerance and Restless legs syndrome. One day following the second dose, the patient developed hematuria. Duration of symptoms was seven days, with spontaneous resolution. At three week follow-up, creatinine and urine protein were	yes	yes	no	2	1	0	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
					Restless legs syndrome(C)				normal. WHO Causality assessment for IgA nephropathy relapse is Probable for this literature case.								
[redacted]		Literature - Non-Study	54	Female	Pharyngitis streptococcal(H); Obesity(C); Hypertension(C); Gastrooesophageal reflux disease(C); IgA nephropathy(C)	ENALAPRIL; HYDROCHLOROTHIAZIDE; PROPRANOLOL	Acute kidney injury, IgA nephropathy	Possible	Literature report of a 54 year old woman with history of IgAN after strep throat infection who had been diagnosed hy biopsy. Other significant co-morbidity includes obesity (BMI 31.6), hypertension, and GERD. She had no prior documented infection with COVID-19. She was on enalapril 20 mg daily, hydrochlorothiazide 12.5 mg daily, and propranolol 120 mg daily. Two days after dose 2 of Spikevax, she developed hematuria, which resolved after two days. Her baseline eGFR dropped from 46 yo 16 and creatinine rose from 1.2 to 3.04. Renal biopsy was performed and, according to the authors of this literature report: "Electron microscopy revealed some mesangial electron-dense deposits (Fig. 1d). Differential diagnosis included IgAN relapse, other de-novo glomerulonephropathies, urinary tract hemorrhage with obstruction, and urinary tract infection, among other causes of hematuria and AKI; however, given her history and kidney biopsy result, IgAN relapse was thought to be the most likely cause." The lack of certainty about IgAN relapse stems in large part from the biospy finding of " Immunofluorescence analysis showed weak IgA staining in mesangium." Given the above, WHO Causality for IgAN relapse is Possible.	yes, by kidney biopsy	yes, history of IgAN	no	2	2	0	[redacted]	0
		Regulatory Authority	55	Male	Chronic hepatitis B(C); Hyperlipidaemia(C); Hyperuricaemia(C); Polycythaemia(C)	BARACLUDE	Altered state of consciousness, Atrial fibrillation, Diarrhoea, Disturbance in attention, IgA nephropathy, Nausea, Oliguria, Renal failure, Renal tubular necrosis, Seizure, Vomiting	Unlikely	This adverse event in a 55 year old male with Chronic hepatitis B; Hyperlipidaemia; Hyperuricaemia; Polycythaemia. Hepatitis B has been independently linked to IgAN. The onset of the adverse event was 50 days after dose 1 of Spikevax. Hepatitis B infection is a confounder, and the time to onset is quite long--therefore, this case is considered WHO Causality Unlikely.	yes, by kidney biopsy	no	no	I	50	0		0
		Literature -	57	Male	Chronic kidney	0	IgA nephropathy	Possible	In this multi-patient case series of 29 cases, there were not numerous details on each case. The onset of symptoms was one day	yes	no	no	2	1	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
		Non-Study			disease(H)				after dose 2. This case was reported as having chronic kidney disease; however, the type of disease was not further specified. So this case cannot surely be considered a flare of IgA nephropathy. WHO Causality is Possible due to temporal association.							[redacted]	
[redacted]		Regulatory Authority	58	Male	Gout(C); Hypertension(C); Psoriasis (C)	ALLOPURINOL; AMLODIPINE; ASA; LISINOPRIL; METOPROLOL XL	Acute kidney injury, Cutaneous vasculitis, Glomerulonephritis, Haematuria, Henoch-Schonlein purpura, IgA nephropathy, Proteinuria, Purpura	Possible	f ACUTE KIDNEY INJURY (Acute kidney injury), CUTANEOUS VASCULITIS (Cutaneous vasculitis), IGA NEPHROPATHY (IgA nephropathy), HAEMATURIA (Haematuria), HENOCH-SCHONLEIN PURPURA (Henoch-Schonlein purpura), PROTEINURIA (Proteinuria) and PURPURA (Purpuric rash) in a 58-year-old male patient who received mRNA-1273 (Moderna COVID-19 Vaccine) for COVID-19 vaccination. Concurrent medical conditions included Gout, Hypertension and Psoriasis. Concomitant products included ALLOPURINOL, AMLODIPINE, ASA, LISINOPRIL and METOPROLOL TARTRATE (METOPROLOL XL) for an unknown indication. Eleven days after the first dose of Spikevax on 23-Mar-2021, the patient experienced ACUTE KIDNEY INJURY (Acute kidney injury) CUTANEOUS VASCULITIS (Cutaneous vasculitis) based on a biopsy 2 months and five days after vaccination, IGA NEPHROPATHY (IgA nephropathy) (seriousness criteria hospitalization and medically significant), HAEMATURIA (Haematuria) (seriousness criterion hospitalization), HENOCH-SCHONLEIN PURPURA (Henoch-Schonlein purpura) (seriousness criterion hospitalization), PROTEINURIA (Proteinuria) (seriousness criterion hospitalization) and PURPURA (Purpuric rash) (seriousness criterion hospitalization). DIAGNOSTIC RESULTS showed increasing blood creatine levels over time: On 23-Apr-2021, Blood creatinine: 0.9 mg/dl (Inconclusive) serum creatinine 0.9 mg/dL. On 23-Apr-2021, Urine analysis: abnormal (abnormal) abnormal. On 10-May-2021, Blood creatinine: 3.67 mg/dl (Inconclusive) 3.67 mg/dL. On 12-May-2021, Blood creatinine: 3.98	yes, by kidney biopsy	no	no	1	11	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									mg/dl (Inconclusive) 3.98 mg/dL. WHO Causality assessment is Possible because although there is a temporal association with vaccination, there have been reports of IgA nephropathy in conjunction with psoriasis so that is an alternative explanation.								
[redacted]	[redacted]	Regulatory Authority	64	Male	COVID-19 immunisation(H); Toxic nodular goitre(H); Hypertension(C); COVID-19 immunisation(H)	LOSARTAN	Blood urine present, Chills, COVID-19 immunisation, IgA nephropathy, Myalgia, Pyrexia	Unassessable	Other than the mention of hematuria and a diagnosis of IgA nephropathy, this report provides no other clinical or laboratory data, and therefore WHO Causality is Unassessable.	yes	no	no	3	0	0	[redacted]	3006273
		Regulatory Authority	66	Male	IgA nephropathy(C); Diabetes mellitus(C); Nephritis(H)	0	Decreased appetite, Discomfort, Fatigue, Generalised oedema, Hypoalbuminaemia, IgA nephropathy, Proteinuria	Conditional	This report is hard to interpret and needs clarification. The patient had previously diagnosed diabetes (which may have played a contributory role to kidney pathology) and IgA nephropathy. In particular, the prior history and pattern of the patient's relapses, if any, were not specified. It was only stated that his illness had been in remission for 6 months, but the experience before that was not stated; on the day of the first dose, "Protein total: 1000 (abnormal) Abnormal" was reported which indicates there was a problem before the adverse event that occurred 2 weeks after dose 2; " The patient was reminded to take medicine regularly," suggesting perhaps that he had not been taking his previously prescribed medicines. WHO Causality is Conditional because more detail and precision is needed in this report.	yes, but no biopsy	yes, history of IgAN	no	2	14	0		0
		Literature - Non-Study	66	Male	0	0	IgA nephropathy, Pericarditis	Possible	Literature report of a 66 year old male who developed IgAN 2 weeks after dose 1, with hematuria, proteinuria, normal serum albumin, and slightly elevated serum creatinine. Pericarditis was also reported; this case is the only case with both IgAN and pericarditis in the MAH's postmarketing safety database so there is no concerning pattern with regard to co-occurrence of these two adverse events.	yes, but no biopsy	no	no	1	11	0		0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									Reported details on this case are limited. Based on temporal association between IgAN and Spikevax, this case is WHO Causality: Possible.								
[redacted]	[redacted]	Regulatory Authority	66	Female	Nephrotic syndrome(C); Dyslipidaemia(C); Goitre(H); Uterine leiomyoma(C)	0	IgA nephropathy, Nephrotic syndrome	Possible	A 66-year-old female patient diagnosed with nephrotic syndrome and IgA nephropathy (by biopsy nearly one year earlier) had a relapse of nephrotic syndrome 9 days after dose 1 of Spikevax. The patient's past medical history included Goiter (Thyroid goiter s/p unilateral thyroidectomy). Other concurrent medical conditions included dyslipidemia and Uterine leiomyoma. Whether the patient had been free of relapses/flairs since initial diagnosis of IgAN was not reported. Absence of other exposures that might have led to a flair was also not reported. At the time of the report, NEPHROTIC SYNDROME (Nephrotic syndrome with IgA nephropathy) and IGA NEPHROPATHY (Nephrotic syndrome with IgA nephropathy) was resolving. WHO Causality for a relapse is Possible because of temporal association following one vaccination. Rechallenge was not reported.	yes	yes	no	I	9	0	[redacted]	0
		Regulatory Authority	66	Male	0	0	IgA nephropathy	Unassessable	No clinical details	yes	no	no	3	3	0		216001
		Regulatory Authority	71	Female	Hypertension(C); Hepatic steatosis (C); Pain(H); Pyrexia(H); Peripheral swelling (H)	0	Acute kidney injury, IgA nephropathy, Malaise	Conditional	71 year old female experience reactogenicity to Spikevax on the day and day after vaccination. She developed hematuria and proteinuria on the day following dose 1. Renal biopsy found atypical forms of IgA nephropathy. Knowing what was atypical about the biopsy finding is needed to assess this case for causality. WHO Causality: Conditional.	yes, by kidney biopsy	no	no	2	I	Frank hematuria and high level of uric protein with creatinine developed after the 2nd vaccination with the vaccine, and the patient was diagnosed with atypical		3003657

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
															forms of IgA nephropathy (acute kidney injury with frank hematuria). As cases of the same kind have been reported, it is considered that the event was an adverse reaction to the vaccine.The events developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.		
[redacted]		Literature - Non-Study	0.00	Female	0	0	Acute kidney injury, Anti-glomerular basement membrane disease, Decreased appetite, Haematuria, Nausea, Pyrexia	Possible	This literature case adverse event in an "older woman" with previously normal renal function and no significant past medical history, prior coronavirus disease 2019 (COVID-19) infection, or medication use. Two weeks after dose 2, she developed fevers, anorexia, nausea, and gross hematuria. There was acute kidney injury, with peak creatinine of 7.8. Anti-GBM nephritis with mesangial IgA deposits was diagnosed, based on renal biopsy. The author of this report, who best knows the patient, wrote "Whether current cases can be attributed to COVID-19 vaccine–related	yes, by kidney biopsy	no	no	2	14	0	[redacted]	0

Case ID	Country	Report Type	Patient Age (Years)	Patient Gender	Medical History	Concomitant Medications	ALL PT'S	WHO Causality	WHO-UMC Causality and Justification	IgAN	IgA Flare	+Rechallenge	Dose	TTO All Doses	MAH Comment	WW Identifier	Batch/Lot Number
									immune response is speculative but intriguing, and warrants investigation." Based on the above, this report is categorized as WHO causality Possible.								
[redacted]		Regulatory Authority	0.00	Female	IgA nephropathy(C); Blood urine present(H)	0	Blood urine present, IgA nephropathy	Unassessable	This consumer report from a patient with previously diagnosed IgAN lacks basic details beyond the description of bematuria after both doses, and is Unassessable for WHO Causality.	yes, but no biopsy	yes, history of IgAN	no	1,2	?	0	[redacted]	0

Appendix 5 Listing of all MAH-Sponsored Interventional Trials with the Primary Aim of Identifying, Characterising, or Quantifying a Safety Hazard or Confirming the Safety Profile of the Medicinal Product

Table 20.2 Listing of all MAH-Sponsored Interventional Trials with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard or Confirming the Safety Profile of the Medicinal Product

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
mRNA-1273-P201	2a	USA	A Phase 2, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Trial to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine in Adults Aged 18 Years and Older	This is a three-part, Phase 2a study: Part A, Part B, and Part C. Participants in Part A, the Blinded Phase of the study, are blinded to their treatment assignment. Part B, the Open-label Interventional Phase of this study is designed to offer participants who received placebo in Part A of this study an option to receive 2 injections of open-label mRNA-1273. Participants who received 1 or 2 injections of mRNA-1273 (50 µg or 100 µg) in Part A of this study will proceed to Part B, open-label, and will be offered a single booster dose of mRNA-1273 (50	Part A: 50 or 100 µg mRNA-1273 or placebo two Intramuscular (IM) doses, 28 days apart Part B: Placebo recipients from Part A receive 2-100 µg mRNA-1273 doses mRNA recipients from Part A receive a 50µg booster dose of mRNA-1273. Part C: Participants from P301 are enrolled in P201 Part C to receive one of the following boosters: 20 or 50 µg of mRNA-1273.351 or 50 µg of a 1:1 mix	Healthy adults Part A: Age groups: Cohort 1: ≥ 18 to < 55 years (n=300) Cohort 2: ≥ 55 years (n=300) Dose groups: Placebo (n=200) mRNA-1273 50 µg (n = 200), mRNA-1273 100 µg (n=200) Part B: mRNA-1273 50 µg booster (n=400) Part C: mRNA-1273.351 20 µg (n=20) mRNA-1273.351 50 µg (n=20) mRNA-1273 + mRNA-1273.351 (1:1) 50 µg (n=20)	29 May 2020	Part A: 600 Part B:400 Part C:60	Double blinded Phase (Part A) mRNA-1273-558, placebo-42 Open-label Phase (Part B): 158 subjects who took placebo in part A received mRNA-1273, 344 subjects who took mRNA-1273 in part A received mRNA-1273 booster. Part C: mRNA-1273/1273.351 booster – 20; mRNA-1273.351 booster - 40

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				µg). Part C will be a proof-of-concept rollover study of approximately 60 participants, who are currently enrolled in Moderna's Phase 3 mRNA-1273-P301 Corona Virus Efficacy (COVE) study and have previously received 2 doses of mRNA-1273 at least 6 months earlier. Upon enrolment into Part C of this study, they will receive a single IM injection of mRNA-1273.351 (20 µg or 50 µg) or mRNA-1273/mRNA-1273.351 mixture (50 µg total) at least 6 months after receiving the second vaccination in the mRNA-1273-P301 COVE study. At enrolment into this study, their participation in	of mRNA-1273 and mRNA-1273.351				

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				mRNA-1273-P301 COVE study will be terminated. The study is divided into two cohorts by age, Cohort 1 with 300 participants (≥ 18 to < 55 years old) and Cohort 2 with 300 participants (≥ 55 years old). In the blinded Part A, approximately 600 participants will be randomly assigned in a 1:1:1 ratio to mRNA-1273 50 µg, mRNA-1273 100 µg, or placebo. A total of 400 participants will receive mRNA-1273, 200 participants in each dose level, or 100 participants in each age cohort and dose level.					
mRNA-1273-P203	2/3	USA	A Phase 2/3, Randomized, Observer-Blind,	This is a two-part, Phase 2/3, study: Part A and Part B. The study will	Part A 100 µg mRNA-1273 or placebo (2:1) 2 IM doses, 28	Healthy adolescents Age group: 12	09 Dec 2021	3000	mRNA-1273-2,592 Placebo-1,144 EUA+mRNA-1273

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
			Placebo-Controlled, Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 years of age	evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV-2 vaccine in healthy adolescents 12 to < 18 years of age. Participants in Part A, the Blinded Phase of the study, will be randomly assigned to receive injections of either 100 µg of mRNA-1273 vaccine or a placebo control in a 2:1 randomization ratio. Part B, the Open-label Observational Phase of this study, is designed to offer participants who received placebo in Part A of this study, and who meet Emergency Use Authorisation (EUA) eligibility criteria, an option to receive mRNA-1273 in an open-label fashion.	days apart Part B Placebo recipients in Part A receive 100 µg mRNA-1273 2 IM doses, 28 days apart	to < 18 years n=3,000 mRNA-1273 n=2000 placebo n=1000 Randomization will be stratified based on age: 12 to <15 and 15 to <18 years of age. At least 30% of enrolled participants, but not to exceed 50%, will be 12 to <15 years of age			Booster-45 Primary series+mRNA-1273 Booster-1,388

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
mRNA-1273-P204	2/3	USA, Canada	A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA 1273 SARS-CoV 2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age	This is a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study intended to infer the effectiveness of mRNA-1273 in children aged 6 months to < 12 years. The study population will be divided into three age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years), and up to three dose levels (25, 50, and 100 µg) of mRNA-1273 will be evaluated. The study will be conducted in two parts. Part 1 of the study will be open-label and consist of dose-escalation and age de-escalation in approximately 1350	25, 50, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart	Healthy paediatrics Part 1: Age groups: 6 to < 12 years (n = 150) 2 to < 6 years (n=150) 6 months to < 2 years (n=450) mRNA-1273 dose groups: 25 µg (n=150), 50 µg (n=300), 100 µg (n=300), Part 2: Age groups: 6 to < 12 years (n=2,000) 2 to < 6 years (n=2,000) 6 months to < 2 years (n=2,000) mRNA-1273 selected dose (n=4,500) Placebo (n=1,500)	15 Mar 2021	Part 1: 1,500 Part 2: 6000	Part A=mRNA-1273-9,989 Placebo-1,880 mRNA-1273 Booster-2,303

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				participants to select the dose for each age group. Part 2 of the study will be placebo-controlled observer-blind evaluation of the selected dose in approximately 5,700 participants (approximately 1,700 participants in the 6 to < 12 years of age group and approximately 2,000 participants in both the 2 to < 6 years and the 6 months to < 2 years age groups). No participants in Part 1 will participate in Part 2 of the study.					
mRNA-1273-P205	2/3	USA	A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants	This is an open-label, Phase 2/3 study to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1273.211, mRNA-1273, mRNA-1273.617.2, and mRNA-	Participants will be enrolled to receive the 50 or 100 µg dose of mRNA-1273.211 (Part A), 100 µg mRNA-1273 (Part B), 50 or 100 µg mRNA-	Participants will be male or female, 18 to 55 years of age (inclusive), be in good general health and can comply with study procedures at the time of	May 2021	Approximately 300 participants will receive a single booster dose of mRNA-1273.211 50 µg, to	mRNA-1273 Booster-688 mRNA-1273.211 Booster-870 mRNA-1273.213 Booster-954 mRNA-1273.617.2 Booster-1,158 mRNA-1273.211 Booster+mRNA-

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				1273.213. Part A will evaluate the immunogenicity, safety, and reactogenicity of two dose levels of the mRNA-1273.211 vaccine when administered as a single booster dose to adult participants of the mRNA-1273-P301 (COVE) study who have previously received 2 doses of mRNA-1273 as a primary series. Part B will evaluate the immunogenicity, safety, and reactogenicity of the mRNA-1273 vaccine when administered as a single booster dose to adult participants of the mRNA-1273-P301 (COVE) study who have previously received 2 doses of mRNA-	1273.617.2 (Part C), 50 or 100 µg mRNA-1273.213 (Part D). 50 or 100 ug mRNA-1273.529 (part F)	consent. Participants will have clinical screening laboratory evaluations that are within normal reference ranges at the study-designated laboratory, negative pregnancy test for female participants of childbearing potential and negative serology results for SARS-CoV-2 at the screening Visit. In addition, participants will be asymptomatic for any acute or chronic illness requiring medical or surgical care, to include changes in medication in		achieve 270 evaluable participants in the 50 µg dose study arm. Approximately 300 participants will receive a single booster dose of mRNA-1273 100 µg, to achieve 270 evaluable participants in Part B of the study. Approximately 584 participants will receive a single booster dose of mRNA-	1273.214 Booster-25 mRNA-1273.214 Booster-437 mRNA-1273.529 Booster -508

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				1273 as a primary series. Part C will evaluate the immunogenicity, safety, and reactogenicity of two dose levels (50 or 100 µg) of the mRNA-1273.617.2 vaccine when administered as a single booster dose to adults who have previously received 2 doses of mRNA-1273 as a primary series in Study mRNA-1273-P301 (COVE) or under the EUA. Part D will evaluate the immunogenicity, safety, and reactogenicity of two dose levels (50 or 100 µg) of the mRNA-1273.213 vaccine when administered as a single booster dose to adults who have previously received		the past 2 months indicating that chronic illness/disease is not stable (at the discretion of the investigator).		1273.617.2 50 µg, to achieve 526 evaluable participants in the 50 µg dose study arm. Approximately 300 participants will receive a single booster dose of mRNA-1273.529 50 µg, to achieve 270 evaluable participants in the 50 µg dose study arm. Approximately 300 participants will receive a single booster	

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				2 doses of mRNA-1273 as a primary series in Study mRNA-1273-P301 (COVE) or under the EUA.				dose of mRNA-213 50 µg, to achieve 270 evaluable participants in the 50 µg dose study arm.	
mRNA-1273-P301	3	USA	A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older.	This is a two-part Phase 3 study: Part A and Part B. Participants in Part A, the Blinded Phase of this study are blinded to their treatment assignment. Part B, the open-label observational Phase of this study is designed to offer participants who received placebo in Part A of this study and who meet EUA eligibility, an option to request open-label mRNA-1273.	Part A: 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart Part B: Placebo recipients in Part A receive 100 µg mRNA-1273 2 IM doses, 28 days apart	Healthy adults Age groups: ≥18 years (n=30,000) Dose groups: Placebo crossed over to mRNA-1273 (n=15,000) mRNA-1273 100 µg (n=15,000)	27 Jul 2020	30,000	Double blinded Phase: mRNA-1273-27,834 Placebo-2,513 mRNA-1273 Booster-19,609
mRNA-1273-P304	3b	USA	A Phase 3b, Open-Label, Safety and	This is a Phase 3b, open-label study to evaluate the safety,	100 µg mRNA-1273 2 IM doses, 28	Adult liver and kidney transplant	16 Apr 2021	240 adult participants (110	mRNA-1273=81 EUA+mRNA-1273=74

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
			Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls	reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in solid organ transplant recipients and healthy controls.	days apart	recipients and healthy control participants. Age group: ≥18 years (n=240) mRNA-1273 100 µg (n=240)		kidney transplant recipients, 110 liver transplant recipients, and 20 healthy adults)	EUA+mRNA-1273 Booster=57 Primary series+mRNA-1273 Booster=75
mRNA-1273-P305	2/3	UK	A Phase 2/3, Randomized, Observer-blind, Active-controlled, Multicenter Study to Evaluate the Immunogenicity and Safety of mRNA-1273.529 (B.1.1.529, Omicron Variant) in Comparison with mRNA-1273 (Prototype) Booster Vaccine	Approximately 2,924 participants will be randomized in a 1:1 ratio to 1 of 2 study arms to receive a single dose of either 50 µg of mRNA-1273.529 or 50 µg of mRNA-1273 (active control). Randomization will be stratified by age groups (16 to < 65 years or ≥ 65 years) and number of booster doses received (to receive study vaccine as the 4th dose or to receive study vaccine as the 3rd dose). At least ≥	single dose of either 50 µg of mRNA-1273.529 or 50 µg of mRNA-1273	Participants who will receive the 4th dose as part of the study must have previously received a mRNA vaccine (Moderna or Pfizer-BioNTech) as the 3rd dose of a COVID-19 vaccine. Participants who will receive the 3rd dose as part of the study may have previously received 2 doses of an approved/authorized mRNA or a		2,924	3,536

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				90% of participants will receive study vaccine as the 4th dose.		non-mRNA COVID-19 vaccine (a heterologous vaccine regimen is acceptable)			
mRNA-1283-P101	1	USA	A Phase 1, Randomized, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1283 and mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18-55 Years	This is a Phase 1, randomized, observer-blind study in healthy adult participants 18 to 55 years of age. All participants will participate in a Screening Period, Treatment Period, and Follow-up Period. The study duration will be approximately 14 months for each participant: a screening period of up to 1 month and a study period of 13 months that includes the first dose of vaccine on Day 1 and the second dose on Day 29. The participant's final visit will be on Day 394 (Month 13), 12	Three dose levels (10, 30, and 100 µg) of mRNA-1283 (Arms 1 through 3) and one dose level (100 µg) of mRNA-1273 (Arm 5) will each be evaluated in a 2-dose regimen, with the doses administered 28 days apart. One dose level (100 µg) of mRNA-1283 will be evaluated in a single dose regimen (Arm 4). Approximately 125 participants will be randomized in a 1:1:1:1:1 ratio	Participants will be male or female, 18 to 55 years of age (inclusive), be in good general health and can comply with study procedures at the time of consent. Participants will have clinical screening laboratory evaluations that are within normal reference ranges at the study-designated laboratory, negative pregnancy test for female participants of childbearing	02 Mar 2021	Up to 125 participants will be randomized to one of five study arms in a 1:1:1:1:1 ratio, with up to 25 per arm to achieve 20 evaluable participants per arm.	Placebo+mRNA-1283=13 Placebo+mRNA-1283+mRNA-1273=5 mRNA-1273=22 mRNA-1283=64

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				months after the second dose of vaccine on Day 29 (Month 1). Three dose levels (10, 30, and 100 µg) of mRNA-1283 (Arms 1 through 3) and one dose level (100 µg) of mRNA-1273 (Arm 5) will each be evaluated in a 2-dose regimen, with the doses administered 28 days apart. One dose level (100 µg) of mRNA-1283 will be evaluated in a single dose regimen (Arm 4). Approximately 125 participants will be randomized in a 1:1:1:1:1 ratio to receive an Investigational Product, with approximately 25 participants randomized to each study arm. All study arms will be enrolled in parallel.	to receive an Investigational Product, with approximately 25 participants randomized to each study arm. All study arms will be enrolled in parallel.	potential and negative serology results for SARS-CoV-2 at the screening Visit. In addition, participants will be asymptomatic for any acute or chronic illness requiring medical or surgical care, to include changes in medication in the past 2 months indicating that chronic illness/disease is not stable (at the discretion of the investigator).			

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				The full study comprises eight scheduled study site visits: Screening, Day 1, Day 8, Day 29 (Month 1), Day 36, Day 57 (Month 2), Day 209 (Month 7), and Day 394 (Month 13). There are also scheduled monthly safety phone calls to collect medically attended adverse events, adverse events of special interest, adverse events leading to withdrawal, serious adverse events, and information about concomitant medications associated with these events, as well as to collect information about receipt of non-study vaccinations temporally associated with these events.					

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
mRNA-1283-P201	2	US	A Phase 2a, randomized, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2	This is an observer-blind, Phase 2a, stratified, randomized study to evaluate the immunogenicity, safety, and reactogenicity of mRNA-1283, mRNA-1283.211, and potentially of other study vaccines, administered as a single booster dose to participants 18 years and older who were previously vaccinated with mRNA-1273. This study will assess whether a single dose of mRNA-1283 at three different dose levels (2.5 µg, or 5 µg, or 10 µg) or mRNA-1283.211 at two different dose levels (5 µg or 10 µg) will boost antibody responses to the Wuhan-Hu-1 (ancestral strain of	Each injection will have a volume of 0.25 mL. The vaccines will contain mRNA-1283 at the doses of 2.5 µg, 5 µg, and 10 µg (dose volume 0.25 mL), mRNA-1283.211 at the doses of 5 µg and 10 µg (dose volume 0.25 mL) and mRNA-1273 at the dose of 50 µg (dose volume 0.25 mL).	Enrolment in this study will be stratified by age with two age strata: 18-55 years of age and ≥ 56 years of age, with at least 20% but no more than 50% of participants 56 years of age or older. Those with documented prior SARS-CoV-2 infection are eligible to participate if also previously vaccinated with mRNA-1273. Prior infection status will be confirmed by anti-nucleocapsid antibody testing of all participants	29 Nov 2021	Approximately 420 participants previously vaccinated for COVID-19 with mRNA-1273 will receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or a single dose of the active comparator, mRNA-1273, in a 1:1:1:1:1:1 ratio, ie,	543

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				the SARS-CoV-2) virus, and to the B.1.351 variant, and potentially other SARS-CoV-2 variants, and inform dose selection for mRNA-1283 booster vaccines for subsequent clinical evaluation. The study will include an active comparator group of participants who will receive mRNA-1273 (50 µg). Participants who received the primary series of mRNA-1273 (100 µg) with appropriate documentation at least 6 months prior will be randomized 1:1:1:1:1:1 to receive a single boost of mRNA-1283 at one of three dose levels, a single boost of mRNA-1283.211 at one of two dose levels, or				70 participants per treatment group	

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				a single dose of the active comparator, mRNA-1273.					
mRNA-CRID-001	Phase 1b	US	Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Modified mRNA Vaccines Using a Systems Biology Approach in Healthy Adults	An open-label, randomized, 2-part, Phase 1b study to evaluate the safety, reactogenicity and immunogenicity of modified mRNA vaccines using a systems biology approach in healthy adults aged 18 to 75 years old. Approximately 8 sites in the US will participate in the study. The vaccines to be tested in the study contain single mRNAs encoding cell-membrane associated antigens (ie, SARS-CoV-2, RSV, CMV) and multiple mRNAs encoding influenza hemagglutinin (HA). The different arms for the study will include: •mRNA-1273	Generally healthy adults (to include 2 age groups: 18 to < 50 years of age and ≥ 50 to ≤ 75 years of age) will be screened and enrolled in each study part. In the mRNA-1647 study arms, healthy adults aged 18 to < 50 years old will be screened and enrolled. This study will have a 2:1:1 randomization in Part 1 and 2:2:2 randomization in Part 2, and parallel enrolment between arms. The study will enroll up to 60	Up to 300 generally, healthy adults will be enrolled in this study, with 30-60 participants per study arm	Apr 2022	Up to 300 participants will be enrolled and randomized in the study	There is no active dosing

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				(SARS-CoV-2) •mRNA-1010 (influenza HA) •mRNA-1345 (RSV) •mRNA-1647 (CMV) •Active comparator: adjuvanted (MF59), inactivated, quadrivalent seasonal influenza vaccine (FLUAD) Part 1 will enroll approximately 120 participants without a laboratory-confirmed infection or vaccination for RSV within 6 months of screening. Participants will be randomized to receive either a single dose of mRNA-1345, two doses of mRNA-1647 (Day [D]1 and D57), or three doses of mRNA-1647 on study D1, D57 and D169. Study participants in other	participants into each study arm with a balanced age group distribution of approximately 1:1 including two age groups of 18 to < 50 years of age and ≥ 50 to ≤ 75 years of age.				

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				arms may be CMV-neg or CMV-pos. Part 2 will enroll approximately 180 participants without a laboratory-confirmed infection or vaccination for SARS-CoV-2 within 4 months, or influenza within 6 months of screening. Participants will be randomized to receive either a single dose of mRNA-1273, mRNA-1010, or FLUAD (active comparator) on study D1. Study participants randomized to the mRNA-1273 arm may receive either mRNA-1273 (prototype strain) or mRNA-1273 encoding spike protein(s) that more closely matches circulating variant strains of SARS-					

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Start Date (FVFP[a])	Planned Enrolment	Subject Exposure [b]
				CoV-2, such as the bivalent mRNA-1273.214 vaccine that encodes spike proteins for the prototype Wuhan and Omicron strains. Selection of the final mRNA-1273 vaccine will occur prior to enrolment in Part 2 and depends on current recommendations for booster vaccination and/or predominant SARS-CoV-2 strain(s) in circulation					

Appendix 6 Listing of all the MAH-sponsored Non-interventional Studies with the Primary Aim of Identifying, Characterising, or Quantifying a Safety Hazard; Confirming the Safety Profile of the Medicinal Product; or Measuring the Effectiveness of Risk Management Measures

Table 20.3 List of all the MAH-sponsored Non-interventional Studies

Study ID	Country	Study Title	Study Design	Study Population	Milestones	Due dates
mRNA-1273-P902	EU, Canada, US	Moderna mRNA-1273 Observational pregnancy outcome study	Primary data collection cohort study.	Pregnant women exposed to mRNA-1273 recruited from the general population and live-born infants from Germany, Italy, Finland, Canada, and the United States. European Surveillance of Congenital Anomalies (EUROCAT) network data, Metropolitan Atlanta Congenital Defects Program (MACDP) data, and other published data will provide an external comparator.	Protocol submission Interim updates Final study report	31 Jan 2021 31 Jul 2021, 31 Jan 2022, 31 Jul 2022, 31 Jan 2023, 31 Jul 2023, 31 Jan 2024 30 June 2024
mRNA-1273-P903	US	Post-Authorisation Safety of SARS-CoV-2 mRNA 1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity.	Secondary database analysis using retrospective analyses of pre-vaccination data as well as prospectively updating data during the vaccination period. It will include estimation of background rates of observed versus expected rates, and self-	A sample of paediatric, adolescent and adult individuals enrolled in health plans contributing data to HealthVerify will be used for calculation of background rates. Patients from this dataset as well as additional patients with evidence of SARS CoV 2 vaccination will be included as vaccine uptake increases.	Protocol submission Interim updates Final study report	31 Jan 2021 30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022, 30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Dec 2022 30 June 2023

Study ID	Country	Study Title	Study Design	Study Population	Milestones	Due dates
			controlled risk interval analyses.			
mRNA-1273-P904	Denmark, Norway, Italy, Spain, United Kingdom	Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU.	Paediatric, adolescent, and adult individuals within the catchment area of participating data partners from the VAC4EU network	Protocol submission Interim updates Final study report	30 Jun 2021 30 Sep 2021, 31 Mar 2022, 30 Sep 2022, 31 Mar 2023 31 Dec 2023
mRNA-1273-P905	Denmark, Norway, Italy, Spain, United Kingdom	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries.	Secondary database analysis comparing birth prevalence of study outcomes for pregnancies with and without COVID-19 Vaccine Moderna exposure.	The study population will encompass all pregnancies, identifiable in the databases, ending in a live or still birth; a spontaneous abortion; or an induced abortion, as identifiable in the participating databases	Protocol submission Interim updates Final study report	30 Jun 2021 31 Mar 2022, 30 Sep 2022, 31 Mar 2023 31 Dec 2023
mRNA-1273-P910	Norway, Denmark, United Kingdom, Spain	Natural history and clinical outcomes of vaccine associated myocarditis	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults	Observational cohort study	Analyses will be conducted using two populations. A case-cohort design will be applied that includes a sample a elasomeran - exposed individuals an all exposed	Protocol submission: 26 Apr 2022 Interim report: 30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024 Final study report:

Study ID	Country	Study Title	Study Design	Study Population	Milestones	Due dates
					cases. A cohort will also be followed, and will include cases of myocarditis following elasomeran as well as cases not secondary to vaccines targeting SARS CoV-2.	28 Feb 2025
mRNA-1273-P911	United States	Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA)	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX).	Observational cohort study	Cases of myocarditis identified in routine clinical practice meeting the CDC case definition, including those occurring following administration of elasomeran as well as cases not secondary to vaccines targeting SARS CoV-2	Protocol submission: 30 Apr 2022 Interim report: 31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027 Final study report: 31 Oct 2028
mRNA-1273-P912	Korea	Post-marketing Surveillance (PMS) Use-Result Surveillance with Moderna's COVID-19 vaccines including SPIKEVAX ® and MODERNA	A Multi-centre, Prospective, Observational Post-marketing Surveillance to Investigate the Long-term Safety of Moderna's COVID-19 vaccines including	Individuals who will be vaccinated with Moderna's COVID-19 vaccines as per label	NA	NA

Study ID	Country	Study Title	Study Design	Study Population	Milestones	Due dates
		SPIKEVAX®	SPIKEVAX® and MODERNA SPIKEVAX® Under Routine Clinical Care in Korea			
mRNA-1273-P913	United States	Real-world Comparative Effectiveness of the mRNA-1273 Vaccine vs. BNT162b2 Vaccine Among Immunocompromised Adults in the United States	This observational retrospective comparative effectiveness cohort study will use the HealthVerity aggregated medical and pharmacy claims database. HealthVerity data elements include provider-submitted claims, adjudicated insurance claims, and pharmacy billing manager claims submissions. Hospitalizations are included in the data at a summary level	The study population will be selected from HealthVerity's aggregated medical and pharmacy claims database that represents healthcare utilization for participants between 01 Dec 2018 and 10 Jan 2022	Actual study start date Actual Primary Completion Date Actual Study Completion Date	10 Sep 2021 04 Feb 2022 21 Mar 2022
mRNA-1273-P914		Discoveries - Different Immunization boosters for COVID-19: Effect on Response In antibodies	Study is observational with self blood collection for assessing antibody levels over time in participants previously boosted with a COVID	Participants previously boosted with a COVID vaccine	Start date	12 Apr 2022

Study ID	Country	Study Title	Study Design	Study Population	Milestones	Due dates
			vaccine			

[a] FVFP = First Visit First Patient.
[b] Based upon total number of subjects recruited as of 18 Jun 2022 and applied randomization schemes.

Appendix 7 List of the Sources of Information Used to Prepare the PBRER (if desired by the MAH)

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Appendix 8 EU Regional Appendices

Appendix 8.1 Proposed Product Information

Not applicable.

Appendix 8.2 Reference Information Comparison

Not applicable.

Appendix 8.3 Proposed Additional Pharmacovigilance and Risk Minimisation Activities

Not applicable.

Appendix 8.4 Summary of Ongoing Safety Concerns

A list of safety concerns from RMP v1.2 available at the beginning of the reporting period is presented in Section 16.1 of this report.

During the reporting period, elasomeran RMP 1.2 was updated to v2.3 approved on 10 Feb 2022 which was the merge of v2.0 and v2.1 to include data on adolescent indication and the two new important identified risks of myocarditis and pericarditis, respectively. Later, RMP v2.3 was updated to RMP v3.0 (approved on 01 Mar 2022) with no additional changes to the list of safety concerns. RMP v3.0 was further updated to RMP v4.0 approved on 23 Jun 2022 (after the DLP) to remove 'anaphylaxis' as an important identified risk and reclassify it as an identified risk (not important); while anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine.

Appendix 8.5 Reporting of Results from Post-authorisation Safety Studies

Not applicable.

Appendix 8.6 Effectiveness of Risk Minimisation

Not applicable.

Appendix 8.7 Medication Errors

EU Regional Appendix: Medication Errors

	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non-Serious			Serious	
PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
***** HLT TOTAL *****	**1**	**2**	**2**	**36**	**38**	**0**	**0**
Accidental exposure to product	1	2	2	36	38	0	0
***** HLT TOTAL *****	**31**	**52**	**414**	**894**	**946**	**0**	**0**
Circumstance or information capable of leading to device use error	0	0	1	1	1	0	0
Circumstance or information capable of leading to medication error	0	0	19	28	28	0	0
Device difficult to use	0	0	0	1	1	0	0
Device use error	0	0	0	2	2	0	0
Device use issue	0	0	0	5	5	0	0
Dose calculation error	0	0	0	5	5	0	0
Expired device used	0	0	1	2	2	0	0
Inadequate aseptic technique in use of product	0	0	0	5	5	0	0
Incorrect disposal of product	0	0	0	1	1	0	0
Intercepted medication error	0	0	2	2	2	0	0
Medication error	28	37	329	411	448	0	0
Multiple use of single-use product	0	0	0	3	3	0	0
Product substitution error	0	0	0	1	1	0	0
Product use complaint	0	0	1	4	4	0	0
Product use in unapproved indication	0	0	2	5	5	0	0

	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non-Serious			Serious	
PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Product use issue	1	5	14	29	34	0	0
Vaccination error	0	1	20	142	143	0	0
Wrong dose	0	0	0	1	1	0	0
Wrong drug	0	0	0	1	1	0	0
Wrong patient	0	0	0	3	3	0	0
Wrong route	0	0	0	1	1	0	0
Wrong schedule	1	2	1	6	8	0	0
Wrong technique in device usage process	0	1	5	82	83	0	0
Wrong technique in product usage process	1	6	19	153	159	0	0
***** HLT TOTAL *****	**20**	**274**	**11531**	**36254**	**36528**	**0**	**0**
Accidental overdose	0	7	277	778	785	0	0
Accidental underdose	0	0	217	572	572	0	0
Booster dose missed	0	1	0	1	2	0	0
Contraindicated product administered	0	0	0	3	3	0	0
Counterfeit product administered	0	0	1	6	6	0	0
Drug administered in wrong device	0	0	0	1	1	0	0
Drug dose omission by device	0	1	0	0	1	0	0
Duplicate therapy error	0	0	0	1	1	0	0
Expired product administered	0	3	5930	12155	12158	0	0
Extra dose administered	0	40	227	798	838	0	0

	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non-Serious			Serious	
PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Inappropriate schedule of product administration	3	96	1189	5911	6007	0	0
Inappropriate schedule of product discontinuation	0	0	0	4	4	0	0
Incomplete course of vaccination	0	33	5	165	198	0	0
Incorrect dosage administered	0	0	0	6	6	0	0
Incorrect dose administered	0	7	90	1059	1066	0	0
Incorrect dose administered by device	0	0	0	8	8	0	0
Incorrect dose administered by product	0	0	0	6	6	0	0
Incorrect drug administration rate	0	0	0	1	1	0	0
Incorrect product administration duration	1	1	2	35	36	0	0
Incorrect product dosage form administered	0	0	0	1	1	0	0
Incorrect product formulation administered	0	0	1	62	62	0	0
Incorrect route of product administration	1	19	36	840	859	0	0
Intercepted product administration error	0	0	1	3	3	0	0
Lack of injection site rotation	0	0	0	1	1	0	0
Poor quality product administered	1	1	3240	5009	5010	0	0
Product administered at inappropriate site	8	35	14	289	324	0	0
Product administered by wrong person	0	0	1	2	2	0	0
Product administered to patient of inappropriate age	3	8	200	4565	4573	0	0
Product administration error	2	5	37	403	408	0	0
Product administration interrupted	0	0	1	65	65	0	0

	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non-Serious			Serious	
PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Product dose omission in error	0	0	0	18	18	0	0
Product dose omission issue	1	14	45	3180	3194	0	0
Recalled product administered	0	0	0	1	1	0	0
Wrong patient received product	0	0	0	7	7	0	0
Wrong product administered	0	3	17	298	301	0	0
***** HLT TOTAL *****	**0**	**0**	**12**	**60**	**60**	**0**	**0**
Device use confusion	0	0	0	2	2	0	0
Product dosage form confusion	0	0	0	1	1	0	0
Product label confusion	0	0	12	56	56	0	0
Product packaging confusion	0	0	0	1	1	0	0
***** HLT TOTAL *****	**0**	**0**	**16**	**36**	**36**	**0**	**0**
Device dispensing error	0	0	0	1	1	0	0
Drug dispensed to wrong patient	0	0	0	4	4	0	0
Product dispensing error	0	0	16	20	20	0	0
Product dispensing issue	0	0	0	11	11	0	0
***** HLT TOTAL *****	**0**	**1**	**1**	**5**	**6**	**0**	**0**
Documented hypersensitivity to administered product	0	0	0	1	1	0	0
Labelled drug-drug interaction issue	0	0	0	1	1	0	0
Labelled drug-food interaction medication error	0	1	0	0	1	0	0
Medical device monitoring error	0	0	1	1	1	0	0

	Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
	Serious		Non-Serious			Serious	
PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Product monitoring error	0	0	0	2	2	0	0
***** HLT TOTAL *****	**0**	**1**	**17**	**90**	**91**	**0**	**0**
Product preparation error	0	0	15	40	40	0	0
Product preparation issue	0	1	2	50	51	0	0
***** HLT TOTAL *****	**1**	**3**	**1**	**4**	**7**	**0**	**0**
Contraindicated product prescribed	0	2	0	1	3	0	0
Intercepted product prescribing error	0	0	0	1	1	0	0
Product prescribing error	1	1	0	0	1	0	0
Product prescribing issue	0	0	1	2	2	0	0
***** HLT TOTAL *****	**0**	**0**	**7**	**11**	**11**	**0**	**0**
Product selection error	0	0	7	11	11	0	0
***** HLT TOTAL *****	**0**	**2**	**3039**	**5973**	**5975**	**0**	**0**
Intercepted product storage error	0	0	0	1	1	0	0
Product storage error	0	2	3039	5972	5974	0	0
***** HLT TOTAL *****	**1**	**1**	**1**	**3**	**4**	**0**	**0**
Product communication issue	1	1	0	0	1	0	0
Transcription medication error	0	0	1	3	3	0	0
***** HLT TOTAL *****	**54**	**336**	**15041**	**43366**	**43702**	**0**	**0**

Appendix 9 US Regional Appendices

Not applicable

Appendix 10 Canada Regional appendix

Appendix 10.1 Introduction

Together with the annual Periodic Benefit-Risk Evaluation Report (PBRER) covering [01 Jan 2022 to 18 Jun 2022], the Market Authorisation Holder provides details of all ADRs that occurred in Canada for COVID-19 mRNA Vaccine and Canadian-specific data.

Appendix 10.2 Adverse Drug Reactions Occurring in Canada

Sources of post-marketed ADRs in Canada include events reported directly by the reporter to the Company, solicited reports which include market research and patient support programs and published literature. As required by Health Canada guidelines, Company monitors the Moderna GSDB to identify cases potentially involving Company products which have been reported directly to Health Canada.

Post-marketed Reports from Canada

During this reporting period, 3,163 new adverse reaction case reports (ADRs) were identified for COVID-19 mRNA Vaccine from the Canada Vigilance Adverse Reaction Online Database search.

Table 20.4 Summary of ADRs Occurring in Canada

	Serious Events	Non-serious Events	Total Events
Spontaneous (including literature)	808	2,355	**3,163**
Non-interventional postmarketing study and reports from other solicited sources	0	0	**0**

*Refer to attachment for more detailed case summaries. As per PBRER ADR inclusion criteria, only serious events/cases are presented from non-interventional studies and solicited sources

