Neurological and other Adverse events in Clinical Trials.

Links to FDA documents:

https://www.fda.gov/media/144416/download

https://www.fda.gov/media/144673/download

https://www.fda.gov/media/146338/download

Pfizer Evaluation of Booster Dose (3rd dose):

https://www.fda.gov/media/152161/download

Links to EMA documents:

https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf

https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf

https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-janssen-epar-public-assessment-report_en.pdf

Each of the available vaccines had neurological adverse events in clinical trial.

Pfizer showed 1158 cases of"Nervous System Disorders", 6.2% of trial participants. Pfizer and Moderna had cases of Bells Palsy in the clinical trials and have since had post-marketing reports of the same.

Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum

System Organ Class Preferred Term	BNT162b2 N=18801 n (%)	Placebo N=18785 n (%)	Total N=37586 n (%)
Nervous system disorders	1158 (6.2)	460 (2.4)	1618 (4.3)
Headache	973 (5.2)	304 (1.6)	1277 (3.4)
Gastrointestinal disorders	565 (3.0)	368 (2.0)	933 (2.5)
Diarrhoea	194 (1.0)	149 (0.8)	343 (0.9)
Nausea	216 (1.1)	63 (0.3)	279 (0.7)

Source: FDA analysis.
Adverse events in any PT = at least one adverse event experienced (regardless of the MedDRA Preferred Term)
%: n/N. n = number of participants reporting at least 1 occurrence of the specified event.
of any event. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
Data analysis cutoff date: November 14, 2020.

Subgroup analyses by age

16 and 17 years of age: the table below represents an FDA-generated summary of unsolicited AEs consistent with reactogenicity and AEs that occurred at >1% and higher in the BNT162b2

Moderna had 1215 “medically-attended Adverse Events” with 91 participants being discontinued from the trial due to the AE. 23.9% of the trial participants reported an “unsolicited AE”

Moderna COVID-19 Vaccine
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Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Moderna had 651 reports of nervous system disorders.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0

Johnson and Johnson had a case of Gillan Barre Syndrome in the vaccine arm, 6 reports of Tinnitus, with none in placebo arm.

Reports of bells palsy and other facial paralysis as well as autonomic disfunction, myo and peri-carditis and urticaria were also noted in the vaccine arm.

The SMQ for "hearing and vestibular disorders" included the PT "tinnitus" for which was a numerical imbalance was observed across treatment groups. Tinnitus was reported in 6 vaccine recipients (6 events) compared to no placebo recipients. Events of tinnitus are summarized in the table below.

Table 30. Tinnitus in Vaccine Recipients, Full Analysis Set, Study 3001

Investigational Product	Age/Sex	Day of Onset	Resolution Status	Grade/ SAE[a]	Possible Risk Factor(s)	Related[a]
Ad26.COV2.S	58/M	1	Resolving	1/N	Hypertension	No
Ad26.COV2.S	63/F	1	Resolved	1/N	Hypothyroidism	Yes
Ad26.COV2.S	25/F	2	Resolved	1/N	Allergic rhinitis, medication use	Yes
Ad26.COV2.S	51/M	12	Unresolved	1/N	Hypertension, hypothyroidism, medication use	No
Ad26.COV2.S	54/M	17	Resolving	1/N	Allergic rhinitis	No
Ad26.COV2.S	65/F	22	Resolving	2/N	History of tinnitus	No

[a] Classification of events as SAEs and relatedness determined by study investigators

An additional event of tinnitus was reported in the clinical development of Ad26.COV2.S. The event, reported in Study 1002, occurred in 21-year-old male with no reported past medical history and no concomitant medications who experienced sudden hearing loss on Day 34 post-vaccination with Ad26.COV2.S. The hearing loss was associated with tinnitus and blocked ear sensation. Testing revealed sensorineural hearing loss. Workup for etiology including laboratory tests and imaging did not reveal an etiology. Hearing improved and the event was resolved by Day 69. The event was not considered related to the study product by the investigator or the Sponsor.

were assessed by the investigator as related to study vaccination (Table 31). Of the 7 SAEs in the vaccine group, the Sponsor assessed 3 as related/likely related, 2 as possibly related, 2 as unrelated to the vaccine.