Summary Tabulations of Post-Marketing Adverse Drug Reactions occurring in Canada

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Blood and lymphatic system disorders	*** SOC TOTAL ***	1	17	10	69	86	0	0
	Anaemia	0	1	0	1	2	0	0
	Blood disorder	0	0	0	1	1	0	0
	Coagulopathy	0	1	0	2	3	0	0
	Haemorrhagic diathesis	0	1	0	0	1	0	0
	Leukocytosis	0	1	0	0	1	0	0
	Lymph node pain	0	1	2	8	9	0	0
	Lymphadenitis	0	0	1	1	1	0	0
	Lymphadenopathy	0	5	7	56	61	0	0
	Thrombocytopenia	1	7	0	0	7	0	0
Cardiac disorders	*** SOC TOTAL ***	122	578	16	92	670	0	0
	Acute myocardial infarction	2	5	0	0	5	0	0
	Angina pectoris	3	6	0	0	6	0	0
	Arrhythmia	3	7	0	1	8	0	0
	Atrial enlargement	0	0	1	1	1	0	0
	Atrial fibrillation	3	8	0	0	8	0	0
	Atrial flutter	0	1	0	0	1	0	0
	Bradycardia	0	2	0	0	2	0	0
	Bundle branch block left	0	1	0	0	1	0	0
	Bundle branch block right	0	1	0	0	1	0	0
	Cardiac aneurysm	0	1	0	0	1	0	0
	Cardiac arrest	1	4	0	0	4	0	0
	Cardiac discomfort	1	1	1	7	8	0	0
	Cardiac disorder	1	1	3	7	8	0	0
	Cardiac failure	1	6	0	0	6	0	0
	Cardiac flutter	0	5	0	0	5	0	0
	Cardio-respiratory arrest	0	1	0	0	1	0	0
	Cardiomegaly	1	1	0	0	1	0	0
	Cardiomyopathy	0	1	0	0	1	0	0
	Cardiovascular disorder	0	0	0	1	1	0	0
	Carditis	0	0	0	2	2	0	0
	Coronary artery disease	2	2	0	0	2	0	0
	Coronary artery stenosis	1	1	0	0	1	0	0
	Diabetic cardiomyopathy	0	1	0	0	1	0	0
	Extrasystoles	1	1	0	1	2	0	0
	Hypersensitivity myocarditis	1	1	0	0	1	0	0
	Left atrial enlargement	0	1	0	0	1	0	0
	Left ventricular dysfunction	0	3	0	0	3	0	0
	Mitral valve incompetence	0	1	0	0	1	0	0
	Myocardial infarction	1	5	1	1	6	0	0
	Myocardial injury	0	4	0	0	4	0	0
	Myocardial oedema	0	2	0	0	2	0	0
	Myocarditis	42	166	0	2	168	0	0
	Myopericarditis	21	156	0	1	157	0	0
	Palpitations	4	21	9	57	78	0	0
	Pericardial cyst	0	1	0	0	1	0	0
	Pericardial effusion	2	12	0	0	12	0	0
	Pericarditis	25	112	0	3	115	0	0
	Sinus arrhythmia	1	2	0	1	3	0	0
	Sinus bradycardia	0	4	0	0	4	0	0
	Sinus tachycardia	0	7	0	2	9	0	0
	Stress cardiomyopathy	1	1	0	0	1	0	0
	Supraventricular tachycardia	0	2	0	0	2	0	0
	Tachycardia	3	10	1	5	15	0	0
	Tricuspid valve incompetence	0	2	0	0	2	0	0
	Ventricular dysfunction	0	1	0	0	1	0	0
	Ventricular enlargement	0	1	0	0	1	0	0
	Ventricular failure	0	1	0	0	1	0	0
	Ventricular fibrillation	0	1	0	0	1	0	0
	Ventricular tachycardia	1	4	0	0	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
Congenital, familial and genetic disorders	*** SOC TOTAL ***	2	4	0	0	4	0	0
	Cerebral palsy	0	1	0	0	1	0	0
	Dermoid cyst	1	1	0	0	1	0	0
	Labial tie	1	1	0	0	1	0	0
	Porphyria acute	0	1	0	0	1	0	0
Ear and labyrinth disorders	*** SOC TOTAL ***	9	23	13	55	78	0	0
	Deafness	1	3	0	0	3	0	0
	Deafness neurosensory	0	2	0	0	2	0	0
	Ear discomfort	1	2	0	4	6	0	0
	Ear pain	3	3	1	6	9	0	0
	Ear swelling	0	0	1	1	1	0	0
	External ear pain	0	0	0	1	1	0	0
	Hyperacusis	0	1	0	0	1	0	0
	Hypoacusis	0	0	1	3	3	0	0
	Motion sickness	0	0	0	1	1	0	0
	Sudden hearing loss	0	1	0	0	1	0	0
	Tinnitus	1	3	7	22	25	0	0
	Vertigo	3	7	2	15	22	0	0
	Vertigo positional	0	1	1	2	3	0	0
Endocrine disorders	*** SOC TOTAL ***	0	2	0	6	8	0	0
	Autoimmune thyroiditis	0	1	0	0	1	0	0
	Endocrine disorder	0	0	0	1	1	0	0
	Goitre	0	0	0	2	2	0	0
	Hyperthyroidism	0	1	0	0	1	0	0
	Thyroid cyst	0	0	0	1	1	0	0
	Thyroid disorder	0	0	0	2	2	0	0
Eye disorders	*** SOC TOTAL ***	15	46	18	118	164	0	0
	Abnormal sensation in eye	0	0	1	3	3	0	0
	Accommodation disorder	0	0	0	1	1	0	0
	Anisocoria	0	0	0	1	1	0	0
	Asthenopia	0	0	0	2	2	0	0
	Blepharitis	0	0	1	2	2	0	0
	Blepharospasm	1	1	0	3	4	0	0
	Blindness	1	3	0	0	3	0	0
	Blindness transient	0	2	0	0	2	0	0
	Blindness unilateral	0	1	0	0	1	0	0
	Central serous chorioretinopathy	0	1	0	0	1	0	0
	Chalazion	0	0	0	1	1	0	0
	Cogan's syndrome	0	1	0	0	1	0	0
	Corneal disorder	0	0	0	1	1	0	0
	Diplopia	0	2	0	1	3	0	0
	Dry eye	0	0	1	8	8	0	0
	Excessive eye blinking	0	0	0	1	1	0	0
	Eye colour change	0	0	0	1	1	0	0
	Eye disorder	0	0	0	2	2	0	0
	Eye inflammation	0	0	1	2	2	0	0
	Eye irritation	0	0	1	5	5	0	0
	Eye movement disorder	0	1	0	0	1	0	0
	Eye pain	1	1	0	9	10	0	0
	Eye pruritus	1	1	1	7	8	0	0
	Eye swelling	1	1	1	11	12	0	0
	Eyelid oedema	0	0	1	1	1	0	0
	Glaucoma	0	2	0	0	2	0	0
	Halo vision	0	0	0	1	1	0	0
	Hypoaesthesia eye	0	0	0	1	1	0	0
	Lacrimation increased	0	0	1	3	3	0	0
	Lagophthalmos	1	1	0	0	1	0	0
	Macular oedema	0	2	0	0	2	0	0
	Mydriasis	0	1	0	0	1	0	0
	Neurological eyelid disorder	0	0	0	1	1	0	0
	Ocular discomfort	1	2	0	4	6	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Ocular hyperaemia	1	1	3	10	11	0	0
	Ophthalmoplegia	0	1	0	0	1	0	0
	Periorbital oedema	0	0	0	1	1	0	0
	Periorbital swelling	1	1	1	5	6	0	0
	Photophobia	0	3	0	2	5	0	0
	Pupillary disorder	0	0	0	1	1	0	0
	Retinal degeneration	0	1	0	0	1	0	0
	Retinal detachment	0	1	0	0	1	0	0
	Retinal oedema	0	1	0	0	1	0	0
	Retinal tear	0	1	0	0	1	0	0
	Retinal vein occlusion	0	2	0	0	2	0	0
	Swelling of eyelid	0	0	2	4	4	0	0
	Vision blurred	2	4	2	15	19	0	0
	Visual field defect	0	1	0	0	1	0	0
	Visual impairment	3	4	1	8	12	0	0
	Vitreous detachment	0	1	0	0	1	0	0
	Vitreous floaters	1	1	0	0	1	0	0
Gastrointestinal disorders	*** SOC TOTAL ***	67	180	57	459	639	0	0
	Abdominal discomfort	2	3	1	17	20	0	0
	Abdominal distension	0	2	1	4	6	0	0
	Abdominal pain	5	10	1	27	37	0	0
	Abdominal pain lower	1	1	0	0	1	0	0
	Abdominal pain upper	2	7	3	26	33	0	0
	Anaesthesia oral	0	0	0	2	2	0	0
	Anal fissure	0	0	1	1	1	0	0
	Anorectal discomfort	0	0	1	1	1	0	0
	Bowel movement irregularity	0	0	0	1	1	0	0
	Cardiospasm	1	1	0	0	1	0	0
	Cheilitis	0	0	1	2	2	0	0
	Coeliac disease	0	2	0	0	2	0	0
	Colitis	0	1	0	0	1	0	0
	Colitis ulcerative	3	3	0	0	3	0	0
	Constipation	2	4	0	8	12	0	0
	Crohn's disease	1	2	0	0	2	0	0
	Diarrhoea	7	21	7	79	100	0	0
	Diarrhoea haemorrhagic	0	1	0	0	1	0	0
	Dry mouth	0	0	1	4	4	0	0
	Duodenogastric reflux	0	1	0	0	1	0	0
	Dyspepsia	3	6	2	10	16	0	0
	Dysphagia	1	3	1	6	9	0	0
	Enlarged uvula	0	0	0	1	1	0	0
	Eructation	0	0	1	2	2	0	0
	Faeces discoloured	1	1	0	1	2	0	0
	Flatulence	0	0	0	4	4	0	0
	Food poisoning	0	0	1	1	1	0	0
	Frequent bowel movements	3	4	1	2	6	0	0
	Gastric dilatation	0	1	0	0	1	0	0
	Gastric ulcer	1	1	0	0	1	0	0
	Gastrointestinal disorder	0	0	0	2	2	0	0
	Gastrointestinal haemorrhage	0	2	0	0	2	0	0
	Gastrointestinal pain	0	0	0	1	1	0	0
	Gastrooesophageal reflux disease	0	0	0	2	2	0	0
	Gingival bleeding	0	0	1	1	1	0	0
	Gingival discomfort	0	0	1	1	1	0	0
	Gingival pain	0	0	0	1	1	0	0
	Gingival swelling	0	0	1	1	1	0	0
	Haematochezia	2	3	0	1	4	0	0
	Haemorrhoids	0	0	0	2	2	0	0
	Hyperaesthesia teeth	0	0	0	1	1	0	0
	Hypoaesthesia oral	1	1	0	8	9	0	0
	Inflammatory bowel disease	1	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Infrequent bowel movements	0	0	0	1	1	0	0
	Irritable bowel syndrome	2	2	0	0	2	0	0
	Lip swelling	0	1	4	13	14	0	0
	Loose tooth	0	0	1	1	1	0	0
	Mouth swelling	0	0	1	1	1	0	0
	Mouth ulceration	0	1	0	1	2	0	0
	Nausea	13	46	22	141	187	0	0
	Noninfective gingivitis	0	1	0	0	1	0	0
	Odynophagia	1	2	0	1	3	0	0
	Oesophageal pain	0	1	0	0	1	0	0
	Oral discomfort	0	0	0	2	2	0	0
	Oral mucosal blistering	0	0	0	1	1	0	0
	Oral pain	2	2	0	3	5	0	0
	Pancreatitis	0	1	0	0	1	0	0
	Paraesthesia oral	0	1	0	8	9	0	0
	Rectal haemorrhage	0	1	0	0	1	0	0
	Retching	0	0	0	2	2	0	0
	Saliva discolouration	0	1	0	0	1	0	0
	Stomatitis	0	1	0	1	2	0	0
	Swollen tongue	1	2	1	4	6	0	0
	Teething	0	0	1	1	1	0	0
	Tongue discomfort	0	1	0	3	4	0	0
	Tongue disorder	0	2	0	0	2	0	0
	Tongue dry	0	0	0	1	1	0	0
	Tongue geographic	0	1	0	0	1	0	0
	Tooth loss	0	0	0	1	1	0	0
	Toothache	2	2	0	4	6	0	0
	Vomiting	9	29	1	48	77	0	0
	Vomiting projectile	0	0	0	1	1	0	0
General disorders and administration site conditions	*** SOC TOTAL ***	131	733	412	2560	3293	0	0
	Administration site joint erythema	1	1	0	0	1	0	0
	Administration site joint pain	1	1	0	0	1	0	0
	Administration site pain	1	1	0	0	1	0	0
	Administration site swelling	1	1	0	0	1	0	0
	Adverse drug reaction	1	1	0	1	2	0	0
	Adverse event	0	0	0	3	3	0	0
	Adverse reaction	0	0	0	2	2	0	0
	Asthenia	8	24	12	82	106	0	0
	Axillary pain	0	0	3	12	12	0	0
	Chest discomfort	9	61	6	53	114	0	0
	Chest pain	13	174	12	84	258	0	0
	Chills	6	55	30	164	219	0	0
	Condition aggravated	1	6	1	20	26	0	0
	Crying	0	0	1	2	2	0	0
	Cyst	0	0	0	1	1	0	0
	Death	0	6	0	0	6	0	0
	Decreased activity	0	0	0	1	1	0	0
	Developmental delay	0	0	0	1	1	0	0
	Discomfort	0	5	8	19	24	0	0
	Disease progression	0	2	0	0	2	0	0
	Disease recurrence	0	1	0	0	1	0	0
	Drug ineffective	0	0	2	4	4	0	0
	Drug interaction	1	3	0	0	3	0	0
	Effusion	0	1	0	0	1	0	0
	Exercise tolerance decreased	1	1	1	1	2	0	0
	Face oedema	0	0	1	1	1	0	0
	Facial discomfort	0	0	0	3	3	0	0
	Facial pain	0	1	1	6	7	0	0
	Fatigue	16	65	44	285	350	0	0
	Feeling abnormal	3	8	24	87	95	0	0
	Feeling cold	2	5	5	21	26	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Feeling drunk	0	0	0	3	3	0	0
	Feeling hot	1	5	8	63	68	0	0
	Feeling jittery	0	0	0	1	1	0	0
	Feeling of body temperature change	0	0	1	5	5	0	0
	Gait disturbance	2	9	7	37	46	0	0
	Gait inability	0	5	3	9	14	0	0
	General physical health deterioration	1	4	1	1	5	0	0
	General symptom	0	1	0	0	1	0	0
	Generalised oedema	0	0	1	1	1	0	0
	Granuloma	0	0	1	2	2	0	0
	Hunger	0	0	1	1	1	0	0
	Hyperthermia	0	2	0	0	2	0	0
	Illness	1	4	11	43	47	0	0
	Induration	0	0	0	5	5	0	0
	Inflammation	1	4	0	14	18	0	0
	Influenza like illness	0	7	13	39	46	0	0
	Infusion site erythema	2	2	0	0	2	0	0
	Infusion site haemorrhage	2	2	0	0	2	0	0
	Infusion site pruritus	2	2	0	0	2	0	0
	Infusion site warmth	2	2	0	0	2	0	0
	Injected limb mobility decreased	0	0	2	2	2	0	0
	Injection site bruising	0	0	0	1	1	0	0
	Injection site discharge	0	0	0	1	1	0	0
	Injection site discomfort	0	0	0	1	1	0	0
	Injection site erythema	1	8	1	22	30	0	0
	Injection site induration	0	2	0	4	6	0	0
	Injection site inflammation	0	2	0	3	5	0	0
	Injection site irritation	0	0	0	1	1	0	0
	Injection site joint swelling	0	0	0	1	1	0	0
	Injection site mass	0	1	0	3	4	0	0
	Injection site pain	0	2	0	22	24	0	0
	Injection site paraesthesia	0	0	0	1	1	0	0
	Injection site pruritus	0	2	0	10	12	0	0
	Injection site rash	0	3	0	7	10	0	0
	Injection site reaction	2	3	1	3	6	0	0
	Injection site swelling	1	6	0	12	18	0	0
	Injection site urticaria	0	0	0	1	1	0	0
	Injection site warmth	0	4	0	12	16	0	0
	Injury associated with device	0	0	1	1	1	0	0
	Localised oedema	0	1	0	0	1	0	0
	Malaise	8	28	11	73	101	0	0
	Mass	0	0	0	7	7	0	0
	Moaning	1	1	0	0	1	0	0
	No adverse event	0	0	0	1	1	0	0
	Nodule	1	1	2	3	4	0	0
	Non-cardiac chest pain	0	0	0	1	1	0	0
	Oedema	0	2	0	1	3	0	0
	Oedema peripheral	4	5	1	2	7	0	0
	Pain	9	41	37	142	183	0	0
	Peripheral swelling	9	19	15	56	75	0	0
	Pre-existing condition improved	0	0	0	1	1	0	0
	Pyrexia	7	79	42	238	317	0	0
	Screaming	0	0	1	1	1	0	0
	Secretion discharge	0	1	0	0	1	0	0
	Sensation of blood flow	0	1	0	1	2	0	0
	Sensation of foreign body	0	0	1	1	1	0	0
	Shoulder injury related to vaccine administration	1	2	0	0	2	0	0
	Sluggishness	0	0	0	3	3	0	0
	Sudden death	1	1	0	0	1	0	0
	Swelling	1	9	11	49	58	0	0
	Swelling face	0	3	5	19	22	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Systemic inflammatory response syndrome	0	1	0	0	1	0	0
	Temperature intolerance	1	1	0	1	2	0	0
	Tenderness	2	3	1	7	10	0	0
	Therapeutic product effect decreased	0	0	1	1	1	0	0
	Therapeutic response shortened	0	0	1	1	1	0	0
	Therapeutic response unexpected	0	0	2	8	8	0	0
	Thirst	0	0	2	5	5	0	0
	Unevaluable event	0	3	1	2	5	0	0
	Vaccination failure	1	1	0	0	1	0	0
	Vaccination site anaesthesia	0	0	1	1	1	0	0
	Vaccination site bruising	0	0	0	8	8	0	0
	Vaccination site discolouration	0	0	0	6	6	0	0
	Vaccination site discomfort	0	0	3	8	8	0	0
	Vaccination site dysaesthesia	0	0	0	1	1	0	0
	Vaccination site erythema	0	1	9	122	123	0	0
	Vaccination site haematoma	0	1	0	0	1	0	0
	Vaccination site haemorrhage	0	0	0	5	5	0	0
	Vaccination site hypersensitivity	0	0	0	1	1	0	0
	Vaccination site hypoaesthesia	0	0	0	4	4	0	0
	Vaccination site induration	0	0	0	11	11	0	0
	Vaccination site inflammation	0	0	3	8	8	0	0
	Vaccination site joint pain	0	1	0	0	1	0	0
	Vaccination site joint warmth	0	1	0	0	1	0	0
	Vaccination site lymphadenopathy	0	0	3	10	10	0	0
	Vaccination site mass	0	0	3	12	12	0	0
	Vaccination site movement impairment	0	1	2	11	12	0	0
	Vaccination site nodule	0	0	0	2	2	0	0
	Vaccination site oedema	0	0	1	1	1	0	0
	Vaccination site pain	1	13	27	214	227	0	0
	Vaccination site paraesthesia	0	1	0	3	4	0	0
	Vaccination site plaque	0	0	0	2	2	0	0
	Vaccination site pruritus	0	0	3	73	73	0	0
	Vaccination site rash	0	2	2	52	54	0	0
	Vaccination site reaction	0	0	5	43	43	0	0
	Vaccination site scab	0	0	0	1	1	0	0
	Vaccination site swelling	1	3	10	94	97	0	0
	Vaccination site urticaria	0	0	0	6	6	0	0
	Vaccination site vesicles	0	0	0	4	4	0	0
	Vaccination site warmth	0	1	3	48	49	0	0
Hepatobiliary disorders	*** SOC TOTAL ***	1	5	2	6	11	0	0
	Cholelithiasis	0	0	0	1	1	0	0
	Gallbladder rupture	0	2	0	0	2	0	0
	Hepatic lesion	0	0	0	1	1	0	0
	Hepatic pain	0	0	1	1	1	0	0
	Hepatitis	0	1	0	1	2	0	0
	Hepatomegaly	0	0	1	1	1	0	0
	Liver disorder	1	1	0	1	2	0	0
	Liver injury	0	1	0	0	1	0	0
Immune system disorders	*** SOC TOTAL ***	14	34	31	125	159	0	0
	Allergy to arthropod sting	0	0	0	1	1	0	0
	Allergy to vaccine	0	0	0	5	5	0	0
	Anaphylactic reaction	5	13	0	0	13	0	0
	Anaphylactic shock	0	1	0	0	1	0	0
	Autoimmune disorder	1	1	0	0	1	0	0
	Decreased immune responsiveness	1	1	0	1	2	0	0
	Drug hypersensitivity	0	1	0	0	1	0	0
	Dust allergy	0	0	0	1	1	0	0
	Food allergy	0	0	0	3	3	0	0
	Haemophagocytic lymphohistiocytosis	0	1	0	0	1	0	0
	Hypersensitivity	3	7	3	29	36	0	0
	Immune system disorder	0	1	0	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Immunisation reaction	2	5	28	78	83	0	0
	Immunosuppression	0	1	0	0	1	0	0
	Multisystem inflammatory syndrome in adults	1	1	0	0	1	0	0
	Reaction to excipient	0	0	0	1	1	0	0
	Seasonal allergy	0	0	0	1	1	0	0
	Sensitisation	0	0	0	1	1	0	0
	Transplant rejection	1	1	0	0	1	0	0
	Type IV hypersensitivity reaction	0	0	0	3	3	0	0
Infections and infestations	*** SOC TOTAL ***	25	88	36	109	197	0	0
	Appendicitis	0	1	0	0	1	0	0
	Bed bug infestation	1	1	0	0	1	0	0
	Bronchitis	0	1	0	1	2	0	0
	COVID-19	6	6	14	26	32	0	0
	Cellulitis	0	17	0	1	18	0	0
	Chlamydial infection	0	0	1	1	1	0	0
	Cystitis	3	3	1	2	5	0	0
	Encephalitis	0	1	0	0	1	0	0
	Encephalitis brain stem	1	1	0	0	1	0	0
	Epstein-Barr viraemia	0	1	0	0	1	0	0
	Escherichia urinary tract infection	0	1	0	0	1	0	0
	Eye infection	0	0	0	1	1	0	0
	Furuncle	0	0	0	1	1	0	0
	Gingivitis	0	0	1	1	1	0	0
	Herpes virus infection	0	0	1	1	1	0	0
	Herpes zoster	4	11	3	19	30	0	0
	Herpes zoster oticus	0	1	0	0	1	0	0
	Impetigo	0	0	0	1	1	0	0
	Infection	0	2	0	5	7	0	0
	Infectious mononucleosis	0	1	0	0	1	0	0
	Influenza	0	1	3	9	10	0	0
	Injection site cellulitis	1	3	0	0	3	0	0
	Labyrinthitis	0	0	0	2	2	0	0
	Latent tuberculosis	0	0	1	1	1	0	0
	Lip infection	0	0	0	1	1	0	0
	Liver abscess	0	1	0	0	1	0	0
	Lyme disease	0	3	0	0	3	0	0
	Mastitis	0	1	0	0	1	0	0
	Nasopharyngitis	1	2	7	16	18	0	0
	Oral herpes	0	0	1	1	1	0	0
	Otitis externa	0	0	0	1	1	0	0
	Pharyngitis	0	0	1	1	1	0	0
	Pneumonia	2	11	0	0	11	0	0
	Pneumonia aspiration	0	1	0	0	1	0	0
	Pneumonia bacterial	0	1	0	0	1	0	0
	Post viral fatigue syndrome	1	1	0	0	1	0	0
	Post-acute COVID-19 syndrome	0	0	0	1	1	0	0
	Postoperative wound infection	0	0	0	1	1	0	0
	Purulent discharge	0	0	0	1	1	0	0
	Rhinitis	0	1	0	0	1	0	0
	Sepsis	0	2	0	0	2	0	0
	Sinusitis	0	0	0	2	2	0	0
	Skin infection	1	1	0	0	1	0	0
	Streptococcal infection	0	1	0	0	1	0	0
	Suspected COVID-19	0	0	1	3	3	0	0
	Tonsillitis	2	2	0	0	2	0	0
	Tooth abscess	0	0	0	1	1	0	0
	Tooth infection	0	0	0	1	1	0	0
	Upper respiratory tract infection	1	1	0	0	1	0	0
	Urinary tract infection	1	3	1	2	5	0	0
	Vaccination site abscess	0	0	0	1	1	0	0
	Vaccination site cellulitis	0	2	0	3	5	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Vaginal infection	0	0	0	1	1	0	0
	Vulvovaginal mycotic infection	0	1	0	0	1	0	0
	Wound infection	0	1	0	0	1	0	0
Injury, poisoning and procedural complications	*** SOC TOTAL ***	30	63	1092	2234	2297	0	0
	Accidental overdose	0	0	25	46	46	0	0
	Accidental underdose	0	0	7	21	21	0	0
	Bone fragmentation	0	0	0	1	1	0	0
	Chest injury	1	1	0	0	1	0	0
	Circumstance or information capable of leading to device use error	0	0	1	1	1	0	0
	Circumstance or information capable of leading to medication error	0	0	3	3	3	0	0
	Concussion	0	0	0	1	1	0	0
	Contusion	3	5	0	10	15	0	0
	Corneal laceration	0	0	0	1	1	0	0
	Counterfeit product administered	0	0	1	1	1	0	0
	Dermal filler reaction	0	0	1	1	1	0	0
	Drug dose omission by device	0	1	0	0	1	0	0
	Expired product administered	0	0	478	772	772	0	0
	Exposure during pregnancy	1	1	0	32	33	0	0
	Exposure to SARS-CoV-2	0	0	0	1	1	0	0
	Exposure via breast milk	0	0	0	10	10	0	0
	Extra dose administered	0	1	66	68	69	0	0
	Fall	3	4	2	13	17	0	0
	Foetal exposure during pregnancy	1	1	0	0	1	0	0
	Foot fracture	1	3	0	0	3	0	0
	Head injury	0	0	0	1	1	0	0
	Heat illness	0	0	0	1	1	0	0
	Inadequate aseptic technique in use of product	0	0	0	4	4	0	0
	Inappropriate schedule of product administration	0	1	248	551	552	0	0
	Inappropriate schedule of product discontinuation	0	0	0	1	1	0	0
	Incision site erythema	0	1	0	0	1	0	0
	Incision site rash	0	1	0	0	1	0	0
	Incomplete course of vaccination	0	0	0	2	2	0	0
	Incorrect dose administered	0	0	4	17	17	0	0
	Incorrect product formulation administered	0	0	1	6	6	0	0
	Incorrect route of product administration	0	0	3	9	9	0	0
	Injury	0	1	0	1	2	0	0
	Intentional dose omission	0	0	0	7	7	0	0
	Intentional product use issue	2	2	0	3	5	0	0
	Intercepted product administration error	0	0	1	1	1	0	0
	Joint dislocation	0	0	1	1	1	0	0
	Ligament sprain	0	0	0	2	2	0	0
	Limb injury	2	3	1	2	5	0	0
	Maternal exposure before pregnancy	0	0	1	4	4	0	0
	Maternal exposure during breast feeding	0	0	2	6	6	0	0
	Maternal exposure during pregnancy	1	3	13	65	68	0	0
	Muscle injury	2	3	0	0	3	0	0
	Muscle strain	1	3	0	2	5	0	0
	Occupational exposure to product	0	0	0	1	1	0	0
	Off label use	5	9	2	46	55	0	0
	Overdose	0	0	2	4	4	0	0
	Periorbital haemorrhage	0	0	0	1	1	0	0
	Poor quality product administered	0	0	3	18	18	0	0
	Postoperative wound complication	0	1	0	0	1	0	0
	Product administered at inappropriate site	0	0	1	3	3	0	0
	Product administered to patient of inappropriate age	0	0	8	83	83	0	0
	Product administration error	0	0	1	12	12	0	0
	Product administration interrupted	0	0	0	6	6	0	0
	Product dose omission issue	0	2	3	86	88	0	0
	Product preparation error	0	0	0	1	1	0	0
	Product preparation issue	0	0	0	4	4	0	0
	Product storage error	0	0	205	261	261	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Product use issue	1	3	1	1	4	0	0
	Rib fracture	1	1	0	1	2	0	0
	Scar	0	0	0	1	1	0	0
	Scratch	0	0	1	2	2	0	0
	Skin injury	0	1	0	0	1	0	0
	Sunburn	0	0	1	3	3	0	0
	Thermal burn	0	0	0	1	1	0	0
	Tooth fracture	0	0	0	1	1	0	0
	Underdose	0	1	2	19	20	0	0
	Vaccination complication	2	3	1	4	7	0	0
	Vaccination error	0	0	0	1	1	0	0
	Vasoplegia syndrome	1	1	0	0	1	0	0
	Wound	2	2	0	1	3	0	0
	Wound complication	0	1	0	0	1	0	0
	Wrong product administered	0	2	1	3	5	0	0
	Wrong technique in product usage process	0	1	1	2	3	0	0
Investigations	*** SOC TOTAL ***	27	55	14	60	115	0	0
	Antipsychotic drug level increased	1	1	0	0	1	0	0
	Blast cells present	0	1	0	0	1	0	0
	Blood cholesterol increased	0	0	0	1	1	0	0
	Blood creatine phosphokinase increased	1	1	0	0	1	0	0
	Blood creatinine increased	1	1	0	0	1	0	0
	Blood glucose decreased	2	2	0	1	3	0	0
	Blood glucose increased	2	3	0	1	4	0	0
	Blood insulin decreased	2	2	0	0	2	0	0
	Blood insulin increased	2	2	0	0	2	0	0
	Blood pressure abnormal	0	0	0	1	1	0	0
	Blood pressure decreased	1	2	0	0	2	0	0
	Blood pressure increased	0	2	1	4	6	0	0
	Body temperature fluctuation	0	0	1	1	1	0	0
	Breath sounds abnormal	1	1	0	0	1	0	0
	Faecal volume increased	0	0	0	1	1	0	0
	Fibrin D dimer increased	2	4	0	0	4	0	0
	Foetal heart rate decreased	1	1	0	0	1	0	0
	Glomerular filtration rate decreased	0	0	1	1	1	0	0
	Grip strength decreased	1	1	0	0	1	0	0
	Haemoglobin decreased	0	1	0	0	1	0	0
	Heart rate decreased	1	2	0	1	3	0	0
	Heart rate increased	1	4	3	18	22	0	0
	Heart rate irregular	2	2	1	4	6	0	0
	International normalised ratio increased	0	0	0	1	1	0	0
	Lymphocyte count abnormal	0	0	0	1	1	0	0
	Muscle strength abnormal	1	1	0	0	1	0	0
	Oxygen consumption decreased	0	0	0	1	1	0	0
	Platelet count decreased	2	6	1	2	8	0	0
	Pulse abnormal	0	0	1	1	1	0	0
	Quality of life decreased	0	0	0	1	1	0	0
	Respiratory rate decreased	0	0	0	1	1	0	0
	Respiratory rate increased	0	0	0	2	2	0	0
	SARS-CoV-2 test positive	0	0	1	2	2	0	0
	Thyroid hormones increased	0	0	1	1	1	0	0
	Troponin increased	1	5	0	0	5	0	0
	Vitamin B12 decreased	0	1	0	0	1	0	0
	Weight decreased	1	6	3	11	17	0	0
	Weight increased	1	2	0	2	4	0	0
	White blood cell count decreased	0	1	0	0	1	0	0
Metabolism and nutrition disorders	*** SOC TOTAL ***	7	32	10	46	78	0	0
	Abnormal loss of weight	0	0	0	1	1	0	0
	Alcohol intolerance	0	0	0	1	1	0	0
	Dawn phenomenon	0	0	0	1	1	0	0
	Decreased appetite	3	9	7	30	39	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Dehydration	2	4	1	3	7	0	0
	Diabetes mellitus	0	2	0	0	2	0	0
	Diabetes mellitus inadequate control	0	1	0	0	1	0	0
	Diabetic ketoacidosis	1	1	0	0	1	0	0
	Feeding disorder	1	3	2	4	7	0	0
	Gout	0	2	0	3	5	0	0
	Hyperglycaemia	0	1	0	1	2	0	0
	Hypophagia	0	3	0	0	3	0	0
	Hypovolaemia	0	2	0	0	2	0	0
	Ketoacidosis	0	2	0	0	2	0	0
	Latent autoimmune diabetes in adults	0	0	0	1	1	0	0
	Metabolic disorder	0	1	0	0	1	0	0
	Type 1 diabetes mellitus	0	1	0	0	1	0	0
	Vitamin B12 deficiency	0	0	0	1	1	0	0
Musculoskeletal and connective tissue disorders	*** SOC TOTAL ***	59	195	163	900	1095	0	0
	Ankylosing spondylitis	0	0	1	1	1	0	0
	Arthralgia	5	28	19	101	129	0	0
	Arthritis	0	0	3	16	16	0	0
	Axillary mass	0	0	1	1	1	0	0
	Back pain	3	8	8	36	44	0	0
	Bone pain	0	0	2	14	14	0	0
	Bone swelling	0	0	1	3	3	0	0
	Bursitis	1	2	0	0	2	0	0
	Costochondritis	1	1	0	1	2	0	0
	Fibromyalgia	0	1	0	0	1	0	0
	Flank pain	0	1	0	2	3	0	0
	Groin pain	0	0	1	2	2	0	0
	Joint range of motion decreased	0	0	0	1	1	0	0
	Joint stiffness	0	0	0	4	4	0	0
	Joint swelling	1	1	2	12	13	0	0
	Joint warmth	0	0	0	2	2	0	0
	Limb discomfort	0	3	3	29	32	0	0
	Mastication disorder	0	0	1	2	2	0	0
	Mobility decreased	0	6	9	29	35	0	0
	Muscle contracture	0	0	1	1	1	0	0
	Muscle disorder	0	0	0	1	1	0	0
	Muscle fatigue	0	0	0	2	2	0	0
	Muscle necrosis	1	1	0	0	1	0	0
	Muscle rigidity	0	0	0	1	1	0	0
	Muscle spasms	6	12	1	24	36	0	0
	Muscle tightness	1	2	0	8	10	0	0
	Muscle twitching	0	2	2	10	12	0	0
	Muscular weakness	3	7	3	15	22	0	0
	Musculoskeletal chest pain	0	2	0	4	6	0	0
	Musculoskeletal discomfort	1	1	1	6	7	0	0
	Musculoskeletal disorder	0	1	0	1	2	0	0
	Musculoskeletal pain	0	1	1	4	5	0	0
	Musculoskeletal stiffness	1	3	7	31	34	0	0
	Myalgia	10	45	36	239	284	0	0
	Myopathy	0	1	0	0	1	0	0
	Myositis	0	2	0	1	3	0	0
	Neck mass	1	1	2	2	3	0	0
	Neck pain	3	9	2	22	31	0	0
	Osteitis	0	0	0	1	1	0	0
	Pain in extremity	14	34	55	257	291	0	0
	Pain in jaw	2	5	0	5	10	0	0
	Polyarthritis	0	1	0	0	1	0	0
	Polymyositis	0	1	0	0	1	0	0
	Psoriatic arthropathy	1	1	0	0	1	0	0
	Rhabdomyolysis	1	2	0	0	2	0	0
	Rheumatoid arthritis	0	4	0	0	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Rotator cuff syndrome	2	2	0	0	2	0	0
	Sacroiliitis	0	0	1	1	1	0	0
	Spinal pain	1	1	0	2	3	0	0
	Spinal stenosis	0	1	0	0	1	0	0
	Spinal synovial cyst	0	0	0	1	1	0	0
	Still's disease	0	1	0	0	1	0	0
	Synovial cyst	0	0	0	1	1	0	0
	Systemic lupus erythematosus	0	1	0	0	1	0	0
	Tendon disorder	0	0	0	1	1	0	0
	Tendonitis	0	0	0	2	2	0	0
	Tenosynovitis	0	0	0	1	1	0	0
plasms benign, malignant and unspecified (incl cysts and pol	*** SOC TOTAL ***	5	9	1	1	10	0	0
	Breast cancer	0	1	0	0	1	0	0
	Colon cancer	0	1	0	0	1	0	0
	Diffuse large B-cell lymphoma	1	1	0	0	1	0	0
	Glioblastoma	1	1	0	0	1	0	0
	Haematological malignancy	0	1	0	0	1	0	0
	Neoplasm malignant	0	1	0	0	1	0	0
	Neoplasm skin	0	0	1	1	1	0	0
	Plasma cell myeloma	2	2	0	0	2	0	0
	Skin papilloma	1	1	0	0	1	0	0
Nervous system disorders	*** SOC TOTAL ***	104	361	154	866	1227	0	0
	Accessory nerve disorder	0	0	0	1	1	0	0
	Ageusia	0	0	0	7	7	0	0
	Altered state of consciousness	0	2	0	1	3	0	0
	Amnesia	0	0	1	2	2	0	0
	Anosmia	0	0	0	2	2	0	0
	Aphasia	1	2	1	3	5	0	0
	Aura	0	0	0	1	1	0	0
	Autonomic nervous system imbalance	0	1	0	0	1	0	0
	Balance disorder	2	6	3	16	22	0	0
	Bell's palsy	4	12	0	2	14	0	0
	Bradykinesia	0	0	0	1	1	0	0
	Brain injury	0	1	0	0	1	0	0
	Burning sensation	3	10	5	31	41	0	0
	Carpal tunnel syndrome	0	1	0	0	1	0	0
	Cerebellar stroke	1	1	0	0	1	0	0
	Cerebral disorder	0	0	0	1	1	0	0
	Cerebral infarction	0	1	0	0	1	0	0
	Cerebral mass effect	0	1	0	0	1	0	0
	Cerebral microembolism	0	1	0	0	1	0	0
	Cerebral thrombosis	0	2	0	0	2	0	0
	Cerebral venous thrombosis	0	1	0	0	1	0	0
	Cerebrovascular accident	4	11	0	0	11	0	0
	Cognitive disorder	0	1	0	1	2	0	0
	Cold-stimulus headache	0	0	1	1	1	0	0
	Coma	0	1	0	0	1	0	0
	Complex regional pain syndrome	0	0	1	1	1	0	0
	Coordination abnormal	0	0	0	1	1	0	0
	Cranial nerve disorder	1	1	0	0	1	0	0
	Depressed level of consciousness	1	3	0	1	4	0	0
	Disturbance in attention	1	2	1	7	9	0	0
	Dizziness	11	33	13	121	154	0	0
	Dizziness postural	0	1	1	2	3	0	0
	Dysaesthesia	0	0	1	1	1	0	0
	Dysarthria	1	4	1	4	8	0	0
	Dysgeusia	1	2	1	14	16	0	0
	Dysgraphia	0	0	1	1	1	0	0
	Dyskinesia	0	1	0	3	4	0	0
	Dyslexia	0	1	0	0	1	0	0
	Dyspraxia	0	0	1	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Dysstasia	0	0	S	9	9	0	0
	Electric shock sensation	0	0	2	10	10	0	0
	Embolic stroke	1	1	0	0	1	0	0
	Facial paralysis	3	6	0	2	8	0	0
	Febrile convulsion	0	0	0	1	1	0	0
	Generalised tonic-clonic seizure	0	2	0	0	2	0	0
	Guillain-Barre syndrome	1	S	0	0	S	0	0
	Haemorrhagic transformation stroke	0	2	0	0	2	0	0
	Head discomfort	1	1	2	12	13	0	0
	Headache	14	55	49	248	303	0	0
	Hemiparaesthesia	0	1	0	0	1	0	0
	Hemiparesis	0	3	0	0	3	0	0
	Hemiplegia	0	2	0	0	2	0	0
	Hyperaesthesia	0	0	0	1	1	0	0
	Hypersomnia	1	1	2	S	6	0	0
	Hypoaesthesia	8	20	13	73	93	0	0
	Hypogeusia	1	1	0	0	1	0	0
	Hypokinesia	2	3	1	3	6	0	0
	Hyporeflexia	0	2	0	0	2	0	0
	Hyposmia	1	1	0	0	1	0	0
	Hypotonic-hyporesponsive episode	0	0	0	1	1	0	0
	Intellectual disability	0	1	0	0	1	0	0
	Intensive care unit acquired weakness	1	1	0	0	1	0	0
	Intraventricular haemorrhage	0	2	0	0	2	0	0
	Ischaemic stroke	0	1	0	0	1	0	0
	Lethargy	4	9	2	9	18	0	0
	Loss of consciousness	4	23	2	2	25	0	0
	Memory impairment	2	3	3	7	10	0	0
	Mental impairment	1	1	0	1	2	0	0
	Migraine	1	6	4	30	36	0	0
	Miller Fisher syndrome	0	1	0	0	1	0	0
	Motor dysfunction	0	1	0	0	1	0	0
	Movement disorder	2	3	0	3	6	0	0
	Multiple sclerosis	1	3	0	0	3	0	0
	Multiple sclerosis relapse	2	2	1	1	3	0	0
	Muscle contractions involuntary	0	0	1	S	S	0	0
	Myelitis transverse	0	1	0	0	1	0	0
	Myoclonic epilepsy	0	1	0	0	1	0	0
	Myoclonus	0	0	0	3	3	0	0
	Nervous system disorder	0	1	1	1	2	0	0
	Neuralgia	1	3	2	9	12	0	0
	Neuralgic amyotrophy	1	3	0	0	3	0	0
	Neurologic neglect syndrome	0	2	0	0	2	0	0
	Neurological symptom	0	0	0	3	3	0	0
	Neuropathy peripheral	1	4	0	0	4	0	0
	Noninfective encephalitis	0	1	0	0	1	0	0
	Paraesthesia	S	20	12	76	96	0	0
	Paralysis	1	4	2	3	7	0	0
	Parosmia	0	0	1	1	1	0	0
	Periodic limb movement disorder	0	0	1	1	1	0	0
	Petit mal epilepsy	0	1	0	0	1	0	0
	Polyneuropathy	1	1	0	0	1	0	0
	Presyncope	2	S	0	7	12	0	0
	Radiculopathy	0	0	0	1	1	0	0
	Restless legs syndrome	0	0	2	2	2	0	0
	Retinal migraine	0	0	0	1	1	0	0
	Sciatica	2	2	0	1	3	0	0
	Seizure	1	13	0	0	13	0	0
	Sensory disturbance	0	1	1	2	3	0	0
	Sensory loss	0	1	0	3	4	0	0
	Sleep deficit	0	0	0	2	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Somnolence	1	5	4	32	37	0	0
	Speech disorder	0	0	0	4	4	0	0
	Stupor	1	1	0	0	1	0	0
	Subarachnoid haemorrhage	0	2	0	0	2	0	0
	Syncope	0	5	1	2	7	0	0
	Taste disorder	1	1	0	14	15	0	0
	Tension headache	0	1	0	4	5	0	0
	Tongue paralysis	0	2	0	1	3	0	0
	Transient ischaemic attack	0	1	0	0	1	0	0
	Tremor	3	9	8	39	48	0	0
	Trigeminal neuralgia	0	0	0	2	2	0	0
	Unresponsive to stimuli	1	3	0	0	3	0	0
	Upper motor neurone lesion	0	1	0	0	1	0	0
	Vascular headache	0	0	0	1	1	0	0
	Vestibular migraine	0	0	0	1	1	0	0
Pregnancy, puerperium and perinatal conditions	*** SOC TOTAL ***	6	15	0	6	21	0	0
	Abortion spontaneous	0	1	0	0	1	0	0
	Foetal death	0	3	0	0	3	0	0
	Gestational diabetes	1	2	0	0	2	0	0
	Haemorrhage in pregnancy	0	1	0	1	2	0	0
	Morning sickness	0	0	0	2	2	0	0
	Neonatal disorder	0	0	0	1	1	0	0
	Placenta praevia	1	2	0	0	2	0	0
	Placental disorder	1	1	0	0	1	0	0
	Pregnancy	0	0	0	1	1	0	0
	Premature delivery	1	2	0	0	2	0	0
	Prolonged labour	1	1	0	0	1	0	0
	Stillbirth	1	2	0	0	2	0	0
	Umbilical cord around neck	0	0	0	1	1	0	0
Product issues	*** SOC TOTAL ***	0	2	8	42	44	0	0
	Device connection issue	0	0	0	9	9	0	0
	Drug delivery system malfunction	0	1	0	0	1	0	0
	Needle issue	0	0	0	3	3	0	0
	Product availability issue	0	0	0	7	7	0	0
	Product colour issue	0	0	0	1	1	0	0
	Product contamination	0	0	0	1	1	0	0
	Product lot number issue	0	0	1	1	1	0	0
	Product quality issue	0	1	0	1	2	0	0
	Product supply issue	0	0	0	1	1	0	0
	Product temperature excursion issue	0	0	6	15	15	0	0
	Suspected counterfeit product	0	0	1	1	1	0	0
	Syringe issue	0	0	0	2	2	0	0
Psychiatric disorders	*** SOC TOTAL ***	25	55	38	163	218	0	0
	Abnormal dreams	0	0	0	2	2	0	0
	Agitation	1	1	0	2	3	0	0
	Anger	0	1	0	1	2	0	0
	Anticipatory anxiety	1	1	0	0	1	0	0
	Antisocial behaviour	0	1	0	0	1	0	0
	Anxiety	7	9	3	21	30	0	0
	Confusional state	0	2	0	10	12	0	0
	Conversion disorder	0	0	0	1	1	0	0
	Delirium	0	2	0	0	2	0	0
	Depressed mood	0	1	0	2	3	0	0
	Depression	0	1	1	5	6	0	0
	Derealisation	0	0	0	1	1	0	0
	Disorientation	0	2	2	7	9	0	0
	Dissociation	1	1	1	1	2	0	0
	Drug abuse	0	1	0	0	1	0	0
	Eating disorder	0	0	0	2	2	0	0
	Emotional disorder	0	0	1	1	1	0	0
	Emotional distress	0	0	3	3	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Enuresis	0	0	1	1	1	0	0
	Euphoric mood	0	0	0	1	1	0	0
	Fear	0	1	1	2	3	0	0
	Fear of death	1	1	0	0	1	0	0
	Fear of falling	0	0	0	1	1	0	0
	Generalised anxiety disorder	0	1	0	0	1	0	0
	Insomnia	5	7	11	46	53	0	0
	Irritability	0	0	0	4	4	0	0
	Listless	1	1	0	0	1	0	0
	Loss of libido	0	0	1	1	1	0	0
	Major depression	0	1	0	0	1	0	0
	Mental disorder	0	2	1	5	7	0	0
	Mental fatigue	0	0	0	1	1	0	0
	Mood altered	0	0	2	3	3	0	0
	Near death experience	0	1	1	1	2	0	0
	Nervousness	0	1	0	2	3	0	0
	Nightmare	1	1	0	1	2	0	0
	Panic attack	2	5	2	5	10	0	0
	Paranoia	0	0	0	2	2	0	0
	Post-traumatic stress disorder	2	2	0	0	2	0	0
	Psychomotor retardation	1	2	0	0	2	0	0
	Psychotic disorder	0	0	0	1	1	0	0
	Restlessness	0	0	1	3	3	0	0
	Sleep disorder	0	0	3	12	12	0	0
	Sleep disorder due to general medical condition, insomnia type	0	0	0	1	1	0	0
	Social avoidant behaviour	0	0	0	1	1	0	0
	Stress	1	1	3	8	9	0	0
	Suicidal behaviour	0	1	0	0	1	0	0
	Suicidal ideation	1	4	0	0	4	0	0
	Thinking abnormal	0	0	0	2	2	0	0
Renal and urinary disorders	*** SOC TOTAL ***	5	17	7	14	31	0	0
	Acute kidney injury	0	4	0	0	4	0	0
	Bladder pain	2	2	0	0	2	0	0
	Bladder stenosis	0	1	0	0	1	0	0
	Chromaturia	0	0	2	4	4	0	0
	Dysuria	0	0	3	5	5	0	0
	Haematuria	0	0	1	1	1	0	0
	Micturition urgency	0	0	0	1	1	0	0
	Nephrolithiasis	1	1	0	0	1	0	0
	Oliguria	0	1	0	0	1	0	0
	Pollakiuria	0	1	0	2	3	0	0
	Proteinuria	0	1	0	0	1	0	0
	Renal failure	0	1	0	0	1	0	0
	Renal impairment	0	1	0	0	1	0	0
	Renal pain	1	1	0	0	1	0	0
	Urinary incontinence	0	0	1	1	1	0	0
	Urinary retention	1	3	0	0	3	0	0
Reproductive system and breast disorders	*** SOC TOTAL ***	13	26	32	111	137	0	0
	Abnormal uterine bleeding	1	1	0	0	1	0	0
	Amenorrhoea	0	1	1	5	6	0	0
	Breast discomfort	0	0	0	1	1	0	0
	Breast mass	0	0	0	1	1	0	0
	Breast pain	0	1	4	8	9	0	0
	Breast swelling	0	0	2	2	2	0	0
	Dysmenorrhoea	0	1	2	10	11	0	0
	Endometriosis	2	2	0	0	2	0	0
	Genital discomfort	0	0	0	1	1	0	0
	Genital pain	0	0	1	1	1	0	0
	Genital rash	0	0	1	1	1	0	0
	Heavy menstrual bleeding	1	3	3	19	22	0	0
	Hypomenorrhoea	0	0	1	2	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Infertility	0	0	1	1	1	0	0
	Intermenstrual bleeding	1	1	1	6	7	0	0
	Menstrual disorder	2	2	2	9	11	0	0
	Menstruation delayed	1	2	2	10	12	0	0
	Menstruation irregular	1	1	0	11	12	0	0
	Nipple pain	0	1	0	0	1	0	0
	Oligomenorrhoea	0	0	2	3	3	0	0
	Pelvic pain	0	1	1	1	2	0	0
	Penile pain	0	0	0	1	1	0	0
	Polymenorrhoea	0	0	1	6	6	0	0
	Postmenopausal haemorrhage	1	3	3	3	6	0	0
	Premenstrual pain	1	1	0	0	1	0	0
	Premenstrual syndrome	0	0	1	1	1	0	0
	Sexual dysfunction	0	0	0	1	1	0	0
	Suppressed lactation	0	0	1	2	2	0	0
	Testicular pain	1	1	0	0	1	0	0
	Vaginal haemorrhage	1	3	0	2	5	0	0
	Vulvovaginal burning sensation	0	0	1	1	1	0	0
	Vulvovaginal pruritus	0	1	0	1	2	0	0
	Vulvovaginal swelling	0	0	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders	*** SOC TOTAL ***	48	201	51	289	490	0	0
	Acute respiratory distress syndrome	0	1	0	0	1	0	0
	Aphonia	0	0	0	1	1	0	0
	Apnoea	1	2	0	0	2	0	0
	Asthma	1	3	0	3	6	0	0
	Atelectasis	0	3	0	0	3	0	0
	Bronchospasm	0	0	0	3	3	0	0
	Cheyne-Stokes respiration	1	1	0	0	1	0	0
	Choking	0	1	0	0	1	0	0
	Choking sensation	0	1	0	0	1	0	0
	Cough	0	15	9	37	52	0	0
	Dry throat	0	0	1	4	4	0	0
	Dysphonia	0	1	0	6	7	0	0
	Dyspnoea	13	88	19	106	194	0	0
	Dyspnoea at rest	0	1	0	0	1	0	0
	Dyspnoea exertional	0	2	0	1	3	0	0
	Epistaxis	0	1	2	7	8	0	0
	Haemoptysis	0	1	2	3	4	0	0
	Hyperventilation	0	2	0	0	2	0	0
	Increased upper airway secretion	0	1	0	0	1	0	0
	Interstitial lung disease	1	1	0	0	1	0	0
	Irregular breathing	0	0	0	1	1	0	0
	Lung disorder	0	2	0	1	3	0	0
	Nasal congestion	0	0	2	6	6	0	0
	Nasal discomfort	0	0	0	1	1	0	0
	Nasal dryness	0	0	0	1	1	0	0
	Nasal oedema	0	0	0	1	1	0	0
	Nasal septum deviation	0	0	0	1	1	0	0
	Obstructive airways disorder	1	1	0	1	2	0	0
	Oropharyngeal discomfort	2	3	1	5	8	0	0
	Oropharyngeal pain	2	6	5	37	43	0	0
	Orthopnoea	0	0	0	1	1	0	0
	Painful respiration	0	0	0	1	1	0	0
	Pharyngeal paraesthesia	0	0	0	1	1	0	0
	Pharyngeal swelling	1	4	1	5	9	0	0
	Pleural effusion	1	4	0	0	4	0	0
	Pleuritic pain	0	15	0	7	22	0	0
	Pneumomediastinum	1	1	0	0	1	0	0
	Pneumonitis	1	1	0	0	1	0	0
	Pneumothorax	0	1	0	0	1	0	0
	Pneumothorax spontaneous	1	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Productive cough	0	1	2	4	5	0	0
	Pulmonary calcification	0	1	0	0	1	0	0
	Pulmonary embolism	4	9	0	0	9	0	0
	Pulmonary fibrosis	1	1	0	0	1	0	0
	Pulmonary oedema	0	1	0	0	1	0	0
	Respiration abnormal	1	1	0	0	1	0	0
	Respiratory disorder	0	0	0	1	1	0	0
	Respiratory distress	0	1	0	0	1	0	0
	Respiratory failure	2	2	0	0	2	0	0
	Respiratory tract congestion	0	0	1	1	1	0	0
	Rhinalgia	0	0	0	1	1	0	0
	Rhinorrhoea	2	2	1	11	13	0	0
	Sinus congestion	2	2	0	0	2	0	0
	Sinus pain	0	0	0	1	1	0	0
	Sleep apnoea syndrome	0	0	0	1	1	0	0
	Sneezing	0	0	0	3	3	0	0
	Stridor	1	1	0	0	1	0	0
	Suffocation feeling	0	0	0	3	3	0	0
	Tachypnoea	1	3	0	0	3	0	0
	Throat clearing	0	0	1	1	1	0	0
	Throat irritation	3	5	1	5	10	0	0
	Throat tightness	3	6	1	8	14	0	0
	Tonsillar hypertrophy	0	0	0	1	1	0	0
	Upper-airway cough syndrome	0	0	1	2	2	0	0
	Wheezing	1	1	1	5	6	0	0
Skin and subcutaneous tissue disorders	*** SOC TOTAL ***	59	176	139	662	838	0	0
	Acne	0	0	3	8	8	0	0
	Alopecia	3	3	6	10	13	0	0
	Angioedema	2	9	0	0	9	0	0
	Blister	0	1	2	9	10	0	0
	Blister rupture	0	0	0	1	1	0	0
	Butterfly rash	0	0	0	1	1	0	0
	Chronic spontaneous urticaria	0	0	3	3	3	0	0
	Cold sweat	0	3	4	7	10	0	0
	Cutaneous vasculitis	0	1	0	0	1	0	0
	Dermatitis	0	0	1	3	3	0	0
	Dermatitis acneiform	0	0	0	1	1	0	0
	Dermatitis allergic	0	0	1	2	2	0	0
	Dermatitis bullous	0	1	0	0	1	0	0
	Dermatitis contact	0	0	0	2	2	0	0
	Drug eruption	0	0	0	1	1	0	0
	Dry skin	1	2	0	2	4	0	0
	Ecchymosis	0	1	0	0	1	0	0
	Eczema	3	3	1	4	7	0	0
	Erythema	6	24	15	99	123	0	0
	Haemorrhage subcutaneous	0	1	0	0	1	0	0
	Hair colour changes	0	0	2	2	2	0	0
	Hand dermatitis	0	0	1	1	1	0	0
	Hyperhidrosis	8	30	3	30	60	0	0
	Hyperkeratosis follicularis et parafollicularis	2	2	0	0	2	0	0
	Lichen planus	0	1	0	1	2	0	0
	Livedo reticularis	1	2	0	1	3	0	0
	Mechanical urticaria	0	0	2	2	2	0	0
	Miliaria	0	0	1	2	2	0	0
	Night sweats	0	0	0	6	6	0	0
	Onychalgia	0	0	0	1	1	0	0
	Pain of skin	0	0	0	2	2	0	0
	Palmar-plantar erythrodysaesthesia syndrome	0	0	0	1	1	0	0
	Papule	0	0	1	4	4	0	0
	Pemphigoid	1	1	0	0	1	0	0
	Petechiae	2	2	0	1	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Photosensitivity reaction	0	1	0	3	4	0	0
	Piloerection	0	0	1	1	1	0	0
	Pityriasis rosea	0	0	0	1	1	0	0
	Pruritus	6	17	23	134	1S1	0	0
	Psoriasis	1	1	4	4	S	0	0
	Purpura	0	1	0	0	1	0	0
	Rash	7	19	17	101	120	0	0
	Rash erythematous	2	6	6	29	3S	0	0
	Rash macular	0	1	1	10	11	0	0
	Rash maculo-papular	0	0	2	2	2	0	0
	Rash papular	2	6	2	7	13	0	0
	Rash pruritic	0	3	S	17	20	0	0
	Rash vesicular	0	0	0	1	1	0	0
	Scab	0	0	0	1	1	0	0
	Sensitive skin	0	1	0	3	4	0	0
	Skin burning sensation	1	3	1	6	9	0	0
	Skin discharge	0	1	0	0	1	0	0
	Skin discolouration	0	2	3	11	13	0	0
	Skin discomfort	0	0	0	2	2	0	0
	Skin disorder	0	0	0	2	2	0	0
	Skin exfoliation	1	3	0	0	3	0	0
	Skin fissures	1	1	0	0	1	0	0
	Skin haemorrhage	0	0	1	2	2	0	0
	Skin hyperpigmentation	0	0	0	1	1	0	0
	Skin irritation	0	0	1	3	3	0	0
	Skin lesion	0	1	1	3	4	0	0
	Skin mass	0	0	0	6	6	0	0
	Skin oedema	0	0	1	1	1	0	0
	Skin plaque	1	1	1	2	3	0	0
	Skin reaction	0	0	1	6	6	0	0
	Skin swelling	0	1	0	2	3	0	0
	Skin texture abnormal	0	0	0	1	1	0	0
	Skin tightness	0	0	1	1	1	0	0
	Skin warm	1	S	0	10	1S	0	0
	Urticaria	7	1S	20	81	96	0	0
	Urticaria chronic	0	0	1	1	1	0	0
Social circumstances	*** SOC TOTAL ***	2	18	13	4S	63	0	0
	Bedridden	0	1	2	S	6	0	0
	Immobile	0	2	0	0	2	0	0
	Impaired driving ability	0	1	0	1	2	0	0
	Impaired quality of life	0	0	1	2	2	0	0
	Impaired work ability	1	4	4	11	1S	0	0
	Job dissatisfaction	0	0	0	1	1	0	0
	Loss of personal independence in daily activities	1	7	6	18	2S	0	0
	Menopause	0	0	0	1	1	0	0
	Physical disability	0	1	0	0	1	0	0
	Sight disability	0	0	0	1	1	0	0
	Sitting disability	0	0	0	1	1	0	0
	Stress at work	0	1	0	0	1	0	0
	Walking aid user	0	0	0	3	3	0	0
	Walking disability	0	1	0	0	1	0	0
	Wheelchair user	0	0	0	1	1	0	0
Surgical and medical procedures	*** SOC TOTAL ***	9	17	29	138	1SS	0	0
	Appendicectomy	0	1	0	0	1	0	0
	COVID-19 immunisation	3	3	0	3	6	0	0
	Coronary artery bypass	1	1	0	0	1	0	0
	Cryotherapy	0	0	1	1	1	0	0
	Hospitalisation	0	1	0	0	1	0	0
	Interchange of vaccine products	3	8	28	133	141	0	0
	Knee arthroplasty	0	0	0	1	1	0	0
	Pain management	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
	Specialist consultation	1	1	0	0	1	0	0
	Therapy change	1	1	0	0	1	0	0
Vascular disorders	*** SOC TOTAL ***	22	70	9	67	137	0	0
	Arteriosclerosis	1	1	0	0	1	0	0
	Behcet's syndrome	0	0	0	1	1	0	0
	Blood pressure fluctuation	1	1	0	1	2	0	0
	Blue toe syndrome	0	0	0	1	1	0	0
	Circulatory collapse	0	1	0	0	1	0	0
	Cryoglobulinaemia	0	1	0	0	1	0	0
	Cyanosis	0	2	0	1	3	0	0
	Deep vein thrombosis	1	8	0	0	8	0	0
	Flushing	1	2	0	8	10	0	0
	Haematoma	1	1	0	0	1	0	0
	Haemorrhage	2	4	0	0	4	0	0
	Hot flush	0	1	3	14	15	0	0
	Hyperaemia	0	1	0	0	1	0	0
	Hypertension	1	6	0	7	13	0	0
	Hypertensive crisis	0	0	0	1	1	0	0
	Hypertensive emergency	0	1	0	0	1	0	0
	Hypotension	2	7	1	9	16	0	0
	Ischaemia	0	1	0	0	1	0	0
	Jugular vein distension	1	1	0	0	1	0	0
	Lymphoedema	0	0	1	1	1	0	0
	Microangiopathy	1	1	0	0	1	0	0
	Pallor	3	3	0	2	5	0	0
	Pelvic venous thrombosis	0	1	0	0	1	0	0
	Peripheral artery occlusion	1	1	0	0	1	0	0
	Peripheral coldness	0	3	0	3	6	0	0
	Peripheral embolism	0	1	0	0	1	0	0
	Poor peripheral circulation	0	0	2	3	3	0	0
	Raynaud's phenomenon	1	1	2	2	3	0	0
	Shock	0	1	0	0	1	0	0
	Superficial vein thrombosis	0	1	0	2	3	0	0
	Thrombophlebitis	0	2	0	2	4	0	0
	Thrombosis	5	14	0	1	15	0	0
	Vascular pain	0	0	0	2	2	0	0
	Vasculitis	0	1	0	1	2	0	0
	Vasoconstriction	0	0	0	1	1	0	0
	Vasodilatation	0	0	0	2	2	0	0
	Vein disorder	0	0	0	1	1	0	0
	Venous thrombosis	0	1	0	0	1	0	0
	Vessel perforation	0	0	0	1	1	0	0
[Total]		808	3022	2355	9243	12265	0	0

Appendix 10.3 Epidemiology of the Medical Condition(s) or Risk Factors that Reflect the Authorized Indications(s) in Canada

SARS-CoV-2 continues to spread within Canada following the first domestic report of COVID-19 on 25 Jan 2020 in a patient returning to Toronto from Wuhan, China (Silverstein et al. 2020). Early transmission of COVID-19 within Canada was strongly associated with international travel and accounted for approximately half of cases in Jan 2020. Ontario, British Columbia, and Quebec were the first provinces with cases and have the largest and most centralized populations. Despite these early efforts, progressive community transmission ensued in Mar, with rising case counts across Canada during the first epidemic wave, peaking in mid-Apr 2020. As the epidemic has progressed, Canadians have become less adherent to public health recommendations, and these trends in self-reported public behavior coincided with a national R0 exceeding 1.0 in early Aug 2020, and the emergence of a "second wave"[1]. A sharp fall in cases was recorded in early 2021, but the country started to experience a third wave of infection in Mar and again in Dec of 2021. As of 24 Jun 2022, there had been almost 3.9 million confirmed coronavirus cases and 41 thousand deaths from the disease in Canada [2]. Risk factors for severe disease in Canadians include age (>60 years old), male sex, and the presence of pre-existing medical conditions (such as diabetes, high blood pressure, chronic lung disease, and obesity). Risk factors for death mirroring those factors associated with severe disease-namely age and pre-existing medical conditions. In fact, those aged 80 years and older have accounted for around 61 percent of the deaths in Canada[3]. By 18 Jun 2022, the number of reported coronavirus (COVID-19) cases in Canada had reached 3.91 million. This statistic shows the cumulative number of coronavirus (COVID-19) cases in Canada from 01 Feb 2020 to 18 Jun 2022, by date.[4]. The most widespread SARS-CoV-2 variant in Canada is variant B.1.1.7, which was first identified in the United Kingdom, with most cases found in Ontario and Quebec[5]. Current variants of concern in Canada include:

- Alpha (B.1.1.7)
- Beta (B.1.351)
- Gamma (P.1)
- Delta (B.1.617.2)
- Omicron (B.1.1.529)

[1] https://www.facetsjournal.com/doi/full/10.1139/facets-2021-0029
[2] https://www.statista.com/topics/6192/coronavirus-covid-19-in-canada/#dossierKeyfigures
[3] https://www.statista.com/topics/6192/coronavirus-covid-19-in-canada/#dossierKeyfigures
[4] https://www.statista.com/statistics/1107094/covid19-cumulative-cases-by-date-of-symptom-onset-canada/
[5] https://www.statista.com/topics/6192/coronavirus-covid-19-in-canada/#dossierKeyfigures

Appendix 10.4 Canadian Product Monograph for COVID-19 mRNA Vaccine

Current Canadian Product Monograph version 9.0 (dated 01 Jun 2022)

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SPIKEVAX™

Elasomeran mRNA vaccine

Dispersion for intramuscular injection

Multidose Vial, 0.20 mg / mL

Multidose Vial, 0.10 mg / mL

Active Immunizing Agent

ModernaTX, Inc.
200 Technology Square
Cambridge, MA, USA, 02139

Imported and Distributed by:
Innomar Strategies, Inc.
3470 Superior Ct,
Oakville, ON
L6L 0C4

Date of Initial Authorization:
September 16, 2021

Date of Revision:
June 1, 2022

Submission Control Number: 263161

RECENT MAJOR LABEL CHANGES

1. INDICATION	March 2022
4. DOSAGE AND ADMINISTRATION	May 2022
6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	May 2022
7. WARNINGS AND PRECAUTIONS	November 2021
8. ADVERSE REACTIONS	March 2022
14. CLINICAL TRIALS, 14.2 Study Results	March 2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SPIKEVAX (elasomeran mRNA vaccine) is indicated for active immunization against coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in individuals 6 years of age and older.

1.1 Pediatrics

The safety and efficacy of SPIKEVAX in individuals under 6 years of age has not yet been established (see ADVERSE REACTIONS, and CLINICAL TRIALS sections).

1.2 Geriatrics

Clinical studies of SPIKEVAX include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see ADVERSE REACTIONS and CLINICAL TRIALS sections).

2 CONTRAINDICATIONS

SPIKEVAX is contraindicated in individuals who are hypersensitive to the active ingredient or to any ingredients in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see
DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS

At the time of authorization, there are no known serious warnings or precautions associated with this product.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

SPIKEVAX is a dispersion for intramuscular injection that should be administered by a trained healthcare worker. Dose volume will be different depending on which presentation of the vaccine is being administered. Careful attention should be paid to the vial cap colour and the corresponding dose volumes.

Individuals ≥ 12 Years of Age: The primary series is a two-dose regimen of 100 mcg each.

Individuals 6 to 11 Years of Age: The primary series is a two-dose regimen of 50 mcg each.

The SPIKEVAX booster is one dose of50 mcg.

Age Range	Vaccination	Dose	Presentation	Vial Cap Colour	Dose Volume
18 years of age or older	Primary Series	100 mcg*	0.20 mg/mL	Red	0.5 mL
	Booster Dose	50 mcg	0.20 mg/mL	Red	0.25 mL
			0.10 mg/mL	Royal Blue	0.5 mL
12 to 17 years of age	Primary Series	100 mcg*	0.20 mg/mL	Red	0.5 mL
6 to 11 years of age	Primary Series	50 mcg	0.20 mg/mL	Red	0.25 mL
			0.10 mg/mL	Royal Blue	0.5 mL

*The 0.1 mg/mL presentation is not intended for preparation of the 100 mcg dose.

4.2 Recommended Dose and Dosage Adjustment

Primary Series

Individuals ≥ 12 Years of Age: SPIKEVAX is administered intramuscularly as a primary series of two doses of 100 mcg each 4 weeks apart (see CLINICAL TRIALS).

Individuals 6 to 11 Years of Age: SPIKEVAX is administered intramuscularly as a primary series of two doses of 50 mcg each 4 weeks apart (see CLINICAL TRIALS).

There are currently no data available from Moderna clinical trials on the interchangeability of SPIKEVAX with other COVID-19 vaccines to complete the primary vaccination series.

Booster Dose

A booster dose of 50 mcg may be administered intramuscularly at least 6 months after completion of the primary series in individuals 18 years of age or older.

4.3 Reconstitution

SPIKEVAX must not be reconstituted, mixed with other medicinal products, or diluted. No dilution is required prior to administration.

4.4 Administration

Use aseptic technique for preparation and administration.

Preparation

SPIKEVAX multidose vials are supplied as a frozen dispersion that does not contain preservative. Each vial must be thawed prior to administration.

Presentation	Volume in vial	Number of 0.5 mL doses	Number of 0.25 mL doses
0.20 mg / mL	5 mL	10	20*
0.10 mg /mL	2.5 mL	5	N/A

*Do not puncture the 5 mL vial more than 20 times

Thaw each vial before use.

Presentation	Vial Cap Colour	Thaw time under refrigeration between 2° to 8°C (36° to 46°F)	Thaw time at room temperature between 15° to 25°C (59° to 77°F)
0.20 mg/mL	Red	• 2 hours and 30 minutes After thawing, let vial stand at room temperature for 15 minutes before administering.	• 1 hour
0.10 mg/mL	Royal blue	• 2 hours After thawing, let vial stand at room temperature for 15 minutes before administering.	• 45 minutes

Do not re-freeze vials after thawing.

Swirl the vial gently after thawing and between each withdrawal. Do not shake.

Administration

SPIKEVAX is a white to off-white dispersion. It may contain white or translucent product-related particulates. Visually inspect SPIKEVAX vials for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

Administer SPIKEVAX intramuscularly (IM) only. The preferred site is the deltoid muscle of the upper arm. A needle length of ≥1 inch should be used as needles <1 inch may be of insufficient length to penetrate muscle tissue in some adults.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. Withdraw each dose of vaccine from the vial using a new sterile needle and syringe (preferentially a low dead-volume syringe and/or needle) for each injection. Pierce the stopper preferably at a different site each time.

After Vial Puncture: The dose in the syringe should be used as soon as feasible and no later than 24 hours after the vial was first entered (needle-punctured).

SPIKEVAX is preservative free. Once the vial has been entered, it should be discarded after 24 hours. Do not refreeze. Thawed vials and filled syringes can be handled in room light conditions. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

5 OVERDOSAGE

In the case of a suspected vaccine overdose, monitoring of vital functions and symptomatic treatment are recommended. Contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Dispersion, (0.20 mg /mL) Elasomeran (mRNA), encoding the pre fusion stabilized Spike glycoprotein of 2019 novel Coronavirus (SARS-CoV-2) Multidose vial (5 mL)	• Acetic acid • Cholesterol • DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) • Lipid SM-102 • PEG2000-DMG (1,2-dimyristoyl-rac-glycerol,methoxy-polyethyleneglycol) • Sodium acetate trihydrate • Sucrose • Trometamol • Trometamol hydrochloride • Water for injection
Intramuscular injection	Dispersion, (0.10 mg /mL) Elasomeran (mRNA), encoding the pre fusion stabilized Spike glycoprotein of 2019 novel Coronavirus (SARS-CoV-2) Multidose vial (2.5 mL)	• Acetic acid • Cholesterol • DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) • Lipid SM-102 • PEG2000-DMG (1,2-dimyristoyl-rac-glycerol,methoxy-polyethyleneglycol) • Sodium acetate trihydrate • Sucrose • Trometamol • Trometamol hydrochloride • Water for injection

SPIKEVAX is provided as a white to off-white, sterile, preservative-free, frozen dispersion for intramuscular injection. SPIKEVAX contains lipid nanoparticle (LNP), comprised of a messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus and four lipids, formulated with the non-medicinal ingredients listed in Table 1. SPIKEVAX does not contain any preservatives, antibiotics, adjuvants, or human- or animal-derived materials.

SPIKEVAX is supplied in a multi-dose 10R type I glass vial with a 20 mm Fluro Tec-coated chlorobutyl elastomer stopper, 20 mm flip-off aluminum seal. The vial stopper does not contain natural rubber latex. Vials are packaged in a secondary carton containing a total of ten (10) SPIKEVAX vials per carton. The 0.2 mg/mL multi-dose vial is supplied with a red flip-off plastic cap. The 0.1 mg/mL multi-dose vial is supplied with a royal blue flip-off plastic cap.

To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of

administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

7 WARNINGS AND PRECAUTIONS

As with any vaccine, vaccination with SPIKEVAX may not protect all recipients.

Hypersensitivity and Anaphylaxis
Anaphylaxis has been reported. As with all vaccines, appropriate medical treatment, training for immunizers and supervision after immunization should always be readily available in case of a rare anaphylactic event following the administration of this vaccine.

Vaccine recipients should be kept under observation for at least 15 minutes after immunization; 30 minutes is a preferred interval when there is a specific concern about a possible vaccine reaction.

A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of SPIKEVAX.

Cardiovascular

Myocarditis and Pericarditis
Very rare cases of myocarditis and/or pericarditis following vaccination with SPIKEVAX have been reported during post-authorization use. These cases occurred more commonly after the second dose and in adolescents and young adults. Typically, the onset of symptoms has been within a few days following receipt of SPIKEVAX. Available short-term follow-up data suggest that the symptoms resolve in most individuals, but information on long-term sequelae is lacking. The decision to administer SPIKEVAX to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances.

Healthcare professionals are advised to consider the possibility of myocarditis and/or pericarditis in their differential diagnosis if individuals present with chest pain, shortness of breath, palpitations or other signs and symptoms of myocarditis and/or pericarditis following immunization with a COVID-19 vaccine. This could allow for early diagnosis and treatment. Cardiology consultation for management and follow up should be considered.

Acute Illness
Consideration should be given to postponing immunization in persons with severe febrile illness or severe acute infection. Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.

Hematologic-Bleeding
As with other intramuscular injections, SPIKEVAX should be given with caution in individuals with bleeding disorders, such as haemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of haematoma following the injection, and when the potential benefit clearly outweighs the risk of administration.

Immune
Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine. In these individuals, a third dose may be considered as part of the primary series.

Syncope
Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from fainting and manage syncopal reactions.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of SPIKEVAX in pregnant women have not yet been established.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPIKEVAX during pregnancy. Women who are vaccinated with SPIKEVAX during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

7.1.2 Breast-feeding

It is unknown if SPIKEVAX is excreted in human milk. A risk to the newborns/infants cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19.

7.1.3 Pediatrics

The safety and efficacy of SPIKEVAX in children under 6 years of age have not yet been established.

7.1.4 Geriatrics

Clinical studies of SPIKEVAX include participants 65 years of age and older and their data contributes to the overall assessment of safety and efficacy (see ADVERSE REACTIONS and CLINICAL TRIALS sections).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile in participants ≥ 18 years of age presented below is based on data generated from an ongoing Phase 3 placebo- controlled clinical study on subjects ≥ 18 years of age (Study P301, NCT 04470427).

Solicited adverse reactions were reported more frequently among subjects in the vaccine group than in the placebo group. The most frequently reported adverse reactions after any dose were pain at the injection site (92.0%), fatigue (70.0%), headache (64.7%), myalgia (61.5%) and chills (45.4%). The

majority of local and systemic adverse reactions had a median duration of 1 to 3 days.

Overall, there was a higher reported rate of solicited adverse reactions in younger age groups; the incidence of lymphadenopathy (axillary swelling/tenderness), fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, fever was higher in adults 18 to 64 years of age than in those 65 years of age and above. Solicited adverse reactions were also more frequent after the second dose, compared to the first one, including grade 3 local and systemic adverse reactions (see Table 2, Table 3, Table 4 and Table 5 respectively).

Safety data in adolescents (12 to 17 years of age) were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical trial (Study P203, NCT04649151) conducted in the United States involving 3,726 participants who received at least one dose of SPIKEVAX (n=2,486) or placebo (n=1,240). Of these, 1360 adolescents (vaccine=942, placebo=418) have been followed for at least 2 months (60 days) after the second dose of SPIKEVAX at the time of the analysis (cut-off date May 8, 2021). Overall, solicited adverse reactions at any dose were reported more frequently among adolescents in the vaccine group than in the placebo group. The most frequently reported adverse reactions in adolescent subjects were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%), and chills (49.1%) (see Table 6 and Table 7).

Safety data in children (6 to 11 years of age) were collected in an ongoing Phase 2/3 two-part clinical trial (Study P204, NCT04796896) conducted in the United States and Canada. Part 1 is an open-label phase of the trial for safety, dose selection, and immunogenicity involving 380 participants who received at least one dose of SPIKEVAX (0.25 mL, 50 mcg). Part 2 is the placebo-controlled phase for safety, immunogenicity and efficacy; at the time of data snapshot (November 10, 2021) it included 4,002 participants 6 to 11 years of age who received at least one dose (0.25 mL, 50 mcg) of SPIKEVAX (n=3,007) or placebo (n=995), and 2,988 SPIKEVAX participants and 973 placebo participants had received dose 2. No participants in Part 1 participated in Part 2.

In Part 2, the median follow-up duration was 82 days after dose 1 and 51 days after dose 2. A total of 2,981 (99.15%) subjects in the SPIKEVAX group and 966 (97.1%) subjects in the placebo group have been followed for 28 days or more after dose 2. A total of 1,066 subjects in the SPIKEVAX group (35.3%) and 218 subjects in the placebo group (21.9%) have been followed for 56 days or more after dose 2.

Overall, solicited adverse reactions were reported more frequently among children in the vaccine group than in the placebo group. The most frequently reported adverse reactions in children 6 to 11 years of age in Part 2 following administration of the primary series were pain at the injection site (94.8%), fatigue (64.5%), headache (54.3%), chills (30.3%) and myalgia (28.2%) (see Table 8 and Table 9).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse vaccine reactions in real-world use.

Primary Series

Participants 18 Years of Age and Older

Solicited Adverse Reactions

The safety profile presented below is based on data generated in an ongoing Phase 3, placebo-controlled clinical study on subjects ≥ 18 years of age in which pre-specified cohorts of subjects who were either ≥65 years of age or 18 to 64 years of age with comorbid medical conditions were included. At the time of the analysis, the safety analysis set included a total of 30,351 subjects who received at least one dose of SPIKEVAX (n=15,181) or placebo (n=15,170). Subjects were followed for a median of 92 days from first injection and 63 days from second injection.

Solicited adverse reaction data were collected from Day 1 to Day 7 and reported by participants in an electronic diary (e-Diary) after each dose and on electronic case report forms. Reported solicited local and systemic adverse reactions are presented in Table 2, Table 3, Table 4 and Table 5 respectively.

Table 2 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade-Participants 18 to 64 Years of Age (Safety Analysis Set*)

Solicited local AR	Dose 1		Dose 2	
	SPIKEVAX Group n (%) N=11,406	Placebo Group n (%) N=11,407	SPIKEVAX Group n (%) N=10,985	Placebo Group n (%) N=10,918
Pain				
Any grade	9908 (86.9)	2177 (19.1)	9873 (89.9)	2040 (18.7)
Grade 3 or 4[a]	366 (3.2)	23 (0.2)	506 (4.6)	22 (0.2)
Erythema				
Any grade	344 (3.0)	47 (0.4)	982 (8.9)	43 (0.4)
Grade 3 or 4[b]	34 (0.3)	11 (<0.1)	210 (1.9)	12 (0.1)
Swelling/Induration				
Any grade	767 (6.7)	34 (0.3)	1389 (12.6)	36 (0.3)
Grade 3 or 4[b]	62 (0.5)	3 (<0.1)	182 (1.7)	4 (<0.1)
Axillary swelling/ Tenderness				
Any grade	1322 (11.6)	567 (5.0)	1775 (16.2)	470 (4.3)
Grade 3 or 4	37 (0.3)	13 (0.1)	46 (0.4)	11 (0.1)

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
n= # of participants with specified reaction, percentages are based on n/N
N= number of exposed subjects who submitted any data for the event.
[a] Pain - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
[b] Erythema and Swelling/Induration - Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
[c] Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

Table 3 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 65 Years of Age and Older (Safety Analysis Set*)

Solicited local AR	Dose 1		Dose 2	
	SPIKEVAX Group n (%) N=3762	Placebo Group n (%) N=3748	SPIKEVAX Group n (%) N=3692	Placebo Group n (%) N=3648
Pain				
Any grade	2782 (74.0)	481 (12.8)	3070 (83.2)	437 (12.0)
Grade 3 or 4[a]	50 (1.3)	32 (0.9)	98 (2.7)	18 (0.5)
Erythema				
Any grade	86 (2.3)	20 (0.5)	275 (7.5)	13 (0.4)
Grade 3 or 4[b]	8 (0.2)	2 (<0.1)	77 (2.1)	3 (<0.1)
Swelling/Induration				
Any grade	165 (4.4)	18 (0.5)	400 (10.8)	13 (0.4)
Grade 3 or 4[b]	20 (0.5)	3 (<0.1)	72 (2.0)	7 (0.2)
Axillary swelling/ Tenderness				
Any grade	231 (6.1)	155 (4.1)	315 (8.5)	97 (2.7)
Grade 3 or 4	12 (0.3)	14 (0.4)	21 (0.6)	8 (0.2)

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
n= # of participants with specified reaction, percentages are based on n/N
N= number of exposed subjects who submitted any data for the event.
[a] Pain - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
[b] Erythema and Swelling/Induration - Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
[c] Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e., lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

Table 4 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 18 to 64 Years of Age (Safety Analysis Set*)

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group n (%) N=11406	Placebo Group n (%) N=11407	SPIKEVAX Group n (%) N=10985	Placebo Group n (%) N=10918
Fatigue				
Any grade	4,384 (38.4)	3,282 (28.8)	7,430 (67.6)	2,687 (24.6)
Grade 3[a]	120 (1.1)	83 (0.7)	1,174 (10.7)	86 (0.8)
Grade 4[b]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache				

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group n (%) N=11406	Placebo Group n (%) N=11407	SPIKEVAX Group n (%) N=10985	Placebo Group n (%) N=10918
Any grade	4,030 (35.3)	3,304 (29.0)	6,898 (62.8)	2,760 (25.3)
Grade 3[c]	219 (1.9)	162 (1.4)	553 (5.0)	129 (1.2)
Myalgia				
Any grade	2,699 (23.7)	1,628 (14.3)	6,769 (61.6)	1,411 (12.9)
Grade 3[a]	73 (0.6)	38 (0.3)	1,113 (10.1)	42 (0.4)
Arthralgia				
Any grade	1,893 (16.6)	1,327 (11.6)	4,993 (45.5)	1,172 (10.7)
Grade 3[a]	47 (0.4)	29 (0.3)	647 (5.9)	37 (0.3)
Grade 4[b]	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills				
Any grade	1,051 (9.2)	730 (6.4)	5,341 (48.6)	658 (6.0)
Grade 3[d]	17 (0.1)	8 (<0.1)	164 (1.5)	15 (0.1)
Nausea/vomiting				
Any grade	1,068 (9.4)	908 (8.0)	2,348 (21.4)	801 (7.3)
Grade 3[e]	6 (<0.1)	8 (<0.1)	10 (<0.1)	8 (<0.1)
Fever				
Any grade	105 (0.9)	37 (0.3)	1,908 (17.4)	39 (0.4)
Grade 3[f]	10 (<0.1)	1 (<0.1)	184 (1.7)	2 (<0.1)
Grade 4[g]	4 (<0.1)	4 (<0.1)	12 (0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	1,523 (13.4)	6,292 (57.3)	1,248 (11.4)

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
n= # of participants with specified reaction, percentages are based on n/N
N= number of exposed subjects who submitted any data for the event.
[a] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[b] Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.
[c] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[d] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[e] Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
[h] Grade 3 fever: Defined as ≥39.0 – ≤40.0°C / ≥102.1 – ≤104.0°F.
[i] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Table 5 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade - Participants 65 Years of Age and Older (Safety Analysis Set*)

Solicited Systemic AR	Dose 1		Dose 2	
	SPIKEVAX Group n (%) N=3762	Placebo Group n (%) N=3748	SPIKEVAX Group n (%) N=3692	Placebo Group n (%) N=3648
Fatigue				
Any grade	1251 (33.3)	851 (22.7)	2152 (58.3)	716 (19.6)
Grade 3[a]	30 (0.8)	22 (0.6)	254 (6.9)	20 (0.5)
Headache				
Any grade	921 (24.5)	723 (19.3)	1704 (46.2)	650 (17.8)
Grade 3[b]	52 (1.4)	34 (0.9)	106 (2.9)	33 (0.9)
Myalgia				
Any grade	742 (19.7)	443 (11.8)	1739 (47.1)	398 (10.9)
Grade 3[a]	17 (0.5)	9 (0.2)	205 (5.6)	10 (0.3)
Arthralgia				
Any grade	618 (16.4)	456 (12.2)	1291 (35.0)	397 (10.9)
Grade 3[a]	13 (0.3)	8 (0.2)	123 (3.3)	7 (0.2)
Chills				
Any grade	202 (5.4)	148 (4.0)	1141 (30.9)	151 (4.1)
Grade 3[c]	7 (0.2)	6 (0.2)	27 (0.7)	2 (<0.1)
Nausea/vomiting				
Any grade	194 (5.2)	166 (4.4)	437 (11.8)	133 (3.6)
Grade 3[d]	4 (0.1)	4 (0.1)	10 (0.3)	3 (<0.1)
Grade 4[e]	0 (0)	0 (0)	1 (<0.1)	0 (0)
Fever				
Any grade	10 (0.3)	7 (0.2)	370 (10.0)	4 (0.1)
Grade 3[f]	1 (<0.1)	1 (<0.1)	18 (0.5)	0 (0)
Grade 4[g]	0 (0)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	477 (12.7)	1546 (41.9)	329 (9.0)

*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
n= # of participants with specified reaction, percentages are based on n/N
N= number of exposed subjects who submitted any data for the event.
[a] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

[b] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[c] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[d] Grade 3 Nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
[e] Grade 4 Nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.
[f] Grade 3 fever: Defined as ≥39.0 – ≤40.0°C / ≥102.1 – ≤104.0°F.
[g] Grade 4 fever: Defined as >40.0°C / >104.0°F.

Unsolicited Adverse Events

Serious Adverse Events

Serious adverse events were reported in 0.6% of participants who received SPIKEVAX and 0.6% of participants who received a placebo, from the first dose until 28 days following the last vaccination. Serious adverse events were reported in 1% of participants who received SPIKEVAX and 1% of participants who received a placebo, from the first dose until the last observation (cut-off date November 25, 2020). In these analyses, 87.9% of study participants had at least 28 days of follow-up after dose 2, and the median follow-up time for all participants was 9 weeks after dose 2.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

Three serious adverse events were likely related to SPIKEVAX: two cases of facial swelling occurring within 7 days of receiving Dose 2, in female patients aged 46 and 51; one case of nausea and vomiting with headaches and fever occurring within 7 days after Dose 2 and requiring in-hospital treatment in a 61 year old female, with past medical history of headaches with nausea and vomiting requiring hospitalization. One case of Bell's palsy, which occurred 32 days following receipt of vaccine, was classified as a serious adverse event. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine.

No deaths related to the vaccine were reported in the study.

Non-Serious Adverse Events

In the COVE Phase 3 study, unsolicited adverse events occurring within 28 days after each vaccination were reported by 23.9% of subjects who received SPIKEVAX, and 21.6% of subjects who received the placebo. These adverse events were predominantly solicited adverse reactions occurring outside of the conventional 7-day monitoring period after the injection (injection site pain, fatigue, headaches, myalgia, etc.).

Unsolicited adverse events that occurred in ≥ 1% of study participants who received SPIKEVAX and at a rate at least 1.5-fold higher rate than placebo, were lymphadenopathy related events (1.1% of versus 0.6%) and delayed injection site reactions reported >7 days after vaccination (1.2% versus 0.4%). All of the lymphadenopathy events are similar to the axillary swelling/tenderness in the injected arm reported as solicited adverse reactions. Delayed injection site reactions included one or more of the following: erythema, pain and swelling, and are likely related to vaccination. Hypersensitivity events were reported in 1.5% of the SPIKEVAX group compared to 1.1% of the placebo group, but this imbalance was mostly due to injection site rash and injection site erythema/swelling occurring more frequently in the SPIKEVAX group.

There were three reports of Bell's palsy in the SPIKEVAX group (one of which was a serious adverse event), which occurred 22, 29, and 32 days after the second dose of vaccine, and one in the placebo group which occurred 17 days after the first dose of saline. Currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including neurologic, musculoskeletal or inflammatory events) that would suggest a causal relationship to SPIKEVAX.

Adolescents 12 to 17 Years of Age

Solicited Adverse Reactions

Data on solicited local and systemic adverse reactions and use of antipyretic medication were collected on a daily basis in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among adolescent participants receiving SPIKEVAX (n=2,482) and participants receiving placebo (n=1,238) with at least 1 documented dose.[a] Events that persisted for more than 7 days were followed until resolution.

The reported number and percentage of the solicited local and systemic adverse reactions in participants 12 through 17 years of age by dose are presented in Table 6 and Table 7 respectively. Solicited local and systemic adverse reactions reported following administration of SPIKEVAX had a median duration of 1 to 3 days.

Table 6 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 12 to 17 Years of Age (Solicited Safety Analysis Set)[b,c]

	Dose 1		Dose 2	
	Vaccine Group n (%) N=2,482	**Placebo Group[a]** n (%) N=1,238	**Vaccine Group** n (%) N=2,478	**Placebo Group[a]** n (%) N=1,220
Pain				
Any grade	2,310 (93.1)	431 (34.8)	2,290 (92.4)	370 (30.3)
Grade 3[b]	133 (5.4)	1 (<0.1)	126 (5.1)	3 (0.2)
Axillary swelling/ tenderness				
Any grade	578 (23.3)	101 (8.2)	519 (21.0)	61 (5.0)
Grade 3[b]	10 (0.4)	0 (0)	7 (0.3)	0 (0)
Swelling (hardness)				
≥25 mm	403 (16.2)	12 (1.0)	509 (20.5)	12 (1.0)
Grade 3[c]	27 (1.1)	0 (0)	56 (2.3)	0 (0)
Erythema (redness)				
≥25 mm	334 (13.5)	8 (0.6)	484 (19.5)	11 (0.9)
Grade 3[c]	21	0	72	0

	Dose 1		Dose 2	
	Vaccine Group n (%) N=2,482	Placebo Group[a] n (%) N=1,238	Vaccine Group n (%) N=2,478	Placebo Group[a] n (%) N=1,220
	(0.8)	(0)	(2.9)	(0)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
[a] Placebo was a saline solution.
[b] Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.

Table 7 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 12 to 17 Years of Age (Solicited Safety Analysis Set)[d,e]

	Dose 1		Dose 2	
	Vaccine Group n (%) N=2,482	Placebo Group[a] n (%) N=1,238	Vaccine Group n (%) N=2,478	Placebo Group[a] n (%) N=1,220
Fatigue				
Any grade	1,188 (47.9)	453 (36.6)	1,679 (67.8)	353 (28.9)
Grade 3[d]	33 (1.3)	18 (1.5)	188 (7.6)	10 (0.8)
Headache				
Any grade	1,106 (44.6)	477 (38.5)	1,739 (70.2)	370 (30.3)
Grade 3[e]	56 (2.3)	17 (1.4)	112 (4.5)	14 (1.1)
Grade 4[f]	0 (0)	0 (0)	1 (<0.1)	0 (0)
Myalgia				
Any grade	668 (26.9)	205 (16.6)	1,154 (46.6)	153 (12.5)
Grade 3[d]	24 (1.0)	10 (0.8)	129 (5.2)	3 (0.2)
Chills				
Any grade	456 (18.4)	138 (11.1)	1,066 (43.0)	97 (8.0)
Grade 3[g]	4 (0.2)	1 (<0.1)	11 (0.4)	0 (0)
Arthralgia				
Any grade	371 (15.0)	143 (11.6)	716 (28.9)	113 (9.3)
Grade 3[d]	15 (0.6)	5 (0.4)	57 (2.3)	2 (0.2)
Nausea/vomiting				
Any grade	281 (11.3)	110 (8.9)	591 (23.9)	106 (8.7)
Grade 3[h]	2 (<0.1)	0 (0)	2 (<0.1)	0 (0)

	Dose 1		Dose 2	
	Vaccine Group n (%) N=2,482	**Placebo Group[a]** n (%) N=1,238	**Vaccine Group** n (%) N=2,478	**Placebo Group[a]** n (%) N=1,220
Grade 4[i]	0 (0)	0 (0)	1 (<0.1)	0 (0)
Fever				
Any grade	63 (2.5)	12 (1.0)	302 (12.2)	12 (1.0)
Grade 3 (≥39.0° – ≤40.0°C)	9 (0.4)	1 (<0.1)	46 (1.9)	1 (<0.1)
Grade 4 (>40.0°C)	0 (0)	0 (0)	1 (<0.1)	1 (<0.1)
Use of antipyretic or analgesic medications	748 (30.1)	118 (9.5)	1,242 (50.1)	108 (8.9)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
[a] Placebo was a saline solution.
[d] Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.
[e] Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.
[f] Grade 4 headache: Defined as requires emergency room visit or hospitalisation.
[g] Grade 3 chills: Defined as prevents daily activity and requires medical intervention.
[h] Grade 3 nausea/vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
[i] Grade 4 nausea/vomiting: Defined as requires emergency room visit or hospitalisation for hypotensive shock.

Unsolicited Adverse Events

Participants (12 to 17 years of age) were monitored for unsolicited adverse events for up to 28 days following each dose and follow-up is ongoing. Serious adverse events and medically attended adverse events will be recorded for the entire study duration. As of May 8, 2021, 3,726 participants (vaccine=2,486, placebo=1,240) had received at least 1 dose and 97.3% of the study participants had at least 28 days of follow-up after Dose 2. The median follow-up time for all participants was 53 days after Dose 2.

Unsolicited adverse events that occurred within 28 days following each vaccination were reported by 20.5% of participants (n=510) who received SPIKEVAX and 15.9% of participants (n=197) who received placebo. Imbalances in unsolicited adverse events up to 28 days after any injection are primarily attributable to events related to local reactogenicity such as lymphadenopathy.

Serious adverse events within 28 days of any injection were reported by <0.1% (n=2) of participants who received SPIKEVAX and <0.1% (n=1) of participants who received placebo. As of May 8, 2021, serious adverse events during the overall study period were reported by 0.2% (n=6) of participants who received SPIKEVAX and 0.2% (n=2) of participants who received placebo. No SAEs during the study were assessed by the investigator as related to study vaccine.

Children 6 to 11 Years of Age

Solicited Adverse Reactions

Data on solicited local and systemic adverse reactions were collected on a daily basis in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among pediatric participants aged 6 to 11 years receiving SPIKEVAX (n=3,007) and participants receiving placebo (n=995) with at least 1 documented dose, and 2,988 participants receiving SPIKEVAX and 973 participants in the placebo group had received dose 2 in Study P204 Part 2. For events that persisted for more than 7 days the caregiver was prompted to continue to record until resolution.

The reported number and percentage of the solicited local and systemic adverse reactions in participants 6 through 11 years of age by dose are presented in Table 8 and Table 9 respectively. The majority of solicited local adverse reactions following administration of SPIKEVAX occurred within the first 1 to 2 days after any dose and persisted for a median of 3 days.

Table 8 – Solicited Local Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 6 to 11 of Age in Study P204 Part 2 (Solicited Safety Analysis Set)

	Dose 1		Dose 2	
	Vaccine Group 50 mcg n (%) N=3,004	**Placebo Group**[a] n (%) N=993	**Vaccine Group 50 mcg** n (%) N=2,988	**Placebo Group**[a] n (%) N=969
Pain				
Any grade	2796 (93.1)	465 (46.8)	2832 (94.8)	480 (49.5)
Grade 3 [b]	28 (0.9)	0	81 (2.7)	2 (0.2)
Erythema (redness)				
Any grade	349 (11.9)	13 (1.3)	559 (18.7)	10 (1.0)
Grade 3 [c]	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Swelling (hardness)				
Any grade	354 (11.8)	12 (1.2)	507 (17.0)	12 (1.2)
Grade 3[c]	19 (0.6)	1 (0.1)	20 (0.7)	0 (0)
Axillary swelling/ tenderness				
Any grade	465 (15.5)	84 (8.5)	537 (18.0)	65 (6.7)
Grade 3[b]	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
[a] Placebo was a saline solution.
[b] Grade 3 pain and axillary swelling/tenderness: Defined as prevents daily activity.
[c] Grade 3 swelling and erythema: Defined as >100 mm / >10 cm

Table 9 – Solicited Systemic Adverse Reactions Within 7 Days After First and Second Injection by Grade – Participants 6 to 11 Years of Age in Study P204 Part 2 (Solicited Safety Analysis Set)

	Dose 1	Dose 2

	Vaccine Group 50 mcg n (%) N=3,004	Placebo Group[a] n (%) N=993	Vaccine Group 50 mcg n (%) N=2,988	Placebo Group[a] n (%) N=969
Fever				
Any grade	99 (3.3)	15 (1.5)	714 (23.9)	19 (2.0)
Grade 3 (≥39.0° – ≤40.0°C)	17 (0.6)	2 (0.2)	113 (3.8)	2 (0.2)
Headache				
Any grade	938 (31.2)	306 (30.8)	1622 (54.3)	275 (28.4)
Grade 3[b]	18 (0.6)	4 (0.4)	119 (4.0)	8 (0.8)
Fatigue				
Any grade	1298 (43.2)	334 (33.6)	1925 (64.5)	335 (34.6)
Grade 3[b]	31 (1.0)	8 (0.8)	191 (6.4)	8 (0.8)
Myalgia				
Any grade	438 (14.6)	96 (9.7)	843 (28.2)	105 (10.8)
Grade 3[b]	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Arthralgia				
Any grade	260 (8.7)	75 (7.6)	482 (16.1)	84 (8.7)
Grade 3[b]	3 (<0.1)	1 (0.1)	25 (0.8)	0 (0)
Nausea/vomiting				
Any grade	325 (10.8)	107 (10.8)	716 (24.0)	97 (10.0)
Grade 3[c]	5 (0.2)	0 (0)	19 (0.6)	0 (0)
Chills				
Any grade	309 (10.3)	67 (6.7)	904 (30.3)	74 (7.6)
Grade 3[b]	3 (<0.1)	0 (0)	19 (0.6)	0 (0)

n= # of participants with specified reaction, percentages are based on n/N.
N= number of exposed subjects who submitted any data for the event.
[a] Placebo was a saline solution.
[b] Grade 3 headache, fatigue, myalgia, arthralgia and chills: Defined as prevents daily activity.
[c] Grade 3 nausea/vomiting: Defined as prevents daily activity.

Unsolicited Adverse Events

Participants (6 to 11 years of age) were monitored for unsolicited adverse events for up to 28 days following each dose. Serious adverse events and medically attended adverse events will be recorded for the entire study duration. As of November 10, 2021, overall safety data are available for the 4,382 participants enrolled in Study P204 Part 1 and Part 2 which incudes data from 3,387 participants who

received at least one 50 mcg dose of SPIKEVAX (Part 1=380; Part 2=3,007) and 995 placebo participants in Part 2.

Unsolicited adverse events that occurred within 28 days following each vaccination were reported by 29.6% of participants (n=3,007) who received SPIKEVAX and 25.1% of participants (n=995) who received placebo. Unsolicited adverse events that occurred in ≥ 1% of study participants who received SPIKEVAX and at a rate at least 1.5-fold higher rate than placebo, were injection site erythema (3.0% versus 0.1%) and injection site lymphadenopathy (1.7% vs 0.4%). Hypersensitivity events were reported in 4.7% of the SPIKEVAX group compared to 2.5% of the placebo group, but this imbalance was mostly due to injection site rash and urticaria occurring more frequently in the SPIKEVAX group.

Serious adverse events (SAE) within 28 days of any injection were reported by <0.1% (n=4) of participants who received SPIKEVAX. No SAEs during the study were assessed by the investigator as related to study vaccine.

Booster Dose

Study P201 Part B is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of SPIKEVAX in participants 18 years of age and older (NCT04405076). In an open-label phase of this study, 171 participants received a single booster dose (50 mcg) at least 6 months after receiving the second dose (100 mcg) of the SPIKEVAX primary series. At the time of analysis, participants were followed-up for safety for one month after receiving the booster.

The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series. The most common solicited local adverse reactions (ARs) were pain at injection site (84%) and axillary swelling or tenderness (20%). The most common solicited systemic ARs were fatigue (59%), headache (55%), myalgia (49%), arthralgia (41%), and chills (35%). The local and systemic ARs were transient, and most resolved by Day 4. The frequency and severity of solicited ARs was numerically comparable between age cohorts (18 to <55; ≥55 years of age). The most common unsolicited AEs were headache (2.3%) and fatigue (2.3%); these were also solicited AEs that extended beyond Day 7. All unsolicited AEs were mild or moderate in severity. Of the 171 participants who received a booster dose of SPIKEVAX, there were no serious adverse events reported from the booster dose through 29 days after the booster dose.

8.3 Less Common Clinical Trial Adverse Reactions

The following events were reported in the ongoing Phase 3, placebo-controlled clinical study in participants ≥ 18 years of age:

Nervous System Disorders: Acute peripheral facial paralysis†

Skin and Subcutaneous Tissue Disorders: Rash

General Disorders and Administration Site Conditions: Injection site pruritus, injection site rash, injection site swelling, injection site erythema, injection site urticaria, facial swelling§

† Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the SPIKEVAX group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.
§ There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported on Day 1 and Day 3, respectively, relative to day of vaccination.

8.4 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-authorization use of SPIKEVAX.

Immune System Disorders: Anaphylaxis

Cardiac Disorders: Myocarditis and/or pericarditis (see WARNINGS AND PRECAUTIONS).

Skin and Subcutaneous Tissue Disorders: Erythema multiforme

Nervous System Disorders: facial paralysis / Bell's palsy, hypoaesthesia / paraesthesia, dizziness.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

9 DRUG INTERACTIONS

No interaction studies have been performed.

Do not mix SPIKEVAX with other vaccines/products in the same syringe.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

SPIKEVAX encodes for the pre-fusion stabilized Spike (S) protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for expression of the SARS-CoV-2 S antigen. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection. The vaccine induces both neutralizing antibody and cellular immune responses (T-cell and B-cell) to the spike (S) antigen, which may contribute to protection against COVID-19 disease.

11 STORAGE, STABILITY AND DISPOSAL

Storage Prior to Use

As Displayed on the Vial Labels and Cartons

The SPIKEVAX multidose vials are stored frozen between -50° to -15°C (-58° to 5°F). Store in the original carton to protect from light.

Additional Storage Information Not Displayed on the Vial Labels and Cartons

- Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use.
- Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 24 hours.
- Do not refreeze once thawed.

Transportation of Thawed Vials in Liquid State at 2° to 8°C (36° to 46°F)

If transport at -50° to -15°C (-58° to 5°F) is not feasible, available data support transportation of one or more thawed vials in liquid state for up to 12 hours at 2° to 8°C (36° to 46°F) when shipped using shipping containers which have been qualified to maintain 2° to 8°C (36° to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Precautions should be taken (packaging/dunnage) to minimize vibration of vials when transporting at this temperature. Once thawed and transported in liquid state at 2° to 8°C (36° to 46°F), vials should not be refrozen and should be stored at 2° to 8°C (36° to 46°F) until use.

Thawing Vials Prior To Use

The SPIKEVAX multidose vial contains a frozen dispersion that does not contain a preservative and must be thawed prior to administration. Remove the required number of vial(s) from storage and thaw each vial before use.

Presentation	**Vial Cap Colour**	**Thaw time under refrigeration between 2° to 8°C (36° to 46°F)**	**Thaw time at room temperature between 15° to 25°C (59° to 77°F)**
0.20 mg/mL	Red	• 2 hours and 30 minutes After thawing, let vial stand at room temperature for 15 minutes before administering.	• 1 hour
0.10 mg/mL	Royal blue	• 2 hours After thawing, let vial stand at room temperature for 15 minutes before administering.	• 45 minutes

After thawing, do not refreeze.

Storage After Use (Punctured Vials)

SPIKEVAX is preservative-free. Once the vial has been entered (needle-punctured), it can be stored at room temperature or refrigerated, but must be discarded after 24 hours. Do not refreeze.

12 SPECIAL HANDLING INSTRUCTIONS

SPIKEVAX must not be mixed with other medicinal products or diluted. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Elasomeran (mRNA vaccine)

Chemical name: mRNA-1273 LS (Large Scale) Lipid Nanoparticle (LNP)

Product Characteristics

SPIKEVAX is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion that contains elasomeran (mRNA CX-024414) that encodes for the pre-fusion stabilized Spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2) and four lipids which act as protectants and carriers of the mRNA.

SPIKEVAX is supplied as a multidose liquid ready-to-use dispersion at 0.20 mg/mL or 0.1 mg/mL for intramuscular administration. SPIKEVAX is in a 10R clear Type 1 glass vial with a rubber serum stopper and an aluminum seal with flip-off plastic cap.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

14.1.1 Participants 18 Years of Age and Older

The safety and efficacy of SPIKEVAX were evaluated in Study P301, a Phase 3 randomized, placebo-controlled, multicentre study in participants 18 years of age and older (COVE Study). A total of 30,351 (15,181 in the SPIKEVAX group and N=15,170 in the placebo group) participants were randomized equally to receive 2 doses of SPIKEVAX or placebo separated by 28 days. Randomization was stratified by age and risk of severe COVID-19 as follows: ≥ 65 years old, < 65 years old and at increased risk for the complications of COVID-19, and < 65 years old and not at increased risk for the complications of COVID-19.

Pregnant or breastfeeding women and individuals with known history of SARS-CoV-2 infection, immunosuppressive or immunodeficient state, asplenia or recurrent severe infections were excluded from the study. The primary efficacy was symptomatic* COVID-19 infection confirmed by Polymerase Chain Reaction (PCR) and by a clinical adjudication committee. The population for the analysis of the primary efficacy endpoint included participants who did not have evidence of prior infection with SARS-CoV-2 through 14 days after the second dose. Participants are planned to be followed for up to 24 months for assessments of safety and efficacy against COVID-19 disease.

* Symptomatic COVID-19 case definition: At least two of the following systemic symptoms: fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

Table 10 – Demographic Characteristics – Subjects ≥ 18 Years of Age Without Evidence of Infection Prior to 14 Days After Dose 2 – Evaluable Efficacy Population (Data Accrued Through November 21, 2020)

	SPIKEVAX Group (N=14,134) n (%)	Placebo Group (N=14,073) n (%)	Total (N=28,207) n (%)
Sex			
Female	6768 (47.9)	6611 (47.0)	13,379 (47.4)
Male	7366 (52.1)	7462 (53.0)	14,828 (52.6)
Age (years)			
Mean (SD)	51.6 (15.44)	51.6 (15.54)	51.6 (15.49)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
18 to <65	10,551 (74.6)	10,521 (74.8)	21,072 (74.7)
65 and older	3583 (25.4)	3552 (25.2)	7135 (25.3)
Race			
American Indian or Alaska Native	108 (0.8)	111 (0.8)	219 (0.8)
Asian	620 (4.4)	689 (4.9)	1309 (4.6)
Black or African American	1385 (9.8)	1349 (9.6)	2734 (9.7)
Native Hawaiian or Other Pacific Islander	35 (0.2)	31 (0.2)	66 (0.2)
White	11,253 (79.6)	11,174 (79.4)	22,427 (79.5)
Other	299 (2.1)	295 (2.1)	594 (2.1)
Ethnicity			
Hispanic or Latino	2789 (19.7)	2780 (19.8)	5569 (19.7)
Not Hispanic or Latino	11,212 (79.3)	11,165 (79.3)	22,377 (79.3)
Race and Ethnicity			
Non-Hispanic White	9023 (63.8)	8916 (63.4)	17,939 (63.6)
Communities of color	5088 (36.0)	5132 (36.5)	10,220 (36.2)
Occupational Risk*	11,586 (82.0)	11,590 (82.4)	23,176 (82.2)
Healthcare worker	3593 (25.4)	3581 (25.4)	7174 (25.4)
High Risk Condition**			
One high risk condition present	2616 (18.5)	2591 (18.4)	5207 (18.5)
Two or more high risk conditions present	590 (4.2)	576 (4.1)	1166 (4.1)
No high risk condition	10,928 (77.3)	10,906 (77.5)	21,834 (77.4)
Age and Health Risk for Severe COVID-19* **			
18 to <65 years and not at risk	8189 (57.9)	8200 (58.3)	16,389 (58.1)
18 to <65 years and at risk	2367 (16.7)	2324 (16.5)	4691 (16.6)
≥ 65 years	3578 (25.3)	3549 (25.2)	7127 (25.3)

* Occupational risk includes: Healthcare Workers; Emergency Response; Retail/Restaurant Operations; Manufacturing and Production; Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel Personal care and in-home services; Hospitality and Tourism Workers, Pastoral; Social or Public Health Workers; and Educators and Students.

** High risk for severe COVID-19 is defined as patients who meet at least one of the following criteria (protocol-defined):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and
- pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m2)

- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human immunodeficiency virus (HIV) infection

*** Age and health risk for severe COVID-19 is used as stratification factor for randomization.

14.1.2 Adolescents 12 to 17 Years of Age

Safety, efficacy and immunogenicity data for SPIKEVAX in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical trial (Study P203) conducted in the United States involving 3,726 participants 12 through 17 years of age who received at least one dose of SPIKEVAX (n=2,486) or placebo (n=1,240). Overall, 51.4% were male, 48.6% were female, 11.6% were Hispanic or Latino, 83.9% were White, 3.4% were African American, 5.9% were Asian, 0.5% were American Indian or Alaska Native, <0.1% were Native Hawaiian or Pacific Islander, 1.0% were other races, and 4.5% were multiracial. Demographic characteristics were similar among participants who received SPIKEVAX and those who received placebo.

14.1.3 Children 6 to 11 Years of Age

Safety data for SPIKEVAX in children were collected in an ongoing Phase 2/3 two-part clinical trial conducted in the United States and Canada. Part 1 is an open-label phase of the trial for safety, dose selection, and immunogenicity and included 380 participants 6 through 11 years of age who received at least 1 dose (0.25 mL, 50 mcg) of SPIKEVAX. Part 2 is the placebo-controlled phase for safety, immunogenicity and efficacy, and included 4,002 participants 6 through 11 years of age who received at least one dose of SPIKEVAX (n=3,007) or placebo (n=995). No participants in Part 1 participated in Part 2. Overall, in Part 2 50.8% were female and 49.2% male, 18.5% were Hispanic or Latino, 65.6% were White, 10.0% were African American, 9.9% were Asian, 0.4% were American Indian or Alaska Native, <0.1% were Native Hawaiian or Pacific Islander, 2.1% were other races and 10.6% were multiracial. Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.

14.1.4 Booster Dose (Participants ≥ 18 Years of Age)

A booster dose of SPIKEVAX was evaluated in Study P201 Part B, an open-label part assessing immunogenicity following administration of a 50 ug booster dose in participants 18 years of age and older (N=171) who had received a SPIKEVAX primary series in Study P201 Part A. Participants were predominantly female (60.8%), had a mean age of approximately 52 years and were predominantly white (95.9%).

14.2 Study Results

14.2.1 Efficacy in Participants ≥ 18 Years of Age (Based on Cut-off Date of November 21, 2020)

The analysis of the primary efficacy endpoint in the COVE Study (P301) included 28,207 participants 18 years of age and older (14,134 in the SPIKEVAX group and 14,073 in the placebo group). At the time of the final primary efficacy analysis, participants had been followed for symptomatic COVID 19 disease for a median of 2 months after the second dose, corresponding to 3304.9 person years for the SPIKEVAX group and 3273.7 person years in the placebo group.

There were 11 confirmed COVID-19 cases identified in the SPIKEVAX group and 185 in placebo groups, respectively, for the primary efficacy analysis. Compared to placebo, efficacy of SPIKEVAX in participants with first COVID-19 occurrence from 14 days after Dose 2 was 94.1% (two-sided 95% confidence interval of 89.3% to 96.8%). In participants 65 years of age and older, efficacy of SPIKEVAX was 86.4% (two-sided 95% confidence interval of 61.4%% to 95.5%). At the time of primary efficacy analysis, there was a total of 30 severe COVID-19 cases reported in the placebo group starting 14 days after Dose 2, per adjudication committee assessment. No cases of severe COVID-19 were reported in the SPIKEVAX group.

14.2.2 Efficacy and Immunogenicity in Adolescents 12 to 17 Years of Age (Based on Cut-off Date of May 8, 2021)

The vaccine safety, efficacy and immunogenicity in participants 12 to 17 years of age was evaluated in Study P203, an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial. Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732 participants were randomised 2:1 to receive 2 doses of SPIKEVAX or 2 doses of saline placebo 28 days apart. Participants will be followed for efficacy and safety until 1 year after the second dose.

There were 0 confirmed COVID-19 cases identified in the mRNA-1273 COVID-19 Vaccine (N=2,162) and 4 in placebo groups (N=1,073), respectively, for the vaccine efficacy analysis. Compared to placebo, efficacy of mRNA-1273 COVID-19 Vaccine in participants with first COVID-19 occurrence from 14 days after Dose 2 was 100% (two-sided 95% confidence interval of 28.9% to 100%).

An analysis of SARS-CoV-2 50% neutralising titers in randomly selected subsets of participants was performed to demonstrate non-inferior immune responses (within 1.5-fold) comparing adolescents 12 to 17 years of age (from Study P203) to participants 18 to 25 years of age (from Study P301) who had no serological or virological evidence of past SARS-CoV-2 infection. The immune response to SPIKEVAX in adolescents 12 to 17 years of age (n=340) was non-inferior to the immune response in participants 18 to 25 years of age (n=305), based on results for SARS-CoV-2 neutralizing titers at 28 days after the second dose. The geometric mean titers (GMT) ratio of the adolescents 12 to 17 years of age group to the participants 18 to 25 years of age group was 1.08, with a 2-sided 95% CI of 0.93 to 1.24, meeting the 1.5-fold non-inferiority criterion (the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] >0.67).

14.2.3 Immunogenicity and Efficacy in Children 6 to 11 Years of Age (Based on Cut-off Date of November 10, 2021)

The vaccine safety, efficacy and immunogenicity in participants 6 to 11 years of age was evaluated in Study P204 Part 2, an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial. Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,016 participants were randomised 3:1 to receive 2 doses (0.25 mL, 50 mcg) of SPIKEVAX or saline placebo 28 days apart. Participants will be followed for efficacy and safety until 1 year after the second dose. In Part 2, the median length of follow-up at the data cutoff date of November 10, 2021 was 82 days after dose 1 and 51 days after dose 2.

An immunobridging analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in subset of children aged 6 to 11 in the paediatric study (Study P204;

N=320) and in participants 18 through 25 years of age from the Phase 3 efficacy study (Study P301; N=295). Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralising antibody titers in children 6 to 11 years of age compared to the 18- to 25-year-olds was 1.239 (95% CI: 1.072, 1.432). The difference in seroresponse rate was 0.1% (95% CI: -1.9, 2.1). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met (see Table 11).

Table 11 – Immunogenicity Analysis, Neutralizing Antibody Geometric Mean Titers (ID50), Study P204 and Study P301

	Study P204 6 years to < 12 Years SPIKEVAX 50 µg N=320	**Study P301 18 to ≤ 25 Years SPIKEVAX 100 µg N=295**
Baseline GMT	9.250	9.285
GMT Observed at Day 57	1610.203	1299.855
GMR at Day 57 (Study P204 vs P301; model based)(95% CI)[a]	1.239 (1.072, 1.432)	
Participants achieving seroresponse, (%)[b] at Day 57	(99.1)	(99.0)
Difference in seroresponse rate (Study P204 vs P301), % (95% CI)[c]	0.1 (-1.9, 2.1)	

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID50 = 50% inhibitory dose.

[a] The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (children in P204 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.

[c] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

An exploratory efficacy analysis evaluating confirmed COVID-19 cases that accrued up to the data cutoff date of November 10, 2021 was performed in 3497 participants who received two doses of either SPIKEVAX (n=2644) or placebo (n=853), and had a negative baseline SARS-CoV-2 status. There were 3 confirmed cases in each arm, with the incidence rate per 1000 person-years being smaller in the vaccine arm (5.04) than in the placebo arm (16.26).

14.2.4 Immunogenicity in Participants ≥ 18 Years of Age – After Booster Dose

Effectiveness of the single booster dose of 50 mcg of SPIKEVAX in adults 18 years of age and older who received a 2-dose primary series with 100 mcg SPIKEVAX at least 6 months prior to booster was inferred by comparing the antibody titers from Study P201 Part B to the pivotal adult Study P301.

Study P201 Part B was an open-label study assessing immunogenicity responses following administration of a 50 mcg booster of SPIKEVAX to participants primed with 100 mcg doses of SPIKEVAX. Participants with negative baseline SARS-CoV-2 status were randomly selected from Study P301 participants in the SPIKEVAX group to form an Immunogenicity Subset in Study P301, which was used as the comparator arm for the Study P201 Part B immunobridging analysis.

Immunobridging analyses compared the neutralizing antibody titers (ID50) 28 days following the booster dose (201 Part B; N=149) to the corresponding titers 28 days after completion of the primary series in a random subset of participants 18 years of age and older from the Phase 3 efficacy study (P301; N=1055).

In participants who were primed with a 2-dose series of 100 mcg of SPIKEVAX, single booster dose of 50 mcg of SPIKEVAX demonstrated a geometric mean fold rise of 12.99 (95% CI: 11.04, 15.29) from pre-booster values of neutralizing antibodies as compared to 28 days after the booster dose. The geometric mean ratio (comparing the antibody levels on Day 29 in Study P201 Part B vs. the antibody levels on Day 57 after the priming series in Study P301) was 1.76 (95% CI: 1.50, 2.06), successfully meeting the pre-specified non-inferiority criterion of 0.67 corresponding to non-inferiority margin of 1.5. The analysis is summarized in Table 12.

Table 12 – Neutralizing Antibody Geometric Mean Titers (ID50) Against a Pseudovirus Expressing the SARS-CoV-2 Spike Protein at 28 Days After a Booster Dose in Study P201 Part B vs 28 Days After Completion of the Primary Series in Study P301, Participants ≥18 Years of Age, Per-Protocol Immunogenicity Set

Study P201 Part B Booster Dose N[a]=149 GMT[b] (95% CI)	Study P301 Primary Series N[a]=1053 GMT[b] (95% CI)	GMT Ratio (Study P201 Part B/ Study P301)	Met Success Criteria[c]
1802 (1548, 2099)	1027 (968, 1089)	1.76 (1.50, 2.06)	Lower limit of 95% CI ≥0.67 Criterion: Yes Point Estimate ≥1.0 Criterion: Yes

* Per-Protocol Immunogenicity Set included all subjects who had both baseline (or Study P201 Part B Day 1) and post-vaccination immunogenicity samples, did not have SARS-CoV-2 infection at baseline (or Study P201 Part B Day 1), did not have a major protocol deviation that impacted immune response, and had post-injection immunogenicity assessment at timepoint of primary interest (Day 29 for Study P201 Part B and Day 57 for Study P301).
[a]Number of subjects with non-missing data at the corresponding timepoint.
[b]The statistical analysis plan pre-specified an analysis of covariance model for estimating the geometric mean titer that adjusts for differences in age groups (<65 years, ≥65 years).
[c]Immunobridging is declared if the lower limit of the 2-sided 95% CI for the GMR is >0.67 and the point estimate of the GLSM ratio is ≥1.0.
Note: Antibody values < the lower limit of quantitation (LLOQ) are replaced by 0.5 × LLOQ. Values > the upper limit of quantitation (ULOQ) are replaced by the ULOQ if actual values are not available.
GLSM = Geometric least squares mean
GMR = Geometric mean ratio

15 MICROBIOLOGY

No microbiological information is required for this vaccine product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Intramuscular administration of SPIKEVAX (or other Moderna mRNA investigational vaccines) at doses ranging from 9 to 150 mcg/dose administered once every 2 weeks for up to 6 weeks resulted in transient injection site erythema and edema, body temperature increases, and a generalized systemic inflammatory response. Transient hepatocyte vacuolation and/or Kupffer cell hypertrophy, often observed without liver enzyme elevations, was observed and considered secondary to the systemic inflammatory response. In general, all changes resolved within 2 weeks.

Carcinogenicity: SPIKEVAX has not been evaluated for carcinogenicity in animals, as carcinogenicity studies were not considered relevant to this vaccine.

Genotoxicity: SM-102, a proprietary lipid component of SPIKEVAX, is not genotoxic in the bacterial mutagenicity and the human peripheral blood lymphocytes chromosome aberration assays. Two intravenous in vivo micronucleus assays were conducted with mRNA therapies using the same lipid nanoparticle (LNP) formulation as SPIKEVAX. Equivocal results observed at high systemic concentrations were likely driven by micronuclei formation secondary to elevated body temperature induced by a LNP-driven systemic inflammatory response. The genotoxic risk to humans is considered to be low due to minimal systemic exposure following intramuscular administration, limited duration of exposure, and the negative in vitro results.

Reproductive and Developmental Toxicology: In a pre- and post-natal developmental toxicity study, 0.2mL of a vaccine formulation containing the same quantity of mRNA (100 mcg) and other ingredients included in a single human dose of SPIKEVAX was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related adverse effects on female fertility, fetal development or postnatal development were reported in the study.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SPIKEVAX™

Elasomeran mRNA vaccine, Dispersion for Intramuscular Injection

Read this carefully before you start taking **SPIKEVAX**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SPIKEVAX**.

What is SPIKEVAX used for?
SPIKEVAX is a vaccine used to prevent the coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus. It can be given to people aged 6 years and older.

How does SPIKEVAX work?
SPIKEVAX works by causing the body to produce its own protection (antibodies) against the SARS-CoV-2 virus that causes the COVID-19 infection. SPIKEVAX uses a molecule called messenger ribonucleic acid (mRNA, the genetic code for a piece of the virus) to deliver the set of instructions that cells in your body can use to make antibodies to help fight the virus that causes COVID-19. The vaccine is given by injection with a needle in the upper arm. The primary vaccination series will require two doses given 4 weeks apart.

You cannot get COVID-19 from this vaccine.

As with any vaccine, SPIKEVAX may not fully protect all those who receive it. Even after you have had the vaccine, continue to follow the recommendations of local public health officials to prevent spread of COVID-19.

Individuals may not be optimally protected until after receiving the second dose of the vaccine.

What are the ingredients in SPIKEVAX?
Medicinal ingredients: Elasomeran (mRNA)

Non-medicinal ingredients:
- acetic acid
- cholesterol
- DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)
- PEG2000-DMG (1,2-dimyristoyl-rac-glycerol,methoxy-polyethyleneglycol)
- lipid SM-102
- sodium acetate trihydrate
- sucrose
- trometamol
- trometamol hydrochloride
- water for injection

SPIKEVAX comes in the following dosage forms:
White to off-white dispersion for injection provided in a multidose vial. For individuals 12 years of age and older each dose in the primary vaccination series is 100 micrograms of elasomeran (mRNA). For children 6 to 11 years of age each dose in the primary vaccination series is 50 micrograms of elasomeran.

The dose for the booster in individuals 18 years of age and older is 50 micrograms of elasomeran.

Do not receive SPIKEVAX if:
- you are allergic to the active substance or any of the other ingredients of this vaccine (see What are the ingredients in SPIKEVAX?)
- you have had an allergic reaction to a previous dose of SPIKEVAX
- you currently have symptoms that could be due to COVID-19. Talk with your healthcare professional about your symptoms and getting a COVID-19 test. Your healthcare professional will advise you when you are able to receive the vaccine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SPIKEVAX. Talk about any health conditions or problems you may have, including if you:
- have any allergies
- have had previous problems following administration of SPIKEVAX such as an allergic reaction or breathing problems
- have a weakened immune system due to a medical condition or are on a medicine that affects your immune system
- have a bleeding problem, bruise easily or use a blood thinning medication
- have a high fever or severe infection
- have any serious illness
- have previously had episodes of myocarditis (inflammation of the heart muscle) and/or pericarditis (inflammation of the lining outside the heart)
- are pregnant, think you may be pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There is no information on the use of SPIKEVAX with other vaccines. Tell your healthcare professional if you have recently received any other vaccine.

How is SPIKEVAX given:
- Your doctor, pharmacist or nurse will inject the vaccine into a muscle (intramuscular injection) in your upper arm
- During and after each injection of the vaccine, your doctor, pharmacist or nurse will watch over you for around 15 minutes to monitor for signs of an allergic reaction.

Usual dose:
SPIKEVAX will be given to you as two injections (called the primary vaccination series). Each injection will be given on a separate visit 1 month apart. It is very important that you return for the second injection, or the vaccine may not work as well.

- For individuals 12 years of age and older, each dose is 100 mcg.
- For children 6 to 11 years of age, each dose is 50 mcg.

The booster dose is given as one 50 mcg injection. The booster dose may be given on a separate visit at least 6 months after completion of the primary vaccination series in individuals 18 years of age and older.

Overdose:

In the event of suspected overdose with SPIKEVAX, contact your regional poison control centre.

Missed Dose:
If you forget to go back to your healthcare professional at the scheduled time for your next dose, ask your healthcare professional for advice.

What are possible side effects from using SPIKEVAX?
Like all vaccines, SPIKEVAX can cause side effects.

The following are common or very common side effects of SPIKEVAX. Most of these side effects are mild and do not last long. Tell your doctor if you have side effects that bother you:
- pain at the injection site
- tiredness
- headache
- muscle ache and stiffness
- chills
- fever
- swelling or redness at the injection site
- nausea and/or vomiting
- enlarged lymph nodes
- hypoaesthesia (decreased sense of touch or sensation, numbness) or paraesthesia (tingling, itching or pricking sensation)
- dizziness

Non-severe allergic reactions (such as rash, itching, hives or swelling of the face), severe allergic reactions, erythema multiforme (red round patches on the skin) and facial paralysis / Bell's palsy have been reported.

These are not all the possible side effects you may have when taking SPIKEVAX. If you experience any side effects not listed here, tell your healthcare professional.

Should you develop any serious symptoms or symptoms that could be an allergic reaction, seek medical attention right away. Symptoms of an allergic reaction include:
- hives (bumps on the skin that are often very itchy)
- swelling of the face, tongue or throat
- difficulty breathing

If you experience a severe allergic reaction, call 9-1-1, or go to the nearest hospital.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Suspected Side Effects for Vaccines

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional.

Should you require information related to the management of the side effect, please contact your healthcare professional. The Public Health Agency of Canada, Health Canada and ModernaTX, Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/form.html) and send it to your local Health Unit.

Storage:
Your doctor or pharmacist is responsible storing, supplying and administering SPIKEVAX, as well as disposing of any unused product correctly.

Keep out of reach and sight of children.

If you want more information about SPIKEVAX:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.modernacovid19global.com/ca/, or by calling 1-866-MODERNA (1-866-663-3762).

This leaflet was prepared by ModernaTX, Inc.

Last Revised 1 Jun 2022

Appendix 10.5 Information Related to Canadian Patient Exposure

As of DLP, there were 8 studies in Canada with a total of 407 patients exposed in clinical trials to mRNA-1273.

Appendix 10.6 Post-marketing Experience in the Canadian Context

As of DLP, a total of 45,957,240 doses were delivered and 23,752,558 doses were administered in Canada.

Appendix 10.7 Pharmacovigilance Activities within Canada

The information below is described in the Canadian Addendum. Please refer to the Canadian Addendum v3.1 to the EU RMP v4.1 for full detailed information of all Canadian-specific PV activities.

Routine:

- Adverse reactions associated with Moderna COVID-19 Vaccine will be reported to Health Canada in an expedited fashion.
- ModernaTx, Inc. will submit bimonthly safety reports as required per the Post-Authorization Final Terms and Conditions issued for elasomeran which received Notice of Compliance (NOC) on 16 Sep 2021.
- ModernaTx, Inc. will submit Periodic Safety Update Reports (PSURs)/Periodic Benefit Risk Evaluation Reports (PBRERs) every 6 months, as required per the Post-Authorization Final Terms and Conditions issued for elasomeran which received Notice of Compliance (NOC) on 16 September 2021.
- In a timely manner, Moderna will submit an updated Core RMP (EU RMP) and Canadian Addendum if a signal of safety issue is observed in post-authorization surveillance including the information described in the Canadian-specific Addendum.
- If adverse events are received containing sufficient information to identify them as originating from marginalized, remote, or indigenous communities then these will be summarized in a Canadian appendix to the monthly report.

Additional:

A global plan for additional PV activities is proposed that is included in the EU RMP (see section III.3 Summary Table of additional Pharmacovigilance activities). The observational pregnancy outcome study described in section III of the EU RMP has sites planned in Canada in addition to EU and US.

Study mRNA-1273-P204, is currently ongoing in Canada, for investigation of the safety, immunogenicity and dose-ranging of mRNA-1273 in children 6 months to 12 years of age, please refer to EU RMP Section III.2 Additional Pharmacovigilance Activities.

In addition, the following follow-up forms outlined below are used in Canada:

- Moderna Initial Pregnancy Report Form
- Moderna Pregnancy Outcome Form
- Guillain-Barre Syndrome Follow-up Form
- Moderna Vaccine Hypersensitivity Anaphylaxis Follow-up Form
- Moderna Adverse Event Follow-up Form
- Moderna COVID-19 Follow-up Questionnaire
- Moderna COVID-19 Vaccine Failure Questionnaire
- Moderna Myocarditis/Pericarditis Follow-up Questionnaire

Appendix 10.8 Verification of AR records against Health Canada's Canada Vigilance Database

Health Canada publishes Adverse Reaction reports received directly by them on a monthly basis on the Canada Vigilance Adverse Reaction Online database. The last monthly update on the Canada Vigilance Adverse Reaction Online database was on 03 Jun 2022 to include reports until 28 Feb 2022. Moderna has successfully completed the download and processing of all applicable cases related to elasomeran in the Global safety database.

Appendix 10.9 Risk Minimization Strategies and Evaluation Of Effectiveness Of Risk Minimization Activities To The Canadian Context

Moderna is using the Canadian Product Monograph to inform on safety risks and their management. Moderna will monitor adverse events from Canada and will update the safety profile should new adverse drug reactions are identified.