Table 31. SAEs Considered Related by Investigator, Full Analysis Set, Study 3001

Investigational Product	SAE (PT)	Age/Sex	Day of Onset	Resolution Status	Grade	Related (Sponsor Assessment)
Ad26.COV2.S	Radiculitis brachial	30/M	1	Unresolved	3	Yes (Reassessed as injection site pain)
Ad26.COV2.S	Post-vaccination syndrome	35/M	2	Resolved	3	Yes (Reassessed as reactogenicity)
Ad26.COV2.S	Facial paralysis	62/M	3	Resolving	2	No
Ad26.COV2.S	Vaccination site hypersensitivity	42/M	3	Resolved	3	Likely
Ad26.COV2.S	Facial paralysis	43/M	16	Resolving	2	No
Ad26.COV2.S	Guillain-Barre Syndrome	60/F	16	Unresolved	4	Possibly
Ad26.COV2.S	Pericarditis	68/M	17	Resolved	4	Possibly
Placebo	Deep vein thrombosis	44/M	6	Resolving	4	Indeterminate
Placebo	Epstein-Barr infection[a]	69/M	14	Resolved	3	No
Placebo	Atrial flutter[a]	69/M	21	Resolving	3	No

[a] Events occurred the same study participant

In FDA's opinion following review of narratives, the following 3 SAEs in the vaccine group are considered likely related to the study vaccine:

In FDA's opinion following review of narratives, the following 3 SAEs in the vaccine group are considered likely related to the study vaccine:

- A 42-year-old male with no personal or family history of allergic reactions experienced diffuse urticaria beginning on Day 3 following vaccination accompanied with systemic symptoms of fatigue, myalgia and arthralgia. Over the following two days the urticaria progressed, and the participant experienced angioedema of the lips as well as the sensation of itchy and tight throat, but no hypoxia or respiratory distress. The event did not meet Brighton Criteria for anaphylaxis. FDA's assessment is that this event was likely a hypersensitivity reaction to the study vaccine.

- A 30-year-old male was reported to have "brachial neuritis following vaccination" (PT: "radiculitis brachial") with pain at the site of vaccine administration on Day 1 which persisted and worsened over several days and was unresponsive to non-prescription analgesics. Evaluation included electroconductive studies, which revealed intact nerves with no denervation of the evaluated muscles, and MRI of the cervical spine, which did not reveal an etiology of the participant's symptoms. FDA's assessment of this event is that the pain at injection site is likely related to the vaccine, however the diagnosis of brachial neuritis is unlikely given the findings on electroconductive studies.

- A 35-year-old male experienced generalized malaise, weakness, myalgia, shortness of breath, headache, sensation of numbness and tingling in upper extremities, chest pain and fever beginning on Day 2 following vaccination. The participant was hospitalized for exacerbated generalized weakness. Abnormal vital signs included fever (39.4°C), blood pressure (129/103 mmHg), heart rate (112bpm) and respiratory rate (19 breaths per minute). There was no hypoxia. On exam he complained of diffuse tenderness in the extremities. No abnormalities were noted on neurologic exam which included normal reflexes. Abnormal laboratory findings included a mild elevation of creatine kinase attributed to mild myositis. Laboratory testing was negative for COVID-19, influenza and RSV. Symptoms resolved by Day 4. FDA's assessment of this event is that it is likely systemic reactogenicity related to the study vaccine.

For the SAE of pericarditis, as no alternative etiology was determined, FDA's assessment is that the possibility that the vaccine contributed to the event cannot be excluded. Review of Janssen's safety database including all Ad26-based vaccines did not reveal any additional reports of pericarditis.

the treatment groups.

Table 28. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants Within 28 Days Following Vaccination, by MedDRA Primary System Organ Class and Preferred Term, Safety Subset[a], Study 3001