Appendix 11 Other Appendices Supporting PBRER

Appendix 11.1 Worldwide Marketing Authorization status

Table 20.5 Worldwide Marketing Authorization: Adults 18+ Years

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Approval/ Authorization Number	Expiration of Temp Authorization
1.	United States	Moderna COVID-19 Vaccine Suspension for injection	18 Dec 2020	Emergency Use Authorization (FDA)	27073	Valid until Health Emergency ends
2.	United States	SPIKEVAX (COVID-19 Vaccine, mRNA)	31 Jan 2022	Biologics License Application (BLA)	2256	N/A
3.	Canada	SPIKEVAX™ (elasomeran mRNA vaccine) Dispersion for injection	16 Sep 2021	Notice of Compliance (Health Canada)	252733	N/A
4.	Israel	COVID-19 Vaccine Moderna Dispersion for injection	04 Jan 2021	Exceptional Use Authorization (MOH)	Not applicable	TBD
5.	European Economic Area (30 member states)	COVID-19 Vaccine Moderna Dispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA)	EU/1/20/1507/ 001	Valid for 1 year (opportunity to renew) 06 Jan 2023
6.	United Kingdom	COVID-19 Vaccine Moderna Dispersion for injection	31 Mar 2021	Conditional Marketing Authorisation (MHRA)	PLGB 53720/0002 - 0001	Valid for 1 year 31 Mar 2022
7.	Switzerland	COVID-19 Vaccine Moderna Dispersion for injection	12 Jan 2021	Temporary Marketing Approval (SwissMedic)	68267	Valid for 2 years 12 Jan 2023
8.	Qatar	COVID-19 Vaccine Moderna Dispersion for injection	20 Jan 2021	Emergency Use Authorization (MOH)	PDCD/EM/00 04	Valid until Health Emergency ends
9.	Singapore	COVID-19 Vaccine Moderna	03 Feb 2021	Pandemic Special Access Route (PSAR) application	PSAR Ref: 5ff7c74431b81 000117b7397	Valid 1 year

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Approval/ Authorization Number	Expiration of Temp Authorization
		Dispersion for injection				
10.	Paraguay	n/a	29 Dec 2020	Emergency Use Authorization for all COVID19 vaccines authorized by FDA or EMA	n/a	No expiration date
11.	Brunei	Moderna COVID-19 Vaccine (mRNA-1273 Vaccine)	09 Apr 2021	Emergency Use Authorization by BDMCA	(22) BDMCA/SPE _MP/2021	08 Apr 2024
12.	Botswana	COVID-19 Vaccine Moderna dispersion for injection	16 Apr 2021	Emergency Use Authorization	BEU210010	No expiration date
13.	Taiwan	Moderna COVID-19 Vaccine	22 Apr 2021	Special Import Permit	DHS00000000 000	30 Jun 2022
14.	Philippines	COVID-19 Vaccine Moderna	05 May 2021	Emergency Use Authorization	n/a	Expires when the public health emergency ends
15.	Thailand	COVID-19 Vaccine Moderna	13 May 2021	Conditional Authorization for Emergency Use	1C 6/64 (NBC)	12 May 2022
16.	South Korea	COVID-19 Vaccine Moderna	21 May 2021	Conditional Marketing Authorisation	5108	5 years
17.	Japan	SPIKEVAX IM (COVID-19 Vaccine Moderna IM)	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act	n/a	8 years ("re-examination period," no expiry)
18.	Jordan	COVID-19 Vaccine Moderna	08 Jun 2021	Emergency Use Authorization	n/a	unknown
19.	Bhutan	COVID-19 Vaccine Moderna	22 Jun 2021	Emergency Use Authorization	DRA/D4b/01-Gen/20-21/1059	Expires when declaration COVID-19 pandemic is over
20.	UAE	COVID-19 Vaccine Moderna	22 Jun 2021	Emergency Use Authorization	52773-1572-79783	1 year

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Approval/ Authorization Number	Expiration of Temp Authorization
21.	Colombia	COVID-19 Vaccine Moderna	25 Jun 2021	Emergency Use Authorization	n/a	1 year
22.	Saudi Arabia	COVID-19 Vaccine Moderna	26 Jun 2021	Conditional approval		No expiration date
23.	Vietnam	SPIKEVAX	28 Jun 2021	Conditional approval	3122/QĐ-BYT	No expiration date
24.	Sri Lanka	COVID-19 mRNA Vaccine (nucleoside modified) (Moderna) (mRNA1273)	29 Jun 2021	Import License	NMRA/EA/EUP/MED-VAC/07/2021	Not shown
25.	Haiti	Vaccine ARNm 1273	30 Jun 2021	Emergency Use Authorization	n/a	29 Jun 2022
26.	Indonesia	COVID-19 Vaccine Moderna	02 Jul 2021	Emergency Use Authorization	EUA21597001 43A1	Not shown
27.	Ukraine	COVID-19 Vaccine Moderna	08 Jul 2021	Emergency Use Authorization	n/a	Not shown
28.	Tunisia	COVID-19 Vaccine Moderna	25 Jun 2021	Conditional approval	n/a	24 Jun 2022
29.	Algeria	COVID-19 Vaccine Moderna	14 Jul 2021	Conditional approval	n/a	13 Jul 2022
30.	Nigeria	COVID-19 Vaccine Moderna	14 Jul 2021	Emergency Use Authorization	n/a	13 Jul 2022
31.	Ghana	SPIKEVAX	30 Jun 2021	Emergency Use Authorization	FDA/HPT/DHM/VBP/BPV/21/0134	01 Jul 2021
32.	Cambodia	Moderna COVID-19 Vaccine	02 Aug 2021	Emergency Use Authorization	D6H/DDF4016	Expires when the public health emergency ends
33.	Malaysia	SPIKEVAX	05 Aug 2021	Conditional approval	Not provided	04 Aug 2022
34.	Malawi	n/a	05 Aug 2021	Emergency Use Authorization	n/a	Not shown

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Approval/ Authorization Number	Expiration of Temp Authorization
35.	Australia	SPIKEVAX	09 Aug 2021	Provisional approval		
36.	Palestine	n/a	13 Aug 2021	Emergency Use Authorization	Not provided	Not shown
37.	Egypt	COVID-19 Vaccine Moderna	17 Aug 2021	Emergency Use Authorization	Not provided	Not shown
38.	Cabo Verde	SPIKEVAX/ Moderna COVID-19 vaccine	10 Sep 2021	Emergency Use Authorization	0136/2021	09 Sep 2022
39.	Argentina	SPIKEVAXCOVID-19 Vaccine Moderna Intramuscular Injection	05 Oct 2021	Emergency Use Authorization	RESOL-2021-277-APN-MS	Not shown
40.	African Union (55 countries)	SPIKEVAX				
41.	WHO	COVID-19	12 May 2021	Emergency Use Listing	I8-370-43 AMRO	time-limited recommendation
42.	Lebanon	SPIKEVAX	22 Nov 2021	Emergency Use Authorization	Lebanon	SPIKEVAX
43.	South Korea	SPIKEVAX Injection	13 Dec 2021	Conditional Marketing Authorization	1	20 May 2032 (5 years after re-examination period)
44.	Kuwait	SPIKEVAX	Sep 2021	Emergency Use Authorization	n/a (Approval received in September, but provided in Jan 2022 to Moderna as it was gated by the supply date)	1 year
45.	Turkmen-istan	SPIKEVAX	15 Dec 2021	Marketing Authorization	022450	5 years
46.	Seychelles	SPIKEVAX	23 Feb 2022	MAA		
47.	Chile	SPIKEVAX	03 Feb 2022.	Emergency Use Authorization	RM-05888	Expires when the public health

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Approval/ Authorization Number	Expiration of Temp Authorization
						emergency ends
48.	Peru	SPIKEVAX	11 Mar 2022	Conditional Marketing Authorization	BEC-0011	11 Mar 2023

Of note: WHO approved use of SPIKEVAX on 12 May 2021 for adults 18+ years

Abbreviations: AMRO = Americas Regional Office; COVID-19 = Coronavirus disease 2019; BDMCA = Brunei Darussalam Medicines Control Authority; EMA = European Medicines Agency; FDA = US Food and Drug Administration; MHRA = Medicines and Healthcare Regulatory Agency; MOH = Ministry of Health; NA = not applicable; PMD = pharmaceutical and medical devices; PSAR = Pandemic Special Access Route; TBD = to be determined; UAE = United Arab Emirates; WHO = World Health Organization

Table 20.6 Worldwide Marketing Authorisation: 12 to < 18 Years of Age (Adolescents)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
	United States	Moderna COVID-19 Vaccine Suspension for injection	18 Dec 2020	Emergency Use Authorization (FDA) Nbr: 27073	09 Jun 2021	17 Jun 2022
	European Economic Area (30 member states)	SPIKEVAX Dispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA) Nbr: EU/1/20/1507/001	04 Jun 2021	23 Jul 2021 (CHMP Opinion and Commission decision)
	Japan	SPIKEVAXIM (COVID-19 Vaccine Moderna IM)	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act	09 Jun 2021	26 Jul 2021
	Canada	SPIKEVAX™ (elasomeran mRNA vaccine) Dispersion for injection	16 Sep 2021	Notice of Compliance (Health Canada) 252733	NDS: 15 Jun 2021 IO. 04 Jun 2021	16 Sep 2021 (Indication first authorized under Interim Order on 27 Sept 2021)

	Country	Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
	Switzerland	COVID-19 Vaccine Moderna Dispersion for injection	12 Jan 2021	Temporary Marketing Approval (SwissMedic) Nbr: 68267	11 Jun 2021	09 Aug 2021
	Argentina	COVID-19 Vaccine Moderna Intramuscular Injection	Not yet approved	Emergency Use Authorization	26 Jun 2021	05 Oct 2021
	Israel	COVID-19 Vaccine Moderna	04 Jan 2021	Emergency Use Authorization	29 Jun 2021	Pending approval
	Singapore	COVID-19 Vaccine Moderna	03 Feb 2021	Pandemic Special Access Route (PSAR) application	05 Jul 2021	Pending approval
	Qatar	COVID-19 Vaccine Moderna	20 Jan 2021	Emergency Use Authorization (MOH)	05 Jul 2021	09 Sep 2021
).	Taiwan	Moderna COVID-19 Vaccine	22 Apr 2021	Special Import Permit	05 Jul 2021	18 Aug 2021
.	South Korea	COVID-19 Vaccine Moderna	21 May 2021	Conditional Marketing Authorisation	05 Jul 2021	Pending approval
2.	Thailand	COVID-19 Vaccine Moderna	13 May 2021	Conditional Authorization for Emergency Use	05 Jul 2021	11 Oct 2021
3.	Philippines	COVID-19 Vaccine Moderna	05 May 2021	Emergency Use Authorization	05 Jul 2021	03 Sep 2021
4.	Brunei	Moderna COVID-19 Vaccine	09 Apr 2021	Emergency Use Authorization by BDMCA	06 Jul 2021	Pending approval
5.	Botswana	COVID-19 Vaccine Moderna	16 Apr 2021	Emergency Use Authorization	06 Jul 2021	Pending approval
6.	UAE	COVID-19 Vaccine Moderna	22 Jun 2021	Emergency Use Authorization	06 Jul 2021	Pending approval
7.	Vietnam	SPIKEVAX	28 Jun 2021	Conditional approval	06 Jul 2021	26 Sep 2021

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
3.	Saudi Arabia	COVID-19 Vaccine Moderna	26 Jun 2021	Conditional approval	06 Jul 2021	21 Aug 2021
9.	Malaysia	SPIKEVAX	pending	Emergency Use Authorization	07 Jul 2021	Pending approval
0.	Kuwait	SPIKEVAX	Sep 2021	Pending	13Jul 2021	September 2021
.	Great Britain	COVID-19 Vaccine Moderna	31 Mar 2021	Conditional approval	13 Jul 2021 (Reliance route with EMA's approval, as exception as requested by MHRA)	17 Aug 2021
2.	Australia	SPIKEVAX	09 Aug 2021	Provisional approval	Jun 2021	03 Sep 2021
5.	Colombia	COVID-19 Vaccine Moderna	25 Jun 2021	Emergency Use Authorization	17 Sep 2021	21 Sep 2021
4.	Seychelles	SPIKEVAX	23 Feb 2022		23 Feb 2022	23 Feb 2022
5.	Chile	SPIKEVAX	03 Feb 2022	Emergency Use Authorization	RM-05888	Expires when the public health emergency ends
6.	Peru	SPIKEVAX	11 Mar 2022	Conditional Marketing Authorization	BEC-0011	11 Mar 2023

Abbreviations: COVID-19 = Coronavirus disease 2019; BDMCA = Brunei Darussalam Medicines Control Authority; EMA = European Medicines Agency; FDA = US Food and Drug Administration; MHRA = Medicines and Healthcare Regulatory Agency; MOH = Ministry of Health; NA = not applicable; PMD = pharmaceutical and medical devices; PSAR = Pandemic Special Access Route; TBD = to be determined

Table 20.7 List of Approved Countries for the 6 to < 12-Year-Old Indication (Paediatrics)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
1.	United States	Moderna COVID-19 Vaccine Suspension for injection	18 Dec 2020	Emergency Use Authorization (FDA) Nbr: 27073	09 Jun 2021	17 Jun 2022
2.	Canada	SPIKEVAX™ (elasomeran mRNA vaccine)	16 Sep 2021	Notice of Compliance (Health Canada)	15 Nov 2021	17 Mar 2022

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
		Dispersion for injection		252733		
3.	European Economic Area (30 member states)	SPIKEVAXDispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA) Nbr: EU/1/20/1507/001	09 Nov 2021	02 Mar 2022
4.	Switzerland	SPIKEVAXDispersion for injection	12 Jan 2021	Conditional Marketing Authorisation (Swissmedic) 68267	18 Nov 2021	pending
5.	Israel	SPIKEVAXDispersion for injection	04 Jan 2021	Emergency Use Authorization	11 Nov 2021	Pending
6.	Australia	SPIKEVAX	09 Aug 2021	Provisional approval	12 Nov 2021	17 Feb 2022
7.	Colombia	SPIKEVAX COVID-19 Vaccine Moderna	25 Jun 2021	Emergency Use Authorization	02 Dec 2021	pending
8.	Singapore	COVID-19 Vaccine Moderna	03 Feb 2021	Pandemic Special Access Route (PSAR) application	19 Nov 2021	pending
9.	WHO	COVID-19	12 May 2021	Emergency Use Listing	22 Nov 2021	pending
10.	United Kingdom	COVID-19 Vaccine Moderna Dispersion for injection	31 Mar 2021	Conditional Marketing Authorisation (MHRA)	02 Feb 2022	14 Apr 2022 Approved
11.	Philippines	COVID-19 Vaccine Moderna	05 May 2021	Emergency Use Authorization	01 Mar 2022	pending
12.	Taiwan	Moderna COVID-19 Vaccine	22 Apr 2021	Special Import Permit	18 Feb 2022	17Apr2022
13.	Vietnam	SPIKEVAX	28 Jun 2021	Conditional Approval	25-Feb-2022	31 Mar 2022 Approved
14.	Thailand	SPIKEVAX	13 May 2021	Conditional Authorization for Emergency Use	31 Mar 2022	pending
15.	Saudi Arabia	COVID-19 Vaccine Moderna	26 Jun 2021	Conditional approval		Approved on 06 Apr 2022

Table 20.8 List of Approved Countries for the 50 µg Booster Indication (Adults)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
1.	United States	Moderna COVID-19 Vaccine Suspension for injection	18 Dec 2020	Emergency Use Authorization (FDA) Nbr: 27073	01 Sep 2021 followed by 3 Sep for datasets	20 Oct 2021
2.	Canada	SPIKEVAX™ (elasomeran mRNA vaccine) Dispersion for injection	16 Sep 2021	Notice of Compliance (Health Canada) 252733	05 Oct 2021	12 Nov 2021
3.	European Economic Area (30 member states)	SPIKEVAX Dispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA) Nbr: EU/1/20/1507/001	03 Sep 2021	CHMP opinion on 25 Oct 2021 EC decision on 29 Oct 2021
4.	Switzerland	SPIKEVAX Dispersion for injection	12 Jan 2021	Conditional Marketing Authorisation (Swissmedic) 68267	07 Sep 2021	25 Oct 2021
5.	South Korea	SPIKEVAX Dispersion for injection	21 May 2021	Conditional Marketing Authorisation	09 Sep 2021	
6.	Israel	SPIKEVAX Dispersion for injection	04 Jan 2021	Emergency Use Authorization	09 Sep 2021	Approved
7.	Qatar				18 Nov 2021	18 Nov 2021
8.	Malaysia	SPIKEVAX Dispersion for injection	05 Aug 2021	Emergency Use Authorization	29 Sep 2021	
9.	Saudi Arabia	SPIKEVAX Dispersion for injection	26 Jun 2021	Emergency Use Authorization	29 Sep 2021	07 Nov 2021
10.	Great Britain	COVID-19 Vaccine Moderna	31 Mar 2021	Conditional approval	29 Oct 2021 (Reliance route with EMA's	15 Dec 2021

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
					approval, as exception as requested by MHRA)	
11.	UAE	COVID-19 Vaccine Moderna	22 Jun 2021	Emergency Use Authorization		09 Dec 2021 (18yo+)
12.	Australia	SPIKEVAX	09 Aug 2021	Provisional approval	11 May 2021	07 December 2021 (18yo+)
13.	Japan	SPIKEVAXIM (COVID-19 Vaccine Moderna IM)	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act	20 Oct 2021	16 December 2021 (18yo+)
14.	Argentina	SPIKEVAX COVID-19 Vaccine Moderna Intramuscular Injection	05 Oct 2021	Emergency Use Authorization	12 Nov 2021	Under review
15.	Colombia	SPIKEVAX COVID-19 Vaccine Moderna	25 Jun 2021	Emergency Use Authorization	12 Nov 2021	03 Dec 2021
16.	Philippines	SPIKEVAX	05 May 2021	Emergency Use Authorization		10 Dec 2021 (Revised SmPC on 28 Dec 2021, 18+yr)
17.	Taiwan	SPIKEVAX	22 Apr 2021	Special Import Permit	02 Dec 2021	07-Jan-2022 (18+yr)
18.	Vietnam	SPIKEVAX	28 Jun 2021	Conditional approval		19 January 2021
19.	Brunei	SPIKEVAX	09 Apr 2021	Emergency Use Authorization by BDMCA		24 Feb 2022 (18+yr)
20.	Thailand	SPIKEVAX	13 May 2021	Conditional Authorization for Emergency Use		1 Mar 2022 (18+yr)
21.	Seychelles	SPIKEVAX	23 Feb 2022	MAA		23 Feb 2022 (18+yr)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
22.	Chile	SPIKEVAX	03 Feb 2022	Emergency Use Authorization	RM-05888	Expires when the public health emergency ends
23.	Peru	SPIKEVAX	11 Mar 2022	Conditional Marketing Authorization	BEC-0011	11 Mar 2023
24.	Singapore	SPIKEVAX COVID-19 Vaccine Moderna Dispersion for injection	03 Feb 2021	Pandemic Special Access Route (PSAR) application	PSAR Ref: 5ff7c74431b81000117b7397	04 Mar 2022

Abbreviations: COVID-19 = Coronavirus disease 2019; BDMCA = Brunei Darussalam Medicines Control Authority; EMA = European Medicines Agency; FDA = US Food and Drug Administration; MHRA = Medicines and Healthcare Regulatory Agency; MOH = Ministry of Health; NA = not applicable; PMD = pharmaceutical and medical devices; PSAR = Pandemic Special Access Route; TBD = to be determined.

Table 20.9 List of Approved Countries for the 50 µg Booster Indication (Adolescents)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
1.	Canada	SPIKEVAX™ (elasomeran mRNA vaccine) Dispersion for injection	16 Sep 2021	Notice of Compliance (Health Canada) 252733	14 Mar 2022	
2.	European Economic Area (30 member states)	SPIKEVAX Dispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA) Nbr: EU/1/20/1507/001	22 Feb 2022	
3.	Australia	SPIKEVAX	09 Aug 2021	Provisional approval	03 Mar 2022	
4.	United Kingdom	COVID-19 Vaccine Moderna Dispersion for injection	31 Mar 2021	Conditional Marketing Authorisation (MHRA)	04 Mar 2022	

Table 20.10 List of Approved Countries for the 3rd Dose in Immunocompromised Patients

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
1.	United States	Moderna COVID-19 Vaccine Suspension for injection	18 Dec 2020	Emergency Use Authorization (FDA) Nbr: 27073	11 Aug 2021	12 Aug 2021
2.	European Union (member states)	COVID-19 Vaccine Moderna Dispersion for injection	06 Jan 2021	Conditional Marketing Authorisation under Regulation (EC) No. 726/2004 (EMA) Nbr: EU/1/20/1507/001	19 Aug 2021	CHMP opinion 04 Oct 2021 EC decision 05 Oct 2021
3.	Canada	SPIKEVAX™ (elasomeran mRNA vaccine) Dispersion for injection	16 Sep 2021	Notice of Compliance (Health Canada) 252733	01 Sep 2021 (under IO)	16 Sep 2021 under NDS NOC
4.	Switzerland	COVID-19 Vaccine Moderna Dispersion for injection	12 Jan 2021	Temporary Marketing Approval (SwissMedic) Nbr: 68267	06 Sep 2021	25 Oct 2021
5.	Japan	COVID-19 Vaccine Moderna Intramuscular Injection	21 May 2021	Article 14-3, Paragraph 1 of the PMD Act		
6.	Argentina	COVID-19 Vaccine Moderna Intramuscular Injection	05 Oct 2021	Emergency Use Authorization		
7.	Israel	COVID-19 Vaccine Moderna	04 Jan 2021	Emergency Use Authorization		Approved
8.	Singapore	COVID-19 Vaccine Moderna	3 Feb 2021	Pandemic Special Access Route (PSAR) application		
9.	Qatar	COVID-19 Vaccine Moderna	20 Jan 2021	Emergency Use Authorization (MOH)		Approved
10.	Taiwan	Moderna COVID-19 Vaccine	22 Apr 2021	Special Import Permit	02 Dec 2021	07 Jan 2022 (12+ yr)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
11.	South Korea	COVID-19 Vaccine Moderna	21 May 2021	Conditional Marketing Authorisation	24 Dec 2021	
12.	Thailand	COVID-19 Vaccine Moderna	13 May 2021	Conditional Authorization for Emergency Use		1 March 2022 (12+ yr)
13.	Philippines	COVID-19 Vaccine Moderna	05 May 2021	Emergency Use Authorization		10 Dec 2021 for limited group (Revised SmPC approved on 24 Jan 2022, 12+yr)
14.	Brunei	Moderna Covid-19 Vaccine	09 Apr 2021	Emergency Use Authorization by BDMCA		24 Feb 2022 (12+yr)
15.	Botswana	COVID-19 Vaccine Moderna	16 Apr 2021	Emergency Use Authorization		
16.	UAE	COVID-19 Vaccine Moderna	22 June 2021	Emergency Use Authorization		Approved on 09 Dec 2021, for individuals 12+
17.	Vietnam	SPIKEVAX	28 June 2021	Conditional approval		19 Jan 2022
18.	Saudi Arabia	COVID-19 Vaccine Moderna	26 June 2021	Conditional approval	29 Sep 2021	Approved (07 Nov 2021)
19.	Malaysia	SPIKEVAX	05 Aug 2021	Emergency Use Authorization		
20.	Kuwait	SPIKEVAX	pending	Pending		Approved
21.	Great Britain	COVID-19 Vaccine Moderna	31 March 2021	Conditional approval	08 Oct 2021 (Reliance route with EMA's approval, as exception as requested by MHRA)	02 Dec 2021
22.	Australia	SPIKEVAX	03 Sep 2021	Provisional approval	11 May 2021	07 Dec 2021 (12yo+)

Country		Product	Date of Approval or Authorization	Type of Approval or Authorization	Indication Submission	Indication Approval
23.	Colombia	SPIKEVAX COVID-19 Vaccine Moderna	25 Jun 2021	Emergency Use Authorization	12 Nov 2021	03 Dec 2021
24.	Chile	SPIKEVAX	03 Feb 2022	Emergency Use Authorization	RM-05888	Expires when the public health emergency ends
25.	Peru	SPIKEVAX	11 Mar 2022	Conditional Marketing Authorization	BEC-0011	11 Mar 2023
26.	Singapore	SPIKEVAX COVID-19 Vaccine Moderna Dispersion for injection	03 Feb 2021	Pandemic Special Access Route (PSAR) application	PSAR Ref: 5ff7c74431b81000117b7397	04 Mar 2022

Appendix 11.2 Summary of Exposure from Marketing Experience and Distribution and Administration Data

Country	Doses distributed	Doses administered
Angola [1]	40,56,000	20,28,000
Argentina	1,37,59,060	97,83,014
Australia [1]	2,18,43,800	1,09,21,900
Austria	55,86,500	15,95,310
Bangladesh [1]	1,02,81,500	51,40,750
Belgium	1,26,67,000	42,73,085
Benin [1]	5,50,800	2,75,400
Bhutan [1]	4,99,600	2,49,800
Bolivia [1]	19,65,600	9,82,800
Botswana [1]	10,01,340	5,00,670
Brunei Darussalam [1]	4,00,800	2,00,400
Bulgaria	9,58,100	4,97,496
Burkina Faso [1]	3,76,800	1,88,400
Cambodia [1]	1,88,160	94,080
Canada	4,59,57,240	2,37,52,558
Central African Republic [1]	91,200	45,600
Chile [1]	57,00,000	28,50,000
Colombia [1]	1,50,78,340	75,39,170
Croatia	10,49,400	5,12,141
Cyprus [2]	1,67,200	1,98,353
Czech Republic	35,22,600	15,99,431
Democratic Republic of the Congo [1]	18,82,020	9,41,010
Denmark	56,98,800	17,22,193
Dominica [1]	30,240	15,120
Egypt [1]	56,29,440	28,14,720
Estonia	2,72,800	2,35,107
Fiji [1]	1,92,000	96,000
Finland	21,37,900	19,06,111
France	5,71,40,000	2,43,27,556
Germany	8,22,75,600	2,96,34,245
Greece	19,00,800	15,98,812
Grenada [1]	10,080	5,040
Guinea [1]	1,88,400	94,200
Haiti [1]	1,51,200	75,600
Hungary	17,44,800	10,51,421
Iceland	2,62,900	97,372
Indonesia [1]	1,32,80,400	66,40,200
Ireland	26,22,100	12,07,518
Israel [1]	24,54,000	12,27,000
Italy	4,27,80,600	3,36,40,999
Japan	11,05,38,700	3,23,18,674
Kenya [1]	5,64,480	2,82,240
Kuwait [1]	4,99,200	2,49,600
Kyrgyzstan [1]	2,16,000	1,08,000

Latvia	11,68,900	7,02,652
Liechtenstein [3]	.	47,265
Lithuania	5,03,400	3,28,875
Luxembourg [2]	2,12,100	3,03,040
Malta	2,87,800	2,39,737
Mexico [1]	27,72,000	13,86,000
Moldova [1]	3,81,600	1,90,800
Nepal	76,52,800	69,69,264
Netherlands	1,13,27,200	63,89,356
Nigeria [1]	1,22,30,880	61,15,440
Norway	28,81,800	22,73,163
Pakistan [1]	2,63,46,460	1,31,73,230
Palestine [1]	4,53,600	2,26,800
Peru [1]	96,31,800	48,15,900
Philippines [1]	3,08,85,360	1,54,42,680
Poland	1,08,83,000	36,65,735
Portugal	61,95,400	36,42,487
Qatar [1]	34,09,800	17,04,900
Romania	53,12,300	9,76,469
Rwanda [1]	16,24,800	8,12,400
Sao Tome and Principe [1]	1,12,320	56,160
Saudi Arabia [1]	1,40,94,040	70,47,020
Singapore [1]	54,72,000	27,36,000
Slovakia	8,72,400	6,73,807
Slovenia	7,19,200	2,37,307
South Korea	3,06,06,860	2,47,19,242
Spain	2,70,05,600	2,38,77,671
St. Lucia [1]	5,040	2,520
Sweden	72,51,800	36,01,346
Switzerland	1,14,98,200	98,06,302
Taiwan [1]	1,52,77,680	76,38,840
Tajikistan [1]	21,09,840	10,54,920
Tanzania [1]	3,76,320	1,88,160
Thailand [1]	92,39,066	46,19,533
Tunisia [1]	3,00,720	1,50,360
Turkmenistan [1]	4,99,200	2,49,600
Uganda [1]	18,70,800	9,35,400
Ukraine [1, 5]	29,30,300	1465150
United Arab Emirates [1]	99,600	49,800
United Kingdom	2,27,50,600	1,25,00,000
USA	47,09,61,060	22,34,09,934
International donations [4]		4,69,62,026
Uzbekistan [1]	76,88,800	38,44,400
Vanuatu [1]	20,400	10,200
Vietnam [1]	80,35,960	40,17,980
Zambia [1]	1,88,400	94,200
Totals	1,25,23,20,706	66,28,71,167

1: For countries where administration estimates were not available, doses administered was estimated as 50% of the total doses distributed.
2: Whereas doses distributed are derived from internal Moderna supply chain estimates, doses administered are identified based on data shared publically by health authorities. In some instances, doses administered appear to exceed doses distributed, possibly due to redistribution of vaccines after initial delivery by Moderna. Data have been retained as they appeared in the respective sources.
3: Doses distributed to Switzerland are inclusive of doses that were ultimately administered in Liechtenstein.
4: A proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX. Based on data shared for the US, the MAH has estimated that 15% of all Moderna doses distributed may be part of such agreements. It is estimated that approximately 25% of these doses have been administered to date.
5: PBRER2 used OWID data but OWID stopped reporting the Ukraine data in February 2022 and we have started to imput estimates going forward.

Batch	Doses Distributed	Batch	Doses Distributed	Batch	Doses Distributed
7006520004	1,11,600	7006521072	13,66,300	7006521209	13,19,300
7006520005	33,100	7006521073	13,43,000	7006521210	30,23,800
7006520010	36,700	7006521074	12,25,200	7006521211	7,57,400
7006520012	11,09,700	7006521076	12,35,300	7006521212	14,32,900
7006520013	10,85,900	7006521077	13,04,300	7006521213	14,82,400
7006520014	4,43,500	7006521078	23,400	7006521214	14,96,800
7006520015	12,27,300	7006521080	14,32,600	7006521215	9,85,200
7006520016	16,67,600	7006521081	13,47,000	7006521216	15,75,200
7006520017	9,67,300	7006521082	13,28,900	7006521217	9,31,300
7006520018	25,44,400	7006521084	11,92,000	7006521218	11,53,100
7006520019	23,51,200	7006521085	12,25,200	7006521219	4,62,600
7006520020	11,86,000	7006521086	12,34,700	7006521221	10,38,200
7006520021	12,99,600	7006521087	13,20,900	7006521222	19,72,800
7006520022	14,20,600	7006521088	13,35,700	7006521223	13,92,300
7006520023	22,90,600	7006521089	11,10,500	7006521224	14,42,400
7006520024	11,15,100	7006521090	12,15,200	7006521225	14,49,600
7006520025	7,87,500	7006521091	12,40,400	7006521228	14,12,200
7006520026	12,90,600	7006521092	12,72,500	7006521229	12,05,300
7006520027	13,16,700	7006521093	13,59,400	7006521231	11,98,600
7006520028	12,93,300	7006521094	14,02,800	7006521232	14,13,800
7006520029	11,59,800	7006521095	13,67,500	7006521233	6,47,800
7006520030	14,47,100	7006521096	12,65,900	7006521233	8,89,000
7006520031	11,57,300	7006521098	13,89,600	7006521234	21,13,600
7006520032	14,51,300	7006521100	12,93,300	7006521234	3,91,600
7006520033	14,95,400	7006521102	11,63,300	7006522001	29,26,800
7006520034	11,29,200	7006521104	11,27,700	7006522002	30,34,800
7006520035	14,08,600	7006521105	13,98,100	7006522003	29,25,400
7006520036	12,25,800	7006521107	15,52,000	7006522004	31,28,800
7006520037	13,04,600	7006521108	14,78,100	7006522004	1,400
7006520038	14,91,100	7006521110	13,60,800	7006522005	14,30,800
7006520039	12,23,000	7006521113	12,01,700	7006522006	14,86,800
7006520040	11,19,500	7006521114	11,27,700	7006522007	200
7006520042	13,20,100	7006521115	11,67,600	7006522007	9,69,600
7006520043	11,94,700	7006521116	13,14,400	7006522008	14,28,400
7006521001	10,38,300	7006521130	10,83,100	7006522009	14,62,000
7006521002	11,12,700	7006521131	9,61,000	7006522010	15,68,100
7006521003	9,78,300	7006521133	12,33,400	7006522011	14,59,800
7006521004	12,60,500	7006521136	11,32,100	7006522012	14,79,300
7006521005	13,01,800	7006521137	12,02,800	7006522013	13,80,700
7006521006	10,70,300	7006521140	12,87,800	7006522014	14,96,000
7006521007	12,21,500	7006521141	13,63,300	7006522015	14,78,600
7006521008	13,09,700	7006521143	11,92,400	7006522016	14,85,400
7006521009	12,32,400	7006521144	14,71,800	7006522017	13,39,200
7006521010	11,14,400	7006521145	14,73,200	7006522018	6,46,200
7006521011	15,26,000	7006521145	5,62,800	7006522019	14,60,800
7006521012	15,36,000	7006521146	13,04,900	7006522021	12,81,000

7006521013	11,11,300	7006521147	14,48,000	7006522022	9,66,400
7006521014	12,08,400	7006521148	15,84,200	7006522024	10,50,000
7006521015	12,00,400	7006521150	14,44,200	7006522025	12,37,200
7006521016	10,94,500	7006521151	14,66,500	7006522026	8,35,600
7006521017	13,80,200	7006521152	30,58,400	7006522027	11,51,600
7006521018	11,90,400	7006521153	18,39,320	7006522028	11,91,000
7006521019	12,22,400	7006521153	5,23,440	7006522029	12,34,900
7006521020	14,77,200	7006521154	14,09,800	7006522030	12,58,600
7006521021	11,63,600	7006521155	28,03,800	7006522032	11,77,200
7006521022	13,45,600	7006521156	13,14,600	7006522033	8,47,000
7006521023	13,75,400	7006521158	14,80,600	7006522034	8,59,300
7006521024	12,49,200	7006521159	15,03,800	7006522035	8,54,000
7006521025	8,97,600	7006521160	28,66,400	7006522036	10,21,700
7006521026	13,95,500	7006521161	15,25,300	7006522037	3,70,100
7006521027	12,64,600	7006521162	2,200	7006522038	15,79,300
7006521028	10,39,500	7006521162	14,60,300	7006522039	10,94,500
7006521029	12,55,700	7006521163	12,03,000	7006522041	8,60,400
7006521030	7,74,200	7006521164	26,67,400	7006522042	10,99,900
7006521031	13,27,700	7006521165	23,34,800	7006522043	9,96,400
7006521033	14,04,700	7006521166	15,30,700	7006522045	13,03,300
7006521034	12,91,900	7006521167	14,70,900	7006522046	14,78,700
7006521035	13,18,900	7006521168	15,13,200	7006522047	5,74,300
7006521036	12,12,900	7006521169	12,56,700	7006522048	11,15,600
7006521037	11,88,300	7006521170	15,83,400	7006522049	13,53,200
7006521038	11,38,400	7006521171	91,200	7006622001	9,41,700
7006521040	5,37,600	7006521172	14,98,900	7006622002	13,91,800
7006521041	12,82,300	7006521173	23,70,600	7006622003	10,78,200
7006521042	12,95,300	7006521175	11,51,000	7006622004	8,43,600
7006521043	13,17,900	7006521177	12,64,700	7006820801	5,14,300
7006521045	12,34,400	7006521178	14,36,400	7006820802	5,41,800
7006521046	13,07,100	7006521179	12,79,000	7006821001	5,58,300
7006521047	13,01,200	7006521181	12,32,100	7006821002	5,96,400
7006521050	13,42,700	7006521182	25,50,800	7006821003	6,25,500
7006521051	12,60,200	7006521182	19,200	7006821004	5,36,400
7006521052	13,18,300	7006521183	29,40,200	7006821005	5,58,100
7006521053	12,56,600	7006521186	13,83,700	7006821006	4,99,200
7006521054	12,18,000	7006521187	13,53,800	7006821007	5,72,400
7006521055	13,18,600	7006521188	11,15,200	7006821008	5,64,300
7006521056	8,46,700	7006521190	15,35,300	7006821009	5,55,600
7006521057	11,40,000	7006521191	12,26,100	7006821010	5,31,600
7006521058	13,84,900	7006521193	10,01,300	7006821011	5,32,800
7006521059	12,93,700	7006521194	7,25,600	7006821012	5,67,100
7006521060	13,59,600	7006521195	13,29,700	7006821013	5,49,100
7006521061	13,77,300	7006521196	13,01,300	7006821014	5,39,900
7006521062	13,48,300	7006521199	14,84,300	7006821015	5,41,600
7006521063	2,39,500	7006521200	14,97,200	7006821016	5,54,400
7006521065	12,74,800	7006521201	12,34,200	7006821017	5,17,700

7006521066	13,16,300	7006521202	14,95,600	7006821018	5,90,400
7006521067	14,54,100	7006521203	24,19,800	7006821019	6,07,200
7006521068	13,41,200	7006521204	14,52,400	7006821020	6,09,100
7006521069	12,45,800	7006521205	14,77,200	7006821021	6,01,500
7006521070	13,76,500	7006521207	14,91,000	7006821022	5,61,600
7006521071	12,24,200	7006521208	14,92,400	7006821023	5,90,400
7006821024	5,79,200	7006821126	5,39,100	7006821228	12,63,100
7006821025	5,96,200	7006821127	5,12,900	7006821229	12,95,000
7006821026	5,92,300	7006821128	5,14,800	7006821230	13,92,900
7006821027	5,98,600	7006821129	5,49,300	7006821231	9,05,000
7006821028	6,09,300	7006821130	5,74,100	7006821232	11,80,800
7006821029	5,84,400	7006821131	5,85,600	7006821233	13,85,100
7006821030	5,55,300	7006821132	5,68,900	7006821237	10,77,600
7006821031	6,31,200	7006821133	5,17,900	7006821238	6,74,400
7006821032	5,88,300	7006821134	5,15,700	7006821241	12,56,900
7006821034	6,05,300	7006821135	4,80,400	7006821242	12,34,800
7006821035	5,70,600	7006821136	5,64,900	7006821243	12,28,800
7006821036	5,95,000	7006821137	5,74,800	7006821244	11,96,200
7006821037	6,20,200	7006821138	5,68,800	7006821245	14,45,900
7006821038	6,15,100	7006821139	5,80,600	7006821246	10,17,600
7006821039	6,22,800	7006821140	5,16,200	7006821247	11,94,000
7006821040	5,86,700	7006821141	5,55,500	7006821251	10,71,400
7006821041	5,56,300	7006821142	5,65,200	7006821254	13,29,600
7006821042	5,47,400	7006821143	5,95,100	7006821255	12,46,800
7006821043	5,63,000	7006821145	5,59,200	7006821256	5,83,000
7006821046	5,35,200	7006821146	5,54,200	7006821257	6,07,400
7006821047	5,73,500	7006821147	5,74,400	7006821258	5,93,200
7006821048	5,54,600	7006821148	5,62,200	7006821259	5,91,000
7006821049	5,96,700	7006821149	5,67,500	7006821260	5,66,500
7006821050	4,97,900	7006821150	5,45,800	7006821261	5,80,600
7006821051	5,84,100	7006821151	5,72,600	7006821262	5,50,500
7006821052	5,54,400	7006821152	5,82,100	7006821263	5,59,100
7006821053	5,14,800	7006821153	5,61,500	7006821264	6,42,500
7006821054	5,86,800	7006821154	5,12,700	7006821266	13,42,800
7006821055	5,54,200	7006821155	5,58,900	7006821267	12,71,000
7006821056	5,69,200	7006821156	5,60,600	7006821268	12,99,400
7006821057	5,85,000	7006821157	5,69,400	7006821269	12,37,700
7006821058	6,01,000	7006821158	5,74,400	7006821270	13,29,600
7006821059	6,10,100	7006821159	5,31,700	7006821272	13,34,300
7006821060	5,80,600	7006821160	5,28,600	7006821273	13,05,600
7006821061	6,06,600	7006821161	5,66,100	7006821274	12,63,000
7006821062	5,50,900	7006821162	5,92,800	7006821275	13,71,800
7006821063	6,13,200	7006821163	5,58,800	7006821276	12,62,100
7006821064	5,58,000	7006821164	5,67,300	7006821277	13,57,300
7006821065	5,94,600	7006821165	5,74,300	7006821278	15,50,000
7006821066	5,14,700	7006821166	5,40,500	7006821279	14,97,100
7006821067	5,34,400	7006821167	6,35,900	7006821280	14,21,200

7006821068	5,62,100	7006821168	5,52,600	7006821281	5,49,700
7006821069	5,54,400	7006821169	6,20,900	7006821282	5,00,100
7006821070	5,57,400	7006821170	5,63,600	7006821283	5,40,000
7006821071	5,54,300	7006821171	5,91,400	7006821284	5,92,700
7006821072	5,26,200	7006821172	5,87,300	7006821285	5,70,100
7006821073	6,00,700	7006821173	6,25,900	7006821286	5,76,600
7006821074	5,54,000	7006821174	5,89,500	7006821287	6,03,900
7006821075	5,66,200	7006821175	5,74,200	7006821288	12,50,400
7006821076	5,93,500	7006821176	5,72,100	7006821289	13,74,700
7006821077	5,73,900	7006821177	5,96,800	7006821290	14,26,000
7006821078	5,64,200	7006821178	5,53,100	7006821291	11,20,800
7006821079	5,84,900	7006821179	4,89,600	7006821292	11,38,200
7006821080	6,06,700	7006821180	5,36,400	7006821293	14,84,900
7006821081	5,31,500	7006821181	5,77,700	7006821294	13,17,400
7006821082	5,45,700	7006821182	5,81,300	7006821295	62,900
7006821083	5,36,400	7006821183	5,82,300	7006821296	5,00,700
7006821084	3,67,500	7006821184	5,79,500	7006821297	5,56,400
7006821085	5,04,100	7006821185	5,71,700	7006821298	6,01,100
7006821086	5,22,800	7006821186	5,82,000	7006821299	4,93,300
7006821087	5,15,400	7006821187	5,77,100	7006821300	4,98,000
7006821088	5,70,600	7006821188	5,88,500	7006821301	3,26,100
7006821089	5,57,600	7006821189	6,02,200	7006821302	2,16,900
7006821090	5,57,600	7006821190	6,00,900	7006821303	5,36,400
7006821091	5,52,000	7006821191	5,43,000	7006821304	5,62,200
7006821092	5,14,700	7006821192	5,85,200	7006821305	5,49,800
7006821093	4,76,600	7006821193	5,43,000	7006821306	5,22,600
7006821094	5,28,200	7006821194	5,43,300	7006821307	5,84,700
7006821095	5,16,200	7006821195	5,64,300	7006821308	5,82,100
7006821096	5,71,700	7006821196	5,45,200	7006821309	5,29,300
7006821097	5,74,900	7006821197	5,76,900	7006821311	5,38,100
7006821098	6,32,400	7006821198	5,16,600	7006821312	5,81,200
7006821099	6,05,000	7006821199	5,41,200	7006821313	5,30,600
7006821100	5,15,500	7006821200	5,00,400	7006821314	5,22,400
7006821101	5,19,600	7006821201	5,29,200	7006821315	5,56,900
7006821102	5,41,100	7006821202	5,69,100	7006821316	4,89,400
7006821103	5,62,300	7006821203	5,48,200	7006821317	5,65,000
7006821104	5,62,700	7006821204	4,43,300	7006821318	5,90,800
7006821105	5,51,100	7006821205	5,79,900	7006821319	5,87,700
7006821106	4,68,000	7006821206	9,44,400	7006821320	4,18,000
7006821107	4,96,900	7006821207	5,74,900	7006821321	5,25,000
7006821108	5,57,700	7006821208	5,17,400	7006821322	5,35,800
7006821109	5,60,100	7006821209	13,72,800	7006821323	5,89,300
7006821110	5,37,700	7006821210	13,02,600	7006821324	6,10,100
7006821111	6,23,600	7006821211	5,64,800	7006821325	6,37,100
7006821112	6,17,200	7006821212	5,40,000	7006821326	8,59,200
7006821113	6,19,900	7006821213	5,56,300	7006821327	5,54,600
7006821114	5,89,200	7006821214	5,83,700	7006821328	13,14,600

7006821115	5,67,600	7006821215	5,37,500	7006821329	13,38,700
7006821116	5,84,900	7006821217	5,72,100	7006821330	14,87,000
7006821117	5,59,600	7006821218	5,36,000	7006821331	15,04,600
7006821118	4,89,100	7006821219	6,08,500	7006821332	8,54,500
7006821119	5,15,000	7006821220	6,04,300	7006821333	8,52,900
7006821120	5,12,100	7006821221	5,44,800	7006821334	7,93,200
7006821121	5,73,300	7006821222	5,57,100	7006821335	8,82,700
7006821122	6,02,000	7006821223	6,02,700	7006821336	9,15,300
7006821123	5,83,700	7006821224	5,72,600	7006821337	9,62,600
7006821124	5,96,200	7006821225	5,66,600	7006821338	9,50,000
7006821125	5,80,100	7006821227	12,57,600	7006821339	9,63,200
7006821340	8,76,800	7006821447	5,58,500	7006821548	7,64,900
7006821341	13,46,100	7006821448	5,53,300	7006821549	6,01,300
7006821342	13,58,600	7006821449	5,37,600	7006821551	7,35,900
7006821343	13,84,500	7006821450	5,62,700	7006821552	5,48,800
7006821344	14,33,700	7006821451	5,69,100	7006821553	5,51,800
7006821345	14,99,600	7006821452	5,81,700	7006821554	5,41,800
7006821346	13,57,300	7006821453	5,52,900	7006821555	7,27,300
7006821347	15,12,100	7006821454	5,36,200	7006821556	8,96,300
7006821348	14,04,800	7006821455	5,86,100	7006821557	3,30,700
7006821349	12,07,900	7006821456	6,01,900	7006821558	7,39,900
7006821350	13,19,600	7006821457	5,22,100	7006821559	10,86,000
7006821351	12,57,500	7006821458	6,18,000	7006821560	5,37,600
7006821352	14,95,600	7006821459	5,54,000	7006821560	2,88,400
7006821353	15,36,000	7006821460	5,52,800	7006821561	5,30,000
7006821354	14,99,600	7006821461	5,73,100	7006821562	5,42,200
7006821355	15,14,900	7006821462	5,86,700	7006821563	5,86,500
7006821356	14,99,200	7006821463	5,66,200	7006821564	7,19,200
7006821357	14,85,000	7006821464	5,60,400	7006821565	5,93,300
7006821359	14,00,400	7006821465	5,56,200	7006821566	5,43,200
7006821360	13,43,700	7006821466	5,62,100	7006821567	5,65,800
7006821361	6,51,200	7006821467	5,93,500	7006821568	5,16,400
7006821362	6,44,500	7006821468	5,49,700	7006821569	6,25,200
7006821363	6,39,900	7006821469	5,36,700	7006821570	5,49,700
7006821364	6,40,100	7006821470	5,46,300	7006821571	5,53,700
7006821365	6,29,600	7006821471	5,53,200	7006821572	5,17,200
7006821366	6,49,200	7006821472	5,39,300	7006821573	5,02,200
7006821367	5,70,300	7006821473	5,51,700	7006821574	5,08,800
7006821368	5,82,300	7006821474	5,50,900	7006821575	5,91,300
7006821369	8,26,100	7006821475	11,20,800	7006821576	5,60,400
7006821370	8,20,900	7006821475	5,700	7006821578	7,73,800
7006821371	6,86,400	7006821476	5,12,800	7006821579	8,02,600
7006821372	7,35,900	7006821477	7,21,100	7006821580	7,27,400
7006821373	5,67,300	7006821478	7,03,200	7006821581	7,38,500
7006821375	5,97,200	7006821483	15,22,800	7006821582	8,35,900
7006821377	5,75,400	7006821484	14,92,000	7006821583	8,14,700
7006821378	5,59,400	7006821485	14,95,500	7006821585	8,35,000

7006821379	5,97,300	7006821486	14,46,900	7006821586	5,72,800
7006821380	5,75,600	7006821487	86,300	7006821587	5,48,600
7006821381	6,02,000	7006821488	14,41,100	7006821588	8,09,100
7006821382	8,21,700	7006821489	8,86,600	7006821589	7,16,700
7006821383	5,86,800	7006821490	8,17,700	7006821590	6,74,500
7006821384	5,88,800	7006821491	12,28,200	7006821591	15,76,200
7006821385	5,97,300	7006821492	14,50,100	7006821592	52,800
7006821386	30,34,200	7006821493	14,18,500	7006821592	7,61,000
7006821387	31,200	7006821494	14,93,900	7006821593	8,39,400
7006821387	14,34,900	7006821495	12,76,800	7006821594	7,73,800
7006821388	29,06,400	7006821496	11,19,000	7006821595	8,11,100
7006821391	12,30,800	7006821497	14,30,400	7006821596	8,13,900
7006821392	11,78,400	7006821498	15,60,300	7006821599	72,000
7006821393	13,71,600	7006821499	14,05,200	7006821599	8,78,100
7006821395	28,50,400	7006821500	9,20,600	7006821601	8,41,000
7006821396	15,20,900	7006821501	12,70,600	7006821602	9,22,500
7006821397	6,17,400	7006821502	8,27,700	7006822005	2,55,600
7006821398	5,66,200	7006821503	2,61,400	7006822008	2,00,400
7006821399	5,62,700	7006821504	12,70,900	7006822009	14,24,900
7006821400	5,84,500	7006821505	13,59,800	7006822011	14,86,200
7006821401	5,19,100	7006821506	15,70,700	7006822012	12,24,600
7006821402	5,51,900	7006821507	15,09,100	7006822014	11,77,800
7006821403	5,85,900	7006821509	6,13,800	7006822017	12,27,400
7006821404	6,19,100	7006821510	8,43,300	7006822018	12,50,100
7006821405	6,07,900	7006821511	33,600	7006822019	8,21,200
7006821406	7,85,400	7006821511	8,62,900	7006822020	64,800
7006821407	5,48,900	7006821512	7,05,700	7006822020	8,36,300
7006821408	7,69,300	7006821513	7,17,000	7006822021	9,00,200
7006821409	5,71,000	7006821514	5,29,100	7006822023	7,78,000
7006821410	5,36,400	7006821515	5,52,500	7006822024	14,400
7006821411	7,07,300	7006821516	5,81,600	7006822024	7,41,600
7006821412	5,40,100	7006821517	7,60,700	7006822025	14,400
7006821413	5,93,700	7006821518	7,01,500	7006822025	7,32,900
7006821414	3,83,300	7006821519	6,92,700	7006822026	7,67,000
7006821417	5,36,300	7006821520	6,07,800	7006822027	8,09,700
7006821418	5,53,500	7006821521	6,99,400	7006822028	7,85,600
7006821419	5,29,100	7006821522	5,34,200	7006822029	7,40,200
7006821420	5,25,500	7006821523	7,69,300	7006822030	7,00,700
7006821421	5,23,600	7006821524	5,34,200	7006822031	2,97,600
7006821422	5,47,700	7006821525	5,60,700	7006822031	6,78,900
7006821423	5,91,200	7006821526	7,39,000	7006822032	7,88,000
7006821424	5,47,000	7006821527	5,66,600	7006822033	8,52,000
7006821425	5,34,300	7006821528	5,33,800	7006822034	79,200
7006821426	5,09,100	7006821529	5,60,600	7006822034	7,54,100
7006821427	4,06,800	7006821530	3,30,000	7006822035	11,06,100
7006821428	5,37,500	7006821531	5,39,800	7006822037	1,00,800
7006821429	5,47,100	7006821532	26,400	7006822037	7,99,500

7006821430	5,54,000	7006821532	6,80,000	7006822038	7,51,200
7006821431	12,16,900	7006821533	7,20,700	7006822038	4,97,700
7006821432	13,46,500	7006821534	7,38,700	7006822039	8,76,500
7006821433	15,69,700	7006821535	5,66,900	7006822040	11,15,500
7006821434	14,99,900	7006821536	6,82,600	7006822043	5,74,800
7006821435	10,32,400	7006821537	3,50,400	7006822043	5,76,200
7006821436	1,65,400	7006821538	5,45,000	7006822044	8,26,600
7006821437	9,59,000	7006821539	5,45,800	7006822045	8,01,200
7006821438	9,49,700	7006821540	7,43,300	7006822046	10,68,000
7006821439	8,26,100	7006821541	5,88,300	7006822046	3,13,900
7006821440	8,88,800	7006821542	12,84,400	7006822047	59,800
7006821441	9,18,100	7006821543	7,12,800	7006822047	7,70,600
7006821443	5,74,200	7006821544	5,00,200	7006822048	38,400
7006821444	5,13,200	7006821545	5,43,700	7006822048	8,27,800
7006821445	7,97,200	7006821546	5,42,100	7006822049	15,00,000
7006821446	7,71,600	7006821547	5,39,500	7006822049	5,93,100
7006822050	7,22,000	7006822147	7,800	7007021046	5,60,100
7006822051	10,10,500	7006822147	7,39,200	7007021047	5,59,600
7006822053	7,05,600	7006822148	7,45,300	7007021048	5,79,300
7006822054	7,83,300	7006822150	7,34,500	7007021049	5,72,800
7006822055	6,50,400	7006822151	7,34,100	7007021050	5,70,000
7006822055	5,32,300	7006822152	7,93,800	7007021051	5,38,100
7006822056	1,24,800	7006822159	16,99,200	7007021052	6,27,700
7006822056	7,67,700	7006822159	3,67,900	7007021053	5,93,000
7006822058	7,15,600	7006822162	10,83,600	7007021054	5,97,600
7006822059	7,53,800	7006822166	30,800	7007021055	5,53,800
7006822060	7,95,300	7006822166	7,54,000	7007021056	5,64,000
7006822061	8,29,400	7006822167	11,30,400	7007021057	6,22,300
7006822062	6,94,500	7006822168	12,50,400	7007021058	6,01,300
7006822063	5,66,200	7006822172	3,12,000	7007021059	5,98,900
7006822064	5,99,700	7006822172	6,07,200	7007021060	5,43,200
7006822065	4,08,000	7006822173	7,24,100	7007021061	5,36,500
7006822065	6,48,000	7006822174	5,16,000	7007021062	5,98,400
7006822066	8,57,700	7006822174	3,48,900	7007021063	5,71,700
7006822067	8,48,700	7006822176	14,76,700	7007021064	5,15,700
7006822068	4,32,000	7006822177	11,37,000	7007021065	5,40,600
7006822068	3,60,600	7006822178		7007021066	5,84,100
7006822069	5,94,000	7006822179	3,24,000	7007021067	5,99,600
7006822069	3,13,800	7006822179	5,65,200	7007021068	5,60,200
7006822070	3,12,000	7006822186	6,24,000	7007021069	5,46,500
7006822070	4,13,400	7006822186	1,80,600	7007021070	5,84,200
7006822071	6,34,200	7006822187	7,39,200	7007021071	5,97,000
7006822074	15,00,000	7006822188	9,600	7007021072	5,76,600
7006822076	8,96,000	7006822188	7,16,200	7007021073	5,48,400
7006822078	14,95,200	7006822192	7,10,300	7007021074	5,20,900
7006822078	1,04,400	7006822193		7007021075	5,45,100
7006822079	7,62,400	7006822194		7007021076	5,66,500

7006822080	7,83,400	7006822196		7007021077	5,83,400
7006822081	6,03,700	7006822199		7007021078	5,73,800
7006822082	7,42,700	7006822202	14,12,200	7007021079	5,83,200
7006822083	7,51,200	7006822203	4,97,200	7007021080	5,09,900
7006822083	4,78,800	7006822204		7007021081	5,19,700
7006822084	7,93,000	7006822204		7007021082	5,97,800
7006822085	4,99,200	7006822206	15,28,800	7007021083	6,27,900
7006822086	7,03,200	7006822207	3,12,000	7007021084	5,75,300
7006822086	4,20,600	7006822207	1,58,400	7007021085	5,95,900
7006822087	3,12,000	7006822208		7007021086	5,98,100
7006822087	6,08,000	7006822211		7007021087	5,57,600
7006822088	13,99,200	7006822214		7007021088	5,40,500
7006822088		7006822215		7007021089	5,55,200
7006822089	24,000	7006822216		7007021090	4,93,600
7006822089	5,57,200	7006822217		7007021091	5,29,800
7006822090	7,78,200	7006822217		7007021092	6,01,800
7006822095	7,90,200	7006822241	11,00,600	7007021093	5,70,400
7006822096	7,24,600	7006822243	13,28,300	7007021094	5,21,900
7006822099	1,36,800	7006822245	12,70,000	7007021095	5,74,400
7006822099	7,48,800	7006822246	6,03,200	7007021096	5,29,700
7006822100	7,43,700	7006822249	15,08,400	7007021097	6,06,500
7006822101	7,72,400	7006822255	13,69,200	7007021098	5,85,400
7006822102	7,69,600	7006822261		7007021099	6,08,700
7006822104	1,36,800	7006822263	1,99,200	7007021101	5,53,500
7006822104	7,14,800	7006822269	10,00,800	7007021102	5,31,800
7006822106	5,50,800	7006822269	9,47,400	7007021103	5,86,600
7006822107	6,32,800	7006822276	14,47,200	7007021104	5,11,100
7006822109	12,50,900	7007021001	6,04,800	7007021105	5,40,400
7006822110	6,00,000	7007021003	5,69,300	7007022001	5,36,200
7006822111	9,98,400	7007021004	6,11,200	7007022002	7,71,900
7006822111	2,87,500	7007021006	5,92,300	7007022003	7,95,600
7006822114	99,600	7007021007	6,03,500	7007022005	8,00,000
7006822115	7,90,900	7007021008	5,47,900	7007022011	7,88,200
7006822116	8,04,100	7007021009	5,90,900	7007022012	7,96,500
7006822117	7,73,000	7007021010	6,04,500	7007022013	7,98,500
7006822118	7,50,200	7007021011	5,86,400	7007022014	7,62,100
7006822119	7,93,000	7007021012	6,07,400	7007022015	7,91,500
7006822121	5,82,000	7007021013	6,10,000	7007022016	7,07,000
7006822121	3,25,200	7007021014	5,74,900	7007022017	7,84,400
7006822122	16,02,800	7007021015	5,53,400	7007022018	7,80,200
7006822123	1,24,800	7007021016	5,46,700	7007022019	8,44,300
7006822123	5,40,800	7007021017	5,32,500	7007022020	7,69,900
7006822124	7,45,500	7007021018	5,66,100	7007022021	8,19,800
7006822126	7,58,800	7007021019	5,26,900	7007022022	7,62,700
7006822127	7,70,100	7007021020	5,58,400	7007022023	5,73,600
7006822128	16,600	7007021021	5,66,500	7007022024	8,42,300
7006822128	5,61,600	7007021022	5,12,500	7007022025	8,37,700

7006822129	3,12,000	7007021023	5,26,200	7007022026	7,86,200
7006822129	3,92,600	7007021024	5,79,300	7007022027	7,40,900
7006822130	5,42,400	7007021025	5,76,700	7007022028	7,38,400
7006822131	5,49,600	7007021026	5,44,800	7007022029	8,16,400
7006822132	5,91,300	7007021027	5,94,500	7007022030	7,74,400
7006822133	5,51,600	7007021028	5,42,500	7007022031	7,48,700
7006822134	4,32,000	7007021029	6,36,700	7007022032	7,48,600
7006822135	5,42,700	7007021030	5,86,000	7007022033	7,93,000
7006822136	18,43,200	7007021031	5,32,100	7007022034	8,00,600
7006822137	7,75,200	7007021032	5,92,500	7007022035	7,63,800
7006822138	7,78,000	7007021033	5,77,000	7007022036	7,01,800
7006822139	8,24,800	7007021034	5,81,100	7007022037	7,27,300
7006822140	7,41,200	7007021035	6,08,000	7007022038	7,82,800
7006822141	7,72,500	7007021036	5,32,800	7007022039	7,00,100
7006822142	7,37,800	7007021037	6,01,900	7007022042	7,05,700
7006822143	6,000	7007021038	5,65,400	7007022043	7,90,800
7006822143	7,05,600	7007021039	5,23,300	7007022044	7,65,300
7006822144	7,05,700	7007021040	5,41,700	7007022045	7,80,900
7006822145	8,32,900	7007021043	6,06,400	7007022046	7,80,700
7006822146	12,000	7007021044	6,04,400	7007022047	7,72,900
7006822146	7,72,600	7007021045	5,54,600	7007022048	7,63,800
7007022049	6,95,300	7007621036	13,85,020	7007621146	13,76,620
7007022050	7,50,100	7007621037	14,01,120	7007621147	15,58,480
7007022052	8,11,000	7007621038	10,51,680	7007621148	13,21,320
7007022053	8,07,600	7007621039	11,76,840	7007621149	13,06,060
7007022054	8,16,700	7007621040	12,22,900	7007621150	6,85,440
7007022055	7,78,000	7007621041	13,46,800	7007621151	8,44,340
7007022056	8,05,700	7007621042	12,52,720	7007621152	8,05,700
7007022057	7,33,200	7007621043	12,59,860	7007621153	8,40,000
7007022058	7,43,400	7007621044	4,39,600	7007621154	7,20,300
7007022059	7,56,700	7007621045	11,74,880	7007621155	7,97,720
7007022060	7,87,900	7007621046	8,26,700	7007621156	7,58,940
7007022061	7,03,900	7007621047	5,70,780	7009422001	8,23,400
7007022062	7,50,300	7007621048	8,14,800	7009422003	3,83,250
7007022063	7,45,800	7007621049	8,12,700	7009422004	7,87,450
7007022064	7,17,200	7007621050	8,54,140	7009422005	7,38,350
7007521001	8,21,940	7007621051	8,48,260	7009422006	6,33,900
7007521002	9,36,320	7007621052	8,55,960	7009422007	8,59,550
7007521003	7,78,260	7007621053	7,88,200	7009422009	6,55,800
7007521004	8,26,560	7007621056	7,95,760	7009422010	6,81,900
7007521005	9,11,680	7007621057	9,07,200	7009422011	7,04,000
7007521006	9,08,320	7007621058	9,14,900	7009422012	6,95,850
7007521007	8,51,480	7007621059	9,94,560	7009422013	7,31,300
7007521008	7,98,840	7007621060	8,58,760	7009422014	7,03,350
7007521010	7,33,180	7007621061	9,01,180	7009422015	7,13,100
7007521011	8,50,220	7007621062	8,73,600	7009422016	7,30,900
7007521012	8,13,120	7007621063	8,44,340	7009422017	6,96,950

7007521013	6,50,720	7007621065	5,00,640	7009422018	7,23,750
7007521014	8,87,740	7007621066	7,85,960	7009422019	7,18,800
7007521015	8,73,600	7007621068	6,89,220	7009422020	6,93,550
7007521016	8,81,860	7007621069	7,18,200	7009422021	7,09,350
7007521017	8,67,440	7007621071	8,70,800	7009422022	6,77,350
7007521018	8,71,500	7007621072	8,73,320	7009422023	7,40,100
7007521019	11,75,440	7007621073	8,60,300	7009422024	7,18,050
7007521020	13,48,340	7007621074	8,83,820	7009422026	6,98,000
7007521021	14,02,100	7007621075	8,83,820	7009422027	6,13,000
7007521022	12,00,920	7007621076	8,52,460	7009422028	6,45,900
7007521023	14,83,160	7007621077	13,86,700	7009422029	8,24,450
7007521024	9,09,860	7007621078	9,42,760	7009422030	8,14,100
7007521025	13,03,680	7007621079	13,16,280	7009422031	5,91,100
7007521026	13,81,940	7007621080	12,28,780	7009422032	4,07,200
7007521027	7,54,320	7007621081	14,00,420	7009422034	7,47,950
7007521028	8,66,180	7007621082	12,15,900	7009422036	8,13,900
7007521030	9,11,260	7007621083	15,31,460	7009422038	7,85,500
7007521031	4,32,880	7007621084	13,88,940	7009422039	7,99,450
7007521032	8,55,680	7007621085	14,28,560	7009422040	8,03,550
7007521033	8,92,920	7007621086	13,48,620	7009422042	7,98,800
7007521034	8,40,000	7007621087	5,64,480	7009422044	5,64,900
7007521036	8,78,920	7007621088	14,49,280	7009422052	3,38,100
7007521038	7,92,960	7007621089	13,58,840	7009422053	3,55,100
7007521040	2,98,760	7007621091	14,06,720	7009422055	7,58,350
7007521045	4,28,400	7007621092	10,42,160	7009422056	7,48,100
7007521048	7,92,960	7007621093	16,42,620	7009422057	7,81,750
7007522001	8,12,280	7007621094	16,02,160	7009422058	7,48,000
7007522002	1,86,900	7007621095	15,49,520	7009422059	7,27,250
7007522014	13,92,580	7007621096	8,41,260	7009422060	7,04,750
7007522016	4,28,400	7007621097	15,38,180	7009422061	7,25,400
7007522017	14,19,600	7007621098	14,79,660	7009422062	7,26,950
7007522018	17,45,660	7007621099	14,72,800	7009422063	7,27,250
7007522019	14,29,680	7007621100	12,45,020	7009422064	7,30,800
7007522029	5,040	7007621101	15,26,420	7009422065	7,26,300
7007522032	2,41,920	7007621102	13,82,220	7012622006	11,68,700
7007522033	3,76,306	7007621104	8,30,900	7012622009	12,35,400
7007522034	16,24,980	7007621106	11,46,180	7012622011	11,40,000
7007522040	17,44,680	7007621107	12,48,940	7012622012	12,95,500
7007621001	12,89,960	7007621108	12,72,180	7012622013	12,64,300
7007621002	12,63,780	7007621109	12,91,920		
7007621003	9,60,680	7007621110	13,98,040		
7007621004	9,55,780	7007621111	13,15,020		
7007621005	8,78,640	7007621112	10,23,680		
7007621006	12,49,640	7007621113	14,29,820		
7007621007	13,74,380	7007621114	15,65,760		
7007621008	14,14,840	7007621115	16,68,520		
7007621009	13,46,240	7007621116	15,62,260		

7007621010	14,55,580	7007621117	14,70,840
7007621011	16,85,600	7007621118	17,23,540
7007621012	12,72,180	7007621119	13,95,520
7007621013	13,01,300	7007621120	15,69,960
7007621014	12,83,380	7007621122	10,74,780
7007621015	14,96,880	7007621123	4,50,380
7007621016	13,13,760	7007621124	14,27,580
7007621017	13,02,840	7007621125	13,20,760
7007621018	6,46,100	7007621126	12,27,940
7007621019	14,22,960	7007621127	13,77,320
7007621020	13,14,880	7007621128	10,20,740
7007621021	12,91,780	7007621129	15,00,940
7007621022	12,81,560	7007621130	14,09,800
7007621023	13,13,480	7007621131	1,36,080
7007621024	12,84,360	7007621132	12,10,440
7007621025	11,48,420	7007621133	11,83,980
7007621026	13,72,560	7007621134	12,71,060
7007621027	8,71,220	7007621135	12,59,860
7007621028	8,64,500	7007621136	12,51,460
7007621029	8,50,780	7007621139	14,55,020
7007621030	15,31,740	7007621140	13,82,500
7007621031	12,58,600	7007621141	11,50,380
7007621032	12,48,380	7007621142	12,93,600
7007621033	9,87,420	7007621143	12,81,840
7007621034	13,94,820	7007621144	15,00,100
7007621035	14,94,500	7007621145	14,74,620

Appendix 11.3 Observed Expected Appendix

Appendix: Observed-to-Expected Analyses

1.1.1.1.1. Methods

To conduct observed/expected analyses, the MAH has referred to disease incidence rates identified in published sources with a focus on studies describing population-based rates of disease in the US prior to COVID-19. As requested by regulatory authorities, Moderna has also used background rates of AESIs provided by ACCESS, where such information is available (https://vac4eu.org/covid-19-vaccine-monitoring/ last accessed 15 June 2022). The presentation of data available through ACCESS included stratified, site-specific rates calculated using both a broad and a narrow definition. Due to inter-site differences in reported AESI rates among the ACCESS sites, Moderna has chosen the conservative approach of including both high and low recent high and low estimates in a population suitable for assessment of the applicable outcome based on the narrow case defining algorithm to estimate expected cases of AESI observed (unless noted otherwise). A panel of three clinicians determined for each AESI/DME which practice setting(s) were likely to best represent the frequency of reporting newly diagnosed conditions (outpatient, emergency department and/or inpatient). Based upon this, as well as ACCESS descriptions of the databases, the list of sources was examined and a high and low estimate for each condition was selected. Estimated background rates that were substantially higher or lower than other data sources provided through ACCESS were omitted. Use of the narrow case defining algorithm is a more conservative approach that produces lower expected case counts. Exclusion of annual rates from 2020 was considered appropriate because healthcare utilization changed substantially in the early period of the pandemic, which may impact rates ascertained in secondary healthcare databases. Where available, ACCESS rates from 2019 were used to account for possible true secular trends in certain conditions, or changes in knowledge that may impact the probability of reporting and accuracy of coding of conditions.

In order to calculate observed reporting rates, a risk window of 21 days was assigned after each administered vaccine dose unless otherwise specified (e.g., for anaphylaxis, a risk window of 3 days was assigned; for myocarditis, both 21 and 7 day windows were used). This window was selected for consistency with analyses that have been conducted by the US Vaccine Safety Datalink. The sum of all person-time as applicable for the reporting period or cumulative analysis time frame was then used as a denominator to calculate the reporting rate. ACCESS or literature based expected rates were then multiplied by the same person-time estimate to identify the count of expected cases.

Age, gender, and age by gender stratified assessments of observed to expected rates were additionally performed. In some instances, it was not feasible to conduct such analyses (due to paucity of data). Our knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provided the same age strata when sharing this information, and these are not always aligned with age categories presented in ACCESS or literature-based sources of external data on the estimated incidence of conditions of interest. Given the volume of SPIKEVAX doses administered in the US, we applied the US age distribution to the total administered doses of vaccine administered and corresponding person-time accrued. As the second booster is authorized for older age groups, it is incorporated accordingly in the age distribution. Because the Pfizer-BioNTech vaccine was authorized for use in adolescents (12-17 years) earlier than Moderna's Spikevax in the US, it is expected that the large majority of primary series of COVID-19 vaccine doses seen in this age group are not Moderna's SPIKEVAX. To account for this, we limited the total assumed accrued exposure of primary series and first booster in individuals < 18 years to 3% of the total. The estimate of 3% was selected based on the assumption that adolescent use in the United States,

where approximately one third of global administrations have occurred and authorization is limited to age ≥ 18 years until the data lock point for PBRER 03, is substantially lower than use in the European Economic Area, where adolescent use is authorized and approximately 2% of COVID-19 vaccinations across all brands have been administered to individuals < 18. Based on the distribution of adverse event reports of all types in safety database, it is estimated that 95% of doses in individuals <18 years of age have been administered to adolescents. Additionally, sensitivity analyses were conducted to assess the potential impact of under reporting and/or data lags in reporting. In these assessments observed to expected rate ratios were recalculated assuming that cases captured in the observed reporting rate represented 50% or 25% of the true exposed cases. These analyses were performed for all AESI.

For those topics discussed in the PBRER, age and gender-specific incidence rates identified from ACCESS or other published literature were then used to estimate expected cases within each category. Where age groups used in sources of background incidence did not align with the available grouping for population-based vaccine administration, the lower rate of adjacent categories was used to produce more conservative expected case counts. Where sources did not include all required subgroups, available information was used to estimate missing categories. For example, for references including data for age and gender separately but not combined, age-specific incidence estimates within subgroups of gender were estimated by multiplying the applicable age-specific estimate by the ratio of the gender specific estimate to the overall estimate. Where no information on age or gender specific rates could be identified, overall rates were applied to all categories.

Limitations in comparing observed reporting rates and expected background rates include lack of direct visibility regarding patient-level data for administration, and limited availability of details on exposure in special risk groups who have received SPIKEVAX (other than an expectation that governments will distribute SPIKEVAX to the indicated adult population). Because the proportion of SPIKEVAX recipients with relevant comorbidities and other risk factors for the outcomes assessed is unknown, it is possible that estimates are confounded, and subgroup analyses of potential interest are infeasible.

Further, it should be noted that many AESI have highly variable estimates of incidence across sources. Even within ACCESS, for example, the estimated incidence of acute kidney injury ranges from 0.77 to 696.46 cases per 100,000 person-years. Although the sites worked from a common protocol, their implementation necessarily varies based on differences in the underlying data. While the MAH has endeavored to select appropriate background rates on the basis of published literature and plausible care settings suitable to capture of relevant diagnoses, mischaracterization of the background rate has the potential to either exaggerate or mask a potential risk. For this reason, multiple comparisons are presented.

1.1.1.1.2. Overall Observed-to-Expected Analyses, Adverse events of Special Interest (AESI)

Outcome	Interval				Cumulative			
	Cases	Person-years*	Rate	Rate Ratio (95% CI)	Cases	Person-years*	Rate	Rate Ratio (95% CI)
Neurologic								
Acute Disseminated Encephalomyelitis[1]								
Observed: Post authorization	25	11,272,825	0.22		93	38,111,689	0.24	
Expected: US (Gubernot 2021)	45	11,272,825	0.40	0.56 (0.34, 0.91)	152	38,111,689	0.40	0.61 (0.47, 0.79)
Expected: US (Gubernot 2021)	56	11,272,825	0.50	0.45 (0.28, 0.71)	191	38,111,689	0.50	0.49 (0.38, 0.62)
Expected: ACCESS, Spain (FISABIO) 2019	56	11,272,825	0.50	0.45 (0.28, 0.71)	191	38,111,689	0.50	0.49 (0.38, 0.62)
Acute Aseptic Arthritis								
Observed: Post authorization	610	11,272,825	5.41		2,309	38,111,689	6.06	
Expected: US (Esposito, 2018)	8,013	11,272,825	71.08	0.08 (0.07, 0.08)	27,090	38,111,689	71.08	0.09 (0.08, 0.09)
Expected: ACCESS UK, (CPRD) 2019	9,807	11,272,825	87.00	0.06 (0.06, 0.07)	33,157	38,111,689	87.00	0.07 (0.07, 0.07)
Expected: ACCESS (broad), Spain (BIFAP) 2017	88,359	11,272,825	783.82	0.01 (0.01, 0.01)	298,727	38,111,689	783.82	0.01 (0.01, 0.01)
Anosmia/Ageusia, all								
Observed: Post authorization	352	11,272,825	3.12		3,009	38,111,689	7.90	
Expected: ACCESS, Spain (BIFAP PC) 2019	1,190	11,272,825	10.56	0.3 (0.26, 0.33)	4,025	38,111,689	10.56	0.75 (0.71, 0.78)
Expected: ACCESS, Netherlands (PHARMO) 2019	4,936	11,272,825	43.79	0.07 (0.06, 0.08)	16,689	38,111,689	43.79	0.18 (0.17, 0.19)
Bell's Palsy								
Observed: Post authorization	486	11,272,825	4.31		3,176	38,111,689	8.33	
Expected: Publication, Monini, 2010	1,296	11,272,825	11.50	0.38 (0.34, 0.42)	4,383	38,111,689	11.50	0.72 (0.69, 0.76)
Expected: Publication, Rowlands, 2002	2,277	11,272,825	20.20	0.21 (0.19, 0.24)	7,699	38,111,689	20.20	0.41 (0.4, 0.43)
Generalized Convulsions								
Observed: Post authorization	510	11,272,825	4.52		3,111	38,111,689	8.16	
Expected: US, Kammerman 2001	4,960	11,272,825	44.00	0.1 (0.09, 0.11)	16,769	38,111,689	44.00	0.19 (0.18, 0.19)
Expected: ACCESS, NL (PHARMO Hosp) 2019	4,528	11,272,825	40.17	0.11 (0.1, 0.12)	15,309	38,111,689	40.17	0.2 (0.2, 0.21)
Expected: ACCESS, Spain (FISABIO) 2019	25,351	11,272,825	224.89	0.02 (0.02, 0.02)	9,486	38,111,689	24.89	0.33 (0.31, 0.34)
Encephalitis								
Observed: Post authorization	88	11,272,825	0.78		233	38,111,689	0.61	
Expected: Publication, Dubey 2018	90	11,272,825	0.80	0.98 (0.73, 1.31)	305	38,111,689	0.80	0.76 (0.64, 0.91)
Expected: Publication, US Esposito 2018	170	11,272,825	1.51	0.52 (0.4, 0.67)	575	38,111,689	1.51	0.41 (0.35, 0.47)
Expected: Publication, US Gubernot 2021	778	11,272,825	6.90	0.11 (0.09, 0.14)	2,630	38,111,689	6.90	0.09 (0.08, 0.1)
Fibromyalgia								
Observed: Post authorization	82	11,272,825	0.73		274	38,111,689	0.72	

[1] Gubernot et al, 2021 and FISABIO estimate incidence of ADEM from literature review and primary care data respectively. However, data from Italy (ARS) includes individuals with ADEM with hospitalization and emergency department discharge diagnoses, resulting an underestimation of the incidence rate. The estimated incidence rates from Gubernot et al and FISABIO are consistent and likely reflecting true incidence. Hence, the reference rate from ACCESS: Italy (ARS) will not be used from PBRER03.

Outcome	Interval				Cumulative			
	Cases	Person-years*	Rate	Rate Ratio (95% CI)	Cases	Person-years*	Rate	Rate Ratio (95% CI)
Expected: Publication, Weir 2006	5,479	11,272,825	48.60	0.01 (0.01, 0.02)	18,522	38,111,689	48.60	0.01 (0.01, 0.02)
Expected: Publication, Collin, 2017	3,754	11,272,825	33.30	0.02 (0.02, 0.03)	12,691	38,111,689	33.30	0.02 (0.02, 0.02)
Multiple Sclerosis								
Observed: Post authorization	120	11,272,825	1.06		313	38,111,689	0.82	
Expected: Publication, Gubernot, 2021	1,680	11,272,825	14.90	0.07 (0.06, 0.09)	5,679	38,111,689	14.90	0.06 (0.05, 0.06)
Expected: Publication, Alonzo, 2008	225	11,272,825	2.00	0.53 (0.43, 0.67)	762	38,111,689	2.00	0.41 (0.36, 0.47)
Expected: Publication, Alonzo, 2008	406	11,272,825	3.60	0.3 (0.24, 0.36)	1,372	38,111,689	3.60	0.23 (0.2, 0.26)
Optic Neuritis								
Observed: Post authorization	32	11,272,825	0.28		113	38,111,689	0.30	
Expected: Esposito, 2018	440	11,272,825	3.90	0.07 (0.05, 0.1)	1,486	38,111,689	3.90	0.08 (0.06, 0.09)
Expected: Publication, Gubernot, 2021	575	11,272,825	5.10	0.06 (0.04, 0.08)	1,944	38,111,689	5.10	0.06 (0.05, 0.07)
Post Viral Fatigue Syndrome								
Observed: Post authorization	55	11,272,825	0.49		111	38,111,689	0.29	
Expected: Publication, Vincent, 2012	1,531	11,272,825	13.58	0.04 (0.03, 0.05)	5,176	38,111,689	13.58	0.02 (0.02, 0.03)
Expected: Publication, Vincent, 2012	8,042	11,272,825	71.34	0.01 (0.01, 0.01)	27,189	38,111,689	71.34	0 (0, 0)
Expected: Norway, Bakken 2014	2,908	11,272,825	25.80	0.02 (0.01, 0.02)	9,833	38,111,689	25.80	0.01 (0.01, 0.01)
Transverse Myelitis[2]								
Observed: Post authorization	19	11,272,825	0.17		113	38,111,689	0.30	
Expected: Publication, Gubernot, 2021	35	11,272,825	0.31	0.54 (0.31, 0.95)	118	38,111,689	0.31	0.96 (0.74, 1.24)
Expected: Publication, Gubernot, 2021	107	11,272,825	0.95	0.18 (0.11, 0.29)	362	38,111,689	0.95	0.31 (0.25, 0.39)
Expected: ACCESS, Italy (ARS) 2019	104	11,272,825	0.92	0.18 (0.11, 0.3)	351	38,111,689	0.92	0.32 (0.26, 0.4)
Guillain-Barre Syndrome								
Observed: Post authorization	168	11,272,825	1.49		611	38,111,689	1.60	
Expected: US (Gubernot, 2021)	134	11,272,825	1.19	1.25 (1, 1.57)	454	38,111,689	1.19	1.35 (1.19, 1.52)
Expected: US (Gubernot, 2021)	485	11,272,825	4.30	0.35 (0.29, 0.41)	1,639	38,111,689	4.30	0.37 (0.34, 0.41)
Expected: ACCESS, Netherlands (PHARMO Hosp) 2019	136	11,272,825	1.21	1.24 (0.99, 1.55)	461	38,111,689	1.21	1.33 (1.17, 1.5)
Expected: ACCESS, Spain (SIDIAP) 2019	472	11,272,825	4.19	0.36 (0.3, 0.42)	1,597	38,111,689	4.19	0.38 (0.35, 0.42)
Narcolepsy								
Observed: Post authorization	7	11,272,825	0.06		32	38,111,689	0.08	
Expected: US, Silber 2002	154	11,272,825	1.37	0.05 (0.02, 0.1)	522	38,111,689	1.37	0.06 (0.04, 0.09)
Expected: US, Scheer 2019	865	11,272,825	7.67	0.01 (0, 0.02)	2,923	38,111,689	7.67	0.01 (0.01, 0.02)
Expected: ACCESS, UK (CPRD) 2019	105	11,272,825	0.93	0.07 (0.03, 0.14)	354	38,111,689	0.93	0.09 (0.06, 0.13)

[2] The estimated transverse myelitis incidence rates from Gubernot et al., 2021 and ACCESS, Italy (ARS) 2019 are consistent and ranges between 0.31 to 0.95 per 100,000 person-years. The estimated incidence from ACCESS, NL (PHARMO) 2019 was lower than 0.31 per 100,000 person-years. As the incidence estimated from ACCESS, NL (PHARMO) 2019 was based on individuals diagnosed in hospital setting only, it is likely an underestimation. Hence, starting with this report the ACCESS, NL (PHARMO) 2019 reference rate will be updated to utilize the incidence estimated based on individuals diagnosed in primary care and hospital settings.

Outcome	Interval				Cumulative			
	Cases	Person-years*	Rate	Rate Ratio (95% CI)	Cases	Person-years*	Rate	Rate Ratio (95% CI)
Expected: ACCESS, Spain (BIFAP PC) 2019	236	11,272,825	2.09	0.03 (0.01, 0.06)	797	38,111,689	2.09	0.04 (0.03, 0.06)
Narcolepsy and/or Hypersomnia								
Observed: Post authorization	164	11,272,825	1.45		1,495	38,111,689	3.92	
Expected: US, Jaussent 2017	1,730	1,944,279	89.00	0.09 (0.08, 0.11)	3,650	4,101,619	89.00	0.41 (0.39, 0.43)
Cardiovascular								
Cardiac: all events								
Observed: Post authorization	4,373	11,272,825	38.79		14,196	38,111,689	37.25	
Expected: US (Esposito, 2018)	82,614	11,272,825	732.86	0.05 (0.05, 0.05)	279,305	38,111,689	732.86	0.05 (0.05, 0.05)
Expected: ACCESS, Spain (FISABIO) 2017	14,592	11,272,825	129.44	0.3 (0.29, 0.31)	49,332	38,111,689	129.44	0.29 (0.28, 0.29)
Expected: ACCESS, AUH 2010	34,387	11,272,825	305.04	0.13 (0.12, 0.13)	116,256	38,111,689	305.04	0.12 (0.12, 0.12)
Arrhythmia								
Observed: Post authorization	2,454	11,272,825	21.77		7,428	38,111,689	19.49	
Expected: US, Williams, 2020	76,881	11,272,825	682.00	0.03 (0.03, 0.03)	259,922	38,111,689	682.00	0.03 (0.03, 0.03)
Expected: ACCESS, UK (CPRD) 2019	53,502	11,272,825	474.61	0.05 (0.04, 0.05)	180,882	38,111,689	474.61	0.04 (0.04, 0.04)
Expected: ACCESS, Spain (SIDIAP PC) 2019	101,284	11,272,825	898.48	0.02 (0.02, 0.03)	342,426	38,111,689	898.48	0.02 (0.02, 0.02)
Heart Failure								
Observed: Post authorization	218	11,272,825	1.93		1,225	38,111,689	3.21	
Expected: US, Roger 2004	32,578	11,272,825	289.00	0.01 (0.01, 0.01)	110,143	38,111,689	289.00	0.01 (0.01, 0.01)
Expected: ACCESS, NL (PHARMO) 2019	14,453	11,272,825	128.21	0.02 (0.01, 0.02)	48,863	38,111,689	128.21	0.03 (0.02, 0.03)
Expected: ACCESS, Italy (ARS) 2019	63,823	11,272,825	566.17	0 (0, 0)	215,777	38,111,689	566.17	0.01 (0.01, 0.01)
Ischemic Coronary Artery Disease								
Observed: Post authorization	380	11,272,825	3.37		1,626	38,111,689	4.27	
Expected: US, Sanchis Gomar 2016	25,927	11,272,825	230.00	0.01 (0.01, 0.02)	87,657	38,111,689	230.00	0.02 (0.02, 0.02)
Expected: ACCESS, NL (PHARMO Hosp) 2019	10,746	11,272,825	95.33	0.04 (0.03, 0.04)	36,332	38,111,689	95.33	0.04 (0.04, 0.05)
Expected: ACCESS, Italy (ARS) 2019	29,748	11,272,825	263.89	0.01 (0.01, 0.01)	100,573	38,111,689	263.89	0.02 (0.02, 0.02)
Myocarditis (with or without Pericarditis)								
Observed: Post authorization	1,155	11,272,825	10.25		3,772	38,111,689	9.90	
Expected: US, Kang 2021	1,127	11,272,825	10.00	1.02 (0.94, 1.11)	3,811	38,111,689	10.00	0.99 (0.95, 1.04)
Expected: ACCESS, Spain (FISABIO) 2019	379	11,272,825	3.36	3.05 (2.71, 3.42)	1,281	38,111,689	3.36	2.94 (2.76, 3.14)
Expected: ACCESS, Netherlands (PHARMO PC HOSP) 2019	2,669	11,272,825	23.68	0.43 (0.4, 0.46)	9,025	38,111,689	23.68	0.42 (0.4, 0.43)
Pericarditis with or without Myocarditis								
Observed: Post authorization	861	11,272,825	7.64		2,757	38,111,689	7.23	
Expected: Publication, Kumar, 2016 (US)	643	11,272,825	5.70	1.34 (1.21, 1.48)	2,172	38,111,689	5.70	1.27 (1.2, 1.34)
Expected: Publication, Maisch, 2004 (US)	834	11,272,825	7.40	1.03 (0.94, 1.14)	2,820	38,111,689	7.40	0.98 (0.93, 1.03)
Expected: Publication, Kyto, 2014 (Finland)	372	11,272,825	3.30	2.31 (2.05, 2.61)	1,258	38,111,689	3.30	2.19 (2.05, 2.34)

	Interval				Cumulative			
Outcome	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**
Expected: Publication, Imazio, 2008 (Italy)	3,123	11,272,825	27.70	0.28 (0.26, 0.3)	10,557	38,111,689	27.70	0.26 (0.25, 0.27)
Pericarditis without Myocarditis								
Observed: Post authorization	599	11,272,825	5.31		1,750	38,111,689	4.59	
Expected: Publication, Kumar, 2016 (US)	643	11,272,825	5.70	0.93 (0.83, 1.04)	2,172	38,111,689	5.70	0.81 (0.76, 0.86)
Expected: Publication, Maisch, 2004 (US)	834	11,272,825	7.40	0.72 (0.65, 0.8)	2,820	38,111,689	7.40	0.62 (0.58, 0.66)
Expected: Publication, Kyto, 2014 (Finland)	372	11,272,825	3.30	1.61 (1.41, 1.83)	1,258	38,111,689	3.30	1.39 (1.29, 1.5)
Expected: Publication, Imazio, 2008 (Italy)	3,123	11,272,825	27.70	0.19 (0.18, 0.21)	10,557	38,111,689	27.70	0.17 (0.16, 0.17)
Postural Orthostatic Tachycardia Syndrome								
Observed: Post authorization	21	11,272,825	0.19		88	38,111,689	0.23	
Expected: Publication, Adamec, 2020	372	11,272,825	3.30	0.06 (0.04, 0.09)	1,258	38,111,689	3.30	0.07 (0.06, 0.09)
Expected: Publication, Adamec, 2020	1,668	11,272,825	14.80	0.01 (0.01, 0.02)	5,641	38,111,689	14.80	0.02 (0.01, 0.02)
Stress Cardiomyopathy								
Observed: Post authorization	12	11,272,825	0.11		53	38,111,689	0.14	
Expected: US, Codd 1989	676	11,272,825	6.00	0.02 (0.01, 0.03)	2,287	38,111,689	6.00	0.02 (0.02, 0.03)
Expected: ACCESS, Spain (FISABIO) 2019	454	11,272,825	4.03	0.03 (0.01, 0.05)	1,536	38,111,689	4.03	0.03 (0.03, 0.05)
Expected: ACCESS, Italy (ARS) 2019	898	11,272,825	7.97	0.01 (0.01, 0.02)	3,038	38,111,689	7.97	0.02 (0.01, 0.02)
Microangiopathy								
Observed: Post authorization	7	11,272,825	0.06		22	38,111,689	0.06	
Expected: ACCESS, Italy (ARS) 2019	65	11,272,825	0.58	0.11 (0.05, 0.23)	221	38,111,689	0.58	0.1 (0.06, 0.15)
Expected: ACCESS, Spain (FISABIO) 2019	791	11,272,825	7.02	0.01 (0, 0.02)	2,675	38,111,689	7.02	0.01 (0.01, 0.01)
Circulatory								
Any Thromboembolic Event								
Observed: Post authorization	2,692	11,272,825	23.88		11,585	38,111,689	30.40	
Expected: US, Beckman 2010	22,546	11,272,825	200.00	0.12 (0.11, 0.12)	76,223	38,111,689	200.00	0.15 (0.15, 0.15)
Expected: ACCESS, Italy (ARS) 2019	22,251	11,272,825	197.39	0.12 (0.12, 0.13)	75,229	38,111,689	197.39	0.15 (0.15, 0.16)
Expected: ACCESS, Netherlands (PHARMO) 2019	31,807	11,272,825	282.16	0.08 (0.08, 0.09)	107,536	38,111,689	282.16	0.11 (0.11, 0.11)
Thrombosis with thrombocytopenia								
Observed: Post authorization	41	11,272,825	0.36		197	38,111,689	0.52	
Expected: ACCESS, Netherlands (PHARMO) 2019	181	11,272,825	1.61	0.23 (0.16, 0.32)	614	38,111,689	1.61	0.32 (0.27, 0.38)
Expected: ACCESS, Spain (FISABIO) 2019	997	11,272,825	8.84	0.04 (0.03, 0.06)	3,369	38,111,689	8.84	0.06 (0.05, 0.07)
Deep Vein Thrombosis								
Observed: Post authorization	1,170	11,272,825	10.38		4,746	38,111,689	12.45	
Expected: US, Silverstein 1998	5,411	11,272,825	48.00	0.22 (0.2, 0.23)	18,294	38,111,689	48.00	0.26 (0.25, 0.27)
Expected: ACCESS, NL (PHARMO) 2019	4,519	11,272,825	40.09	0.26 (0.24, 0.28)	15,279	38,111,689	40.09	0.31 (0.3, 0.32)

	Interval				Cumulative			
Outcome	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**
Expected: ACCESS, NL (PHARMO - PC/HOSP) 2019	31,807	11,272,825	282.16	0.04 (0.03, 0.04)	107,536	38,111,689	282.16	0.04 (0.04, 0.05)
Pulmonary Embolism								
Observed: Post authorization	693	11,272,825	6.15		2,915	38,111,689	7.65	
Expected: US, Silverstein 1998	7,778	11,272,825	69.00	0.09 (0.08, 0.1)	26,297	38,111,689	69.00	0.11 (0.11, 0.12)
Expected: ACCESS, SIDIAP pop since 2017	4,615	11,272,825	40.94	0.15 (0.14, 0.16)	15,603	38,111,689	40.94	0.19 (0.18, 0.19)
Expected: ACCESS, IPCI pop since 2017	10,718	11,272,825	95.08	0.06 (0.06, 0.07)	36,237	38,111,689	95.08	0.08 (0.08, 0.08)
Stroke, All								
Observed: Post authorization	900	11,272,825	7.98		4,127	38,111,689	10.83	
Expected: American Heart Association 2020	24,800	11,272,825	220.00	0.04 (0.03, 0.04)	83,846	38,111,689	220.00	0.05 (0.05, 0.05)
Expected: ACCESS, Denmark (DCE AU) 2010	18,982	11,272,825	168.39	0.05 (0.04, 0.05)	64,176	38,111,689	168.39	0.06 (0.06, 0.07)
Expected: ACCESS, Spain (FISABIO) 2017	34,205	11,272,825	303.43	0.03 (0.02, 0.03)	115,642	38,111,689	303.43	0.04 (0.03, 0.04)
Expected: WHO standardized incidence 2021	12,062	11,272,825	107.00	0.07 (0.07, 0.08)	40,780	38,111,689	107.00	0.1 (0.1, 0.1)
Stroke, Hemorrhagic								
Observed: Post authorization	160	11,272,825	1.42		697	38,111,689	1.83	
Expected: US (Koton 2014)	5,524	11,272,825	49.00	0.03 (0.02, 0.03)	18,675	38,111,689	49.00	0.04 (0.03, 0.04)
Expected: ACCESS, NL (PHARMO) 2019	2,000	11,272,825	17.74	0.08 (0.07, 0.09)	6,761	38,111,689	17.74	0.1 (0.1, 0.11)
Expected: ACCESS, Italy (ARS), 2019	8,340	11,272,825	73.98	0.02 (0.02, 0.02)	28,195	38,111,689	73.98	0.02 (0.02, 0.03)
Central Sinus Venous Thrombosis								
Observed: Post authorization	50	11,272,825	0.44		187	38,111,689	0.49	
Expected: US (Fairbanks 2018)	166	11,272,825	1.47	0.3 (0.22, 0.41)	560	38,111,689	1.47	0.33 (0.28, 0.39)
Expected: US (Otite 2020)	225	11,272,825	2.00	0.22 (0.16, 0.3)	762	38,111,689	2.00	0.25 (0.21, 0.29)
Expected: ACCESS, Spain (SIDIAP PC HOSP) 2019	81	11,272,825	0.72	0.62 (0.43, 0.88)	274	38,111,689	0.72	0.68 (0.57, 0.82)
Expected: ACCESS, Netherlands (PHARMO) 2019	222	11,272,825	1.97	0.23 (0.17, 0.31)	751	38,111,689	1.97	0.25 (0.21, 0.29)
Central Sinus Venous Thrombosis with Thrombocytopenia								
Observed: Post authorization	1	11,272,825	0.01		5	38,111,689	0.01	
Expected: ACCESS, Denmark (DCE AU) 2011	2	11,272,825	0.02	0.5 (0.05, 5.27)	8	38,111,689	0.02	0.63 (0.2, 1.93)
Expected: ACCESS, Spain (FISABIO) 2017	10	11,272,825	0.09	0.1 (0.01, 0.78)	34	38,111,689	0.09	0.15 (0.06, 0.38)
Splanchnic Venous Thrombosis								
Observed: Post authorization	15	11,272,825	0.13		65	38,111,689	0.17	
Expected: Sweden, Acosta, 2008	304	11,272,825	2.70	0.05 (0.03, 0.08)	1,029	38,111,689	2.70	0.06 (0.05, 0.08)
Disseminated Intravascular Coagulation								
Observed: Post authorization	6	11,272,825	0.05		37	38,111,689	0.10	
Expected: US Singh 2013	214	11,272,825	1.90	0.03 (0.01, 0.06)	724	38,111,689	1.90	0.05 (0.04, 0.07)
Expected: ACCESS, NL (PHARMO Hosp) 2019	79	11,272,825	0.70	0.08 (0.03, 0.17)	267	38,111,689	0.70	0.14 (0.1, 0.2)

	Interval				Cumulative			
Outcome	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**
Expected: ACCESS, Spain (FISABIO) 2019	618	11,272,825	5.48	0.01 (0, 0.02)	2,089	38,111,689	5.48	0.02 (0.01, 0.02)
Single Organ Cutaneous Vasculitis								
Observed: Post authorization	81	11,272,825	0.72		327	38,111,689	0.86	
Expected: US, Watts, 1998	435	11,272,825	3.86	0.19 (0.15, 0.24)	1,471	38,111,689	3.86	0.22 (0.2, 0.25)
Expected: ACCESS, Spain (SIDIAP PC) 2019	497	11,272,825	4.41	0.16 (0.13, 0.21)	1,681	38,111,689	4.41	0.19 (0.17, 0.22)
Expected: ACCESS, UK (CPRD) 2019	1,772	11,272,825	15.72	0.05 (0.04, 0.06)	5,991	38,111,689	15.72	0.05 (0.05, 0.06)
Thrombocytopenia								
Observed: Post authorization	472	11,272,825	4.19		2,115	38,111,689	5.55	
Expected: ACCESS, NL (PHARMO PC Hosp) 2019	4,227	11,272,825	37.50	0.11 (0.1, 0.12)	14,292	38,111,689	37.50	0.15 (0.14, 0.15)
Expected: ACCESS, Spain (SIDIAP PC-HOSP) 2019	15,376	11,272,825	136.40	0.03 (0.03, 0.03)	51,984	38,111,689	136.40	0.04 (0.04, 0.04)
Idiopathic/Immune Thrombocytopenia								
Observed: Post authorization	70	11,272,825	0.62		316	38,111,689	0.83	
Expected: US, Weycker 2020	688	11,272,825	6.10	0.1 (0.08, 0.13)	2,325	38,111,689	6.10	0.14 (0.12, 0.15)
Expected: ACCESS, United Kingdom (CPRD) 2019	711	11,272,825	6.31	0.1 (0.08, 0.13)	2,405	38,111,689	6.31	0.13 (0.12, 0.15)
Expected: ACCESS, Denmark (AUH) 2017	2,719	11,272,825	24.12	0.03 (0.02, 0.03)	9,193	38,111,689	24.12	0.03 (0.03, 0.04)
Hepato-gastrointestinal and renal								
Acute Kidney Injury & Renal failure								
Observed: Post authorization	122	11,272,825	1.08		994	38,111,689	2.61	
Expected: US (Cerda 2008)	9,695	11,272,825	86.00	0.01 (0.01, 0.02)	32,776	38,111,689	86.00	0.03 (0.03, 0.03)
Expected: ACCESS, NL (PHARMO HOSP) 2019	20,912	11,272,825	185.51	0.01 (0, 0.01)	70,701	38,111,689	185.51	0.01 (0.01, 0.01)
Expected: ACCESS, Spain (FISABIO) 2019	78,511	11,272,825	696.46	0 (0, 0)	265,433	38,111,689	696.46	0 (0, 0)
Acute Liver Injury								
Observed: Post authorization	70	11,272,825	0.62		314	38,111,689	0.82	
Expected: US (Bell, 2009)	1,567	11,272,825	13.90	0.04 (0.04, 0.06)	5,298	38,111,689	13.90	0.06 (0.05, 0.07)
Expected: ACCESS, Netherlands (PHARMO) 2019	754	11,272,825	6.69	0.09 (0.07, 0.12)	2,550	38,111,689	6.69	0.12 (0.11, 0.14)
Expected: ACCESS, Spain (SIDIAP PC HOSP) 2019	5,259	11,272,825	46.65	0.01 (0.01, 0.02)	17,779	38,111,689	46.65	0.02 (0.02, 0.02)
Appendicitis								
Observed: Post authorization	36	11,272,825	0.32		298	38,111,689	0.78	
Expected: Publication, US Coward 2016	9,492	11,272,825	84.20	0 (0, 0.01)	32,090	38,111,689	84.20	0.01 (0.01, 0.01)
Expected: Publication, Golz, 2020	11,273	11,272,825	100.00	0 (0, 0)	38,112	38,111,689	100.00	0.01 (0.01, 0.01)
Pancreatitis								
Observed: Post authorization	40	11,272,825	0.35		252	38,111,689	0.66	
Expected: Publication, US Yadav 2011	457	11,272,825	4.05	0.09 (0.06, 0.12)	1,544	38,111,689	4.05	0.16 (0.14, 0.19)
Expected: Publication, Vege, 2007	552	11,272,825	4.90	0.07 (0.05, 0.1)	1,867	38,111,689	4.90	0.13 (0.12, 0.15)
Expected: Publication, Vege, 2007	3,945	11,272,825	35.00	0.01 (0.01, 0.01)	13,339	38,111,689	35.00	0.02 (0.02, 0.02)

Outcome	Interval				Cumulative			
	Cases	Person-years*	Rate	Rate Ratio (95% CI)	Cases	Person-years*	Rate	Rate Ratio (95% CI)
Skin and subcutaneous tissue								
Dermatitis Bullous								
Observed: Post authorization	35	11,272,825	0.31		132	38,111,689	0.35	
Expected: Publication, Stanley, 1999	1,127	11,272,825	10.00	0.03 (0.02, 0.04)	3,811	38,111,689	10.00	0.03 (0.03, 0.04)
Expected: Publication, Stanley, 1999	4,396	11,272,825	39.00	0.01 (0.01, 0.01)	14,864	38,111,689	39.00	0.01 (0.01, 0.01)
Acute Generalised Exanthematous Pustulosis								
Observed: Post authorization	3	11,272,825	0.03		16	38,111,689	0.04	
Expected: Publication, Sidoroff, 2001	11	11,272,825	0.10	0.27 (0.08, 0.97)	38	38,111,689	0.10	0.42 (0.23, 0.75)
Expected: Publication, Sidoroff, 2001	56	11,272,825	0.50	0.05 (0.02, 0.17)	191	38,111,689	0.50	0.08 (0.05, 0.14)
Chilblain Like Lesions								
Observed: Post authorization	33	11,272,825	0.29		91	38,111,689	0.24	
Expected: ACCESS, UK (CPRD) 2019	1,121	11,272,825	9.94	0.03 (0.02, 0.04)	3,788	38,111,689	9.94	0.02 (0.02, 0.03)
Expected: ACCESS, Spain (BIFAP PC) 2019	2,900	11,272,825	25.73	0.01 (0.01, 0.02)	9,806	38,111,689	25.73	0.01 (0.01, 0.01)
Erythema Multiforme/Target Lesion								
Observed: Post authorization	59	11,272,825	0.52		301	38,111,689	0.79	
Expected: Publication, Chan 1990	789	11,272,825	7.00	0.07 (0.06, 0.1)	2,668	38,111,689	7.00	0.11 (0.1, 0.13)
Expected: ACCESS, Spain (BIFAP) 2019	705	11,272,825	6.25	0.08 (0.06, 0.11)	2,382	38,111,689	6.25	0.13 (0.11, 0.14)
Expected: ACCESS, Spain (FISABIO) 2019	1,418	11,272,825	12.58	0.04 (0.03, 0.05)	4,794	38,111,689	12.58	0.06 (0.06, 0.07)
Stevens-Johnsons Syndrome/Toxic Epidermal Necrolysis								
Observed: Post authorization	12	11,272,825	0.11		53	38,111,689	0.14	
Expected: Publication, Yacoub, 2016	225	11,272,825	2.00	0.05 (0.03, 0.1)	762	38,111,689	2.00	0.07 (0.05, 0.09)
Expected: Publication, Yacoub, 2016	789	11,272,825	7.00	0.02 (0.01, 0.03)	2,668	38,111,689	7.00	0.02 (0.02, 0.03)
Exfoliative Rash/Skin Necrosis								
Observed: Post authorization	14	11,272,825	0.12		98	38,111,689	0.26	
Expected: Publication, Sigurdsson, 2001	113	11,272,825	1.00	0.12 (0.07, 0.22)	381	38,111,689	1.00	0.26 (0.21, 0.32)
Drug Reaction with Eosinophilia and Systemic Symptoms								
Observed: Post authorization	4	11,272,825	0.04		27	38,111,689	0.07	
Expected: Publication, Muller, 2003	101	11,272,825	0.90	0.04 (0.01, 0.11)	343	38,111,689	0.90	0.08 (0.05, 0.12)
Expected: Publication, Wolfson, 2019	246	11,272,825	2.18	0.02 (0.01, 0.04)	831	38,111,689	2.18	0.03 (0.02, 0.05)
Other								
Acute Respiratory Distress								
Observed: Post authorization	24	11,272,825	0.21		600	38,111,689	1.57	
Expected: US Rubenfeld 2005	9,695	11,272,825	86.00	0 (0, 0)	32,776	38,111,689	86.00	0.02 (0.02, 0.02)

	Interval				Cumulative			
Outcome	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**
Expected: ACCESS, NL (PHARMO Hosp) 2019	2,618	11,272,825	23.22	0.01 (0.01, 0.01)	8,850	38,111,689	23.22	0.07 (0.06, 0.07)
Expected: ACCESS, Spain (FISABIO) 2019	16,562	11,272,825	146.92	0 (0, 0)	55,994	38,111,689	146.92	0.01 (0.01, 0.01)
Aseptic Meningitis								
Observed: Post authorization	24	11,272,825	0.21		133	38,111,689	0.35	
Expected: Publication, Mount, 2017	845	11,272,825	7.50	0.03 (0.02, 0.04)	2,858	38,111,689	7.50	0.05 (0.04, 0.06)
Expected: Publication, Nicolosi, 1986	1,229	11,272,825	10.90	0.02 (0.01, 0.03)	4,154	38,111,689	10.90	0.03 (0.03, 0.04)
Diabetes Mellitus, Type 1								
Observed: Post authorization	21	11,272,825	0.19		51	38,111,689	0.13	
Expected: US (Mobasseri 2020)	2,142	11,272,825	19.00	0.01 (0.01, 0.02)	7,241	38,111,689	19.00	0.01 (0.01, 0.01)
Expected: ACCESS, Spain (BIFAP PC) 2019	1,261	11,272,825	11.19	0.02 (0.01, 0.03)	4,265	38,111,689	11.19	0.01 (0.01, 0.02)
Expected: ACCES, UK (CPRD) 2019	4,232	11,272,825	37.54	0 (0, 0.01)	14,307	38,111,689	37.54	0 (0, 0)
Multisystem Inflammatory Syndrome[3]								
Observed: Post authorization	63	11,272,825	0.56		401	38,111,689	1.05	
Expected: ACCESS, NL (PHARMO Hosp) 2019	37	11,272,825	0.33	1.7 (1.14, 2.55)	126	38,111,689	0.33	3.18 (2.6, 3.89)
Expected: ACCESS, Spain (FISABIO) 2019	229	11,272,825	2.03	0.28 (0.21, 0.36)	774	38,111,689	2.03	0.52 (0.46, 0.58)
Myasthenia Gravis								
Observed: Post authorization	45	11,272,825	0.4		149	38,111,689	0.39	
Expected: Publication, Carr, 2010	60	11,272,825	0.53	0.7 (0.47, 1.04)	202	38,111,689	0.53	0.68 (0.55, 0.85)
Expected: Publication, Westerberg, 2021	327	11,272,825	2.90	0.13 (0.09, 0.18)	1,105	38,111,689	2.90	0.12 (0.1, 0.15)
Rhabdomyolysis								
Observed: Post authorization	29	11,272,825	0.26		154	38,111,689	0.40	
Expected: Publication, Lutimer 2021	119	11,272,825	1.06	0.24 (0.16, 0.37)	404	38,111,689	1.06	0.38 (0.32, 0.46)
Expected: Publication, Esposito, 2018	338	11,272,825	3.00	0.09 (0.06, 0.13)	1,143	38,111,689	3.00	0.13 (0.11, 0.16)
Expected: Publication, Torres, 2015	2,503	11,272,825	22.20	0.01 (0.01, 0.02)	8,461	38,111,689	22.20	0.02 (0.02, 0.02)
Thyrotoxicosis								
Observed: Post authorization	132	11,272,825	1.17		357	38,111,689	0.94	
Expected: Publication, Esposito, 2018	2,721	11,272,825	24.14	0.05 (0.04, 0.06)	9,200	38,111,689	24.14	0.04 (0.03, 0.04)
Expected: Publication, Esposito, 2018	6,931	11,272,825	61.48	0.02 (0.02, 0.02)	23,431	38,111,689	61.48	0.02 (0.01, 0.02)
New topics added for PBRER3								
Autoimmune Hepatitis								
Observed: Post authorization	45	11,272,825	0.40		211	38,111,689	0.55	
Expected: Publication, Delgado, 2013	76	11,272,825	0.67	0.59 (0.41, 0.86)	255	38,111,689	0.67	0.83 (0.69, 0.99)

[3] The MIS cases were identified using the following MedDRA PTs - Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome, Multiple organ dysfunction syndrome, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, and Autoinflammatory disease.

	Interval				Cumulative			
Outcome	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**	**Cases**	**Person-years***	**Rate**	**Rate Ratio (95% CI)**
Expected: Publication, Esposito, 2018	349	11,272,825	3.10	0.13 (0.09, 0.18)	1,181	38,111,689	3.10	0.18 (0.15, 0.21)
IgA Nephropathy								
Observed: Post authorization	23	11,272,825	0.20		58	38,111,689	0.15	
Expected: Publication, Wyatt, 2013	85	11,272,825	0.75	0.27 (0.17, 0.43)	286	38,111,689	0.75	0.2 (0.15, 0.27)
Neuralgic Amyotrophy								
Observed: Post authorization	63	11,272,825	0.56		180	38,111,689	0.47	
Expected: Publication, Bhegi, 1985	180	11,272,825	1.6	0.35 (0.26, 0.47)	610	38,111,689	1.6	0.3 (0.25, 0.35)
Chronic Urticaria								
Observed: Post authorization	171	11,272,825	1.52		209	38,111,689	0.55	
Expected: Publication, Lapi, 2016	14,655	11,272,825	130	0 (0, 0)	49,545	38,111,689	130	0 (0, 0)
Glomerulonephritis and Nephrotic Syndrome								
Observed: Post authorization	85	11,272,825	0.75		186	38,111,689	0.49	
Expected: Publication, Esposito, 2018	507	11,272,825	4.5	0.17 (0.13, 0.21)	1,715	38,111,689	4.5	0.11 (0.09, 0.13)
Serious Hypertension								
Observed: Post authorization	551	11,272,825	4.89		7,563	38,111,689	19.8	
Expected: Publication, McNaughton, 2006	43,964	11,272,825	390	0.01 (0.01, 0.01)	148,636	38,111,689	390	0.05 (0.05, 0.05)
Acquired Haemophilia								
Observed: Post authorization	6	11272825	0.05		22	38111689	0.06	
Expected: Publication, Collins, 2007	17	11272825	0.148	0.35 (0.14, 0.9)	56	38111689	0.148	0.39 (0.24, 0.64)
Autoimmune Haemolytic Anaemia								
Observed: Post authorization	17	11272825	0.15		64	38111689	0.17	
Expected: Publication, Hansen, 2016	200	11272825	1.77	0.09 (0.05, 0.14)	675	38111689	1.77	0.09 (0.07, 0.12)

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1.1.1.1.3. Age and Sex Stratified Observed-to-Expected Analyses, Anaphylaxis

Outcome	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			
Anaphylaxis								
Review Period:								
All	1,610,404	392	24.34	355	22.07	1.1 (0.96, 1.27)	*2.21 (1.95, 2.5)*	*4.41 (3.93, 4.95)*
By age								
<12	2,122	0	0.00	0	8.86	NA	*NA*	*NA*
12-17	40,308	4	9.92	4	8.86	1.12 (0.28, 4.48)	*2.24 (0.67, 7.44)*	*4.48 (1.5, 13.4)*
18-24	291,589	25	8.57	16	5.37	1.6 (0.85, 2.99)	*3.19 (1.82, 5.61)*	*6.39 (3.77, 10.83)*
25-39	199,918	116	58.02	10	4.85	11.96 (6.27, 22.82)	*23.93 (12.71, 45.06)*	*47.85 (25.58, 89.53)*
40-49	451,808	80	17.71	22	4.96	3.57 (2.23, 5.72)	*7.14 (4.57, 11.15)*	*14.28 (9.27, 22)*
50-64	319,854	98	30.64	19	5.85	5.24 (3.2, 8.56)	*10.47 (6.54, 16.78)*	*20.95 (13.22, 33.2)*
65-74	276,806	29	10.48	18	6.52	1.61 (0.89, 2.89)	*3.21 (1.89, 5.45)*	*6.43 (3.91, 10.56)*
75+	27,996	23	82.16	1	4.38	18.76 (2.53, 138.9)	*37.51 (5.17, 272.03)*	*75.03 (10.46, 538.34)*
By gender								
Male	728,162	107	14.69	54	7.35	2 (1.44, 2.77)	*4 (2.96, 5.39)*	*7.99 (6.02, 10.61)*
Female	882,238	276	31.28	55	6.22	5.03 (3.77, 6.72)	*10.06 (7.63, 13.27)*	*20.12 (15.35, 26.38)*
By age and gender								
Male								
<12	954	0	0.00	0	14.50	NA	*NA*	*NA*
12-17	18,136	1	5.51	3	14.50	0.38 (0.04, 3.66)	*0.76 (0.13, 4.55)*	*1.52 (0.34, 6.8)*
18-24	134,204	10	7.45	8	5.97	1.25 (0.49, 3.16)	*2.5 (1.1, 5.67)*	*4.99 (2.34, 10.67)*
25-39	87,913	31	35.26	5	5.17	6.82 (2.65, 17.54)	*13.64 (5.48, 33.93)*	*27.28 (11.16, 66.7)*
40-49	207,672	16	7.70	11	5.22	1.48 (0.68, 3.18)	*2.95 (1.49, 5.86)*	*5.9 (3.11, 11.19)*
50-64	143,036	28	19.58	10	6.65	2.94 (1.43, 6.06)	*5.89 (3, 11.54)*	*11.77 (6.17, 22.48)*
65-74	125,728	8	6.36	12	9.25	0.69 (0.28, 1.68)	*1.38 (0.65, 2.91)*	*2.75 (1.42, 5.34)*
75+	10,519	9	85.56	0	4.72	NA	*NA*	*NA*
Female								
<12	1,167	0	0.00	0	6.62	NA	*NA*	*NA*
12-17	22,172	3	13.53	1	6.62	2.04 (0.21, 19.65)	*4.09 (0.49, 33.96)*	*8.18 (1.06, 62.88)*
18-24	157,385	15	9.53	13	8.40	1.13 (0.54, 2.38)	*2.27 (1.18, 4.35)*	*4.54 (2.49, 8.27)*
25-39	112,005	83	74.10	5	4.75	15.6 (6.33, 38.47)	*31.2 (12.82, 75.95)*	*62.4 (25.8, 150.92)*
40-49	244,136	62	25.40	14	5.85	4.34 (2.43, 7.75)	*8.68 (5, 15.09)*	*17.36 (10.14, 29.75)*
50-64	176,818	69	39.02	12	6.62	5.89 (3.19, 10.88)	*11.79 (6.54, 21.27)*	*23.58 (13.23, 42.03)*
65-74	151,078	21	13.90	10	6.77	2.05 (0.97, 4.36)	*4.11 (2.06, 8.18)*	*8.21 (4.26, 15.82)*
75+	17,477	14	80.11	1	4.52	17.72 (2.33, 134.78)	*35.45 (4.82, 260.52)*	*70.89 (9.81, 512.12)*
Cumulative:								
All	5,444,527	2,344	43.05	1,202	22.07	1.95 (1.82, 2.09)	*3.9 (3.66, 4.16)*	*7.8 (7.35, 8.29)*
By age								
<12	7,873	0	0.00	1	8.86	NA	*NA*	*NA*
12-17	149,580	20	13.37	13	8.86	1.51 (0.75, 3.03)	*3.02 (1.61, 5.64)*	*6.04 (3.36, 10.85)*
18-24	636,660	239	37.54	34	5.37	6.99 (4.88, 10.01)	*13.98 (9.87, 19.8)*	*27.96 (19.86, 39.37)*
25-39	1,043,425	704	67.47	51	4.85	13.91 (10.47, 18.48)	*27.82 (21.04, 36.79)*	*55.65 (42.19, 73.4)*
40-49	1,026,927	469	45.67	51	4.96	9.21 (6.9, 12.29)	*18.42 (13.89, 24.41)*	*36.83 (27.89, 48.64)*
50-64	1,316,727	504	38.28	77	5.85	6.54 (5.15, 8.32)	*13.09 (10.38, 16.5)*	*26.17 (20.84, 32.86)*
65-74	851,924	197	23.12	56	6.52	3.55 (2.64, 4.77)	*7.09 (5.36, 9.38)*	*14.19 (10.82, 18.6)*
75+	411,408	109	26.49	18	4.38	6.05 (3.67, 9.96)	*12.1 (7.48, 19.56)*	*24.2 (15.1, 38.77)*
By gender								
Male	2,549,371	567	22.24	187	7.35	3.02 (2.56, 3.57)	*6.05 (5.18, 7.06)*	*12.1 (10.42, 14.04)*

Outcome	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			
Female	2,895,153	1,730	59.76	180	6.22	9.61 (8.24, 11.2)	*19.22 (16.54, 22.32)*	*38.44 (33.15, 44.57)*
By age and gender								
Male								
<12	3,686	0	0.00	1	14.50	NA	*NA*	*NA*
12-17	70,040	9	12.85	10	14.50	0.89 (0.36, 2.18)	*1.77 (0.82, 3.84)*	*3.54 (1.76, 7.14)*
18-24	298,113	76	25.49	18	5.97	4.27 (2.55, 7.14)	*8.54 (5.24, 13.92)*	*17.08 (10.62, 27.48)*
25-39	488,579	182	37.25	25	5.17	7.21 (4.74, 10.94)	*14.41 (9.61, 21.61)*	*28.82 (19.34, 42.94)*
40-49	480,853	87	18.09	25	5.22	3.47 (2.22, 5.41)	*6.93 (4.56, 10.54)*	*13.86 (9.24, 20.8)*
50-64	616,551	108	17.52	41	6.65	2.63 (1.84, 3.77)	*5.27 (3.77, 7.36)*	*10.54 (7.65, 14.51)*
65-74	398,909	57	14.29	37	9.25	1.54 (1.02, 2.34)	*3.09 (2.13, 4.48)*	*6.18 (4.37, 8.75)*
75+	192,640	37	19.21	9	4.72	4.07 (1.96, 8.43)	*8.14 (4.07, 16.26)*	*16.28 (8.3, 31.9)*
Female								
<12	4,186	0	0.00	0	6.62	NA	*NA*	*NA*
12-17	79,540	11	13.83	5	6.62	2.09 (0.73, 6.01)	*4.18 (1.58, 11.03)*	*8.36 (3.31, 21.07)*
18-24	338,547	161	47.56	28	8.40	5.66 (3.79, 8.46)	*11.32 (7.7, 16.66)*	*22.65 (15.51, 33.06)*
25-39	554,847	516	93.00	26	4.75	19.58 (13.2, 29.03)	*39.16 (26.53, 57.79)*	*78.31 (53.19, 115.3)*
40-49	546,074	376	68.86	32	5.85	11.77 (8.2, 16.89)	*23.54 (16.53, 33.53)*	*47.08 (33.17, 66.82)*
50-64	700,176	389	55.56	46	6.62	8.39 (6.18, 11.39)	*16.78 (12.47, 22.6)*	*33.57 (25.04, 45.01)*
65-74	453,015	140	30.90	31	6.77	4.56 (3.09, 6.74)	*9.13 (6.3, 13.23)*	*18.26 (12.72, 26.21)*
75+	218,768	72	32.91	10	4.52	7.28 (3.76, 14.11)	*14.56 (7.67, 27.64)*	*29.13 (15.5, 54.71)*

ACCESS, Spain (FISABIO 2017). Only age and age by sex stratified rates were available in the available source material. Overall sex-specific expected rates have been estimated as an average of age specific rates.
For anaphylaxis, 3-day person-time is used for observed-to-expected analyses

1.1.1.1.4. Age and Sex Stratified Observed-to-Expected Analyses, Myocarditis and Pericarditis

Myocarditis, overall analyses, all cases

Outcome	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			
Myocarditis								
Review Period:								
All	11,272,825	1,155	10.25	1,015	9.00	1.14 (1.05, 1.24)	*2.28 (2.11, 2.45)*	*4.55 (4.25, 4.87)*
By age								
<12	14,851	0	0.00	1	4.00	NA	*NA*	*NA*
12-17	282,154	37	13.11	37	13.00	1.01 (0.64, 1.59)	*2.02 (1.36, 2.99)*	*4.03 (2.81, 5.78)*
18-24	2,041,125	238	11.66	265	13.00	0.9 (0.75, 1.07)	*1.79 (1.54, 2.08)*	*3.59 (3.13, 4.11)*
25-39	1,399,426	393	28.08	140	10.00	2.81 (2.32, 3.41)	*5.62 (4.69, 6.72)*	*11.23 (9.45, 13.35)*
40-49	3,162,658	160	5.06	316	10.00	0.51 (0.42, 0.61)	*1.01 (0.87, 1.18)*	*2.02 (1.77, 2.32)*
50-64	2,238,981	163	7.28	179	8.00	0.91 (0.74, 1.13)	*1.82 (1.52, 2.18)*	*3.64 (3.09, 4.29)*
65-74	1,937,639	57	2.94	155	8.00	0.37 (0.27, 0.5)	*0.74 (0.58, 0.94)*	*1.47 (1.2, 1.8)*
75+	195,969	22	11.23	14	7.00	1.6 (0.82, 3.13)	*3.21 (1.76, 5.85)*	*6.42 (3.65, 11.28)*
By gender								
Male	5,097,136	833	16.34	612	12.00	1.36 (1.23, 1.51)	*2.72 (2.48, 2.99)*	*5.45 (5, 5.94)*
Female	6,175,668	301	4.87	371	6.00	0.81 (0.7, 0.95)	*1.62 (1.43, 1.85)*	*3.25 (2.89, 3.65)*
By age and gender								
Male								
<12	6,681	0	0.00	0	5.33	NA	*NA*	*NA*
12-17	126,951	33	25.99	22	17.33	1.5 (0.87, 2.57)	*3 (1.85, 4.86)*	*6 (3.82, 9.42)*
18-24	939,430	209	22.25	163	17.33	1.28 (1.05, 1.58)	*2.57 (2.14, 3.08)*	*5.13 (4.34, 6.07)*
25-39	615,389	302	49.07	82	13.33	3.68 (2.88, 4.7)	*7.36 (5.84, 9.27)*	*14.72 (11.77, 18.41)*
40-49	1,453,704	102	7.02	194	13.33	0.53 (0.41, 0.67)	*1.05 (0.86, 1.28)*	*2.1 (1.77, 2.5)*
50-64	1,001,254	95	9.49	107	10.67	0.89 (0.67, 1.17)	*1.78 (1.4, 2.25)*	*3.56 (2.87, 4.41)*
65-74	880,095	31	3.52	94	10.67	0.33 (0.22, 0.5)	*0.66 (0.48, 0.91)*	*1.32 (1.01, 1.73)*
75+	73,631	9	12.22	7	9.33	1.31 (0.49, 3.52)	*2.62 (1.09, 6.27)*	*5.24 (2.33, 11.77)*
Female								
<12	8,168	0	0.00	0	2.67	NA	*NA*	*NA*
12-17	155,205	4	2.58	13	8.67	0.3 (0.1, 0.91)	*0.59 (0.25, 1.43)*	*1.19 (0.57, 2.47)*
18-24	1,101,696	28	2.54	95	8.67	0.29 (0.19, 0.45)	*0.59 (0.42, 0.82)*	*1.17 (0.89, 1.54)*
25-39	784,037	88	11.22	52	6.67	1.68 (1.19, 2.37)	*3.37 (2.47, 4.59)*	*6.73 (5.03, 9.01)*
40-49	1,708,954	57	3.34	114	6.67	0.5 (0.36, 0.69)	*1 (0.77, 1.3)*	*2 (1.6, 2.51)*
50-64	1,237,727	66	5.33	66	5.33	1 (0.71, 1.41)	*2 (1.49, 2.69)*	*4 (3.05, 5.24)*
65-74	1,057,544	26	2.46	56	5.33	0.46 (0.29, 0.73)	*0.92 (0.63, 1.34)*	*1.84 (1.33, 2.55)*
75+	122,337	13	10.63	6	4.67	2.28 (0.87, 5.99)	*4.55 (1.87, 11.06)*	*9.11 (3.91, 21.21)*
Cumulative:								
All	38,111,689	3,772	9.90	3,430	9.00	1.1 (1.05, 1.15)	*2.2 (2.11, 2.29)*	*4.4 (4.24, 4.56)*
By age								
<12	55,109	0	0.00	2	4.00	NA	*NA*	*NA*
12-17	1,047,062	136	12.99	136	13.00	1 (0.79, 1.27)	*2 (1.63, 2.45)*	*4 (3.31, 4.82)*
18-24	4,456,623	1,031	23.13	579	13.00	1.78 (1.61, 1.97)	*3.56 (3.25, 3.9)*	*7.12 (6.53, 7.77)*
25-39	7,303,976	1,227	16.80	730	10.00	1.68 (1.53, 1.84)	*3.36 (3.09, 3.65)*	*6.72 (6.22, 7.26)*
40-49	7,188,488	409	5.69	719	10.00	0.57 (0.5, 0.64)	*1.14 (1.03, 1.26)*	*2.28 (2.08, 2.48)*
50-64	9,217,086	365	3.96	737	8.00	0.5 (0.44, 0.56)	*0.99 (0.89, 1.1)*	*1.98 (1.81, 2.16)*
65-74	5,963,469	157	2.63	477	8.00	0.33 (0.27, 0.39)	*0.66 (0.57, 0.76)*	*1.32 (1.17, 1.48)*
75+	2,879,855	62	2.15	202	7.00	0.31 (0.23, 0.41)	*0.62 (0.49, 0.77)*	*1.23 (1.02, 1.48)*

Outcome	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			
By gender								
Male	17,845,596	2,825	15.83	2,141	12.00	1.32 (1.25, 1.4)	*2.64 (2.51, 2.77)*	*5.28 (5.04, 5.53)*
Female	20,266,072	884	4.36	1,216	6.00	0.73 (0.67, 0.79)	*1.45 (1.35, 1.56)*	*2.91 (2.72, 3.1)*
By age and gender								
Male								
<12	25,804	0	0.00	1	5.33	NA	*NA*	*NA*
12-17	490,282	124	25.29	85	17.33	1.46 (1.11, 1.92)	*2.92 (2.28, 3.73)*	*5.84 (4.64, 7.35)*
18-24	2,086,791	903	43.27	362	17.33	2.5 (2.21, 2.82)	*4.99 (4.46, 5.59)*	*9.99 (8.96, 11.13)*
25-39	3,420,050	957	27.98	456	13.33	2.1 (1.88, 2.35)	*4.2 (3.79, 4.65)*	*8.39 (7.62, 9.25)*
40-49	3,365,973	258	7.66	449	13.33	0.57 (0.49, 0.67)	*1.15 (1.01, 1.3)*	*2.3 (2.06, 2.57)*
50-64	4,315,854	211	4.89	460	10.67	0.46 (0.39, 0.54)	*0.92 (0.8, 1.05)*	*1.83 (1.64, 2.05)*
65-74	2,792,364	78	2.79	298	10.67	0.26 (0.2, 0.34)	*0.52 (0.43, 0.64)*	*1.05 (0.89, 1.23)*
75+	1,348,477	29	2.15	126	9.33	0.23 (0.15, 0.35)	*0.46 (0.34, 0.63)*	*0.92 (0.72, 1.19)*
Female								
<12	29,304	0	0.00	1	2.67	NA	*NA*	*NA*
12-17	556,781	12	2.16	48	8.67	0.25 (0.13, 0.47)	*0.5 (0.3, 0.81)*	*0.99 (0.67, 1.48)*
18-24	2,369,832	126	5.32	205	8.67	0.61 (0.49, 0.77)	*1.23 (1.02, 1.48)*	*2.45 (2.09, 2.89)*
25-39	3,883,926	261	6.72	259	6.67	1.01 (0.85, 1.2)	*2.02 (1.74, 2.34)*	*4.03 (3.52, 4.62)*
40-49	3,822,515	149	3.90	255	6.67	0.58 (0.48, 0.72)	*1.17 (0.99, 1.38)*	*2.34 (2.02, 2.71)*
50-64	4,901,232	149	3.04	261	5.33	0.57 (0.47, 0.7)	*1.14 (0.97, 1.35)*	*2.28 (1.97, 2.64)*
65-74	3,171,105	79	2.49	169	5.33	0.47 (0.36, 0.61)	*0.93 (0.75, 1.16)*	*1.87 (1.55, 2.25)*
75+	1,531,377	33	2.15	71	4.67	0.46 (0.31, 0.7)	*0.92 (0.66, 1.29)*	*1.85 (1.38, 2.46)*

Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep 2021;70:1228–1232. DOI: http://dx.doi.org/10.15585/mmwr.mm7035e5external icon. Because age by sex stratified estimates of the reference rate were not available in the source material, estimates are obtained by multiplying the age specific rate estimate by the ratio of the sex-specific stratum-specific rate to the overall rate.