System Organ Class Preferred Term	Ad26.COV2.S N=3356 Any Grade n (%)	Ad26.COV2.S N=3356 ≥Grade 3 n (%)	Placebo N=3380 Any Grade n (%)	Placebo N=3380 ≥Grade 3 n (%)
General disorders and administration site	211 (6.3%)	5 (0.1%)	134 (4.0%)	2 (0.1%)
Chills	67 (2.0%)	1 (<0.1%)	19 (0.6%)	0
Fatigue	64 (1.9%)	1 (<0.1%)	77 (2.3%)	1 (<0.1%)
Vaccination site pain	42 (1.3%)	1 (<0.1%)	22 (0.7%)	0
Musculoskeletal and connective tissue disorders	103 (3.1%)	3 (0.1%)	89 (2.6%)	4 (0.1%)
Myalgia	49 (1.5%)	0	58 (1.7%)	2 (0.1%)
Arthralgia	35 (1.0%)	1 (<0.1%)	24 (0.7%)	2 (0.1%)
Nervous system disorders	98 (2.9%)	3 (0.1%)	108 (3.2%)	5 (0.1%)
Headache	72 (2.1%)	1 (<0.1%)	82 (2.4%)	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	93 (2.8%)	3 (0.1%)	88 (2.6%)	4 (0.1%)
Nasal congestion	40 (1.2%)	1 (<0.1%)	38 (1.1%)	2 (0.1%)
Cough	33 (1.0%)	1 (<0.1%)	33 (1.0%)	0

AstraZeneca. Data reported to the European Medicines Agency shows Serious Neurological adverse events reported during clinical trials. 0.6% of participants were discontinued from the study due to adverse events. Cases of Transverse Myelitis, Multiple Sclerosis, Acute Demyelinating Encephalomyelitis (ADEM), Chronic Inflammatory Demyelinating Polyradiculopathy and Peripheral sensory neuropathy were also reported. Many other Neurological System Disorders were also reported.

Three AESIs in total were reported as SAEs: transverse myelitis, myelitis and multiple sclerosis. In both the AZD1222 and the control groups, other SAEs reported in the Nervous System Disorders SOC were: Facial spasm, Migraine, Ischaemic stroke, Presyncope, syncope, Serotonin syndrome, subarachnoid haemorrhage and transient ischaemic attack). The SAEs ischaemic stroke, migraine, subarachnoid haemorrhage, transient ischaemic attack, syncope and presyncope may have cardiovascular aetiology. , After reviewing the narratives of the SAEs in this SOC and given the proximity in time to vaccination, it is considered that only two SAEs (Facial spasm and migraine) may be potentially related to study treatment.

The SAE of Multiple sclerosis was considered unrelated to study treatment according to the neurologist assessment, as the MRI showed new and pre-existent brain lesions. Therefore .it was considered that the biological process leading up to the symptoms preceded study treatment administration.

In addition, in the ongoing US phase 3 clinical trial D8110C00001, which is not included in the CMA, two SAEs one of Peripheral Sensory neuropathy and one event of Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) have been reported.

The incidence of CIDP has been estimated to around 0.33 per 100,000 person-year (Broers et al, Neuroepidemiology 2019;52:161–172). Based on the narrative it is not possible to exclude causality with study intervention nor to confirm it. The Investigator considered the SAE to be related to study intervention.

Regarding the event of Peripheral Sensory Neuropathy, relatedness is unclear.

Further, there was a case of acute encephalopathy in the COVISHIELD study (study not included in the current application for CMA) which is suspected to be a nutritional encephalopathy, however an autoimmune aetiology has not been ruled out.

A single case of a non-serious event of anaphylactic reaction was reported, which is considered not related to study treatment. At least one additional case of a potential hypersensitivity reaction has been noted in the safety database, a subject who experienced erythema multiforme, tongue swelling and urticaria popular, whose relatedness is doubtful. Relevantly, subjects with a history of allergic reactions (angioedema, anaphylaxis or allergic disease or reactions that could possibly be exacerbated by any component of

paracetamol use than in those who did not report prophylactic paracetamol use. The interpretation of this data warrants caution, and the higher rates of solicited reactogenicity in those receiving paracetamol prophylaxis suggests that paracetamol was taken in response to symptoms and that truly prophylactic use was rare.

Prophylactic paracetamol use was not captured in the participant diary for study COV005.

2.6.9. Discontinuation due to adverse events

From the Any dose for safety analysis set, 133 (0.6%) participants discontinued early from the study. The reason for discontinuing was Adverse event in one participant (<0.1%) in control group and non-related deaths in 5 participants (<0.1%) in both groups. Other reasons were: Exclusion criteria met, lost to follow-up, withdrawal by the subject and other causes.

No information has been presented on the number of subjects that did not receive a second dose due to an Adverse Event following the first dose. Whilst there are several indications in individual narratives that this may have been the case, it appears this information has not been collected systematically.

2.6.10. Post marketing experience

There are no post-marketing data as the vaccine. AZD1222 vaccine has only recently been granted emergency approval in several countries (e.g., UK).