Myocarditis, dose-specific analyses, Cases Occurring within 7 Days of a Known Dose, Cumulative Through 18 June 2022

	Observed vs Expected (95% CI)		
	Dose 1	**Dose 2**	**Dose 3**
All	0.7 (0.61, 0.8)	2.51 (2.24, 2.83)	1.16 (0.97, 1.39)
By age			
<12 years	NA	NA	NA
12-17 years	0.49 (0.23, 1.03)	3 (1.7, 5.32)	0.22 (0.05, 1.02)
18-24 years	1.21 (0.91, 1.6)	6.23 (4.81, 8.07)	1.74 (1.17, 2.59)
25-39 years	1.39 (1.09, 1.78)	4.19 (3.31, 5.32)	2.02 (1.43, 2.85)
40-49 years	0.33 (0.23, 0.48)	1.11 (0.83, 1.5)	0.8 (0.52, 1.22)
50-64 years	0.32 (0.22, 0.47)	0.53 (0.37, 0.76)	0.67 (0.43, 1.05)
65-74 years	0.12 (0.06, 0.25)	0.29 (0.17, 0.51)	0.54 (0.3, 0.97)
75+ years	0.16 (0.06, 0.42)	0.17 (0.06, 0.5)	0.52 (0.21, 1.3)
By gender			
Male	0.79 (0.67, 0.93)	3.44 (2.99, 3.97)	1.35 (1.09, 1.67)
Female	0.56 (0.44, 0.71)	0.99 (0.79, 1.26)	0.89 (0.65, 1.22)
By age and gender			
Male			
<12 years	NA	NA	NA
12-17 years	0.62 (0.26, 1.5)	4.3 (2.14, 8.63)	0.18 (0.02, 1.48)
18-24 years	1.61 (1.15, 2.25)	9.07 (6.58, 12.49)	2.41 (1.5, 3.88)
25-39 years	1.65 (1.22, 2.23)	5.9 (4.4, 7.9)	2.41 (1.58, 3.68)
40-49 years	0.31 (0.19, 0.5)	1.28 (0.89, 1.84)	0.8 (0.47, 1.38)
50-64 years	0.2 (0.11, 0.36)	0.55 (0.35, 0.86)	0.69 (0.39, 1.2)
65-74 years	0.11 (0.04, 0.28)	0.26 (0.13, 0.55)	0.5 (0.24, 1.08)
75+ years	0.16 (0.05, 0.53)	0.07 (0.01, 0.52)	0.36 (0.1, 1.34)
Female			
<12 years	NA	NA	NA
12-17 years	0.27 (0.06, 1.31)	0.9 (0.27, 3.02)	0.31 (0.03, 2.94)
18-24 years	0.58 (0.32, 1.03)	1.57 (0.94, 2.63)	0.66 (0.28, 1.53)
25-39 years	0.97 (0.62, 1.51)	1.41 (0.88, 2.26)	1.45 (0.79, 2.68)
40-49 years	0.39 (0.21, 0.71)	0.89 (0.52, 1.51)	0.83 (0.41, 1.68)
50-64 years	0.53 (0.31, 0.9)	0.53 (0.29, 0.98)	0.63 (0.3, 1.35)
65-74 years	0.16 (0.05, 0.45)	0.36 (0.15, 0.85)	0.62 (0.24, 1.6)
75+ years	0.18 (0.04, 0.84)	0.37 (0.1, 1.37)	0.84 (0.22, 3.18)

*Reference rates from Boehmer 2021. Because age by sex stratified estimates of the reference rate were not available in the source material, estimates are obtained by multiplying the age specific rate estimate by the ratio of the sex-specific stratum-specific rate to the overall rate.
* The number of cases of myocarditis after dose 4 were extremely sparse (2 cases) hence no analysis is reported.

Interpretability of the analyses relies on certain critical assumptions related to calculation of the expected rate. The age and sex distribution was specified based on the observed distribution in the US with the assumption that a maximum of 3% of SPIKEVAX doses administered annually were used in individuals <18 for fully vaccinated and first booster and only individuals 50 or older for second booster. These demographic distributions were not available by dose, so the same distribution is applied to each dose series to estimate age-specific rates in each dose group. For dose 3, this approach may underestimate the number of women (who are more often diagnosed with autoimmune conditions leading to immunocompromise, an early indication of a third dose in some countries) and older individuals receiving dose 3. This may explain why

observed vs. expected ratios are at unity for young women (where dose 3 reporting rates may be overestimated) but not for young men (where dose 3 reporting rates may be underestimates).

In interpretation of these results, it should be noted that current data do not fully distinguish between individuals who received a third 100 mcg dose, as is indicated in the context of immunocompromise in some settings, and a 50 ug booster dose. Given differences in the risk factor profile for these individuals and the potential impact of immune status on myocarditis risk, informal comparisons between doses may be confounded.

Pericarditis with or without myocarditis, overall analyses, all cases

			Observed		Expected		*Assuming 50% of cases were reported: RR (95% CI)*	*Assuming 25% of cases were reported: RR (95% CI)*
Outcome	**People**	**Cases**	**Rate**	**Cases**	**Rate**	**As observed: RR (95% CI)**		
Pericarditis with or without myocarditis								
Review Period:								
All	11272825	861	7.637837011	609	5.4	1.41 (1.27, 1.57)	2.83 (2.58, 3.1)	5.66 (5.19, 6.17)
By age								
<12	14850.7	0	0	1	3.7	NA	NA	NA
12-17	282154.3	21	7.44273612	10	3.7	2.01 (0.95, 4.27)	4.02 (2.02, 8.02)	8.05 (4.18, 15.5)
18-24	2041125	117	5.732133015	76	3.7	1.55 (1.16, 2.07)	3.1 (2.39, 4.01)	6.2 (4.86, 7.9)
25-39	1399426	260	18.57904598	52	3.7	5.02 (3.73, 6.76)	10.04 (7.55, 13.36)	20.09 (15.2, 26.54)
40-49	3162658	160	5.059035786	117	3.7	1.37 (1.08, 1.74)	2.73 (2.21, 3.38)	5.47 (4.49, 6.66)
50-64	2238981	173	7.726729258	152	6.8	1.14 (0.91, 1.41)	2.27 (1.88, 2.75)	4.55 (3.81, 5.42)
65-74	1937639	57	2.941724439	165	8.5	0.35 (0.26, 0.47)	0.69 (0.55, 0.88)	1.38 (1.13, 1.69)
75+	195969	25	12.75711975	17	8.7	1.47 (0.79, 2.72)	2.93 (1.69, 5.08)	5.87 (3.51, 9.81)
By gender								
Male	5097136	487	9.554385051	342	6.7	1.43 (1.24, 1.64)	2.85 (2.52, 3.23)	5.7 (5.08, 6.4)
Female	6175668	367	5.94267697	253	4.1	1.45 (1.23, 1.7)	2.9 (2.51, 3.34)	5.8 (5.07, 6.63)
By age and gender								
Male								
<12	6681.3	0	0	0	4.6	NA	NA	NA
12-17	126950.7	16	12.60331767	6	4.6	2.75 (1.07, 7.02)	5.49 (2.3, 13.13)	10.98 (4.76, 25.36)
18-24	939430	89	9.473829876	43	4.6	2.06 (1.43, 2.97)	4.13 (2.96, 5.76)	8.25 (6.02, 11.33)
25-39	615389	159	25.83731591	28	4.6	5.63 (3.77, 8.41)	11.26 (7.65, 16.57)	22.51 (15.42, 32.87)
40-49	1453704	76	5.228024412	67	4.6	1.14 (0.82, 1.58)	2.28 (1.71, 3.04)	4.56 (3.5, 5.93)
50-64	1001254	76	7.590481536	84	8.4	0.9 (0.66, 1.23)	1.8 (1.38, 2.35)	3.6 (2.83, 4.58)
65-74	880095	29	3.295098825	93	10.5	0.31 (0.21, 0.47)	0.62 (0.45, 0.87)	1.25 (0.95, 1.64)
75+	73631	15	20.37185425	8	10.8	1.89 (0.8, 4.45)	3.77 (1.73, 8.23)	7.55 (3.61, 15.79)
Female								
<12	8168.4	0	0	0	2.8	NA	NA	NA
12-17	155204.6	5	3.221554	4	2.8	1.15 (0.31, 4.27)	2.29 (0.72, 7.31)	4.59 (1.57, 13.42)
18-24	1101696	28	2.541535959	31	2.8	0.9 (0.54, 1.51)	1.81 (1.17, 2.81)	3.62 (2.43, 5.39)
25-39	784037	98	12.4994101	22	2.8	4.45 (2.8, 7.07)	8.9 (5.73, 13.83)	17.8 (11.58, 27.34)
40-49	1708954	84	4.915287363	48	2.8	1.75 (1.23, 2.49)	3.5 (2.54, 4.82)	7 (5.17, 9.47)
50-64	1237727	96	7.756153013	64	5.2	1.5 (1.09, 2.06)	3 (2.26, 3.99)	6.01 (4.61, 7.83)

Outcome	People	Cases	Observed		Expected		*Assuming 50% of cases were reported: RR (95% CI)*	*Assuming 25% of cases were reported: RR (95% CI)*
			Rate	Cases	Rate	As observed: RR (95% CI)		
65-74	1057544	28	2.647643975	68	6.5	0.41 (0.26, 0.64)	0.82 (0.58, 1.17)	1.64 (1.21, 2.22)
75+	122337	10	8.174141919	8	6.6	1.24 (0.49, 3.14)	2.47 (1.09, 5.62)	4.95 (2.32, 10.57)
Cumulative:								
All	38111689	2757	7.234001096	2058	5.4	1.34 (1.27, 1.42)	2.68 (2.55, 2.82)	5.36 (5.11, 5.62)
By age								
<12	55109	0	0	2	3.7	NA	NA	NA
12-17	1047062	69	6.589867649	39	3.7	1.78 (1.2, 2.64)	3.56 (2.5, 5.08)	7.12 (5.09, 9.96)
18-24	4456623	536	12.0270438	165	3.7	3.25 (2.73, 3.87)	6.5 (5.52, 7.66)	13 (11.1, 15.23)
25-39	7303976	790	10.81602678	270	3.7	2.92 (2.55, 3.36)	5.85 (5.14, 6.65)	11.69 (10.33, 13.24)
40-49	7188488	372	5.174940822	266	3.7	1.4 (1.19, 1.64)	2.8 (2.43, 3.22)	5.59 (4.91, 6.37)
50-64	9217086	448	4.860538352	627	6.8	0.71 (0.63, 0.81)	1.43 (1.29, 1.58)	2.86 (2.61, 3.13)
65-74	5963469	191	3.202833787	507	8.5	0.38 (0.32, 0.45)	0.75 (0.66, 0.86)	1.51 (1.35, 1.69)
75+	2879855	89	3.090433373	251	8.7	0.36 (0.28, 0.45)	0.71 (0.59, 0.86)	1.42 (1.21, 1.67)
By gender								
Male	17845596	1730	9.694268547	1196	6.7	1.45 (1.34, 1.56)	2.89 (2.71, 3.09)	5.79 (5.44, 6.15)
Female	20266072	998	4.9244866	831	4.1	1.2 (1.1, 1.32)	2.4 (2.22, 2.6)	4.8 (4.46, 5.18)
By age and gender								
Male								
<12	25804	0	0	1	4.6	NA	NA	NA
12-17	490282	57	11.6259622	23	4.6	2.53 (1.56, 4.11)	5.06 (3.24, 7.93)	10.13 (6.6, 15.55)
18-24	2086791	423	20.27035769	96	4.6	4.42 (3.54, 5.51)	8.83 (7.15, 10.91)	17.66 (14.38, 21.69)
25-39	3420050	513	14.9997807	157	4.6	3.27 (2.73, 3.91)	6.53 (5.52, 7.73)	13.07 (11.11, 15.37)
40-49	3365973	197	5.852691035	155	4.6	1.27 (1.03, 1.57)	2.55 (2.12, 3.07)	5.1 (4.29, 6.06)
50-64	4315854	214	4.95846245	364	8.4	0.59 (0.5, 0.7)	1.18 (1.02, 1.35)	2.35 (2.08, 2.66)
65-74	2792364	99	3.545383052	294	10.5	0.34 (0.27, 0.42)	0.67 (0.56, 0.81)	1.34 (1.16, 1.56)
75+	1348477	46	3.411255809	146	10.8	0.32 (0.23, 0.44)	0.63 (0.49, 0.82)	1.26 (1.02, 1.57)
Female								
<12	29304	0	0	1	2.8	NA	NA	NA
12-17	556781	12	2.155245958	16	2.8	0.77 (0.36, 1.62)	1.53 (0.82, 2.89)	3.07 (1.74, 5.4)
18-24	2369832	112	4.726073409	67	2.8	1.68 (1.24, 2.28)	3.36 (2.56, 4.42)	6.73 (5.21, 8.7)
25-39	3883926	270	6.95172874	109	2.8	2.47 (1.98, 3.09)	4.95 (4.03, 6.08)	9.9 (8.13, 12.05)
40-49	3822515	175	4.578137692	107	2.8	1.63 (1.28, 2.07)	3.26 (2.62, 4.05)	6.52 (5.32, 7.99)
50-64	4901232	230	4.692697673	253	5.2	0.91 (0.76, 1.09)	1.82 (1.56, 2.12)	3.64 (3.16, 4.18)
65-74	3171105	91	2.869662152	205	6.5	0.44 (0.35, 0.57)	0.89 (0.73, 1.09)	1.78 (1.5, 2.11)
75+	1531377	42	2.742629673	101	6.6	0.42 (0.29, 0.6)	0.83 (0.62, 1.11)	1.66 (1.3, 2.13)

Pericarditis without myocarditis, overall analyses, all cases

Outcome	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			
Pericarditis without myocarditis								
Review Period:								
All	11272825	599	5.3137	609	5.4	0.98 (0.88, 1.1)	1.97 (1.79, 2.17)	3.94 (3.6, 4.3)
By age								
<12	14850.7	0	0	1	3.7	NA	NA	NA
12-17	282154.3	8	2.8353	10	3.7	0.77 (0.3, 1.94)	1.53 (0.7, 3.38)	3.07 (1.51, 6.24)
18-24	2041125	57	2.7926	76	3.7	0.75 (0.54, 1.06)	1.51 (1.13, 2.02)	3.02 (2.33, 3.91)
25-39	1399426	178	12.72	52	3.7	3.44 (2.52, 4.68)	6.88 (5.14, 9.2)	13.75 (10.38, 18.22)
40-49	3162658	126	3.984	117	3.7	1.08 (0.84, 1.38)	2.15 (1.73, 2.68)	4.31 (3.52, 5.27)
50-64	2238981	144	6.4315	152	6.8	0.95 (0.75, 1.19)	1.89 (1.55, 2.3)	3.78 (3.16, 4.52)
65-74	1937639	47	2.4256	165	8.5	0.29 (0.21, 0.39)	0.57 (0.44, 0.74)	1.14 (0.93, 1.41)
75+	195969	20	10.206	17	8.7	1.17 (0.61, 2.24)	2.35 (1.33, 4.14)	4.69 (2.78, 7.92)
By gender								
Male	5097136	294	5.7679	342	6.7	0.86 (0.74, 1.01)	1.72 (1.51, 1.97)	3.44 (3.05, 3.88)
Female	6175668	301	4.874	253	4.1	1.19 (1.01, 1.41)	2.38 (2.05, 2.75)	4.76 (4.15, 5.45)
By age and gender								
Male								
<12	6681.3	0	0	0	4.6	NA	NA	NA
12-17	126950.7	5	3.9385	6	4.6	0.86 (0.26, 2.81)	1.72 (0.62, 4.72)	3.43 (1.38, 8.55)
18-24	939430	32	3.4063	43	4.6	0.74 (0.47, 1.17)	1.48 (1.01, 2.18)	2.97 (2.1, 4.19)
25-39	615389	96	15.6	28	4.6	3.4 (2.23, 5.18)	6.8 (4.57, 10.1)	13.59 (9.26, 19.95)
40-49	1453704	54	3.7146	67	4.6	0.81 (0.57, 1.16)	1.62 (1.19, 2.2)	3.24 (2.46, 4.26)
50-64	1001254	62	6.1922	84	8.4	0.73 (0.53, 1.02)	1.47 (1.11, 1.94)	2.94 (2.29, 3.76)
65-74	880095	24	2.727	93	10.5	0.26 (0.17, 0.41)	0.52 (0.37, 0.73)	1.03 (0.78, 1.38)
75+	73631	14	19.014	8	10.8	1.76 (0.74, 4.2)	3.52 (1.61, 7.73)	7.05 (3.36, 14.78)
Female								
<12	8168.4	0	0	0	2.8	NA	NA	NA
12-17	155204.6	3	1.9329	4	2.8	0.69 (0.15, 3.07)	1.38 (0.39, 4.88)	2.75 (0.89, 8.53)
18-24	1101696	25	2.2692	31	2.8	0.81 (0.48, 1.37)	1.62 (1.03, 2.53)	3.23 (2.16, 4.83)
25-39	784037	80	10.204	22	2.8	3.63 (2.27, 5.82)	7.26 (4.65, 11.34)	14.53 (9.43, 22.38)
40-49	1708954	72	4.2131	48	2.8	1.5 (1.04, 2.16)	3 (2.16, 4.16)	6 (4.42, 8.14)
50-64	1237727	81	6.5443	64	5.2	1.27 (0.91, 1.76)	2.54 (1.9, 3.39)	5.07 (3.88, 6.63)
65-74	1057544	23	2.1749	68	6.5	0.34 (0.21, 0.54)	0.67 (0.46, 0.98)	1.35 (0.99, 1.84)
75+	122337	6	4.9045	8	6.6	0.74 (0.26, 2.14)	1.48 (0.61, 3.63)	2.97 (1.33, 6.61)
Cumulative:								
All	38111689	1750	4.5918	2058	5.4	0.85 (0.8, 0.91)	1.7 (1.61, 1.8)	3.4 (3.24, 3.57)
By age								
<12	55109	0	0	2	3.7	NA	NA	NA
12-17	1047062	24	2.2921	39	3.7	0.62 (0.37, 1.03)	1.24 (0.81, 1.89)	2.48 (1.71, 3.6)
18-24	4456623	235	5.2731	165	3.7	1.43 (1.17, 1.74)	2.85 (2.39, 3.4)	5.7 (4.83, 6.73)
25-39	7303976	492	6.7361	270	3.7	1.82 (1.57, 2.11)	3.64 (3.18, 4.17)	7.28 (6.41, 8.27)
40-49	7188488	291	4.0481	266	3.7	1.09 (0.93, 1.29)	2.19 (1.89, 2.53)	4.38 (3.83, 5)
50-64	9217086	376	4.0794	627	6.8	0.6 (0.53, 0.68)	1.2 (1.08, 1.33)	2.4 (2.19, 2.63)
65-74	5963469	164	2.7501	507	8.5	0.32 (0.27, 0.39)	0.65 (0.56, 0.74)	1.29 (1.15, 1.45)

Outcome	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			
75+	2879855	75	2.6043	251	8.7	0.3 (0.23, 0.39)	0.6 (0.49, 0.73)	1.2 (1.01, 1.42)
By gender								
Male	17845596	934	5.2338	1196	6.7	0.78 (0.72, 0.85)	1.56 (1.45, 1.68)	3.12 (2.93, 3.33)
Female	20266072	796	3.9277	831	4.1	0.96 (0.87, 1.06)	1.92 (1.76, 2.08)	3.83 (3.55, 4.14)
By age and gender								
Male								
<12	25804	0	0	1	4.6	NA	NA	NA
12-17	490282	16	3.2634	23	4.6	0.71 (0.38, 1.35)	1.42 (0.83, 2.43)	2.84 (1.77, 4.58)
18-24	2086791	150	7.1881	96	4.6	1.57 (1.21, 2.02)	3.13 (2.49, 3.94)	6.26 (5.05, 7.77)
25-39	3420050	275	8.0408	157	4.6	1.75 (1.44, 2.13)	3.5 (2.93, 4.18)	7.01 (5.93, 8.28)
40-49	3365973	143	4.2484	155	4.6	0.93 (0.74, 1.16)	1.85 (1.52, 2.25)	3.7 (3.1, 4.42)
50-64	4315854	174	4.0316	364	8.4	0.48 (0.4, 0.57)	0.96 (0.83, 1.11)	1.91 (1.68, 2.17)
65-74	2792364	87	3.1156	294	10.5	0.3 (0.23, 0.38)	0.59 (0.49, 0.71)	1.18 (1.01, 1.38)
75+	1348477	40	2.9663	146	10.8	0.27 (0.19, 0.39)	0.55 (0.42, 0.72)	1.1 (0.88, 1.38)
Female								
<12	29304	0	0	1	2.8	NA	NA	NA
12-17	556781	8	1.4368	16	2.8	0.51 (0.22, 1.2)	1.02 (0.51, 2.05)	2.05 (1.12, 3.73)
18-24	2369832	84	3.5446	67	2.8	1.26 (0.92, 1.74)	2.52 (1.9, 3.35)	5.05 (3.88, 6.56)
25-39	3883926	211	5.4326	109	2.8	1.93 (1.53, 2.44)	3.87 (3.13, 4.77)	7.74 (6.34, 9.44)
40-49	3822515	148	3.8718	107	2.8	1.38 (1.07, 1.77)	2.76 (2.21, 3.44)	5.51 (4.49, 6.77)
50-64	4901232	199	4.0602	253	5.2	0.79 (0.65, 0.95)	1.57 (1.34, 1.84)	3.15 (2.73, 3.62)
65-74	3171105	76	2.3966	205	6.5	0.37 (0.29, 0.48)	0.74 (0.6, 0.92)	1.49 (1.24, 1.77)
75+	1531377	34	2.2202	101	6.6	0.34 (0.23, 0.5)	0.67 (0.49, 0.91)	1.34 (1.04, 1.74)

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1.1.1.1.5. Observed-to-Expected Analyses, Pregnancy

Reports of pregnant women vaccinated during pregnancy or around the time of conception, and reports of fetuses/neonates/infants whose mothers were vaccinated during pregnancy were identified from the ModernaTx global safety database and are described in this PBRER. The cumulative data (as of 18 June 2022) was reviewed.

The current search strategy to identify "pregnancy-related cases" (Pregnancy [MI-PREG&Pts Preg] is comprised of multiple components:

- Argus field "Patient Pregnant" = Yes OR
- MI-Preg (See PSSF 6.0) = Yes and Patient Preg = No AND gender=female and Age Group= (18-49) OR
- MI-Preg =Yes AND Patient Preg = No AND Age group <2 y/o OR "missing" AND PREG-Fetal Outcome <> (Empty) OR
- MI-Preg = Yes and Patient preg =No AND Argus field "Child Case Only" = Yes

Pregnancy-related cases are pulled by case identification numbers and contain "All PTs" which includes both pregnancy-related and non-pregnancy-related events. The MAH reviews all events reported cumulatively for this subpopulation.

"Pregnancy-related events"/ "Pregnancy-related PTs" (such as maternal exposure, pregnancy/labor/delivery/ post-partum complications, pregnancy outcomes, fetal and neonatal events) within cases are identified by the MI-Preg SMQ described in the PSSF 6.0. Pregnancy-related events include congenital anomalies, cases of which are summarized in the table. The O/E analysis includes congenital anomalies as well.

For Pregnancy Outcomes (included in Appendix 9B) a Pregnancy Outcome (Derived) filter is used with the following criteria:

- If PREG-Fetal Outcome is "Empty" but either MI-ABORT, MI-PRETERM, MI-STILLBIRTH, or MI-FULLTERM = YES then the PT term is entered as outcome OR
- Use PREG-Fetal Outcome is populated
- Otherwise, classified as "undetermined"

For the observed to expected analyses, the estimated total number of exposed pregnancies was used to estimate expected cases based on the incidence proportion or birth prevalence from published sources. Where appropriate, additional analyses showing completed pregnancies as the presumed denominator are also presented. The total number of reported pregnancies was estimated based on the number of pregnant women reporting vaccination during pregnancy to the V-Safe After Vaccination Health Checker published on 14 Feb 2022 (201,075). (Note that V-safe did not publish any further updates to the number of pregnant women reporting vaccination during pregnancy as of 16th June 2022) Assuming patterns of vaccination during pregnancy mirrored vaccine brand use in the general US population, approximately 75,850 of these women are expected to have received SPIKEVAX during pregnancy. The proportion of global SPIKEVAX recipients estimated to be pregnant at the time of vaccination was then extrapolated by multiplying the global vaccine recipient estimate by this proportion. The proportion of women reporting a

pregnancy to the safety database who have completed their pregnancies was then used to estimate the number of completed pregnancies exposed to SPIKEVAX (55,541).As V-Safe has stopped updating the number of pregnant women reporting vaccination during pregnancy and none of the estimates for the pregnancy outcomes have changed over the course of the bi/monthly safety reports, it is proposed that estimated pregnancies will be removed from future reports.

Additional analyses considered alternative denominators (estimating the exposed population) based on the total number of reported pregnancies, and the total number of reported pregnancies collected prospectively. It is expected that this substantially underestimates the number of women who have received SPIKEVAX during pregnancy. As such, we consider the approach of considering pregnancies reported to the safety database to represent a highly conservative sensitivity analysis. Comparisons have also been presented based on reported pregnancies overall and reported pregnancies captured prospectively; however, outcome data appear questionably interpretable at this time given the small number of pregnancies where prospective outcomes are available. Selection of references for identification of the expected incidence prioritized reference rates used by the V-Safe registry, with additional sources added where European rates were available.

Outcome	Pregnancies	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported: RR (95% CI)*
		Cases	%	Cases	%		
Pregnancy outcome							
Spontaneous abortion							
Reference: Dugas 2021							
Pregnancies, estimated	225,044	654	0.3	25880	11.5	0.03 (0.02, 0.03)	*0.05 (0.05, 0.05)*
Pregnancies, estimated, complete	55,720	654	1.2	6408	11.5	0.1 (0.09, 0.11)	*0.2 (0.19, 0.22)*
Reported pregnancies	4,786	654	13.7	550	11.5	1.19 (1.06, 1.33)	*2.38 (2.15, 2.63)*
Reported pregnancies, prospective	3,492	43	1.2	402	11.5	0.11 (0.08, 0.15)	*0.21 (0.17, 0.27)*
Reference: Dugas 2021							
Pregnancies, estimated	225,044	654	0.3	58512	26.0	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*
Pregnancies, estimated, complete	55,720	654	1.2	14487	26.0	0.05 (0.04, 0.05)	*0.09 (0.09, 0.1)*
Reported pregnancies	4,786	654	13.7	1244	26.0	0.53 (0.48, 0.58)	*1.05 (0.97, 1.14)*
Reported pregnancies, prospective	3,492	43	1.2	908	26.0	0.05 (0.03, 0.06)	*0.09 (0.08, 0.12)*
Stillbirth							
Reference: Gubernot 2021							
Pregnancies, estimated	225,044	55	0.0	1350	0.6	0.04 (0.03, 0.05)	*0.08 (0.07, 0.1)*
Pregnancies, estimated, complete	55,720	55	0.1	334	0.6	0.16 (0.12, 0.22)	*0.33 (0.27, 0.41)*
Reported pregnancies	4,786	55	1.1	28	0.6	1.96 (1.24, 3.08)	*3.91 (2.58, 5.92)*
Reported pregnancies, prospective	3,492	5	0.1	21	0.6	0.24 (0.09, 0.63)	*0.48 (0.22, 1.01)*
Reported pregnancies, prospective, complete	178	4	2.2	1	0.6	3.82 (0.44, 32.89)	*7.65 (1, 58.66)*
Preterm Delivery[1]							
Reference: US NCHS/Peristats 2020							
Pregnancies, estimated	225,044	70	0.0	22729	10.1	0 (0, 0)	*0.01 (0.01, 0.01)*
Pregnancies, estimated, complete	55,720	70	0.1	5628	10.1	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*
Reported pregnancies	4,786	70	1.5	483	10.1	0.14 (0.11, 0.19)	*0.29 (0.24, 0.35)*
Reported pregnancies, complete	1,185	54	4.6	120	10.1	0.45 (0.33, 0.62)	*0.9 (0.7, 1.17)*
Reported pregnancies, prospective	3,492	19	0.5	353	10.1	0.05 (0.03, 0.09)	*0.11 (0.08, 0.15)*
Reported pregnancies, prospective, complete	178	4	2.2	18	10.1	0.22 (0.08, 0.66)	*0.44 (0.19, 1.02)*
Reference: Renzo 2011							
Pregnancies, estimated	225,044	70	0.0	25880	11.5	0 (0, 0)	*0.01 (0, 0.01)*
Pregnancies, estimated, complete	55,720	70	0.1	6408	11.5	0.01 (0.01, 0.01)	*0.02 (0.02, 0.03)*
Reported pregnancies	4,786	70	1.5	550	11.5	0.13 (0.1, 0.16)	*0.25 (0.21, 0.31)*
Reported pregnancies, complete	1,185	54	4.6	136	11.5	0.4 (0.29, 0.54)	*0.79 (0.62, 1.02)*

Outcome	Pregnancies	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported: RR (95% CI)*
		Cases	%	Cases	%		
Reported pregnancies, prospective	3,492	19	0.5	402	11.5	0.05 (0.03, 0.07)	*0.09 (0.07, 0.13)*
Reported pregnancies, prospective, complete	178	4	2.2	20	11.5	0.2 (0.07, 0.57)	*0.39 (0.17, 0.88)*
Ectopic pregnancy							
Reference: Rouse 2017							
Pregnancies, estimated	225,044	22	0.0	1350	0.6	0.02 (0.01, 0.02)	*0.03 (0.02, 0.04)*
Pregnancies, estimated, complete	55,720	22	0.0	334	0.6	0.07 (0.04, 0.1)	*0.13 (0.1, 0.18)*
Reported pregnancies	4,786	22	0.5	29	0.6	0.77 (0.44, 1.33)	*1.53 (0.96, 2.45)*
Reported pregnancies, prospective	3,492	5	0.1	21	0.6	0.24 (0.09, 0.63)	*0.48 (0.22, 1.01)*
Pregnancy complications							
Hypertensive disorders of pregnancy							
Reference: Antza 2017							
Pregnancies, estimated	225,044	32	0.0	22504	10.0	0 (0, 0)	*0 (0, 0)*
Pregnancies, estimated, complete	55,720	32	0.1	5572	10.0	0.01 (0, 0.01)	*0.01 (0.01, 0.01)*
Reported pregnancies	4,786	32	0.7	479	10.0	0.07 (0.05, 0.1)	*0.13 (0.1, 0.17)*
Reported pregnancies, complete	1,185	32	2.7	119	10.0	0.27 (0.18, 0.4)	*0.54 (0.4, 0.73)*
Reported pregnancies, prospective	3,492	7	0.2	349	10.0	0.02 (0.01, 0.04)	*0.04 (0.02, 0.07)*
Reported pregnancies, prospective, complete	178	7	3.9	18	10.0	0.39 (0.16, 0.94)	*0.79 (0.39, 1.58)*
Reference: Garovic 2020							
Pregnancies, estimated	225,044	32	0.0	33757	15.0	0 (0, 0)	*0 (0, 0)*
Pregnancies, estimated, complete	55,720	32	0.1	8358	15.0	0 (0, 0.01)	*0.01 (0.01, 0.01)*
Reported pregnancies	4,786	32	0.7	718	15.0	0.04 (0.03, 0.06)	*0.09 (0.07, 0.12)*
Reported pregnancies, complete	1,185	32	2.7	178	15.0	0.18 (0.12, 0.26)	*0.36 (0.27, 0.48)*
Reported pregnancies, prospective	3,492	7	0.2	524	15.0	0.01 (0.01, 0.03)	*0.03 (0.02, 0.05)*
Reported pregnancies, prospective, complete	178	7	3.9	27	15.0	0.26 (0.11, 0.6)	*0.52 (0.27, 1)*
Gestational diabetes							
Reference: Eades 2017							
Pregnancies, estimated	225,044	13	0.0	12152	5.4	0 (0, 0)	*0 (0, 0)*
Pregnancies, estimated, complete	55,720	13	0.0	3009	5.4	0 (0, 0.01)	*0.01 (0.01, 0.01)*
Reported pregnancies	4,786	13	0.3	258	5.4	0.05 (0.03, 0.09)	*0.1 (0.07, 0.15)*
Reported pregnancies, complete	1,185	13	1.1	64	5.4	0.2 (0.11, 0.37)	*0.41 (0.26, 0.64)*
Reported pregnancies, prospective	3,492	11	0.3	189	5.4	0.06 (0.03, 0.11)	*0.12 (0.08, 0.18)*
Reported pregnancies, prospective, complete	178	11	6.2	10	5.4	1.14 (0.48, 2.72)	*2.29 (1.07, 4.88)*
Reference: Behboudi 2019							
Pregnancies, estimated	225,044	13	0.0	15753	7.0	0 (0, 0)	*0 (0, 0)*
Pregnancies, estimated, complete	55,720	13	0.0	3900	7.0	0 (0, 0.01)	*0.01 (0, 0.01)*
Reported pregnancies	4,786	13	0.3	335	7.0	0.04 (0.02, 0.07)	*0.08 (0.05, 0.12)*
Reported pregnancies, complete	1,185	13	1.1	83	7.0	0.16 (0.09, 0.28)	*0.31 (0.2, 0.49)*
Reported pregnancies, prospective	3,492	11	0.3	244	7.0	0.05 (0.02, 0.08)	*0.09 (0.06, 0.14)*
Reported pregnancies, prospective, complete	178	11	6.2	12	7.0	0.88 (0.39, 1.99)	*1.77 (0.88, 3.54)*
Haemorrhage							
Reference: Reale, 2020							
Pregnancies, estimated	225,044	100	0.0	6751	3.0	0.01 (0.01, 0.02)	*0.03 (0.03, 0.03)*
Pregnancies, estimated, complete	55,720	100	0.2	1672	3.0	0.06 (0.05, 0.07)	*0.12 (0.1, 0.14)*
Reported pregnancies	4,786	100	2.1	144	3.0	0.7 (0.54, 0.9)	*1.39 (1.12, 1.73)*
Reported pregnancies, complete	1,185	100	8.4	36	3.0	2.81 (1.92, 4.12)	*5.63 (3.94, 8.04)*
Reported pregnancies, prospective	3,492	54	1.5	105	3.0	0.52 (0.37, 0.72)	*1.03 (0.79, 1.35)*
Reported pregnancies, prospective, complete	178	54	30.3	5	3.0	10.11 (4.16, 24.6)	*20.22 (8.48, 48.22)*
Oligohydramnios							

Outcome	Pregnancies	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported: RR (95% CI)*
		Cases	%	Cases	%		
Reference: Locatelli 2004							
Pregnancies, estimated	225,044	4	0.0	2250	1.0	0 (0, 0)	*0 (0, 0.01)*
Pregnancies, estimated, complete	55,720	4	0.0	557	1.0	0.01 (0, 0.02)	*0.01 (0.01, 0.03)*
Reported pregnancies	4,786	4	0.1	48	1.0	0.08 (0.03, 0.23)	*0.17 (0.08, 0.35)*
Reported pregnancies, complete	1,185	4	0.3	12	1.0	0.34 (0.11, 1.05)	*0.68 (0.28, 1.66)*
Reported pregnancies, prospective	3,492	1	0.0	35	1.0	0.03 (0, 0.21)	*0.06 (0.01, 0.24)*
Reported pregnancies, prospective, complete	178	1	0.6	2	1.0	0.56 (0.05, 6.51)	*1.12 (0.15, 8.47)*
Infant outcome							
Major congenital malformations[2]							
Reference: Dugas 2021							
Pregnancies, estimated, complete	55,720	35	0.1	1672	3.0	0.02 (0.01, 0.03)	*0.04 (0.03, 0.05)*
Assuming 1/3 exposed first trimester	18,573	35	0.2	557	3.0	0.06 (0.04, 0.09)	*0.13 (0.1, 0.16)*
Assuming 1/10 exposed first trimester	5,572	35	0.6	167	3.0	0.21 (0.15, 0.3)	*0.42 (0.32, 0.55)*
Reported pregnancies	3,455	35	1.0	104	3.0	0.34 (0.23, 0.5)	*0.68 (0.5, 0.91)*
Reported pregnancies, complete	1,185	24	2.0	36	3.0	0.68 (0.4, 1.13)	*1.35 (0.88, 2.08)*
Reported pregnancies, prospective	3,492	4	0.1	105	3.0	0.04 (0.01, 0.1)	*0.08 (0.04, 0.16)*
Foetal growth restriction							
Reference: Romo 2009							
Pregnancies, estimated, complete	55,720	23	0.0	1672	3.0	0.01 (0.01, 0.02)	*0.03 (0.02, 0.04)*
Assuming 1/3 exposed first trimester	18,573	23	0.1	557	3.0	0.04 (0.03, 0.06)	*0.08 (0.06, 0.11)*
Assuming 1/10 exposed first trimester	5,572	23	0.4	167	3.0	0.14 (0.09, 0.21)	*0.28 (0.2, 0.38)*
Reported pregnancies	3,455	23	0.7	104	3.0	0.22 (0.14, 0.35)	*0.44 (0.31, 0.63)*
Reported pregnancies, complete	1,185	23	1.9	36	3.0	0.65 (0.38, 1.09)	*1.29 (0.84, 2)*
Reported pregnancies, prospective	3,492	7	0.2	105	3.0	0.07 (0.03, 0.14)	*0.13 (0.08, 0.23)*
Hydrops foetalis							
Reference: Romo 2009							
Pregnancies, estimated, complete	55,720	3	0.0	56	0.1	0.05 (0.02, 0.17)	*0.11 (0.05, 0.25)*
Reported pregnancies	4,786	3	0.1	5	0.1	0.63 (0.15, 2.65)	*1.25 (0.38, 4.17)*
Reported pregnancies, prospective	3,492	1	0.0	3	0.1	0.29 (0.03, 2.64)	*0.57 (0.1, 3.26)*
Neonatal neutropenia							
Reference: Maheshwari 2014							
Pregnancies, estimated, complete	55,720	1	0.0	18	0.0	0.06 (0.01, 0.42)	*0.11 (0.03, 0.48)*
Reported pregnancies	4,786	1	0.0	2	0.0	0.65 (0.05, 8.11)	*1.31 (0.16, 10.71)*
Reported pregnancies, prospective	3,492	0	0.0	1	0.0	NA	*NA*

[1]For PBRER03, the definition of Preterm delivery included PT terms (Premature delivery, premature labour, premature rupture of membranes, premature seperation of placenta, and preterm premature rupture of membranes). This definition of Preterm delivery was refined for BSSR2 to include only two PT terms - premature delivery and premature labour.

[2]All reported congenital malformations were reviewed, adjudicated and classified by physicians using the Metropolitan Atlanta Congenital Defects Program (MACDP), which is a population-based tracking system for birth defects. All major congenital malformations in accordance with MACDP were included in the cumulative observed number of cases. All reported non-major congenital malformations –excluding chromosomal anomalies and congenital anomalies documented in adults unrelated to Spikevax– consisted of minor defects, normal variants, or other conditions and were not reported in BSSR3 as they are never included in MACDP data.

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Outcome	Pregnancies	Observed		Expected		As observed: RR (95% CI)	*Assuming 50% of cases were reported: RR (95% CI)*
		Cases	%	Cases	%		

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1.1.1.1.6. Age and Sex Stratified Observed-to-Expected Analyses, Neuralgic Amyotrophy

Outcome	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			
Neuralgic Amyotrophy								
Review Period:								
All	11,272,825	63	0.56	180	1.60	0.35 (0.26, 0.47)	*0.7 (0.56, 0.88)*	*1.4 (1.15, 1.69)*
By age								
<12	14,851	0	0.00	0	1.60	NA	*NA*	*NA*
12-17	282,154	0	0.00	5	1.60	NA	*NA*	*NA*
18-24	2,041,125	1	0.05	33	1.60	0.03 (0, 0.22)	*0.06 (0.01, 0.26)*	*0.12 (0.04, 0.35)*
25-39	1,399,426	7	0.50	22	1.60	0.31 (0.13, 0.73)	*0.63 (0.32, 1.22)*	*1.25 (0.72, 2.19)*
40-49	3,162,658	25	0.79	51	1.60	0.49 (0.31, 0.8)	*0.99 (0.67, 1.46)*	*1.98 (1.41, 2.77)*
50-64	2,238,981	21	0.94	36	1.60	0.59 (0.34, 1)	*1.17 (0.75, 1.83)*	*2.34 (1.59, 3.46)*
65-74	1,937,639	5	0.26	31	1.60	0.16 (0.06, 0.41)	*0.32 (0.16, 0.66)*	*0.65 (0.37, 1.13)*
75+	195,969	3	1.53	3	1.60	0.96 (0.19, 4.74)	*1.91 (0.48, 7.65)*	*3.83 (1.08, 13.56)*
By gender								
Male	5,097,136	36	0.71	82	1.60	0.44 (0.3, 0.65)	*0.88 (0.64, 1.21)*	*1.77 (1.35, 2.32)*
Female	6,175,668	27	0.44	99	1.60	0.27 (0.18, 0.42)	*0.55 (0.39, 0.76)*	*1.09 (0.83, 1.44)*
By age and gender								
Male								
<12	6,681	0	0.00	0	1.60	NA	*NA*	*NA*
12-17	126,951	0	0.00	2	1.60	NA	*NA*	*NA*
18-24	939,430	1	0.11	15	1.60	0.07 (0.01, 0.5)	*0.13 (0.03, 0.58)*	*0.27 (0.09, 0.8)*
25-39	615,389	3	0.49	10	1.60	0.3 (0.08, 1.11)	*0.61 (0.22, 1.68)*	*1.22 (0.53, 2.82)*
40-49	1,453,704	18	1.24	23	1.60	0.77 (0.42, 1.43)	*1.55 (0.92, 2.61)*	*3.1 (1.94, 4.95)*
50-64	1,001,254	9	0.90	16	1.60	0.56 (0.25, 1.27)	*1.12 (0.57, 2.2)*	*2.25 (1.25, 4.05)*
65-74	880,095	3	0.34	14	1.60	0.21 (0.06, 0.74)	*0.43 (0.16, 1.11)*	*0.85 (0.39, 1.84)*
75+	73,631	2	2.72	1	1.60	1.7 (0.15, 18.72)	*3.4 (0.38, 30.38)*	*6.79 (0.85, 54.3)*
Female								
<12	8,168	0	0.00	0	1.60	NA	*NA*	*NA*
12-17	155,205	0	0.00	2	1.60	NA	*NA*	*NA*
18-24	1,101,696	0	0.00	18	1.60	NA	*NA*	*NA*
25-39	784,037	4	0.51	13	1.60	0.32 (0.1, 0.98)	*0.64 (0.26, 1.54)*	*1.28 (0.61, 2.65)*
40-49	1,708,954	7	0.41	27	1.60	0.26 (0.11, 0.59)	*0.51 (0.27, 0.98)*	*1.02 (0.6, 1.74)*
50-64	1,237,727	12	0.97	20	1.60	0.61 (0.3, 1.24)	*1.21 (0.67, 2.19)*	*2.42 (1.44, 4.08)*
65-74	1,057,544	2	0.19	17	1.60	0.12 (0.03, 0.51)	*0.24 (0.08, 0.7)*	*0.47 (0.2, 1.1)*
75+	122,337	1	0.82	2	1.60	0.51 (0.05, 5.63)	*1.02 (0.14, 7.25)*	*2.04 (0.37, 11.16)*
Cumulative:								
All	38,111,689	180	0.47	610	1.60	0.3 (0.25, 0.35)	*0.59 (0.52, 0.67)*	*1.18 (1.06, 1.32)*
By age								
<12	55,109	0	0.00	1	1.60	NA	*NA*	*NA*
12-17	1,047,062	0	0.00	17	1.60	NA	*NA*	*NA*
18-24	4,456,623	4	0.09	71	1.60	0.06 (0.02, 0.15)	*0.11 (0.05, 0.23)*	*0.22 (0.13, 0.39)*
25-39	7,303,976	21	0.29	117	1.60	0.18 (0.11, 0.29)	*0.36 (0.25, 0.51)*	*0.72 (0.54, 0.95)*
40-49	7,188,488	54	0.75	115	1.60	0.47 (0.34, 0.65)	*0.94 (0.72, 1.22)*	*1.88 (1.5, 2.35)*
50-64	9,217,086	64	0.69	147	1.60	0.43 (0.32, 0.58)	*0.87 (0.68, 1.1)*	*1.74 (1.42, 2.13)*
65-74	5,963,469	23	0.39	95	1.60	0.24 (0.15, 0.38)	*0.48 (0.34, 0.69)*	*0.96 (0.72, 1.28)*
75+	2,879,855	7	0.24	46	1.60	0.15 (0.07, 0.34)	*0.3 (0.17, 0.55)*	*0.61 (0.38, 0.97)*
By gender								
Male	17,845,596	93	0.52	286	1.60	0.33 (0.26, 0.41)	*0.65 (0.54, 0.78)*	*1.3 (1.12, 1.52)*
Female	20,266,072	85	0.42	324	1.60	0.26 (0.21, 0.33)	*0.52 (0.44, 0.63)*	*1.05 (0.9, 1.22)*
By age and gender								
Male								
<12	25,804	0	0.00	0	1.60	NA	*NA*	*NA*
12-17	490,282	0	0.00	8	1.60	NA	*NA*	*NA*
18-24	2,086,791	2	0.10	33	1.60	0.06 (0.01, 0.25)	*0.12 (0.04, 0.34)*	*0.24 (0.11, 0.52)*
25-39	3,420,050	9	0.26	55	1.60	0.16 (0.08, 0.33)	*0.33 (0.19, 0.56)*	*0.66 (0.43, 1)*
40-49	3,365,973	29	0.86	54	1.60	0.54 (0.34, 0.85)	*1.08 (0.74, 1.56)*	*2.15 (1.56, 2.97)*
50-64	4,315,854	31	0.72	69	1.60	0.45 (0.29, 0.69)	*0.9 (0.64, 1.27)*	*1.8 (1.34, 2.41)*

Outcome	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			
65-74	2,792,364	16	0.57	45	1.60	0.36 (0.2, 0.63)	*0.72 (0.46, 1.13)*	*1.43 (0.98, 2.1)*
75+	1,348,477	5	0.37	22	1.60	0.23 (0.09, 0.61)	*0.46 (0.22, 0.98)*	*0.93 (0.51, 1.7)*
Female								
<12	29,304	0	0.00	0	1.60	NA	*NA*	*NA*
12-17	556,781	0	0.00	9	1.60	NA	*NA*	*NA*
18-24	2,369,832	2	0.08	38	1.60	0.05 (0.01, 0.22)	*0.11 (0.04, 0.3)*	*0.21 (0.1, 0.45)*
25-39	3,883,926	11	0.28	62	1.60	0.18 (0.09, 0.34)	*0.35 (0.22, 0.58)*	*0.71 (0.48, 1.04)*
40-49	3,822,515	25	0.65	61	1.60	0.41 (0.26, 0.65)	*0.82 (0.56, 1.19)*	*1.64 (1.19, 2.25)*
50-64	4,901,232	33	0.67	78	1.60	0.42 (0.28, 0.63)	*0.84 (0.61, 1.17)*	*1.68 (1.27, 2.23)*
65-74	3,171,105	7	0.22	51	1.60	0.14 (0.06, 0.3)	*0.28 (0.15, 0.5)*	*0.55 (0.35, 0.88)*
75+	1,531,377	2	0.13	25	1.60	0.08 (0.02, 0.34)	*0.16 (0.06, 0.47)*	*0.33 (0.15, 0.72)*

Beghi E, Kurland LT, Mulder DW, Nicolosi A. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970-1981. Ann Neurol 1985; 18: 320–3.

1.1.1.1.7. Age and Sex Stratified Observed-to-Expected Analyses, Autoimmune Haemolytic Anemia

Outcome	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			
Autoimmune Haemolytic Anemia								
Review Period:								
All	11272825	17	0.1508	200	1.77	0.09 (0.05, 0.14)	0.17 (0.12, 0.25)	0.34 (0.26, 0.45)
By age								
<12	14850.7	0	0	0	0.35	NA	NA	NA
12-17	282154.3	0	0	1	0.35	NA	NA	NA
18-24	2041125	0	0	10	0.51	NA	NA	NA
25-39	1399426	2	0.1429	7	0.51	0.28 (0.06, 1.35)	0.56 (0.16, 1.91)	1.12 (0.41, 3.09)
40-49	3162658	6	0.1897	16	0.51	0.37 (0.15, 0.95)	0.74 (0.35, 1.57)	1.49 (0.79, 2.8)
50-64	2238981	3	0.134	75	3.34	0.04 (0.01, 0.13)	0.08 (0.03, 0.18)	0.16 (0.09, 0.3)
65-74	1937639	5	0.258	65	3.34	0.08 (0.03, 0.19)	0.15 (0.08, 0.3)	0.31 (0.19, 0.51)
75+	195969	0	0	7	3.34	NA	NA	NA
By gender								
Male	5097136	6	0.1177	75	1.48	0.08 (0.03, 0.18)	0.16 (0.09, 0.29)	0.32 (0.2, 0.5)
Female	6175668	11	0.1781	106	1.71	0.1 (0.06, 0.19)	0.21 (0.13, 0.33)	0.42 (0.29, 0.59)
By age and gender								
Male								
<12	6681.3	0	0	0	1.48	NA	NA	NA
12-17	126950.7	0	0	2	1.48	NA	NA	NA
18-24	939430	0	0	14	1.48	NA	NA	NA
25-39	615389	0	0	9	1.48	NA	NA	NA
40-49	1453704	2	0.1376	22	1.48	0.09 (0.02, 0.4)	0.19 (0.06, 0.54)	0.37 (0.17, 0.84)
50-64	1001254	2	0.1997	15	1.48	0.13 (0.03, 0.59)	0.27 (0.09, 0.81)	0.54 (0.23, 1.27)
65-74	880095	1	0.1136	13	1.48	0.08 (0.01, 0.59)	0.15 (0.03, 0.68)	0.31 (0.1, 0.94)
75+	73631	0	0	1	1.48	NA	NA	NA
Female								
<12	8168.4	0	0	0	1.71	NA	NA	NA
12-17	155204.6	0	0	3	1.71	NA	NA	NA
18-24	1101696	0	0	19	1.71	NA	NA	NA
25-39	784037	2	0.2551	13	1.71	0.15 (0.03, 0.66)	0.3 (0.1, 0.92)	0.6 (0.25, 1.44)
40-49	1708954	4	0.2341	29	1.71	0.14 (0.05, 0.39)	0.27 (0.13, 0.6)	0.55 (0.3, 1.01)
50-64	1237727	1	0.0808	21	1.71	0.05 (0.01, 0.35)	0.09 (0.02, 0.4)	0.19 (0.06, 0.55)
65-74	1057544	4	0.3782	18	1.71	0.22 (0.07, 0.65)	0.44 (0.19, 1.02)	0.88 (0.45, 1.73)
75+	122337	0	0	2	1.71	NA	NA	NA
Cumulative:								
All	38111689	64	0.1679	675	1.77	0.09 (0.07, 0.12)	0.19 (0.16, 0.23)	0.38 (0.33, 0.44)
By age								
<12	55109	1	1.8146	0	0.35	NA	NA	NA
12-17	1047062	0	0	4	0.35	NA	NA	NA
18-24	4456623	0	0	23	0.51	NA	NA	NA
25-39	7303976	7	0.0958	37	0.51	0.19 (0.08, 0.42)	0.38 (0.2, 0.7)	0.75 (0.46, 1.23)
40-49	7188488	10	0.1391	37	0.51	0.27 (0.14, 0.55)	0.55 (0.32, 0.94)	1.09 (0.7, 1.71)
50-64	9217086	16	0.1736	308	3.34	0.05 (0.03, 0.09)	0.1 (0.07, 0.15)	0.21 (0.16, 0.27)
65-74	5963469	15	0.2515	199	3.34	0.08 (0.04, 0.13)	0.15 (0.1, 0.22)	0.3 (0.23, 0.4)
75+	2879855	12	0.4167	96	3.34	0.12 (0.07, 0.23)	0.25 (0.16, 0.39)	0.5 (0.35, 0.71)
By gender								
Male	17845596	27	0.1513	264	1.48	0.1 (0.07, 0.15)	0.2 (0.15, 0.27)	0.41 (0.33, 0.51)
Female	20266072	36	0.1776	347	1.71	0.1 (0.07, 0.15)	0.21 (0.16, 0.27)	0.42 (0.34, 0.5)
By age and gender								
Male								
<12	25804	1	3.8754	0	1.48	NA	NA	NA
12-17	490282	0	0	7	1.48	NA	NA	NA
18-24	2086791	0	0	31	1.48	NA	NA	NA
25-39	3420050	1	0.0292	51	1.48	0.02 (0, 0.14)	0.04 (0.01, 0.16)	0.08 (0.03, 0.22)
40-49	3365973	4	0.1188	50	1.48	0.08 (0.03, 0.22)	0.16 (0.08, 0.34)	0.32 (0.18, 0.56)
50-64	4315854	6	0.139	64	1.48	0.09 (0.04, 0.22)	0.19 (0.1, 0.35)	0.38 (0.24, 0.6)
65-74	2792364	7	0.2507	41	1.48	0.17 (0.08, 0.38)	0.34 (0.18, 0.62)	0.68 (0.42, 1.1)
75+	1348477	7	0.5191	20	1.48	0.35 (0.15, 0.83)	0.7 (0.35, 1.39)	1.4 (0.79, 2.49)
Female								

Outcome	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			
<12	29304	0	0	1	1.71	NA	NA	NA
12-17	556781	0	0	10	1.71	NA	NA	NA
18-24	2369832	0	0	41	1.71	NA	NA	NA
25-39	3883926	6	0.1545	66	1.71	0.09 (0.04, 0.21)	0.18 (0.1, 0.33)	0.36 (0.23, 0.58)
40-49	3822515	6	0.157	65	1.71	0.09 (0.04, 0.21)	0.18 (0.1, 0.34)	0.37 (0.23, 0.59)
50-64	4901232	10	0.204	84	1.71	0.12 (0.06, 0.23)	0.24 (0.15, 0.39)	0.48 (0.33, 0.7)
65-74	3171105	8	0.2523	54	1.71	0.15 (0.07, 0.31)	0.3 (0.17, 0.52)	0.59 (0.38, 0.91)
75+	1531377	5	0.3265	26	1.71	0.19 (0.07, 0.5)	0.38 (0.18, 0.79)	0.76 (0.43, 1.37)

Hansen DL, Overgaard UM, Pedersen L, Frederiksen H. Positive predictive value of diagnosis coding for hemolytic anemias in the Danish National Patient Register. Clin Epidemiology. 2016;8:241-252. doi:10.2147/clep.s93643

1.1.1.1.8. Age and Sex Stratified Observed-to-Expected Analyses, Acquired Haemophilia

Outcome	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			
Acquired Haemophilia								
Review Period:								
All	11272825	6	0.1	17	0.148	0.36 (0.14, 0.91)	0.72 (0.34, 1.51)	1.44 (0.77, 2.68)
By age								
<12	14850.7	0	0.0	0	0.0045	NA	NA	NA
12-17	282154.3	0	0.0	0	0.0045	NA	NA	NA
18-24	2041125	0	0.0	1	0.029	NA	NA	NA
25-39	1399426	0	0.0	0	0.029	NA	NA	NA
40-49	3162658	0	0.0	1	0.029	NA	NA	NA
50-64	2238981	1	0.0	1	0.029	1.54 (0.1, 24.62)	3.08 (0.28, 33.97)	6.16 (0.69, 55.12)
65-74	1937639	2	0.1	12	0.597	0.17 (0.04, 0.77)	0.35 (0.11, 1.07)	0.69 (0.28, 1.69)
75+	195969	3	1.5	1	0.597	2.56 (0.27, 24.65)	5.13 (0.62, 42.6)	10.26 (1.33, 78.89)
By gender								
Male	5097136	5	0.1	8	0.148	0.66 (0.22, 2.03)	1.33 (0.52, 3.36)	2.65 (1.17, 6.02)
Female	6175668	1	0.0	9	0.148	0.11 (0.01, 0.86)	0.22 (0.05, 1.01)	0.44 (0.13, 1.42)
By age and gender								
Male								
<12	6681.3	0	0.0	0	0.0045	NA	NA	NA
12-17	126950.7	0	0.0	0	0.0045	NA	NA	NA
18-24	939430	0	0.0	0	0.029	NA	NA	NA
25-39	615389	0	0.0	0	0.029	NA	NA	NA
40-49	1453704	0	0.0	0	0.029	NA	NA	NA
50-64	1001254	1	0.1	0	0.029	NA	NA	NA
65-74	880095	2	0.2	5	0.597	0.38 (0.07, 1.96)	0.76 (0.2, 2.84)	1.52 (0.5, 4.65)
75+	73631	2	2.7	0	0.597	NA	NA	NA
Female								
<12	8168.4	0	0.0	0	0.0045	NA	NA	NA
12-17	155204.6	0	0.0	0	0.0045	NA	NA	NA
18-24	1101696	0	0.0	0	0.029	NA	NA	NA
25-39	784037	0	0.0	0	0.029	NA	NA	NA
40-49	1708954	0	0.0	0	0.029	NA	NA	NA
50-64	1237727	0	0.0	0	0.029	NA	NA	NA
65-74	1057544	0	0.0	6	0.597	NA	NA	NA
75+	122337	1	0.8	1	0.597	1.37 (0.09, 21.89)	2.74 (0.25, 30.2)	5.48 (0.61, 49)
Cumulative:								
All	38111689	22	0.1	56	0.148	0.39 (0.24, 0.64)	0.78 (0.53, 1.16)	1.56 (1.12, 2.18)
By age								
<12	55109	0	0.0	0	0.0045	NA	NA	NA
12-17	1047062	0	0.0	0	0.0045	NA	NA	NA
18-24	4456623	0	0.0	1	0.029	NA	NA	NA
25-39	7303976	0	0.0	2	0.029	NA	NA	NA
40-49	7188488	1	0.0	2	0.029	0.48 (0.04, 5.29)	0.96 (0.14, 6.81)	1.92 (0.35, 10.48)
50-64	9217086	5	0.1	3	0.029	1.87 (0.45, 7.83)	3.74 (1.03, 13.59)	7.48 (2.22, 25.18)
65-74	5963469	5	0.1	36	0.597	0.14 (0.06, 0.36)	0.28 (0.14, 0.57)	0.56 (0.33, 0.97)
75+	2879855	11	0.4	17	0.597	0.64 (0.3, 1.37)	1.28 (0.68, 2.41)	2.56 (1.46, 4.48)
By gender								
Male	17845596	9	0.1	26	0.148	0.34 (0.16, 0.73)	0.68 (0.37, 1.24)	1.36 (0.82, 2.26)
Female	20266072	13	0.1	30	0.148	0.43 (0.23, 0.83)	0.87 (0.51, 1.47)	1.73 (1.11, 2.72)
By age and gender								
Male								
<12	25804	0	0.0	0	0.0045	NA	NA	NA
12-17	490282	0	0.0	0	0.0045	NA	NA	NA
18-24	2086791	0	0.0	1	0.029	NA	NA	NA
25-39	3420050	0	0.0	1	0.029	NA	NA	NA

Outcome	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			
40-49	3365973	0	0.0	1	0.029	NA	NA	NA
50-64	4315854	1	0.0	1	0.029	0.8 (0.05, 12.77)	1.6 (0.14, 17.62)	3.2 (0.36, 28.59)
65-74	2792364	2	0.1	17	0.597	0.12 (0.03, 0.52)	0.24 (0.08, 0.71)	0.48 (0.21, 1.11)
75+	1348477	6	0.4	8	0.597	0.75 (0.26, 2.15)	1.49 (0.61, 3.65)	2.98 (1.34, 6.64)
Female								
<12	29304	0	0.0	0	0.0045	NA	NA	NA
12-17	556781	0	0.0	0	0.0045	NA	NA	NA
18-24	2369832	0	0.0	1	0.029	NA	NA	NA
25-39	3883926	0	0.0	1	0.029	NA	NA	NA
40-49	3822515	1	0.0	1	0.029	0.9 (0.06, 14.42)	1.8 (0.16, 19.9)	3.61 (0.4, 32.29)
50-64	4901232	4	0.1	1	0.029	2.81 (0.31, 25.18)	5.63 (0.7, 45)	11.26 (1.49, 84.89)
65-74	3171105	3	0.1	19	0.597	0.16 (0.05, 0.54)	0.32 (0.13, 0.79)	0.63 (0.31, 1.31)
75+	1531377	5	0.3	9	0.597	0.55 (0.18, 1.63)	1.09 (0.44, 2.69)	2.19 (1, 4.8)

Peter W. Collins, Sybil Hirsch, Trevor P. Baglin, Gerard Dolan, John Hanley, Michael Makris, David M. Keeling, Ri Liesner, Simon A. Brown, Charles R. M. Hay, UK Haemophilia Centre Doctors' Organisation; Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007; 109 (5): 1870–1877. doi: https://doi.org/10.1182/blood-2006-06-02985

1.1.1.1.9. Age and Sex Stratified Observed-to-Expected Analyses, Myasthenia Gravis

Outcome	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			
Myasthesnia Gravis								
Review Period:								
All	11272825	45	0.399190088	77	0.68	0.59 (0.41, 0.85)	1.17 (0.87, 1.59)	2.35 (1.8, 3.07)
By age								
<12	14850.7	0	0	0	0.28	NA	NA	NA
12-17	282154.3	0	0	1	0.28	NA	NA	NA
18-24	2041125	1	0.04899259	8	0.38	0.13 (0.02, 1.03)	0.26 (0.05, 1.21)	0.52 (0.16, 1.71)
25-39	1399426	2	0.142915738	6	0.44	0.32 (0.07, 1.61)	0.65 (0.18, 2.3)	1.3 (0.45, 3.74)
40-49	3162658	5	0.158094868	18	0.58	0.27 (0.1, 0.73)	0.55 (0.25, 1.18)	1.09 (0.58, 2.06)
50-64	2238981	15	0.669947623	21	0.92	0.73 (0.38, 1.41)	1.46 (0.83, 2.54)	2.91 (1.77, 4.79)
65-74	1937639	7	0.361264405	32	1.66	0.22 (0.1, 0.49)	0.44 (0.23, 0.82)	0.87 (0.52, 1.45)
75+	195969	11	5.613132689	3	1.76	3.19 (0.89, 11.43)	6.38 (1.91, 21.31)	12.76 (3.96, 41.08)
By gender								
Male	5097136	19	0.372758349	35	0.68	0.55 (0.31, 0.96)	1.1 (0.69, 1.74)	2.19 (1.47, 3.27)
Female	6175668	24	0.388621927	42	0.68	0.57 (0.35, 0.94)	1.14 (0.76, 1.73)	2.29 (1.59, 3.29)
By age and gender								
Male								
<12	6681.3	0	0	0	0.28	NA	NA	NA
12-17	126950.7	0	0	0	0.28	NA	NA	NA
18-24	939430	0	0	4	0.38	NA	NA	NA
25-39	615389	1	0.162498842	3	0.44	0.37 (0.04, 3.55)	0.74 (0.12, 4.42)	1.48 (0.33, 6.6)
40-49	1453704	1	0.068789795	8	0.58	0.12 (0.01, 0.95)	0.24 (0.05, 1.12)	0.47 (0.14, 1.58)
50-64	1001254	7	0.699123299	9	0.92	0.76 (0.28, 2.04)	1.52 (0.66, 3.51)	3.04 (1.43, 6.44)
65-74	880095	3	0.340872292	15	1.66	0.21 (0.06, 0.71)	0.41 (0.16, 1.06)	0.82 (0.38, 1.75)
75+	73631	6	8.148741698	1	1.76	4.63 (0.56, 38.46)	9.26 (1.2, 71.22)	18.52 (2.51, 136.9)
Female								
<12	8168.4	0	0	0	0.28	NA	NA	NA
12-17	155204.6	0	0	0	0.28	NA	NA	NA
18-24	1101696	1	0.090769141	4	0.38	0.24 (0.03, 2.14)	0.48 (0.09, 2.61)	0.96 (0.24, 3.82)
25-39	784037	1	0.127545001	3	0.44	0.29 (0.03, 2.79)	0.58 (0.1, 3.47)	1.16 (0.26, 5.18)
40-49	1708954	4	0.234061303	10	0.58	0.4 (0.13, 1.29)	0.81 (0.32, 2.05)	1.61 (0.73, 3.56)
50-64	1237727	7	0.565552824	11	0.92	0.61 (0.24, 1.59)	1.23 (0.56, 2.71)	2.46 (1.22, 4.94)
65-74	1057544	4	0.378234854	18	1.66	0.23 (0.08, 0.67)	0.46 (0.2, 1.05)	0.91 (0.46, 1.79)
75+	122337	5	4.08707096	2	1.76	2.32 (0.45, 11.97)	4.64 (1.02, 21.2)	9.29 (2.17, 39.74)
Cumulative:								
All	38111689	149	0.390956171	259	0.68	0.57 (0.47, 0.7)	1.15 (0.97, 1.36)	2.3 (1.99, 2.66)
By age								
<12	55109	0	0	0	0.28	NA	NA	NA
12-17	1047062	1	0.095505328	3	0.28	0.34 (0.04, 3.28)	0.68 (0.11, 4.08)	1.36 (0.31, 6.1)
18-24	4456623	1	0.022438515	17	0.38	0.06 (0.01, 0.44)	0.12 (0.03, 0.51)	0.24 (0.08, 0.7)
25-39	7303976	8	0.109529385	32	0.44	0.25 (0.11, 0.54)	0.5 (0.27, 0.91)	1 (0.61, 1.63)
40-49	7188488	13	0.180844706	42	0.58	0.31 (0.17, 0.58)	0.62 (0.38, 1.02)	1.25 (0.83, 1.87)
50-64	9217086	36	0.390578975	85	0.92	0.42 (0.29, 0.63)	0.85 (0.62, 1.16)	1.7 (1.3, 2.22)
65-74	5963469	49	0.821669401	99	1.66	0.49 (0.35, 0.7)	0.99 (0.75, 1.31)	1.98 (1.55, 2.52)
75+	2879855	35	1.215338967	51	1.76	0.69 (0.45, 1.06)	1.38 (0.96, 1.98)	2.76 (2, 3.81)
By gender								
Male	17845596	80	0.448289875	121	0.68	0.66 (0.5, 0.87)	1.32 (1.04, 1.67)	2.64 (2.14, 3.25)
Female	20266072	66	0.325667451	138	0.68	0.48 (0.36, 0.64)	0.96 (0.75, 1.22)	1.92 (1.56, 2.35)
By age and gender								

Outcome	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			
Male								
<12	25804	0	0	0	0.28	NA	NA	NA
12-17	490282	0	0	1	0.28	NA	NA	NA
18-24	2086791	0	0	8	0.38	NA	NA	NA
25-39	3420050	2	0.058478677	15	0.44	0.13 (0.03, 0.58)	0.27 (0.09, 0.8)	0.53 (0.23, 1.25)
40-49	3365973	2	0.059418183	20	0.58	0.1 (0.02, 0.44)	0.2 (0.07, 0.6)	0.41 (0.18, 0.93)
50-64	4315854	23	0.532918861	40	0.92	0.58 (0.35, 0.97)	1.16 (0.76, 1.77)	2.32 (1.6, 3.36)
65-74	2792364	28	1.002734601	46	1.66	0.6 (0.38, 0.97)	1.21 (0.82, 1.78)	2.42 (1.71, 3.41)
75+	1348477	23	1.705627905	24	1.76	0.97 (0.55, 1.72)	1.94 (1.18, 3.17)	3.88 (2.47, 6.07)
Female								
<12	29304	0	0	0	0.28	NA	NA	NA
12-17	556781	1	0.17960383	2	0.28	0.64 (0.06, 7.07)	1.28 (0.18, 9.11)	2.57 (0.47, 14.01)
18-24	2369832	1	0.042197084	9	0.38	0.11 (0.01, 0.88)	0.22 (0.05, 1.03)	0.44 (0.14, 1.44)
25-39	3883926	6	0.154482861	17	0.44	0.35 (0.14, 0.89)	0.7 (0.34, 1.47)	1.4 (0.75, 2.61)
40-49	3822515	11	0.287768655	22	0.58	0.5 (0.24, 1.02)	0.99 (0.55, 1.79)	1.98 (1.19, 3.31)
50-64	4901232	12	0.2448364	45	0.92	0.27 (0.14, 0.5)	0.53 (0.32, 0.87)	1.06 (0.71, 1.6)
65-74	3171105	21	0.662229727	53	1.66	0.4 (0.24, 0.66)	0.8 (0.53, 1.2)	1.6 (1.13, 2.25)
75+	1531377	12	0.783608478	27	1.76	0.45 (0.23, 0.88)	0.89 (0.51, 1.54)	1.78 (1.11, 2.85)

Chen J, Tian DC, Zhang C, Li Z, Zhai Y, Xiu Y, Gu H, Li H, Wang Y, Shi FD. Incidence, mortality, and economic burden of myasthenia gravis in China: A nationwide population-based study. Lancet Reg Health West Pac. 2020 Nov 27;5:100063. doi: 10.1016/j.lanwpc.2020.100063. PMID: 34327399; PMCID: PMC8315547.

1.1.1.1.10. Age and Sex Stratified Observed-to-Expected Analyses, Chronic Urticaria

Outcome	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			
Chronic urticaria								
Review Period:								
All	11,272,825	171	1.52	14,655	130.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.03)*	*0.05 (0.04, 0.05)*
By age								
<12	14,851	0	0.00	19	130.00	NA	*NA*	*NA*
12-17	282,154	0	0.00	367	130.00	NA	*NA*	*NA*
18-24	2,041,125	13	0.64	2,653	130.00	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.01, 0.03)*
25-39	1,399,426	80	5.72	1,819	130.00	0.04 (0.04, 0.06)	*0.09 (0.07, 0.1)*	*0.18 (0.16, 0.2)*
40-49	3,162,658	41	1.30	4,111	130.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.03, 0.05)*
50-64	2,238,981	28	1.25	2,911	130.00	0.01 (0.01, 0.01)	*0.02 (0.01, 0.03)*	*0.04 (0.03, 0.05)*
65-74	1,937,639	2	0.10	2,519	130.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0.01)*
75+	195,969	1	0.51	255	130.00	0 (0, 0.03)	*0.01 (0, 0.03)*	*0.02 (0.01, 0.04)*
By gender								
Male	5,097,136	62	1.22	4,078	80.00	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.06 (0.05, 0.07)*
Female	6,175,668	105	1.70	9,881	160.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.04, 0.05)*
By age and gender								
Male								
<12	6,681	0	0.00	5	80.00	NA	*NA*	*NA*
12-17	126,951	0	0.00	102	80.00	NA	*NA*	*NA*
18-24	939,430	4	0.43	752	80.00	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.02 (0.01, 0.03)*
25-39	615,389	32	5.20	492	80.00	0.06 (0.05, 0.09)	*0.13 (0.1, 0.17)*	*0.26 (0.21, 0.32)*
40-49	1,453,704	13	0.89	1,163	80.00	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*	*0.04 (0.03, 0.06)*
50-64	1,001,254	12	1.20	801	80.00	0.01 (0.01, 0.03)	*0.03 (0.02, 0.04)*	*0.06 (0.04, 0.08)*
65-74	880,095	0	0.00	704	80.00	NA	*NA*	*NA*
75+	73,631	0	0.00	59	80.00	NA	*NA*	*NA*
Female								
<12	8,168	0	0.00	13	160.00	NA	*NA*	*NA*
12-17	155,205	0	0.00	248	160.00	NA	*NA*	*NA*
18-24	1,101,696	9	0.82	1,763	160.00	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.02 (0.01, 0.03)*
25-39	784,037	45	5.74	1,254	160.00	0.04 (0.03, 0.05)	*0.07 (0.06, 0.09)*	*0.14 (0.12, 0.17)*
40-49	1,708,954	28	1.64	2,734	160.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.03)*	*0.04 (0.03, 0.05)*
50-64	1,237,727	16	1.29	1,980	160.00	0.01 (0, 0.01)	*0.02 (0.01, 0.02)*	*0.03 (0.03, 0.04)*
65-74	1,057,544	2	0.19	1,692	160.00	0 (0, 0)	*0 (0, 0.01)*	*0 (0, 0.01)*
75+	122,337	1	0.82	196	160.00	0.01 (0, 0.04)	*0.01 (0, 0.04)*	*0.02 (0.01, 0.05)*
Cumulative:								
All	38,111,689	209	0.55	49,545	130.00	0 (0, 0)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
By age								
<12	55,109	0	0.00	72	130.00	NA	*NA*	*NA*
12-17	1,047,062	0	0.00	1,361	130.00	NA	*NA*	*NA*
18-24	4,456,623	16	0.36	5,794	130.00	0 (0, 0)	*0.01 (0, 0.01)*	*0.01 (0.01, 0.01)*
25-39	7,303,976	91	1.25	9,495	130.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.03, 0.04)*
40-49	7,188,488	48	0.67	9,345	130.00	0.01 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
50-64	9,217,086	37	0.40	11,982	130.00	0 (0, 0)	*0.01 (0, 0.01)*	*0.01 (0.01, 0.01)*
65-74	5,963,469	7	0.12	7,753	130.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0.01)*
75+	2,879,855	1	0.03	3,744	130.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0)*
By gender								
Male	17,845,596	69	0.39	14,276	80.00	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
Female	20,266,072	133	0.66	32,426	160.00	0 (0, 0)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
By age and gender								
Male								
<12	25,804	0	0.00	21	80.00	NA	*NA*	*NA*
12-17	490,282	0	0.00	392	80.00	NA	*NA*	*NA*
18-24	2,086,791	4	0.19	1,669	80.00	0 (0, 0.01)	*0 (0, 0.01)*	*0.01 (0.01, 0.02)*
25-39	3,420,050	32	0.94	2,736	80.00	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*	*0.05 (0.04, 0.06)*
40-49	3,365,973	16	0.48	2,693	80.00	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.02 (0.02, 0.03)*
50-64	4,315,854	15	0.35	3,453	80.00	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.01, 0.02)*

Outcome	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			
65-74	2,792,364	1	0.04	2,234	80.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0)*
75+	1,348,477	0	0.00	1,079	80.00	NA	*NA*	*NA*
Female								
<12	29,304	0	0.00	47	160.00	NA	*NA*	*NA*
12-17	556,781	0	0.00	891	160.00	NA	*NA*	*NA*
18-24	2,369,832	12	0.51	3,792	160.00	0 (0, 0.01)	*0.01 (0, 0.01)*	*0.01 (0.01, 0.02)*
25-39	3,883,926	56	1.44	6,214	160.00	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.04 (0.03, 0.04)*
40-49	3,822,515	32	0.84	6,116	160.00	0.01 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
50-64	4,901,232	22	0.45	7,842	160.00	0 (0, 0)	*0.01 (0, 0.01)*	*0.01 (0.01, 0.01)*
65-74	3,171,105	5	0.16	5,074	160.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0.01)*
75+	1,531,377	1	0.07	2,450	160.00	0 (0, 0)	*0 (0, 0)*	*0 (0, 0)*

*Compared to PBRER2, for PBRER3 - conservative reference rate was used estimated using a population-based study in Italy.
Lapi F, Cassano N, Pegoraro V, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. Brit J Dermatol. 2016;174(5):996-1004. doi:10.1111/bjd.14470

1.1.1.1.11. Age and Sex Stratified Observed-to-Expected Analyses, Autoimmune Hepatitis

Outcome	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			
Autoimmune hepatitis								
Review Period:								
All	11,272,825	45	0.40	349	3.10	0.13 (0.09, 0.18)	*0.26 (0.2, 0.32)*	*0.52 (0.43, 0.62)*
By age								
<12	14,851	0	0.00	0	0.49	NA	*NA*	*NA*
12-17	282,154	0	0.00	1	0.49	NA	*NA*	*NA*
18-24	2,041,125	4	0.20	27	1.32	0.15 (0.05, 0.42)	*0.3 (0.13, 0.65)*	*0.59 (0.32, 1.1)*
25-39	1,399,426	9	0.64	33	2.39	0.27 (0.13, 0.56)	*0.54 (0.3, 0.96)*	*1.08 (0.67, 1.73)*
40-49	3,162,658	10	0.32	76	2.39	0.13 (0.07, 0.26)	*0.26 (0.16, 0.43)*	*0.53 (0.36, 0.78)*
50-64	2,238,981	8	0.36	114	5.07	0.07 (0.03, 0.14)	*0.14 (0.08, 0.24)*	*0.28 (0.19, 0.42)*
65-74	1,937,639	4	0.21	122	6.31	0.03 (0.01, 0.09)	*0.07 (0.03, 0.13)*	*0.13 (0.08, 0.22)*
75+	195,969	7	3.57	12	6.31	0.57 (0.22, 1.44)	*1.13 (0.52, 2.45)*	*2.26 (1.15, 4.45)*
By gender								
Male	5,097,136	18	0.35	67	1.31	0.27 (0.16, 0.45)	*0.54 (0.36, 0.81)*	*1.08 (0.77, 1.5)*
Female	6,175,668	26	0.42	296	4.80	0.09 (0.06, 0.13)	*0.18 (0.13, 0.24)*	*0.35 (0.28, 0.44)*
By age and gender								
Male								
<12	6,681	0	0.00	0	0.21	NA	*NA*	*NA*
12-17	126,951	0	0.00	0	0.21	NA	*NA*	*NA*
18-24	939,430	2	0.21	5	0.56	0.38 (0.07, 1.96)	*0.76 (0.2, 2.83)*	*1.52 (0.5, 4.65)*
25-39	615,389	6	0.97	6	1.01	0.97 (0.31, 2.99)	*1.93 (0.72, 5.14)*	*3.86 (1.58, 9.45)*
40-49	1,453,704	4	0.28	15	1.01	0.27 (0.09, 0.82)	*0.54 (0.23, 1.29)*	*1.09 (0.54, 2.2)*
50-64	1,001,254	2	0.20	21	2.14	0.09 (0.02, 0.4)	*0.19 (0.06, 0.54)*	*0.37 (0.17, 0.84)*
65-74	880,095	1	0.11	23	2.67	0.04 (0.01, 0.32)	*0.09 (0.02, 0.36)*	*0.17 (0.06, 0.49)*
75+	73,631	1	1.36	2	2.67	0.51 (0.05, 5.61)	*1.02 (0.14, 7.22)*	*2.03 (0.37, 11.11)*
Female								
<12	8,168	0	0.00	0	0.76	NA	*NA*	*NA*
12-17	155,205	4	2.58	1	0.76	3.39 (0.38, 30.34)	*6.78 (0.85, 54.23)*	*13.56 (1.8, 102.29)*
18-24	1,101,696	2	0.18	22	2.04	0.09 (0.02, 0.38)	*0.18 (0.06, 0.52)*	*0.36 (0.16, 0.8)*
25-39	784,037	3	0.38	29	3.70	0.1 (0.03, 0.34)	*0.21 (0.09, 0.5)*	*0.41 (0.21, 0.81)*
40-49	1,708,954	6	0.35	63	3.70	0.09 (0.04, 0.22)	*0.19 (0.1, 0.35)*	*0.38 (0.24, 0.61)*
50-64	1,237,727	6	0.48	97	7.85	0.06 (0.03, 0.14)	*0.12 (0.07, 0.22)*	*0.25 (0.16, 0.39)*
65-74	1,057,544	3	0.28	103	9.77	0.03 (0.01, 0.09)	*0.06 (0.03, 0.13)*	*0.12 (0.06, 0.21)*
75+	122,337	6	4.90	12	9.77	0.5 (0.19, 1.34)	*1 (0.45, 2.23)*	*2.01 (1, 4.02)*
Cumulative:								
All	38,111,689	211	0.55	1,181	3.10	0.18 (0.15, 0.21)	*0.36 (0.32, 0.4)*	*0.71 (0.65, 0.78)*
By age								
<12	55,109	1	1.81	0	0.49	NA	*NA*	*NA*
12-17	1,047,062	1	0.10	5	0.49	0.19 (0.02, 1.67)	*0.39 (0.08, 2.01)*	*0.78 (0.21, 2.9)*
18-24	4,456,623	7	0.16	59	1.32	0.12 (0.05, 0.26)	*0.24 (0.13, 0.43)*	*0.48 (0.3, 0.75)*
25-39	7,303,976	40	0.55	175	2.39	0.23 (0.16, 0.32)	*0.46 (0.35, 0.6)*	*0.92 (0.74, 1.14)*
40-49	7,188,488	35	0.49	172	2.39	0.2 (0.14, 0.29)	*0.41 (0.31, 0.54)*	*0.81 (0.65, 1.02)*
50-64	9,217,086	47	0.51	467	5.07	0.1 (0.07, 0.14)	*0.2 (0.16, 0.25)*	*0.4 (0.34, 0.48)*
65-74	5,963,469	44	0.74	376	6.31	0.12 (0.09, 0.16)	*0.23 (0.19, 0.29)*	*0.47 (0.39, 0.56)*
75+	2,879,855	29	1.01	182	6.31	0.16 (0.11, 0.24)	*0.32 (0.24, 0.43)*	*0.64 (0.51, 0.81)*
By gender								
Male	17,845,596	85	0.48	234	1.31	0.36 (0.28, 0.47)	*0.73 (0.6, 0.89)*	*1.45 (1.23, 1.72)*
Female	20,266,072	124	0.61	973	4.80	0.13 (0.11, 0.15)	*0.25 (0.22, 0.29)*	*0.51 (0.46, 0.57)*
By age and gender								
Male								
<12	25,804	0	0.00	0	0.21	NA	*NA*	*NA*
12-17	490,282	0	0.00	1	0.21	NA	*NA*	*NA*
18-24	2,086,791	4	0.19	12	0.56	0.34 (0.11, 1.06)	*0.68 (0.28, 1.67)*	*1.37 (0.65, 2.89)*
25-39	3,420,050	15	0.44	35	1.01	0.43 (0.24, 0.8)	*0.87 (0.53, 1.41)*	*1.74 (1.14, 2.64)*
40-49	3,365,973	12	0.36	34	1.01	0.35 (0.18, 0.68)	*0.71 (0.42, 1.19)*	*1.41 (0.91, 2.19)*

Outcome	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			
50-64	4,315,854	21	0.49	92	2.14	0.23 (0.14, 0.37)	*0.45 (0.32, 0.66)*	*0.91 (0.68, 1.22)*
65-74	2,792,364	22	0.79	75	2.67	0.3 (0.18, 0.47)	*0.59 (0.41, 0.86)*	*1.18 (0.87, 1.61)*
75+	1,348,477	7	0.52	36	2.67	0.19 (0.09, 0.44)	*0.39 (0.21, 0.72)*	*0.78 (0.47, 1.27)*
Female								
<12	29,304	0	0.00	0	0.76	NA	*NA*	*NA*
12-17	556,781	1	0.18	4	0.76	0.24 (0.03, 2.11)	*0.47 (0.09, 2.58)*	*0.95 (0.24, 3.78)*
18-24	2,369,832	3	0.13	48	2.04	0.06 (0.02, 0.2)	*0.12 (0.05, 0.29)*	*0.25 (0.13, 0.47)*
25-39	3,883,926	25	0.64	144	3.70	0.17 (0.11, 0.27)	*0.35 (0.25, 0.48)*	*0.7 (0.54, 0.9)*
40-49	3,822,515	23	0.60	141	3.70	0.16 (0.1, 0.25)	*0.33 (0.23, 0.45)*	*0.65 (0.5, 0.85)*
50-64	4,901,232	26	0.53	385	7.85	0.07 (0.05, 0.1)	*0.14 (0.1, 0.18)*	*0.27 (0.22, 0.34)*
65-74	3,171,105	22	0.69	310	9.77	0.07 (0.05, 0.11)	*0.14 (0.1, 0.19)*	*0.28 (0.22, 0.36)*
75+	1,531,377	22	1.44	150	9.77	0.15 (0.09, 0.23)	*0.29 (0.21, 0.41)*	*0.59 (0.45, 0.77)*

Esposito D, Titievsky L, Beachler DC, et al. Incidence of outcomes relevant to vaccine safety monitoring in a US commercially-insured population. Vaccine. 2018;36(52):8084-8093. doi:10.1016/j.vaccine.2018.10.052

1.1.1.1.12. Age and Sex Stratified Observed-to-Expected Analyses, Single organ cutaneous vasculitis

Outcome	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			
Single organ cutaneous vasculitis								
Review Period:								
All	11,272,825	81	0.72	680	6.03	0.12 (0.09, 0.15)	*0.24 (0.2, 0.28)*	*0.48 (0.42, 0.54)*
By age								
<12	14,851	0	0.00	2	12.63	NA	*NA*	*NA*
12-17	282,154	1	0.35	36	12.63	0.03 (0, 0.2)	*0.06 (0.01, 0.23)*	*0.11 (0.04, 0.32)*
18-24	2,041,125	1	0.05	59	2.89	0.02 (0, 0.12)	*0.03 (0.01, 0.14)*	*0.07 (0.02, 0.19)*
25-39	1,399,426	16	1.14	22	1.59	0.72 (0.38, 1.37)	*1.44 (0.84, 2.47)*	*2.88 (1.77, 4.67)*
40-49	3,162,658	9	0.28	90	2.84	0.1 (0.05, 0.2)	*0.2 (0.12, 0.33)*	*0.4 (0.27, 0.59)*
50-64	2,238,981	29	1.30	81	3.61	0.36 (0.23, 0.55)	*0.72 (0.51, 1.01)*	*1.44 (1.08, 1.91)*
65-74	1,937,639	13	0.67	107	5.54	0.12 (0.07, 0.22)	*0.24 (0.16, 0.37)*	*0.48 (0.35, 0.67)*
75+	195,969	9	4.59	16	7.95	0.58 (0.26, 1.31)	*1.16 (0.59, 2.27)*	*2.31 (1.28, 4.16)*
By gender								
Male	5,097,136	28	0.55	294	5.77	0.1 (0.06, 0.14)	*0.19 (0.14, 0.25)*	*0.38 (0.31, 0.47)*
Female	6,175,668	51	0.83	409	6.62	0.12 (0.09, 0.17)	*0.25 (0.2, 0.31)*	*0.5 (0.42, 0.59)*
By age and gender								
Male								
<12	6,681	0	0.00	1	12.88	NA	*NA*	*NA*
12-17	126,951	0	0.00	16	12.88	NA	*NA*	*NA*
18-24	939,430	1	0.11	11	1.15	0.09 (0.01, 0.72)	*0.19 (0.04, 0.84)*	*0.37 (0.12, 1.16)*
25-39	615,389	5	0.81	3	0.53	1.53 (0.37, 6.41)	*3.07 (0.84, 11.14)*	*6.13 (1.82, 20.64)*
40-49	1,453,704	4	0.28	30	2.06	0.13 (0.05, 0.38)	*0.27 (0.12, 0.58)*	*0.53 (0.29, 0.98)*
50-64	1,001,254	11	1.10	40	3.99	0.28 (0.14, 0.54)	*0.55 (0.33, 0.93)*	*1.1 (0.72, 1.69)*
65-74	880,095	2	0.23	58	6.55	0.03 (0.01, 0.14)	*0.07 (0.03, 0.19)*	*0.14 (0.07, 0.29)*
75+	73,631	5	6.79	5	6.13	1.11 (0.32, 3.83)	*2.22 (0.76, 6.48)*	*4.43 (1.66, 11.81)*
Female								
<12	8,168	0	0.00	1	12.38	NA	*NA*	*NA*
12-17	155,205	1	0.64	19	12.38	0.05 (0.01, 0.39)	*0.1 (0.02, 0.45)*	*0.21 (0.07, 0.61)*
18-24	1,101,696	0	0.00	51	4.67	NA	*NA*	*NA*
25-39	784,037	11	1.40	21	2.64	0.53 (0.26, 1.1)	*1.06 (0.58, 1.93)*	*2.13 (1.26, 3.58)*
40-49	1,708,954	5	0.29	62	3.62	0.08 (0.03, 0.2)	*0.16 (0.08, 0.32)*	*0.32 (0.2, 0.54)*
50-64	1,237,727	18	1.45	40	3.24	0.45 (0.26, 0.78)	*0.9 (0.57, 1.41)*	*1.8 (1.22, 2.64)*
65-74	1,057,544	11	1.04	48	4.57	0.23 (0.12, 0.44)	*0.46 (0.27, 0.75)*	*0.91 (0.6, 1.37)*
75+	122,337	4	3.27	12	9.49	0.34 (0.11, 1.07)	*0.69 (0.28, 1.69)*	*1.38 (0.65, 2.91)*
Cumulative:								
All	38,111,689	327	0.86	2,298	6.03	0.14 (0.13, 0.16)	*0.28 (0.26, 0.31)*	*0.57 (0.53, 0.61)*
By age								
<12	55,109	0	0.00	7	12.63	NA	*NA*	*NA*
12-17	1,047,062	2	0.19	132	12.63	0.02 (0, 0.06)	*0.03 (0.01, 0.08)*	*0.06 (0.03, 0.12)*
18-24	4,456,623	5	0.11	129	2.89	0.04 (0.02, 0.09)	*0.08 (0.04, 0.15)*	*0.16 (0.1, 0.25)*
25-39	7,303,976	53	0.73	116	1.59	0.46 (0.33, 0.63)	*0.91 (0.7, 1.19)*	*1.83 (1.46, 2.29)*
40-49	7,188,488	43	0.60	204	2.84	0.21 (0.15, 0.29)	*0.42 (0.33, 0.54)*	*0.84 (0.69, 1.03)*
50-64	9,217,086	108	1.17	333	3.61	0.32 (0.26, 0.4)	*0.65 (0.55, 0.77)*	*1.3 (1.13, 1.5)*
65-74	5,963,469	60	1.01	330	5.54	0.18 (0.14, 0.24)	*0.36 (0.29, 0.45)*	*0.73 (0.62, 0.86)*
75+	2,879,855	43	1.49	229	7.95	0.19 (0.14, 0.26)	*0.38 (0.29, 0.48)*	*0.75 (0.62, 0.92)*
By gender								
Male	17,845,596	96	0.54	1,030	5.77	0.09 (0.08, 0.11)	*0.19 (0.16, 0.22)*	*0.37 (0.33, 0.42)*
Female	20,266,072	221	1.09	1,342	6.62	0.16 (0.14, 0.19)	*0.33 (0.3, 0.37)*	*0.66 (0.61, 0.72)*
By age and gender								
Male								
<12	25,804	0	0.00	3	12.88	NA	*NA*	*NA*
12-17	490,282	1	0.20	63	12.88	0.02 (0, 0.11)	*0.03 (0.01, 0.13)*	*0.06 (0.02, 0.17)*
18-24	2,086,791	1	0.05	24	1.15	0.04 (0.01, 0.31)	*0.08 (0.02, 0.35)*	*0.17 (0.06, 0.48)*
25-39	3,420,050	13	0.38	18	0.53	0.72 (0.35, 1.46)	*1.43 (0.79, 2.62)*	*2.87 (1.68, 4.9)*

Outcome	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			
40-49	3,365,973	13	0.39	69	2.06	0.19 (0.1, 0.34)	*0.37 (0.24, 0.59)*	*0.75 (0.52, 1.07)*
50-64	4,315,854	35	0.81	172	3.99	0.2 (0.14, 0.29)	*0.41 (0.31, 0.54)*	*0.81 (0.65, 1.02)*
65-74	2,792,364	17	0.61	183	6.55	0.09 (0.06, 0.15)	*0.19 (0.13, 0.27)*	*0.37 (0.28, 0.49)*
75+	1,348,477	16	1.19	83	6.13	0.19 (0.11, 0.33)	*0.39 (0.26, 0.58)*	*0.77 (0.56, 1.07)*
Female								
<12	29,304	0	0.00	4	12.38	NA	*NA*	*NA*
12-17	556,781	1	0.18	69	12.38	0.01 (0, 0.1)	*0.03 (0.01, 0.12)*	*0.06 (0.02, 0.16)*
18-24	2,369,832	4	0.17	111	4.67	0.04 (0.01, 0.1)	*0.07 (0.04, 0.15)*	*0.14 (0.09, 0.24)*
25-39	3,883,926	39	1.00	103	2.64	0.38 (0.26, 0.55)	*0.76 (0.57, 1.02)*	*1.52 (1.19, 1.95)*
40-49	3,822,515	30	0.78	138	3.62	0.22 (0.15, 0.32)	*0.43 (0.32, 0.59)*	*0.87 (0.68, 1.11)*
50-64	4,901,232	73	1.49	159	3.24	0.46 (0.35, 0.61)	*0.92 (0.73, 1.15)*	*1.84 (1.52, 2.23)*
65-74	3,171,105	43	1.36	145	4.57	0.3 (0.21, 0.42)	*0.59 (0.45, 0.77)*	*1.19 (0.95, 1.48)*
75+	1,531,377	27	1.76	145	9.49	0.19 (0.12, 0.28)	*0.37 (0.27, 0.51)*	*0.74 (0.58, 0.95)*

ACCESS, Spain (BIFAP PC) 2019

1.1.1.1.13. Age and Sex Stratified Observed-to-Expected Analyses, Glomerulonephritis and Nephrotic Syndrome

Outcome	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			
Glomerulonephritis and Nephrotic Syndrome								
Review Period:								
All	11,272,825	85	0.75	457	4.05	0.19 (0.15, 0.23)	*0.37 (0.31, 0.44)*	*0.74 (0.65, 0.86)*
By age								
<12	14,851	0	0.00	0	1.41	NA	*NA*	*NA*
12-17	282,154	5	1.77	4	1.41	1.26 (0.34, 4.68)	*2.51 (0.79, 8.01)*	*5.03 (1.72, 14.71)*
18-24	2,041,125	6	0.29	27	1.34	0.22 (0.09, 0.53)	*0.44 (0.22, 0.87)*	*0.88 (0.51, 1.52)*
25-39	1,399,426	18	1.29	19	1.34	0.96 (0.5, 1.83)	*1.92 (1.1, 3.35)*	*3.84 (2.32, 6.37)*
40-49	3,162,658	15	0.47	42	1.34	0.35 (0.2, 0.64)	*0.71 (0.44, 1.13)*	*1.42 (0.95, 2.1)*
50-64	2,238,981	21	0.94	124	5.55	0.17 (0.11, 0.27)	*0.34 (0.24, 0.48)*	*0.68 (0.51, 0.89)*
65-74	1,937,639	12	0.62	200	10.33	0.06 (0.03, 0.11)	*0.12 (0.08, 0.18)*	*0.24 (0.18, 0.33)*
75+	195,969	6	3.06	20	10.33	0.3 (0.12, 0.74)	*0.59 (0.29, 1.21)*	*1.19 (0.65, 2.15)*
By gender								
Male	5,097,136	42	0.82	246	4.82	0.17 (0.12, 0.24)	*0.34 (0.27, 0.44)*	*0.68 (0.56, 0.83)*
Female	6,175,668	41	0.66	205	3.32	0.2 (0.14, 0.28)	*0.4 (0.31, 0.52)*	*0.8 (0.65, 0.98)*
By age and gender								
Male								
<12	6,681	0	0.00	0	1.68	NA	*NA*	*NA*
12-17	126,951	2	1.58	2	1.68	0.94 (0.13, 6.66)	*1.88 (0.34, 10.24)*	*3.75 (0.8, 17.66)*
18-24	939,430	3	0.32	15	1.59	0.2 (0.06, 0.69)	*0.4 (0.16, 1.04)*	*0.8 (0.38, 1.72)*
25-39	615,389	10	1.62	10	1.59	1.02 (0.43, 2.46)	*2.04 (0.96, 4.37)*	*4.09 (2.04, 8.17)*
40-49	1,453,704	4	0.28	23	1.59	0.17 (0.06, 0.5)	*0.35 (0.15, 0.77)*	*0.69 (0.37, 1.31)*
50-64	1,001,254	13	1.30	66	6.61	0.2 (0.11, 0.36)	*0.39 (0.25, 0.62)*	*0.79 (0.55, 1.13)*
65-74	880,095	9	1.02	108	12.29	0.08 (0.04, 0.16)	*0.17 (0.1, 0.27)*	*0.33 (0.23, 0.49)*
75+	73,631	1	1.36	9	12.29	0.11 (0.01, 0.87)	*0.22 (0.05, 1.02)*	*0.44 (0.14, 1.44)*
Female								
<12	8,168	0	0.00	0	1.16	NA	*NA*	*NA*
12-17	155,205	3	1.93	2	1.16	1.67 (0.28, 9.97)	*3.33 (0.67, 16.51)*	*6.67 (1.49, 29.78)*
18-24	1,101,696	3	0.27	12	1.10	0.25 (0.07, 0.88)	*0.5 (0.19, 1.32)*	*0.99 (0.44, 2.2)*
25-39	784,037	8	1.02	9	1.10	0.93 (0.36, 2.4)	*1.86 (0.82, 4.2)*	*3.71 (1.77, 7.77)*
40-49	1,708,954	10	0.59	19	1.10	0.53 (0.25, 1.14)	*1.06 (0.57, 1.99)*	*2.13 (1.23, 3.67)*
50-64	1,237,727	8	0.65	56	4.55	0.14 (0.07, 0.3)	*0.28 (0.16, 0.5)*	*0.57 (0.37, 0.88)*
65-74	1,057,544	3	0.28	90	8.47	0.03 (0.01, 0.11)	*0.07 (0.03, 0.15)*	*0.13 (0.07, 0.24)*
75+	122,337	5	4.09	10	8.47	0.48 (0.16, 1.41)	*0.97 (0.4, 2.32)*	*1.93 (0.9, 4.12)*
Cumulative:								
All	38,111,689	186	0.49	1,544	4.05	0.12 (0.1, 0.14)	*0.24 (0.22, 0.27)*	*0.48 (0.44, 0.53)*
By age								
<12	55,109	0	0.00	1	1.41	NA	*NA*	*NA*
12-17	1,047,062	6	0.57	15	1.41	0.41 (0.16, 1.05)	*0.81 (0.38, 1.74)*	*1.63 (0.85, 3.1)*
18-24	4,456,623	21	0.47	60	1.34	0.35 (0.21, 0.58)	*0.7 (0.47, 1.04)*	*1.41 (1.01, 1.96)*
25-39	7,303,976	38	0.52	98	1.34	0.39 (0.27, 0.56)	*0.78 (0.58, 1.05)*	*1.55 (1.2, 2)*
40-49	7,188,488	29	0.40	96	1.34	0.3 (0.2, 0.46)	*0.6 (0.43, 0.83)*	*1.2 (0.92, 1.58)*
50-64	9,217,086	42	0.46	512	5.55	0.08 (0.06, 0.11)	*0.16 (0.13, 0.21)*	*0.33 (0.28, 0.39)*
65-74	5,963,469	25	0.42	616	10.33	0.04 (0.03, 0.06)	*0.08 (0.06, 0.11)*	*0.16 (0.13, 0.2)*
75+	2,879,855	18	0.63	297	10.33	0.06 (0.04, 0.1)	*0.12 (0.09, 0.17)*	*0.24 (0.19, 0.31)*
By gender								
Male	17,845,596	98	0.55	860	4.82	0.11 (0.09, 0.14)	*0.23 (0.2, 0.27)*	*0.46 (0.4, 0.51)*
Female	20,266,072	82	0.40	673	3.32	0.12 (0.1, 0.15)	*0.24 (0.21, 0.29)*	*0.49 (0.43, 0.56)*
By age and gender								
Male								
<12	25,804	0	0.00	0	1.68	NA	*NA*	*NA*
12-17	490,282	2	0.41	8	1.68	0.24 (0.05, 1.14)	*0.49 (0.15, 1.61)*	*0.97 (0.36, 2.59)*
18-24	2,086,791	14	0.67	33	1.59	0.42 (0.23, 0.79)	*0.84 (0.51, 1.4)*	*1.69 (1.1, 2.59)*
25-39	3,420,050	20	0.58	54	1.59	0.37 (0.22, 0.61)	*0.74 (0.49, 1.11)*	*1.47 (1.04, 2.08)*
40-49	3,365,973	11	0.33	54	1.59	0.21 (0.11, 0.39)	*0.41 (0.25, 0.67)*	*0.82 (0.55, 1.22)*

Outcome	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			
50-64	4,315,854	25	0.58	285	6.61	0.09 (0.06, 0.13)	*0.18 (0.13, 0.24)*	*0.35 (0.28, 0.44)*
65-74	2,792,364	17	0.61	343	12.29	0.05 (0.03, 0.08)	*0.1 (0.07, 0.14)*	*0.2 (0.15, 0.26)*
75+	1,348,477	9	0.67	166	12.29	0.05 (0.03, 0.11)	*0.11 (0.07, 0.18)*	*0.22 (0.15, 0.31)*
Female								
<12	29,304	0	0.00	0	1.16	NA	*NA*	*NA*
12-17	556,781	4	0.72	6	1.16	0.62 (0.17, 2.19)	*1.24 (0.43, 3.57)*	*2.48 (0.97, 6.33)*
18-24	2,369,832	6	0.25	26	1.10	0.23 (0.09, 0.56)	*0.46 (0.23, 0.91)*	*0.92 (0.53, 1.6)*
25-39	3,883,926	18	0.46	43	1.10	0.42 (0.24, 0.73)	*0.84 (0.54, 1.31)*	*1.69 (1.16, 2.46)*
40-49	3,822,515	17	0.44	42	1.10	0.4 (0.23, 0.71)	*0.81 (0.51, 1.27)*	*1.62 (1.1, 2.38)*
50-64	4,901,232	17	0.35	223	4.55	0.08 (0.05, 0.12)	*0.15 (0.11, 0.22)*	*0.3 (0.23, 0.4)*
65-74	3,171,105	8	0.25	269	8.47	0.03 (0.01, 0.06)	*0.06 (0.04, 0.1)*	*0.12 (0.08, 0.17)*
75+	1,531,377	9	0.59	130	8.47	0.07 (0.04, 0.14)	*0.14 (0.08, 0.23)*	*0.28 (0.19, 0.4)*

Esposito D, Titievsky L, Beachler DC, Hawes JCL, Isturiz R, Scott DA, Gangemi K, Maroko R, Hall-Murray CK, Lanes S. Incidence of outcomes relevant to vaccine safety monitoring in a US commercially-insured population. Vaccine. 2018 Dec 18;36(52):8084-8093. doi: 10.1016/j.vaccine.2018.10.052. Epub 2018 Nov 15. PMID: 30448335.).

1.1.1.1.14. Age and Sex Stratified Observed-to-Expected Analyses, Polymyalgia Rheumatica

Outcome	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			
Polymyalgia Rheumatica								
Review Period:								
All	11,272,825	72	0.64	10,811	95.90	0.01 (0.01, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.02, 0.03)*
By age								
<12	14,851	0	0.00	0	3.20	NA	*NA*	*NA*
12-17	282,154	0	0.00	9	3.20	NA	*NA*	*NA*
18-24	2,041,125	0	0.00	65	3.20	NA	*NA*	*NA*
25-39	1,399,426	0	0.00	45	3.20	NA	*NA*	*NA*
40-49	3,162,658	1	0.03	101	3.20	0.01 (0, 0.07)	*0.02 (0, 0.08)*	*0.04 (0.01, 0.11)*
50-64	2,238,981	28	1.25	618	27.60	0.05 (0.03, 0.07)	*0.09 (0.07, 0.12)*	*0.18 (0.15, 0.22)*
65-74	1,937,639	25	1.29	2,048	105.70	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*	*0.05 (0.04, 0.06)*
75+	195,969	12	6.12	533	272.10	0.02 (0.01, 0.04)	*0.05 (0.03, 0.07)*	*0.09 (0.07, 0.12)*
By gender								
Male	5,097,136	40	0.78	3,283	64.40	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*	*0.05 (0.04, 0.06)*
Female	6,175,668	29	0.47	7,732	125.20	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.01, 0.02)*
By age and gender								
Male								
<12	6,681	0	0.00	0	2.15	NA	*NA*	*NA*
12-17	126,951	0	0.00	3	2.15	NA	*NA*	*NA*
18-24	939,430	0	0.00	20	2.15	NA	*NA*	*NA*
25-39	615,389	0	0.00	13	2.15	NA	*NA*	*NA*
40-49	1,453,704	0	0.00	31	2.15	NA	*NA*	*NA*
50-64	1,001,254	15	1.50	186	18.53	0.08 (0.05, 0.14)	*0.16 (0.11, 0.24)*	*0.32 (0.24, 0.43)*
65-74	880,095	17	1.93	625	70.98	0.03 (0.02, 0.04)	*0.05 (0.04, 0.08)*	*0.11 (0.08, 0.14)*
75+	73,631	7	9.51	135	182.72	0.05 (0.02, 0.11)	*0.1 (0.06, 0.18)*	*0.21 (0.14, 0.31)*
Female								
<12	8,168	0	0.00	0	4.18	NA	*NA*	*NA*
12-17	155,205	0	0.00	6	4.18	NA	*NA*	*NA*
18-24	1,101,696	0	0.00	46	4.18	NA	*NA*	*NA*
25-39	784,037	0	0.00	33	4.18	NA	*NA*	*NA*
40-49	1,708,954	1	0.06	71	4.18	0.01 (0, 0.1)	*0.03 (0.01, 0.11)*	*0.06 (0.02, 0.15)*
50-64	1,237,727	13	1.05	446	36.03	0.03 (0.02, 0.05)	*0.06 (0.04, 0.09)*	*0.12 (0.09, 0.16)*
65-74	1,057,544	8	0.76	1,459	137.99	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.02 (0.02, 0.03)*
75+	122,337	5	4.09	435	355.23	0.01 (0, 0.03)	*0.02 (0.01, 0.04)*	*0.05 (0.03, 0.07)*
Cumulative:								
All	38,111,689	224	0.59	36,549	95.90	0.01 (0.01, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.03)*
By age								
<12	55,109	0	0.00	2	3.20	NA	*NA*	*NA*
12-17	1,047,062	0	0.00	34	3.20	NA	*NA*	*NA*
18-24	4,456,623	0	0.00	143	3.20	NA	*NA*	*NA*
25-39	7,303,976	0	0.00	234	3.20	NA	*NA*	*NA*
40-49	7,188,488	6	0.08	230	3.20	0.03 (0.01, 0.06)	*0.05 (0.03, 0.09)*	*0.1 (0.07, 0.16)*
50-64	9,217,086	53	0.58	2,544	27.60	0.02 (0.02, 0.03)	*0.04 (0.03, 0.05)*	*0.08 (0.07, 0.1)*
65-74	5,963,469	90	1.51	6,303	105.70	0.01 (0.01, 0.02)	*0.03 (0.02, 0.03)*	*0.06 (0.05, 0.06)*
75+	2,879,855	65	2.26	7,836	272.10	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.03 (0.03, 0.04)*
By gender								
Male	17,845,596	108	0.61	11,493	64.40	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.03, 0.04)*
Female	20,266,072	113	0.56	25,373	125.20	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
By age and gender								
Male								
<12	25,804	0	0.00	1	2.15	NA	*NA*	*NA*
12-17	490,282	0	0.00	11	2.15	NA	*NA*	*NA*
18-24	2,086,791	0	0.00	45	2.15	NA	*NA*	*NA*
25-39	3,420,050	0	0.00	73	2.15	NA	*NA*	*NA*
40-49	3,365,973	1	0.03	72	2.15	0.01 (0, 0.1)	*0.03 (0.01, 0.11)*	*0.06 (0.02, 0.15)*
50-64	4,315,854	31	0.72	800	18.53	0.04 (0.03, 0.06)	*0.08 (0.06, 0.1)*	*0.16 (0.13, 0.19)*

Outcome	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			
65-74	2,792,364	51	1.83	1,982	70.98	0.03 (0.02, 0.03)	*0.05 (0.04, 0.06)*	*0.1 (0.09, 0.12)*
75+	1,348,477	23	1.71	2,464	182.72	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.04 (0.03, 0.05)*
Female								
<12	29,304	0	0.00	1	4.18	NA	*NA*	*NA*
12-17	556,781	0	0.00	23	4.18	NA	*NA*	*NA*
18-24	2,369,832	0	0.00	99	4.18	NA	*NA*	*NA*
25-39	3,883,926	0	0.00	162	4.18	NA	*NA*	*NA*
40-49	3,822,515	5	0.13	160	4.18	0.03 (0.01, 0.08)	*0.06 (0.03, 0.12)*	*0.13 (0.08, 0.2)*
50-64	4,901,232	22	0.45	1,766	36.03	0.01 (0.01, 0.02)	*0.02 (0.02, 0.03)*	*0.05 (0.04, 0.06)*
65-74	3,171,105	39	1.23	4,376	137.99	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.04 (0.03, 0.04)*
75+	1,531,377	42	2.74	5,440	355.23	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.03 (0.03, 0.04)*

Partington RJ, Muller S, Helliwell T, Mallen CD, Abdul Sultan A. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Ann Rheum Dis. 2018 Dec;77(12):1750-1756. doi: 10.1136/annrheumdis-2018-213883. Epub 2018 Oct 8. PMID: 30297332.

1.1.1.1.15. Age and Sex Stratified Observed-to-Expected Analyses, Multisystem Inflammatory Syndrome

Outcome	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			
Multisystem inflammatory syndrome								
Review Period:								
All	11,272,825	63	0.56	229	2.03	0.28 (0.21, 0.36)	*0.55 (0.44, 0.68)*	*1.1 (0.92, 1.32)*
By age								
<12	14,851	0	0.00	1	6.51	NA	*NA*	*NA*
12-17	282,154	2	0.71	18	6.51	0.11 (0.03, 0.47)	*0.22 (0.07, 0.64)*	*0.44 (0.19, 1)*
18-24	2,041,125	2	0.10	16	0.78	0.13 (0.03, 0.55)	*0.25 (0.08, 0.75)*	*0.5 (0.22, 1.17)*
25-39	1,399,426	8	0.57	19	1.35	0.42 (0.19, 0.97)	*0.85 (0.44, 1.65)*	*1.69 (0.96, 2.99)*
40-49	3,162,658	6	0.19	18	0.58	0.33 (0.13, 0.82)	*0.65 (0.32, 1.36)*	*1.31 (0.71, 2.41)*
50-64	2,238,981	17	0.76	15	0.66	1.15 (0.57, 2.3)	*2.3 (1.25, 4.22)*	*4.6 (2.63, 8.05)*
65-74	1,937,639	12	0.62	13	0.67	0.92 (0.42, 2.03)	*1.85 (0.94, 3.63)*	*3.7 (2, 6.82)*
75+	195,969	10	5.10	2	1.05	4.86 (1.06, 22.18)	*9.72 (2.27, 41.58)*	*19.44 (4.7, 80.44)*
By gender								
Male	5,097,136	31	0.61	128	2.50	0.24 (0.16, 0.36)	*0.49 (0.36, 0.66)*	*0.97 (0.76, 1.24)*
Female	6,175,668	31	0.50	142	2.30	0.22 (0.15, 0.32)	*0.44 (0.32, 0.59)*	*0.87 (0.69, 1.11)*
By age and gender								
Male								
<12	6,681	0	0.00	0	7.47	NA	*NA*	*NA*
12-17	126,951	1	0.79	9	7.47	0.11 (0.01, 0.83)	*0.21 (0.05, 0.98)*	*0.42 (0.13, 1.37)*
18-24	939,430	1	0.11	7	0.77	0.14 (0.02, 1.12)	*0.28 (0.06, 1.33)*	*0.55 (0.16, 1.89)*
25-39	615,389	1	0.16	6	0.90	0.18 (0.02, 1.5)	*0.36 (0.07, 1.79)*	*0.72 (0.2, 2.56)*
40-49	1,453,704	1	0.07	7	0.45	0.15 (0.02, 1.24)	*0.31 (0.06, 1.47)*	*0.61 (0.18, 2.09)*
50-64	1,001,254	12	1.20	5	0.53	2.26 (0.8, 6.42)	*4.52 (1.73, 11.85)*	*9.05 (3.6, 22.72)*
65-74	880,095	8	0.91	6	0.71	1.28 (0.44, 3.69)	*2.56 (1, 6.54)*	*5.12 (2.14, 12.25)*
75+	73,631	4	5.43	1	1.73	3.14 (0.35, 28.1)	*6.28 (0.79, 50.22)*	*12.56 (1.67, 94.72)*
Female								
<12	8,168	0	0.00	0	5.49	NA	*NA*	*NA*
12-17	155,205	1	0.64	9	5.49	0.12 (0.01, 0.93)	*0.23 (0.05, 1.09)*	*0.47 (0.14, 1.52)*
18-24	1,101,696	1	0.09	9	0.79	0.11 (0.01, 0.91)	*0.23 (0.05, 1.06)*	*0.46 (0.14, 1.49)*
25-39	784,037	6	0.77	14	1.80	0.43 (0.16, 1.11)	*0.85 (0.39, 1.84)*	*1.7 (0.88, 3.29)*
40-49	1,708,954	5	0.29	12	0.71	0.41 (0.15, 1.17)	*0.82 (0.36, 1.91)*	*1.65 (0.81, 3.37)*
50-64	1,237,727	5	0.40	10	0.79	0.51 (0.17, 1.5)	*1.02 (0.43, 2.46)*	*2.05 (0.96, 4.37)*
65-74	1,057,544	4	0.38	7	0.64	0.59 (0.17, 2.02)	*1.18 (0.43, 3.26)*	*2.36 (0.97, 5.75)*
75+	122,337	6	4.90	3	2.67	1.84 (0.46, 7.34)	*3.67 (1.04, 13.02)*	*7.35 (2.21, 24.4)*
Cumulative:								
All	38,111,689	401	1.05	774	2.03	0.52 (0.46, 0.58)	*1.04 (0.94, 1.14)*	*2.07 (1.9, 2.26)*
By age								
<12	55,109	0	0.00	4	6.51	NA	*NA*	*NA*
12-17	1,047,062	8	0.76	68	6.51	0.12 (0.06, 0.24)	*0.23 (0.14, 0.4)*	*0.47 (0.31, 0.71)*
18-24	4,456,623	15	0.34	35	0.78	0.43 (0.24, 0.79)	*0.86 (0.53, 1.41)*	*1.73 (1.14, 2.62)*
25-39	7,303,976	36	0.49	99	1.35	0.37 (0.25, 0.53)	*0.73 (0.54, 0.99)*	*1.46 (1.13, 1.89)*
40-49	7,188,488	36	0.50	42	0.58	0.86 (0.55, 1.35)	*1.73 (1.18, 2.53)*	*3.45 (2.45, 4.87)*
50-64	9,217,086	83	0.90	61	0.66	1.36 (0.98, 1.9)	*2.73 (2.03, 3.66)*	*5.46 (4.15, 7.17)*
65-74	5,963,469	110	1.84	40	0.67	2.75 (1.92, 3.95)	*5.51 (3.93, 7.71)*	*11.01 (7.97, 15.22)*
75+	2,879,855	99	3.44	30	1.05	3.27 (2.18, 4.93)	*6.55 (4.46, 9.61)*	*13.1 (9.04, 18.98)*
By gender								
Male	17,845,596	191	1.07	447	2.50	0.43 (0.36, 0.51)	*0.85 (0.75, 0.98)*	*1.71 (1.52, 1.92)*
Female	20,266,072	206	1.02	466	2.30	0.44 (0.38, 0.52)	*0.88 (0.78, 1.01)*	*1.77 (1.58, 1.98)*
By age and gender								
Male								
<12	25,804	0	0.00	2	7.47	NA	*NA*	*NA*
12-17	490,282	4	0.82	37	7.47	0.11 (0.04, 0.31)	*0.22 (0.1, 0.47)*	*0.44 (0.24, 0.79)*
18-24	2,086,791	8	0.38	16	0.77	0.5 (0.21, 1.16)	*1 (0.5, 1.99)*	*1.99 (1.09, 3.63)*
25-39	3,420,050	12	0.35	31	0.90	0.39 (0.2, 0.76)	*0.78 (0.46, 1.33)*	*1.56 (0.99, 2.45)*

Outcome	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			
40-49	3,365,973	11	0.33	15	0.45	0.73 (0.33, 1.58)	*1.45 (0.75, 2.8)*	*2.9 (1.62, 5.22)*
50-64	4,315,854	43	1.00	23	0.53	1.88 (1.13, 3.12)	*3.76 (2.37, 5.96)*	*7.52 (4.87, 11.62)*
65-74	2,792,364	57	2.04	20	0.71	2.88 (1.73, 4.78)	*5.75 (3.58, 9.25)*	*11.5 (7.28, 18.16)*
75+	1,348,477	52	3.86	23	1.73	2.23 (1.36, 3.64)	*4.46 (2.84, 7)*	*8.92 (5.8, 13.72)*
Female								
<12	29,304	0	0.00	2	5.49	NA	*NA*	*NA*
12-17	556,781	4	0.72	31	5.49	0.13 (0.05, 0.37)	*0.26 (0.12, 0.57)*	*0.52 (0.29, 0.96)*
18-24	2,369,832	7	0.30	19	0.79	0.37 (0.16, 0.89)	*0.75 (0.37, 1.49)*	*1.5 (0.84, 2.68)*
25-39	3,883,926	23	0.59	70	1.80	0.33 (0.21, 0.53)	*0.66 (0.45, 0.95)*	*1.32 (0.96, 1.8)*
40-49	3,822,515	25	0.65	27	0.71	0.92 (0.53, 1.59)	*1.84 (1.15, 2.94)*	*3.68 (2.41, 5.64)*
50-64	4,901,232	40	0.82	39	0.79	1.03 (0.66, 1.61)	*2.07 (1.41, 3.03)*	*4.13 (2.91, 5.86)*
65-74	3,171,105	53	1.67	20	0.64	2.61 (1.56, 4.37)	*5.22 (3.24, 8.42)*	*10.45 (6.6, 16.52)*
75+	1,531,377	47	3.07	41	2.67	1.15 (0.76, 1.75)	*2.3 (1.59, 3.32)*	*4.6 (3.28, 6.45)*

ACCESS, Spain (FISABIO 2019). Only age and age by sex stratified rates were available in the available source material. Overall sex-specific expected rates have been estimated as an average of age specific rates.

1.1.1.1.16. Age and Sex Stratified Observed-to-Expected Analyses, Guillain-barre syndrome

Outcome	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			
Guillain-barre syndrome								
Review Period:								
All	11,272,825	168	1.49	326	2.90	0.51 (0.43, 0.62)	*1.03 (0.88, 1.2)*	*2.06 (1.8, 2.35)*
By age								
<12	14,851	0	0.00	0	0.61	NA	*NA*	*NA*
12-17	282,154	4	1.42	2	0.61	2.32 (0.43, 12.69)	*4.65 (0.99, 21.89)*	*9.3 (2.14, 40.43)*
18-24	2,041,125	3	0.15	40	1.98	0.07 (0.02, 0.24)	*0.15 (0.06, 0.35)*	*0.3 (0.16, 0.57)*
25-39	1,399,426	22	1.57	28	1.98	0.8 (0.46, 1.39)	*1.59 (0.99, 2.56)*	*3.18 (2.08, 4.87)*
40-49	3,162,658	27	0.85	95	2.99	0.29 (0.19, 0.44)	*0.57 (0.41, 0.8)*	*1.14 (0.87, 1.5)*
50-64	2,238,981	45	2.01	95	4.24	0.47 (0.33, 0.68)	*0.95 (0.71, 1.27)*	*1.9 (1.48, 2.43)*
65-74	1,937,639	34	1.75	95	4.88	0.36 (0.24, 0.53)	*0.72 (0.53, 0.98)*	*1.44 (1.11, 1.87)*
75+	195,969	22	11.23	12	5.89	1.91 (0.94, 3.85)	*3.82 (2.02, 7.22)*	*7.63 (4.17, 13.95)*
By gender								
Male	5,097,136	89	1.75	167	3.28	0.53 (0.41, 0.69)	*1.06 (0.86, 1.31)*	*2.13 (1.77, 2.56)*
Female	6,175,668	75	1.21	155	2.51	0.48 (0.37, 0.64)	*0.97 (0.77, 1.21)*	*1.94 (1.6, 2.35)*
By age and gender								
Male								
<12	6,681	0	0.00	0	0.65	NA	*NA*	*NA*
12-17	126,951	1	0.79	1	0.65	1.21 (0.08, 19.38)	*2.42 (0.22, 26.73)*	*4.85 (0.54, 43.37)*
18-24	939,430	2	0.21	18	1.92	0.11 (0.03, 0.48)	*0.22 (0.08, 0.66)*	*0.44 (0.19, 1.02)*
25-39	615,389	10	1.62	12	1.92	0.85 (0.37, 1.96)	*1.69 (0.83, 3.46)*	*3.39 (1.78, 6.45)*
40-49	1,453,704	12	0.83	47	3.25	0.25 (0.13, 0.48)	*0.51 (0.31, 0.83)*	*1.02 (0.68, 1.52)*
50-64	1,001,254	28	2.80	53	5.29	0.53 (0.33, 0.84)	*1.06 (0.73, 1.54)*	*2.11 (1.53, 2.93)*
65-74	880,095	20	2.27	50	5.69	0.4 (0.24, 0.67)	*0.8 (0.53, 1.21)*	*1.6 (1.12, 2.27)*
75+	73,631	10	13.58	5	6.90	1.97 (0.67, 5.76)	*3.94 (1.48, 10.49)*	*7.87 (3.11, 19.95)*
Female								
<12	8,168	0	0.00	0	0.57	NA	*NA*	*NA*
12-17	155,205	3	1.93	1	0.57	3.39 (0.35, 32.6)	*6.78 (0.82, 56.34)*	*13.56 (1.76, 104.32)*
18-24	1,101,696	1	0.09	22	2.03	0.04 (0.01, 0.33)	*0.09 (0.02, 0.38)*	*0.18 (0.06, 0.52)*
25-39	784,037	12	1.53	16	2.03	0.75 (0.36, 1.59)	*1.51 (0.8, 2.84)*	*3.02 (1.71, 5.31)*
40-49	1,708,954	15	0.88	47	2.73	0.32 (0.18, 0.57)	*0.64 (0.41, 1.02)*	*1.29 (0.88, 1.88)*
50-64	1,237,727	17	1.37	39	3.18	0.43 (0.24, 0.76)	*0.86 (0.55, 1.37)*	*1.73 (1.17, 2.56)*
65-74	1,057,544	14	1.32	43	4.07	0.33 (0.18, 0.59)	*0.65 (0.4, 1.05)*	*1.3 (0.87, 1.94)*
75+	122,337	12	9.81	6	4.87	2.01 (0.76, 5.37)	*4.03 (1.65, 9.85)*	*8.06 (3.45, 18.83)*
Cumulative:								
All	38,111,689	611	1.60	1,103	2.90	0.55 (0.5, 0.61)	*1.11 (1.02, 1.2)*	*2.22 (2.06, 2.38)*
By age								
<12	55,109	0	0.00	0	0.61	NA	*NA*	*NA*
12-17	1,047,062	5	0.48	6	0.61	0.78 (0.24, 2.57)	*1.57 (0.57, 4.31)*	*3.13 (1.26, 7.8)*
18-24	4,456,623	29	0.65	88	1.98	0.33 (0.22, 0.5)	*0.66 (0.47, 0.92)*	*1.32 (1, 1.74)*
25-39	7,303,976	85	1.16	144	1.98	0.59 (0.45, 0.77)	*1.18 (0.94, 1.47)*	*2.36 (1.94, 2.86)*
40-49	7,188,488	97	1.35	215	2.99	0.45 (0.36, 0.57)	*0.9 (0.74, 1.1)*	*1.81 (1.53, 2.13)*
50-64	9,217,086	173	1.88	390	4.24	0.44 (0.37, 0.53)	*0.89 (0.77, 1.02)*	*1.77 (1.57, 2.01)*
65-74	5,963,469	118	1.98	291	4.88	0.41 (0.33, 0.5)	*0.81 (0.68, 0.96)*	*1.62 (1.4, 1.88)*
75+	2,879,855	78	2.71	169	5.89	0.46 (0.35, 0.6)	*0.92 (0.74, 1.14)*	*1.84 (1.53, 2.22)*
By gender								
Male	17,845,596	308	1.73	586	3.28	0.53 (0.46, 0.6)	*1.05 (0.94, 1.18)*	*2.1 (1.91, 2.32)*
Female	20,266,072	293	1.45	508	2.51	0.58 (0.5, 0.67)	*1.15 (1.02, 1.3)*	*2.31 (2.08, 2.56)*
By age and gender								
Male								
<12	25,804	0	0.00	0	0.65	NA	*NA*	*NA*
12-17	490,282	1	0.20	3	0.65	0.31 (0.03, 3.02)	*0.63 (0.1, 3.76)*	*1.26 (0.28, 5.61)*
18-24	2,086,791	15	0.72	40	1.92	0.37 (0.21, 0.68)	*0.75 (0.47, 1.2)*	*1.5 (1, 2.23)*
25-39	3,420,050	30	0.88	66	1.92	0.46 (0.3, 0.7)	*0.91 (0.64, 1.3)*	*1.83 (1.35, 2.47)*
40-49	3,365,973	43	1.28	109	3.25	0.39 (0.28, 0.56)	*0.79 (0.59, 1.04)*	*1.57 (1.24, 2)*

Outcome	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			
50-64	4,315,854	95	2.20	228	5.29	0.42 (0.33, 0.53)	*0.83 (0.69, 1.01)*	*1.66 (1.41, 1.96)*
65-74	2,792,364	67	2.40	159	5.69	0.42 (0.32, 0.56)	*0.84 (0.67, 1.06)*	*1.69 (1.39, 2.05)*
75+	1,348,477	46	3.41	93	6.90	0.49 (0.35, 0.7)	*0.99 (0.74, 1.32)*	*1.98 (1.54, 2.54)*
Female								
<12	29,304	0	0.00	0	0.57	NA	*NA*	*NA*
12-17	556,781	4	0.72	3	0.57	1.26 (0.28, 5.63)	*2.52 (0.67, 9.5)*	*5.04 (1.47, 17.3)*
18-24	2,369,832	14	0.59	48	2.03	0.29 (0.16, 0.53)	*0.58 (0.37, 0.93)*	*1.16 (0.79, 1.71)*
25-39	3,883,926	55	1.42	79	2.03	0.7 (0.49, 0.98)	*1.4 (1.04, 1.86)*	*2.79 (2.16, 3.61)*
40-49	3,822,515	54	1.41	104	2.73	0.52 (0.37, 0.72)	*1.03 (0.79, 1.35)*	*2.07 (1.64, 2.62)*
50-64	4,901,232	78	1.59	156	3.18	0.5 (0.38, 0.66)	*1 (0.8, 1.25)*	*2 (1.65, 2.43)*
65-74	3,171,105	49	1.55	129	4.07	0.38 (0.27, 0.53)	*0.76 (0.58, 0.99)*	*1.52 (1.22, 1.9)*
75+	1,531,377	32	2.09	75	4.87	0.43 (0.28, 0.65)	*0.86 (0.61, 1.2)*	*1.72 (1.29, 2.28)*

Li X, Ostropolets A, Makadia R, et al. Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study. Preprint. medRxiv. 2021;2021.03.25.21254315. Published 2021 Apr 17. doi:10.1101/2021.03.25.21254315 (Optum EHR data utilized)

1.1.1.1.17. Age and Sex Stratified Observed-to-Expected Analyses, Death

Outcome	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			
Death								
Review Period:								
All	11,272,825	920	8.16	93,147	826.30	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.04, 0.04)*
By age								
<12	14,851	4	26.93	9	59.90	0.45 (0.14, 1.46)	*0.9 (0.35, 2.33)*	*1.8 (0.79, 4.07)*
12-17	282,154	7	2.48	169	59.90	0.04 (0.02, 0.09)	*0.08 (0.05, 0.14)*	*0.17 (0.11, 0.25)*
18-24	2,041,125	13	0.64	1,874	91.80	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.02, 0.04)*
25-39	1,399,426	68	4.86	1,503	107.40	0.05 (0.04, 0.06)	*0.09 (0.08, 0.11)*	*0.18 (0.16, 0.21)*
40-49	3,162,658	65	2.06	9,561	302.30	0.01 (0.01, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.02, 0.03)*
50-64	2,238,981	217	9.69	19,952	891.10	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.04, 0.05)*
65-74	1,937,639	184	9.50	38,772	2001.00	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.02)*
75+	195,969	306	156.15	15,060	7685.10	0.02 (0.02, 0.02)	*0.04 (0.04, 0.04)*	*0.08 (0.08, 0.09)*
By gender								
Male	5,097,136	535	10.50	44,865	880.20	0.01 (0.01, 0.01)	*0.02 (0.02, 0.03)*	*0.05 (0.05, 0.05)*
Female	6,175,668	353	5.72	50,597	819.30	0.01 (0.01, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.03, 0.03)*
By age and gender								
Male								
<12	6,681	3	44.90	4	63.81	0.7 (0.16, 3.14)	*1.41 (0.4, 4.99)*	*2.81 (0.91, 8.73)*
12-17	126,951	4	3.15	81	63.81	0.05 (0.02, 0.13)	*0.1 (0.05, 0.2)*	*0.2 (0.12, 0.34)*
18-24	939,430	6	0.64	919	97.79	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.03 (0.02, 0.04)*
25-39	615,389	49	7.96	704	114.41	0.07 (0.05, 0.09)	*0.14 (0.11, 0.17)*	*0.28 (0.24, 0.33)*
40-49	1,453,704	44	3.03	4,681	322.02	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.03, 0.04)*
50-64	1,001,254	151	15.08	9,504	949.23	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.06 (0.06, 0.07)*
65-74	880,095	110	12.50	18,759	2131.53	0.01 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.03)*
75+	73,631	150	203.72	6,028	8186.40	0.02 (0.02, 0.03)	*0.05 (0.04, 0.06)*	*0.1 (0.09, 0.11)*
Female								
<12	8,168	1	12.24	5	59.39	0.21 (0.02, 1.76)	*0.41 (0.08, 2.13)*	*0.82 (0.22, 3.07)*
12-17	155,205	3	1.93	92	59.39	0.03 (0.01, 0.1)	*0.07 (0.03, 0.15)*	*0.13 (0.07, 0.24)*
18-24	1,101,696	6	0.54	1,003	91.02	0.01 (0, 0.01)	*0.01 (0.01, 0.02)*	*0.02 (0.02, 0.04)*
25-39	784,037	16	2.04	835	106.49	0.02 (0.01, 0.03)	*0.04 (0.03, 0.05)*	*0.08 (0.06, 0.1)*
40-49	1,708,954	19	1.11	5,122	299.74	0 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.01 (0.01, 0.02)*
50-64	1,237,727	64	5.17	10,936	883.55	0.01 (0, 0.01)	*0.01 (0.01, 0.01)*	*0.02 (0.02, 0.03)*
65-74	1,057,544	73	6.90	20,982	1984.05	0 (0, 0)	*0.01 (0.01, 0.01)*	*0.01 (0.01, 0.02)*
75+	122,337	154	125.88	9,322	7620.00	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.07 (0.06, 0.07)*
Cumulative:								
All	38,111,689	6,204	16.28	314,917	826.30	0.02 (0.02, 0.02)	*0.04 (0.04, 0.04)*	*0.08 (0.08, 0.08)*
By age								
<12	55,109	9	16.33	33	59.90	0.27 (0.13, 0.57)	*0.55 (0.31, 0.97)*	*1.09 (0.68, 1.75)*
12-17	1,047,062	14	1.34	627	59.90	0.02 (0.01, 0.04)	*0.04 (0.03, 0.07)*	*0.09 (0.07, 0.12)*
18-24	4,456,623	53	1.19	4,091	91.80	0.01 (0.01, 0.02)	*0.03 (0.02, 0.03)*	*0.05 (0.05, 0.06)*
25-39	7,303,976	274	3.75	7,844	107.40	0.03 (0.03, 0.04)	*0.07 (0.06, 0.08)*	*0.14 (0.13, 0.15)*
40-49	7,188,488	285	3.96	21,731	302.30	0.01 (0.01, 0.01)	*0.03 (0.02, 0.03)*	*0.05 (0.05, 0.06)*
50-64	9,217,086	1,056	11.46	82,133	891.10	0.01 (0.01, 0.01)	*0.03 (0.02, 0.03)*	*0.05 (0.05, 0.05)*
65-74	5,963,469	1,404	23.54	119,329	2001.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.05 (0.05, 0.05)*
75+	2,879,855	2,843	98.72	221,320	7685.10	0.01 (0.01, 0.01)	*0.03 (0.03, 0.03)*	*0.05 (0.05, 0.05)*
By gender								
Male	17,845,596	3,558	19.94	157,077	880.20	0.02 (0.02, 0.02)	*0.05 (0.04, 0.05)*	*0.09 (0.09, 0.09)*
Female	20,266,072	2,494	12.31	166,040	819.30	0.02 (0.01, 0.02)	*0.03 (0.03, 0.03)*	*0.06 (0.06, 0.06)*
By age and gender								
Male								
<12	25,804	6	23.25	16	63.81	0.36 (0.14, 0.93)	*0.73 (0.34, 1.54)*	*1.46 (0.77, 2.74)*
12-17	490,282	9	1.84	313	63.81	0.03 (0.01, 0.06)	*0.06 (0.04, 0.09)*	*0.12 (0.08, 0.16)*
18-24	2,086,791	31	1.49	2,041	97.79	0.02 (0.01, 0.02)	*0.03 (0.02, 0.04)*	*0.06 (0.05, 0.07)*
25-39	3,420,050	180	5.26	3,913	114.41	0.05 (0.04, 0.05)	*0.09 (0.08, 0.1)*	*0.18 (0.17, 0.2)*
40-49	3,365,973	186	5.53	10,839	322.02	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.07 (0.06, 0.07)*
50-64	4,315,854	642	14.88	40,967	949.23	0.02 (0.01, 0.02)	*0.03 (0.03, 0.03)*	*0.06 (0.06, 0.07)*
65-74	2,792,364	881	31.55	59,520	2131.53	0.01 (0.01, 0.02)	*0.03 (0.03, 0.03)*	*0.06 (0.06, 0.06)*

Outcome	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			
75+	1,348,477	1,543	114.43	110,392	8186.40	0.01 (0.01, 0.01)	*0.03 (0.03, 0.03)*	*0.06 (0.05, 0.06)*
Female								
<12	29,304	1	3.41	17	59.39	0.06 (0.01, 0.43)	*0.11 (0.03, 0.5)*	*0.23 (0.08, 0.68)*
12-17	556,781	5	0.90	331	59.39	0.02 (0.01, 0.04)	*0.03 (0.02, 0.06)*	*0.06 (0.04, 0.09)*
18-24	2,369,832	20	0.84	2,157	91.02	0.01 (0.01, 0.01)	*0.02 (0.01, 0.03)*	*0.04 (0.03, 0.05)*
25-39	3,883,926	86	2.21	4,136	106.49	0.02 (0.02, 0.03)	*0.04 (0.04, 0.05)*	*0.08 (0.07, 0.09)*
40-49	3,822,515	93	2.43	11,458	299.74	0.01 (0.01, 0.01)	*0.02 (0.01, 0.02)*	*0.03 (0.03, 0.04)*
50-64	4,901,232	404	8.24	43,305	883.55	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.04, 0.04)*
65-74	3,171,105	515	16.24	62,916	1984.05	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.03 (0.03, 0.03)*
75+	1,531,377	1,285	83.91	116,691	7620.00	0.01 (0.01, 0.01)	*0.02 (0.02, 0.02)*	*0.04 (0.04, 0.05)*
CDC Wonder: https://wonder.cdc.gov/								

Appendix 11.4a Anaphylaxis: Adolescents ages 12 to 17 years_Medical Review with Brighton Collaboration

Case ID	Country	Patient Age (Years)	Patient Gender	Medical History	ALL PT'S	Case Seriousness	Concomitant Medications	Med Review Dose	Med Review TTO	Brighton Collaboration Case Definition	MAH Comment/Justification of causality (risk factors, alternate etiology, etc.)	WW Identifier	Batch/Lot Number
[redacted]	[redacted]	17	Male	0	Anaphylactic reaction, Malaise, Pallor, Syncope, Visual impairment	Serious	0	Received Epinephrine	Within 24 hours	Insufficient information to meet Brighton criteria	Possible based on temporal association	[redacted]	032B21A
		17	Male	0	Anaphylactic reaction, Product administered to patient of inappropriate age	Serious	0	not stated	Within 24 hours	No information on signs or symptoms	Possible based on temporal association		3002184
		16	Male	0	Anaphylactic shock	Serious	0	not stated	Within 24 hours	No information on signs or symptoms	Possible based on temporal association		3004234
		13	Male	0	Asthenia, Pain in extremity, Type I hypersensitivity	Serious	0	not stated	Within 24 hours	Insufficient information to meet Brighton criteria	Possible based on temporal association		214021
		12	Female	Asthma(H)	Anaphylactic reaction	Serious	VENTOLINE [SALBUTAMOL]	not stated	Within 24 hours	No information on signs or symptoms	Possible based on temporal association. Patient has history of asthma and salbutamol was concurrent medication		214018
		16	Male	0	Anaphylactic reaction, Presyncope, Visual impairment	Serious	0	Lactated ringer's solution 500 mL, d-chlorpheniramine maleate 1A, and famotidine 1A were administered. Adrenaline 0.3 mg was injected intramuscularly	30 minutes	Insufficient information to meet Brighton criteria	Possible based on temporal association.		0
		16	Male	0	Anaphylactic reaction	Serious	0	None	Within 24 hours	Insufficient information to meet Brighton criteria	Possible based on temporal association		214008
		16	Female	0	Anaphylactic reaction	Serious	0	Not stated	15 minutes	Insufficient information to meet Brighton criteria	Possible based on temporal association.		3005289
		14	Female	Urticaria(H)	Anaphylactic shock	Serious	0	not stated	unknown	Insufficient information to meet Brighton criteria	Conditional as inormation on time to onset needed. History of urticaria.		3005701; 3005235
		12	Male	0	Anaphylactic reaction	Serious	0	not stated	Within 24 hours	No information on signs or symptoms	Possible based on temporal association		3004731
		16	Female	Hypersensitivity(C)	Anaphylactic reaction	Serious	0	d-chlorpheniramine maleate	30 minutes	Insufficient information to meet Brighton criteria	Possible based on temporal association. History of allergy.		3005890
		16	Female	Mite allergy; Allergy to animal; Allergy to animal; Seasonal allergy; Food allergy; Food allergy; Food allergy	Anaphylactic shock	Serious	0	Intramuscular injection of adrenaline, intravenous injection of methylprednisolone sodium succinate, oral administration of fexofenadine hydrochloride, and intravenous injection of d-chlorpheniramine maleate and famotidine.	17 minutes	Meets Brighton criteria for Level 1 anaphylaxis	Possible based on temporal association. Has a history of muliple allergies.		0
		14	Female	Depression(C); Diabetes mellitus(C)	Anaphylactic reaction, Pruritus, Rash	Serious	REXULTI; SERTRALINE	Administration of antihistaminic famotidine and d-chlorpheniramine maleate, and steroidal methylprednisolone sodium succinate 125 mg	14 minutes	Insufficient information to meet Brighton criteria	Possible based on temporal association.		3005694; 3005694
		14	Female	0	Circulatory collapse, Dizziness, Pyrexia, Vomiting	Serious	0	not stated	Greater than 24 hours	Insufficient information to meet Brighton criteria	Unassessable. Long latency and no clinical details.		3004215
		17	Female	0	Anaphylactic reaction, Dyspnoea, Fatigue, Myalgia, Pruritus, Pyrexia	Non Serious	0	not stated	Within 24 hours	Insufficient information to meet Brighton criteria	Possible based on temporal association.		0
		17	Male	0	Anaphylactic shock, Dizziness, Nausea	Serious	0	not stated	Within 24 hours	Insufficient information to meet Brighton criteria	Possible based on temporal association		012F21A
		14	Female	0	Anaphylactic reaction, Nausea, Pruritus, Pyrexia, Rash, Vomiting	Non Serious	0	not stated	Unknown	Insufficient information to meet Brighton criteria	Conditional as inormation on time to onset needed.		0
		15	Female	0	Anaphylactic reaction	Serious	0	not stated	Within 24 hours	No positive signs or symptoms presented. No erythema was stated.	Unassessable. no clinical details.		022D21A
		16	Female	0	Anaphylactic reaction, Immunisation reaction, Rash	Serious	0	not stated	Within 24 hours	No signs or symptoms given.	Unasssessable. No clinical details.		940885
		15	Male	0	Anaphylactic reaction, Pain, Rash, Swelling	Serious	0	not stated	21 days	Insufficient information to meet Brighton criteria	Unlikely given the latency.		O24D217

Appendix 11.4b Anaphylaxis: Adolescents ages 12 to 17 years_Medical Review with Brighton Collaboration -Narratives

Case ID	Narrative (Complete)
[redacted]	This case was received via [redacted] VAERS (Reference number: [redacted] on 01-Jun-2021 and was forwarded to Moderna on 01-Jun-2021. This regulatory authority case was reported by an other health care professional and describes the occurrence of SYNCOPE (Syncope) and ANAPHYLACTIC REACTION (Anaphylactic reaction) in a 17-year-old male patient who received mRNA-1273 (Moderna COVID-19 Vaccine) (batch no. 032B21A) for COVID-19 vaccination. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On 09-Apr-2021, the patient received dose of mRNA-1273 (Moderna COVID-19 Vaccine) (unknown route) 1 dosage form. On 09-Apr-2021, the patient experienced SYNCOPE (Syncope) (seriousness criterion medically significant), ANAPHYLACTIC REACTION (Anaphylactic reaction) (seriousness criterion medically significant), MALAISE (Malaise), PALLOR (Pallor) and VISUAL IMPAIRMENT (Visual impairment). The patient was treated with EPINEPHRINE (EPIPEN) (intramuscular) at a dose of 1 dosage form. At the time of the report, SYNCOPE (Syncope), ANAPHYLACTIC REACTION (Anaphylactic reaction), MALAISE (Malaise), PALLOR (Pallor) and VISUAL IMPAIRMENT (Visual impairment) had resolved. DIAGNOSTIC RESULTS (normal ranges are provided in parenthesis if available): On 09-Apr-2021, Heart rate: decreased (Low) decreased. On an unknown date, Blood pressure measurement: 112/64 mmHg (Inconclusive) Before EpiPen Administration and 143/75, mmHg (Inconclusive) After EpiPen Administration and Emergency medical service arrived. On an unknown date, Heart rate: 47 breaths per minute (Inconclusive) Before EpiPen Administration, 57 breaths per minute (Inconclusive) After EpiPen Administration and Emergency medical service arrived and 62 breaths per minute (Inconclusive) After EpiPen Administration and remained stable. On an unknown date, Oxygen saturation: 95 % (Inconclusive) Before EpiPen Administration, 94 % (Inconclusive) After EpiPen Administration and Emergency medical service arrived and 94 % (Inconclusive) After EpiPen Administration and remained stable. On an unknown date, Respiratory rate: 16 (Inconclusive) Before EpiPen Administration. The action taken with mRNA-1273 (Moderna COVID-19 Vaccine) (Unknown) was unknown. For mRNA-1273 (Moderna COVID-19 Vaccine) (Unknown), the reporter did not provide any causality assessments. Concomitant product was not provided by the reporter. Patient reported that getting vaccine from nurse after some minutes he show signs of anaphylaxis reaction. On assessment he said that he was not feeling good. He was unable to read how many fingers held up due to leaning his head backward. He complained that he cannot see and slow in responding. Patient had losing consciousness eyes closed color of face became pale. After treatment patient continued to monitor and check vital signs. Patient starts to open his eyes and responding. He was taken to the Emergency room. Followed up with the patient's parent, mom stated that he was stable and doing better. Company comments: Based on the current available information and temporal association between the use of the product and the start date of the events, a causal relationship cannot be excluded.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by a physician and describes the occurrence of ANAPHYLACTIC REACTION (Anaphylactic reaction) in a 17-year-old male patient who received mRNA-1273 (COVID 19 Vaccine Moderna) (batch no. 3002184) for COVID-19 vaccination. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On 10-May-2021, the patient received first dose of mRNA-1273 (COVID 19 Vaccine Moderna) (Intramuscular) 1 dosage form. On 10-May-2021, after starting mRNA-1273 (COVID 19 Vaccine Moderna), the patient experienced PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE (Inappropriate age at vaccine administration). On 10-May-2021 at 1:50 PM, the patient experienced ANAPHYLACTIC REACTION (Anaphylactic reaction) (seriousness criterion medically significant). On 10-May-2021, PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE (Inappropriate age at vaccine administration) had resolved. At the time of the report, ANAPHYLACTIC REACTION (Anaphylactic reaction) outcome was unknown. The action taken with mRNA-1273 (COVID 19 Vaccine Moderna) (Intramuscular) was unknown. For mRNA-1273 (COVID 19 Vaccine Moderna) (Intramuscular), the reporter considered ANAPHYLACTIC REACTION (Anaphylactic reaction) to be probably related. No further causality assessment was provided for PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE (Inappropriate age at vaccine administration). Concomitant medication use was not provided. No Treatment information was provided. Most recent FOLLOW-UP information incorporated above includes: On 07-Jun-2021: Translation document received on 15 June 2021 does not contain any new information.

Case ID	Narrative (Complete)
[redacted]	This case was received via European Medicines Agency (Reference number: [redacted] on 19-Aug-2021 and was forwarded to Moderna on 19-Aug-2021. This regulatory authority case was reported by a physician and describes the occurrence of ANAPHYLACTIC SHOCK (Anaphylactic shock) in a 16-year-old male patient who received mRNA-1273 (Spikevax) (batch no. 3004234) for COVID-19 vaccination. No Medical History information was reported. On 04-Aug-2021, the patient received first dose of mRNA-1273 (Spikevax) (Intramuscular) 1 dosage form. On 04-Aug-2021, after starting mRNA-1273 (Spikevax), the patient experienced ANAPHYLACTIC SHOCK (Anaphylactic shock) (seriousness criteria hospitalization and medically significant). At the time of the report, ANAPHYLACTIC SHOCK (Anaphylactic shock) had not resolved. For mRNA-1273 (Spikevax) (Intramuscular), the reporter did not provide any causality assessments. No relevant concomitant and treatment medications were reported Company Comment Based on the current available information and temporal association between the use of the product and the start date of the event, a causal relationship cannot be excluded. Most recent FOLLOW-UP information incorporated above includes: On 19-Aug-2021: Translated document received on 23 Aug 21 contain no new information

Case ID	Narrative (Complete)
[redacted]	This case was received via European Medicines Agency (Reference number: [redacted] on 17-Sep-2021 and was forwarded to Moderna on 17-Sep-2021. This regulatory authority case was reported by a physician and describes the occurrence of TYPE I HYPERSENSITIVITY (Immediate hypersensitivity reaction) in a 13-year-old male patient who received mRNA-1273 (Spikevax) (batch no. 214021) for SARS-CoV-2 vaccination. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On 04-Sep-2021, the patient received dose of mRNA-1273 (Spikevax) (Intramuscular) 1 dosage form. On 04-Sep-2021, the patient experienced TYPE I HYPERSENSITIVITY (Immediate hypersensitivity reaction) (seriousness criteria hospitalization and medically significant), PAIN IN EXTREMITY (Pain in arm) and ASTHENIA (Asthenia). At the time of the report, TYPE I HYPERSENSITIVITY (Immediate hypersensitivity reaction) had resolved and PAIN IN EXTREMITY (Pain in arm) and ASTHENIA (Asthenia) had not resolved. The action taken with mRNA-1273 (Spikevax) (Intramuscular) was unknown. For mRNA-1273 (Spikevax) (Intramuscular), the reporter did not provide any causality assessments. No concomitant medications reported by reporter. No treatment medications provided by the reporter. Company Comment: This case concerns a 13 year-old, male patient with no relevant medical history, who experienced the unexpected event of Type I hypersensitivity reaction. The event occurred on the same day after the first dose of Spikevax (Moderna COVID-19 vaccine) requiring hospitalization. The rechallenge was not applicable since the event occurred after the first dose. The benefit-risk relationship of Spikevax (Moderna COVID-19 vaccine) is not affected by this report. Most recent FOLLOW-UP information incorporated above includes: On 17-Sep-2021: Translation received on 21-Sep-2021 and contain no new information.

Case ID	Narrative (Complete)
[redacted]	This case was received via European Medicines Agency (Reference number: [redacted] on 16-Sep-2021 and was forwarded to Moderna on 16-Sep-2021. This regulatory authority case was reported by a physician and describes the occurrence of ANAPHYLACTIC REACTION (Anaphylactic reaction) in a 12-year-old female patient who received mRNA-1273 (Spikevax) (batch no. 214018) for COVID-19 vaccination. The patient's past medical history included Allergic asthma since an unknown date. Concomitant products included SALBUTAMOL (VENTOLINE [SALBUTAMOL]) for an unknown indication. On 23-Aug-2021, the patient received first dose of mRNA-1273 (Spikevax) (Intramuscular) 1 dosage form. On 23-Aug-2021, the patient experienced ANAPHYLACTIC REACTION (Anaphylactic reaction) (seriousness criterion medically significant). At the time of the report, ANAPHYLACTIC REACTION (Anaphylactic reaction) had not resolved. For mRNA-1273 (Spikevax) (Intramuscular), the reporter did not provide any causality assessments. The treatment information was not provided. This case concerns a 12-year-old, female with a history of asthma , who experienced the expected event Anaphylactic reaction . The event occurred on the same day after the first dose of mRNA-1273 Moderna vaccine (Spikevax). The rechallenge was not applicable since this is the case for the first dose. The event is consistent with the current understanding of the mechanism of action of the study medication . The medical history of could be a potentially confounder. The benefit-risk relationship of mRNA-1273 Moderna vaccine in not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This case was received via Takeda Pharmaceuticals (Reference number: [redacted] on 13-Sep-2021 and was forwarded to Moderna on 23-Sep-2021. This case, reported by a vaccinator (other than a physician), was received by Takeda via Moderna's adverse reaction reporting site [redacted], and reported to the [redacted] by a vaccinator (other than a physician), was received via the [redacted] (Ref, [redacted]. On 11-Sep-2021, at 11:00, the patient received the 1st dose of this vaccine. At 11:05, anaphylaxis possibly developed suddenly. At 11:30, vasovagal reflex developed. Queasy and dimmed vision were noted. Lactated ringer's solution 500 mL, d-chlorpheniramine maleate 1A, and famotidine 1A were administered in bed. Improvement was confirmed, and when the patient walked home, queasy developed again. Adrenaline 0.3 mg was injected intramuscularly in bed, but the symptoms did not improve. The patient was raced to a hospital and was hospitalized. On 12-Sep-2021, the patient had queasy but was discharged from the hospital at the patient's request. On 13-Sep-2021, it was confirmed that the symptoms were resolving. The outcome of possibility of anaphylaxis, vasovagal reflex, and dimmed vision was reported as resolving. Follow-up investigation will be made. Company Comment: The events developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship. Company Comment: This case concerns a 16-year-old, male patient with no medical history, who experienced the expected event of Anaphylactic reaction. The event occurred immediately within 30 minutes after the first dose of mRNA-1273 (Moderna COVID-19 Vaccine). The patient also experienced serious events of Presyncope and Visual impairment. Event seriousness assessed as per Regulatory Authority reporting. The rechallenge was not applicable. The reporter assessed the events as possible. The benefit-risk relationship of mRNA-1273 (Moderna COVID-19 Vaccine) is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This case was received via European Medicines Agency (Reference number:[redacted] on 05-Oct-2021 and was forwarded to Moderna on 05-Oct-2021. This regulatory authority case was reported by a consumer and describes the occurrence of ANAPHYLACTIC REACTION ([redacted] in a 16-year-old male patient who received mRNA-1273 (Spikevax) (batch no. 214008) for COVID-19 vaccination. No Medical History information was reported. On 19-Sep-2021, the patient received dose of mRNA-1273 (Spikevax) (unknown route) 1 dosage form. On 19-Sep-2021, the patient experienced ANAPHYLACTIC REACTION ([redacted] (seriousness criteria hospitalization and medically significant). On 19-Sep-2021, ANAPHYLACTIC REACTION ([redacted] had resolved. The action taken with mRNA-1273 (Spikevax) (Unknown) was unknown. Concomitant medication was not provided. Treatment medication was not provided. Patient had experienced questionable anaphylactic reaction which started at 8.15 am and lasted until 8.54 am. Patient had also experienced hemodynamic instability and vomiting and no medication was taken for that. Patient had[redacted]Surname). Company Comment: This case concerns a 16-year-old, male patient with no previous relevant medical history, who experienced the expected event of Anaphylactic reaction. The event occurred on the same day after the first dose of Spikevax. The rechallenge was not applicable since only information about the first dose was disclosed. The reporter assessed the events as possible. The benefit-risk relationship of Spikevax is not affected by this report. Most recent FOLLOW-UP information incorporated above includes: On 05-Oct-2021: Translation received on 07-OCT-2021: No new information was upadated

Case ID	Narrative (Complete)
[redacted]	This case was received via Takeda Pharmaceuticals (Reference number: [redacted] on 30-Sep-2021 and was forwarded to Moderna on 06-Oct-2021. This case, reported by a health care worker, was received by Takeda via Moderna's adverse reaction reporting site [redacted], and this case, initially reported to the [redacted] by a physician, was received via the [redacted] (Ref, [redacted]. The patient had an allergic history of house dust. The patient underwent surgery for endocardial defect at the age of 4 years. On an unknown date, the patient received the 1st dose of this vaccine. On an unknown date, body temperature before the vaccination: 35.6 degrees Celsius. On 22-Sep-2021, at 16:44, the patient received the 2nd dose of this vaccine. Immediately after the vaccination, pruritus in the pharynx developed. At 16:59, anaphylaxis developed. The onset was sudden and the symptoms were rapidly progressive. Within several minutes, right chest pain, mild queasy, and abdominal pain developed. Vital signs showed only mild hypertension (BP: 169/81 and P: 62). BP was usually the 120s. The primary care clinic got contacted and ordered an emergency transportation. The patient waited in a first-aid room until transportation. The patient was awake and alert, and there were no agony-like symptoms. At 17:40, the patient was able to transfer alone. The outcome of anaphylaxis was unknown. Follow-up investigation will be made. Company Comment: The event developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.

Case ID	Narrative (Complete)
[redacted]	This case was initially received via Takeda Pharmaceuticals (Reference number: [redacted] on 06-Oct-2021. The most recent information was received on 08-Feb-2022 and was forwarded to Moderna on 15-Feb-2022. This regulatory authority case was reported by a physician and describes the occurrence of ANAPHYLACTIC SHOCK (Anaphylactic shock) in a 14-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna Intramuscular Injection) (batch nos. 3005701 and 3005235) for COVID-19 vaccination. The patient's past medical history included Urticaria. On 04-Sep-2021, the patient received first dose of mRNA-1273 (COVID-19 Vaccine Moderna Intramuscular Injection) (Intramuscular) 1 dosage form. On 02-Oct-2021, received second dose of mRNA-1273 (COVID-19 Vaccine Moderna Intramuscular Injection) (Intramuscular) dosage was changed to 1 dosage form. On an unknown date, the patient experienced ANAPHYLACTIC SHOCK (Anaphylactic shock) (seriousness criteria hospitalization and medically significant). At the time of the report, ANAPHYLACTIC SHOCK (Anaphylactic shock) had resolved. DIAGNOSTIC RESULTS (normal ranges are provided in parenthesis if available): On 03-Oct-2021, Blood pressure measurement: recovered Test Result:Recovered. On 03-Oct-2021, Body temperature: 37.6 cel (degree celsius) 37.6 Cel (degree Celsius). On 03-Oct-2021, Coma scale: decreased Test Result:Decreased and recovered Test Result:Recovered. On an unknown date, Body temperature: 36.1 cel (degree celsius) 36.1 Cel (degree Celsius). For mRNA-1273 (COVID-19 Vaccine Moderna Intramuscular Injection) (Intramuscular), the reporter considered ANAPHYLACTIC SHOCK (Anaphylactic shock) to be possibly related. The timing of onset was late, but the symptoms were severe, so this case was reported. There is no other possible cause other than this vaccine, but it is unknown whether this vaccine was the cause of the adverse event. Most recent FOLLOW-UP information incorporated above includes: On 08-Feb-2022: Significant Follow-up received: Patient demographics, Dosage text were updated. Events Depressed level of consciousness, Eyelid oedema, malaise, urticaria, dyspnea, blood pressure decreased were deleted. Results of tests and procedures relevant to the investigation of the patient were updated.

Case ID	Narrative (Complete)
[redacted]	This case was received via European Medicines Agency (Reference number: [redacted] on 20-Oct-2021 and was forwarded to Moderna on 20-Oct-2021. This regulatory authority case was reported by a consumer and describes the occurrence of ANAPHYLACTIC REACTION (Anaphylactic reaction) in a 12-year-old male patient who received mRNA-1273 (Spikevax) (batch no. 3004731) for COVID-19 vaccination. No Medical History information was reported. On 03-Oct-2021, the patient received dose of mRNA-1273 (Spikevax) (unknown route) 1 dosage form. On an unknown date, the patient experienced ANAPHYLACTIC REACTION (Anaphylactic reaction) (seriousness criteria medically significant and life threatening). At the time of the report, ANAPHYLACTIC REACTION (Anaphylactic reaction) had resolved. The action taken with mRNA-1273 (Spikevax) (Unknown) was unknown. Concomitant product use was not provided by reporter. Treatment information was not provided. Patient reported that Initials: [redacted](Last name, first name) After the intramuscular injection, the vaccine recipient developed an anaphylactic reaction at approximately 11:30 a.m. Outpatient treatment was required. Vaccination took place at the [redacted]vaccination center. Company Comment: This case concerns a 12-year-old male patient with no previous relevant medical history, who experienced the unexpected serious event of Anaphylactic reaction after Spikevax (mRNA- 1273 vaccine / Moderna COVID-19 Vaccine). The event occurred immediately after the dose of Spikevax, dose number unknown. Outpatient treatment was required, but not specified. No further information was provided. The rechallenge is not applicable, since no further doses should be expected. Anaphylactic reaction is consistent with the known safety profile of the vaccine in adults, but since the event was reported in an adolescent, it is currently considered unexpected. The benefit-risk relationship of Spikevax vaccine is not affected by this report. The event was assessed as Life-threatening as per regulatory authority report. There is insufficient evidence to support this seriousness assessment from a clinical or regulatory standpoint. Most recent FOLLOW-UP information incorporated above includes: On 20-Oct-2021: Translation received on 21-OCT-2021 is significant. Sender's comment is updated and added in inarrative.

Case ID	Narrative (Complete)
[redacted]	This case was received via Takeda Pharmaceuticals (Reference number [redacted] on 20-Oct-2021 and was forwarded to Moderna on 28-Oct-2021. This case, initially reported to the [redacted] by a (physician), was received via the [redacted] (Ref, [redacted]. Anaphylaxis was assessed as serious by the MAH. The patient visited a hospital regularly for allergy. On an unknown date, body temperature before the vaccination: 36.3 degrees Celsius. On 16-Oct-2021, around 09:30, the patient received this vaccine (unknown number of doses). At 10:00, anaphylaxis developed. About 30 minutes after the vaccination, skin rash gradually developed. Vital signs showed stable respiratory symptoms. Redness and wheals spread from the limbs to the trunk. The symptoms tended to improve by administration of d-chlorpheniramine maleate, but skin rash increased. Hydrocortisone sodium succinate was administered. The patient was instructed to visit a medical institution. Afterwards, the symptoms were resolving. The outcome of anaphylaxis was reported as resolving. Follow-up investigation will be made. Company Comment: The event developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.

Case ID	Narrative (Complete)
[redacted]	This case was initially received via Takeda Pharmaceuticals (Reference number: [redacted]) on 23-Oct-2021. The most recent information was received on 10-Feb-2022 and was forwarded to Moderna on 16-Feb-2022. This case, initially reported to the [redacted] by a physician, was received via the [redacted] (Ref, [redacted]. On 10-Feb-2022, follow-up information was received from a physician. On 16-Oct-2021, at 09:43, the patient received the 1st dose of this vaccine. At 10:00, several tens of minutes after vaccination, anaphylactic shock developed. The patient had urticaria in the neck, both upper limbs, abdomen, and back, and dyspnoea and tachypnea were noted. Body temperature was 36.6 degrees Celsius, and temporary hypotension of 90/- was noted. The patient was considered to have anaphylaxis and visited the emergency outpatient department of the reporting hospital. The patient was admitted to the hospital after treatments including intramuscular injection of adrenaline, intravenous injection of methylprednisolone sodium succinate, oral administration of fexofenadine hydrochloride, and intravenous injection of d-chlorpheniramine maleate and famotidine. At 13:00, chest X-ray was performed to show no abnormalities. On 17-Oct-2021, at 09:32, the symptoms disappeared. Resolution of the symptoms was recognized, and the patient was discharged from the hospital. The outcome of anaphylactic shock was reported as recovered. No follow-up investigation will be made. Follow-up received on 10-FEB-2022 Updated: Patient Information, Other Relevant History, Lab Data, Product Information, Event Information, Narrative, Reporter Comments Company Comment: The event developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.. Company comment: This regulatory case concerns a 16-year-old, female patient with relevant medical history of allergy to food, pets and dust, who experienced serious unexpected event of Anaphylactic shock few minutes after receiving first dose of mRNA-1273 Vaccine. Within few minutes after vaccination patient had urticaria in the neck, both upper limbs, abdomen, back, dyspnoea and tachypnea. Body temperature was 36.6 degrees Celsius and temporary hypotension. The patient was treated with intramuscular injection of adrenaline, intravenous injection of methylprednisolone sodium succinate, oral administration of fexofenadine hydrochloride, and intravenous injection of d-chlorpheniramine maleate and famotidine. History of various allergies could be confounder to the event. At the time of reporting, the event had recovered. The benefit-risk relationship of mRNA-1273 is not affected by this report. Event seriousness assessed as per Regulatory Authority reporting.
	This case was initially received via Takeda Pharmaceuticals (Reference number [redacted] on 26-Oct-2021. The most recent information was received on 10-Feb-2022 and was forwarded to Moderna on 17-Feb-2022. This case, initially reported to the [redacted] by a physician, was received via the [redacted] (Ref, [redacted] On 10-Feb-2022, follow-up information was received from a physician. On 25-Sep-2021, at 13:58, the patient received the 1st dose of this vaccine. Mild pruritus developed. On 23-Oct-2021, at 14:58, the patient received the 2nd dose of this vaccine. At 15:12, anaphylactic reaction developed. The patient had redness of the chest and limbs, localized pruritus and urticaria, ocular hyperaemia and pruritus, abdominal pain, and vomiting. The patient moved to an emergency outpatient department. At 15:30, the patient was diagnosed with anaphylaxis in the examination by a physician of the emergency outpatient department. Body temperature: 37.4 degrees Celsius, and blood pressure: 122/87. Administration of antihistaminic famotidine and d-chlorpheniramine maleate, and steroidal methylprednisolone sodium succinate 125 mg was performed. The patient was admitted to the pediatrics department in the reporting hospital for follow-up with improvement in the symptoms. Oral administration of fexofenadine hydrochloride was started. On 24-Oct-2021, although dizziness developed, pruritus improved. The symptoms resolved after 24 hours of follow-up, and the patient was discharged to home. Outpatient follow-up was made. On 26-Oct-2021, the patient returned to the hospital for persistent urticaria. Prescription of fexofenadine hydrochloride for two weeks was continued. On 28-Oct-2021, the patient returned to the hospital again, and the examination was completed. The outcome of skin eruption and pruritus was unknown. The outcome of anaphylaxis was reported as resolved. No follow-up investigation will be made. Follow-up received on 10-FEB-2022 Updated: Patient Information, Other Relevant History, Lab Data, Product Information, Event Information, Narrative, Reporter Comments Company Comment: The events developed after the administration of COVID-19 vaccine mRNA (mRNA 1273) and there is temporal relationship.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by a consumer and describes the occurrence of CIRCULATORY COLLAPSE (Circulatory collapse) in a 14-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna) (batch no. 3004215) for COVID-19 vaccination. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On 19-Aug-2021, the patient received first dose of mRNA-1273 (COVID-19 Vaccine Moderna) (unknown route) 1 dosage form. On 16-Sep-2021, received second dose of mRNA-1273 (COVID-19 Vaccine Moderna) (unknown route) dosage was changed to 1 dosage form. On 17-Sep-2021, the patient experienced CIRCULATORY COLLAPSE (Circulatory collapse) (seriousness criterion medically significant), DIZZINESS (Dizziness), VOMITING (Vomiting) and PYREXIA (Fever). On 18-Sep-2021, CIRCULATORY COLLAPSE (Circulatory collapse), DIZZINESS (Dizziness), VOMITING (Vomiting) and PYREXIA (Fever) was resolving. Concomitant medication were not provided. Treatment medication were not reported. Company comment: This case concerns a 14-year-old, female patient with no relevant medical historyreported, who experienced the unexpected event of CIRCULATORY COLLAPSE. The event occurred the following day of the second dose of Moderna COVID-19 vaccine. The rechallenge was not applicable as no information about additional dosing was disclosed. The benefit-risk relationship of Moderna COVID-19 vaccine is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by an other health care professional and describes the occurrence of DYSPNOEA (SHORTNESS OF BREATH), PRURITUS (Itching), ANAPHYLACTIC REACTION (Anaphylaxis), MYALGIA (Muscle pain) and FATIGUE (Fatigue) in a 17-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna) for an unknown indication. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On 13-Dec-2021, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) 1 dosage form. On 13-Dec-2021, the patient experienced PRURITUS (Itching). On 13-Dec-2021 at 6:00 PM, the patient experienced ANAPHYLACTIC REACTION (Anaphylaxis). On 14-Dec-2021, the patient experienced MYALGIA (Muscle pain), FATIGUE (Fatigue) and FATIGUE (Tiredness). On 14-Dec-2021 at 8:00 AM, the patient experienced PYREXIA (Fever). On 22-Dec-2021, the patient experienced DYSPNOEA (SHORTNESS OF BREATH). At the time of the report, DYSPNOEA (SHORTNESS OF BREATH), PRURITUS (Itching), ANAPHYLACTIC REACTION (Anaphylaxis), MYALGIA (Muscle pain), FATIGUE (Fatigue) and FATIGUE (Tiredness) had not resolved and PYREXIA (Fever) was resolving. The action taken with mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) was unknown. For mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular), the reporter did not provide any causality assessments. No concomitant medication was provided by reporter. 12/13/21 night started to had hives all over the body and itcheness 12/14/21 morning - had fever for 3 days until now patient still experience hives, itchiness all over the body and develop to wounds, body ache, body malaise, easy fatigability and shorthness of breath. According to her mother she give amoxicillin and ceterizine but symptoms not relieved. Also, according to her she reported to her [redacted] and was give prescription however un able to buy it (not available in their area) immediately she advised her mother to bring her to [redacted] infirmary for immediate consult since she is having shortness of breath. Contacted [redacted] to follow up with the patient, and she coordinated with infirmary physician This is a regulatory authority case concerning a 17-year-old, female patient with no relevant medical history, who experienced the unexpexted non-serious events of Dyspnoea, Pruritus and Expected Non-serious events of Anaphylactic reaction, Myalgia, Fatigue, Fatigue, Pyrexia. The events occurred approximately on the same day after the unknown dose of mRNA-1273 COVID 19 Vaccine. The rechallenge was not applicable, as information about further dosing was not disclosed. The events were reported as resolving. The benefit-risk relationship of mRNA-1273 COVID 19 Vaccine, is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by an other health care professional and describes the occurrence of ANAPHYLACTIC SHOCK (Anaphylactic shock), DIZZINESS (Dizziness), DIZZINESS (Light headedness) and NAUSEA (Nausea) in a 17-year-old male patient who received mRNA-1273 (COVID-19 Vaccine Moderna) (batch no. 012F21A) for an unknown indication. No Medical History information was reported. On 20-Dec-2021, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) 1 dosage form. On 20-Dec-2021, the patient experienced ANAPHYLACTIC SHOCK (Anaphylactic shock) (seriousness criterion hospitalization), DIZZINESS (Dizziness) (seriousness criterion hospitalization), DIZZINESS (Light headedness) (seriousness criterion hospitalization) and NAUSEA (Nausea) (seriousness criterion hospitalization). At the time of the report, ANAPHYLACTIC SHOCK (Anaphylactic shock), DIZZINESS (Dizziness), DIZZINESS (Light headedness) and NAUSEA (Nausea) was resolving. The action taken with mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) was unknown. For mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular), the reporter did not provide any causality assessments. Treatment information was not provided. List of concomitant medication were not given This is a regulatory authority case concerning a 17-year-old, male patient with no relevant medical history, who experienced the unexpected serious events of Anaphylactic shock, Dizziness, Dizziness, Nausea. The events occurred approximately on the same day after the unknown dose of mRNA-1273 COVID 19 Vaccine. The rechallenge was not applicable, as information about further dosing was not disclosed. The events were reported as resolving. The benefit-risk relationship of mRNA-1273 COVID 19 Vaccine, is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by an other health care professional and describes the occurrence of ANAPHYLACTIC REACTION (Anaphylaxis (FEVER, ITCHING, NAUSEA, RASH ALL OVER THE BODY, VOMITING, DOB,)), PYREXIA (Fever ≥38°C), VOMITING (Vomiting), PRURITUS (Itching) and NAUSEA (Nausea) in a 14-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna) for an unknown indication. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On an unknown date, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (unknown route) 1 dosage form. On 15-Feb-2022 at 10:00 PM, the patient experienced ANAPHYLACTIC REACTION (Anaphylaxis (FEVER, ITCHING, NAUSEA, RASH ALL OVER THE BODY, VOMITING, DOB,)), PYREXIA (Fever ≥38°C), VOMITING (Vomiting), PRURITUS (Itching), NAUSEA (Nausea) and RASH (Skin rash). At the time of the report, ANAPHYLACTIC REACTION (Anaphylaxis (FEVER, ITCHING, NAUSEA, RASH ALL OVER THE BODY, VOMITING, DOB,)), PYREXIA (Fever ≥38°C), VOMITING (Vomiting), PRURITUS (Itching), NAUSEA (Nausea) and RASH (Skin rash) was resolving. The action taken with mRNA-1273 (COVID-19 Vaccine Moderna) (Unknown) was unknown. For mRNA-1273 (COVID-19 Vaccine Moderna) (Unknown), the reporter did not provide any causality assessments. No concomitant medications reported. No treatment medications provided.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by an other health care professional and describes the occurrence of ANAPHYLACTIC REACTION (Anaphylaxis) in a 15-year-old female patient who received mRNA-1273 (Spikevax) (batch no. 022D21A) for an unknown indication. No Medical History information was reported. On 01-Oct-2021, the patient received first dose of mRNA-1273 (Spikevax) (unknown route) 1 dosage form. On 01-Oct-2021, the patient experienced ANAPHYLACTIC REACTION (Anaphylaxis) (seriousness criterion medically significant). At the time of the report, ANAPHYLACTIC REACTION (Anaphylaxis) had resolved. DIAGNOSTIC RESULTS (normal ranges are provided in parenthesis if available): On an unknown date, SARS-CoV-2 test: negative (Negative) No. The action taken with mRNA-1273 (Spikevax) (Unknown) was unknown. For mRNA-1273 (Spikevax) (Unknown), the reporter did not provide any causality assessments. The dose number of suspect product was reported as 1st dose. Patient did not receive any other vaccine. Relevant concomitant product usage were not reported by the reporter. Patient had no swelling, pain, erythema, induration, ulceration, abscess, other, crying incoercible, irritability, confusion, seizures, headache, hypotonia, rash, syncope vasovagal, fever, invagineumoniaion intestinal or diarrhea. No treatment details were added. Company comment: This regulatory authority case concerns a 15-year-old female patient, with no medical history reported, who experienced the expected event of anaphylactic reaction, which was considered as medically significant. The event occurred on the same day after the first dose of mRNA-1273. No detailed information regarding symptoms, diagnostic findings or course of event was provided. The rechallenge was unknown since events occurred after first dose and no information about the second dose was disclosed. The benefit-risk relationship of mRNA-1273 is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This regulatory authority case was reported by an other health care professional and describes the occurrence of VACCINATION COMPLICATION (OTHER SYMPTOMS) and ANAPHYLACTIC REACTION (Anaphylaxis) in a 16-year-old female patient who received mRNA-1273 (Spikevax) (batch no. 940885) for an unknown indication. No Medical History information was reported. On 12-Jan-2022, the patient received first dose of mRNA-1273 (Spikevax) (unknown route) 1 dosage form. On 12-Jan-2022, the patient experienced VACCINATION COMPLICATION (OTHER SYMPTOMS) (seriousness criteria hospitalization and life threatening) and ANAPHYLACTIC REACTION (Anaphylaxis) (seriousness criteria hospitalization and life threatening). At the time of the report, VACCINATION COMPLICATION (OTHER SYMPTOMS) and ANAPHYLACTIC REACTION (Anaphylaxis) had not resolved. DIAGNOSTIC RESULTS (normal ranges are provided in parenthesis if available): On an unknown date, SARS-CoV-2 test: negative (Negative) Negative. The action taken with mRNA-1273 (Spikevax) (Unknown) was unknown. For mRNA-1273 (Spikevax) (Unknown), the reporter did not provide any causality assessments. Concomitant medication list was not provided. Treatment information was not provided. The patient does not received dose previously and other vaccine. This is a regulatory case concerning a 16-year-old female patient with no medical history reported, who experienced the unexpected events of vaccination complication and anaphylactic reaction. The events occurred on the same day after the first dose of mRNA – 1273 vaccine. Both the events were reported as life threatening and causing hospitalization and at the time of report both have not resolved. The reporter's assessment was not provided. The benefit-risk relationship of the vaccine is not affected by this report.

Case ID	Narrative (Complete)
[redacted]	This case was received via an unknown source (no reference has been entered for a health authority or license partner) on 15-Mar-2022 and was forwarded to Moderna on 17-Mar-2022. This regulatory authority case was reported by an other health care professional and describes the occurrence of SWELLING (Swelling), PAIN (Pain), RASH (Rash) and ANAPHYLACTIC REACTION (Anaphylaxis) in a 15-year-old male patient who received mRNA-1273 (Spikevax) (batch no. O24D217) for an unknown indication. No Medical History information was reported. On 12-Oct-2021, the patient received first dose of mRNA-1273 (Spikevax) (unknown route) 1 dosage form. On 02-Nov-2021, the patient experienced SWELLING (Swelling) (seriousness criterion medically significant), PAIN (Pain) (seriousness criterion medically significant), RASH (Rash) (seriousness criterion medically significant) and ANAPHYLACTIC REACTION (Anaphylaxis) (seriousness criterion medically significant). At the time of the report, SWELLING (Swelling), PAIN (Pain), RASH (Rash) and ANAPHYLACTIC REACTION (Anaphylaxis) had resolved. The action taken with mRNA-1273 (Spikevax) (Unknown) was unknown. For mRNA-1273 (Spikevax) (Unknown), the reporter did not provide any causality assessments. Diagnosis was Anaphylaxis. No concomitant medications reported. No treatment information reported. This is a regulatory case concerning a 15-year-old male patient with no medical history reported, who experienced the unexpected events of swelling, pain, rash, and anaphylactic reaction. The events occurred approximately 21 days after the first dose of mRNA – 1273 vaccine. All the events were reported as medically significant but at the time of report all have resolved. The reporter's assessment was not provided. The benefit-risk relationship of the vaccine is not affected by this report.

Appendix 11.4c Anaphylaxis: Literature Search Methodology

((((((((((((anaphylaxis) OR (Anaphylactic reaction)) OR (Anaphylactic shock)) OR (Anaphylactoid reaction)) OR (Type I hypersensitivity)) OR (Anaphylactoid shock)) OR (anaphylaxis[MeSH Terms])) OR (Anaphylactic reaction[MeSH Terms])) OR (Anaphylactic shock[MeSH Terms])) OR (Anaphylactoid reaction[MeSH Terms])) OR (Type I hypersensitivity[MeSH Terms])) OR (Anaphylactoid shock[MeSH Terms])) AND (("mrna vaccines"[MeSH Terms] OR "2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] AND "vaccine"[All Fields] AND "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mRNA 1273"[All Fields] OR "mRNA 1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] AND "vaccine"[All Fields] AND "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mrna1273"[All Fields]) OR ("modernatx"[All Fields] AND "1273"[All Fields]) OR "1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] AND "vaccine"[All Fields] AND "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "m 1273"[All Fields]) OR "m 1273"[All Fields] OR ("moderna"[All Fields] AND ("covid 19 vaccines"[MeSH Terms] OR ("covid 19"[All Fields] AND "vaccines"[All Fields]) OR "covid 19 vaccines"[All Fields] OR ("covid19"[All Fields] AND "vaccine"[All Fields]) OR "covid19 vaccine"[All Fields])) OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "SPIKEVAX"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] AND "vaccine"[All Fields] AND "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "elasomeran"[All Fields]) OR "CX-024414"[All Fields] OR "tak 919"[All Fields] OR "tak 919"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] AND "vaccine"[All Fields] AND "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields])))))) AND (("2020/12/18"[Date - Publication] : "2022/06/18"[Date - Publication])).