2.6.11. Discussion on clinical safety

Exposure

The assessment of AZD1222 safety is based on the interim analysis of the results from all studies pooled in the total Safety analysis Set, comprising 23,745 participants (12,021 subjects: any dose of AZD1222, 11,724: control vaccine or placebo) from four individual studies, COV001, COV002, COV003 and COV005.

interpretation of an effect due to the dose interval should be undertaken with caution.

The most frequently reported solicited local AEs in AZD1222 group were tenderness, followed by pain. The most frequently reported solicited systemic AEs in AZD1222 group were fatigue and headache, followed by muscle pain, malaise, feverishness, chills, joint pain and nausea.

Unsolicited Adverse events: Any unsolicited AEs were reported more frequently in AZD1222 group than in control treatment and generally reflected reactions to vaccination such as vaccination site pain, headache, pyrexia and myalgia. A majority of events was mild to moderate in severity, showing a reduction of the percentages (related or not) after the second dose in both the study vaccine and the comparator. The most frequently reported unsolicited AEs predominantly occurred within ≤7 days of any dose. There were no unsolicited AEs reported by preferred term in more than 2% of subjects within 8-28 days after any dose either AZD1222 or control grou

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A noticeable imbalance in the frequency of unsolicited AEs in the Nervous System Disorder class between the AZD1222 and the control group is observed in the pooled results for the any dose safety analysis set. Further, the imbalance is also present in the reported unsolicited AEs related to the ADZ1222 vaccine.

There were 3 cases of facial paralysis in the AZD1222 group and 3 in the control group. For one of the cases in the AZD1222 group, causality to the vaccine could not be excluded. There was no imbalance between the study groups in the occurrence of Bell's palsy. No risk is identified as only a single case occurred for which

and transient ischaemic attack). The SAEs ischaemic stroke, migraine, subarachnoid haemorrhage, transient ischaemic attack, syncope and presyncope may have cardiovascular aetiology. , After reviewing the narratives of the SAEs in this SOC and given the proximity in time to vaccination, it is considered that only two SAEs (Facial spasm and migraine) may be potentially related to study treatment.

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A single case of a non-serious event of anaphylactic reaction was reported, which is considered not related to study treatment. At least one additional case of a potential hypersensitivity reaction has been noted in the safety database, a subject who experienced erythema multiforme, tongue swelling and urticaria popular, whose relatedness is doubtful. Relevantly, subjects with a history of allergic reactions (angioedema, anaphylaxis or allergic disease or reactions that could possibly be exacerbated by any component of AZD1222, MenACWY or paracetamol) were excluded from participation in the studies. Therefore, it may be that more immunologic reactions will be observed if the vaccine is used in the general public.

The neurological events prompted the EMA to include a note about special concerns to watch for as the vaccine was rolled out.

2.7. Risk Management Plan

2.7.1. Safety concerns

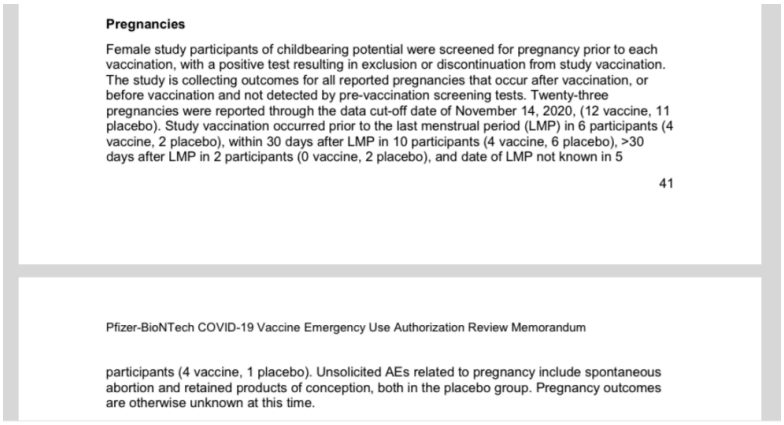
The applicant has submitted an RMP including the following summary of safety concerns:

Table 36: Summary of safety concerns

Important identified risks	None
Important potential risks	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis

Each of the vaccines showed adverse reactions in the clinical trials, reactions that are now being seen in the general population as the vaccine roll-out continues.

Each clinical trial excluded those that were pregnant or excluded those that became pregnant during the trial. Pfizer example verbiage:



Pregnancies

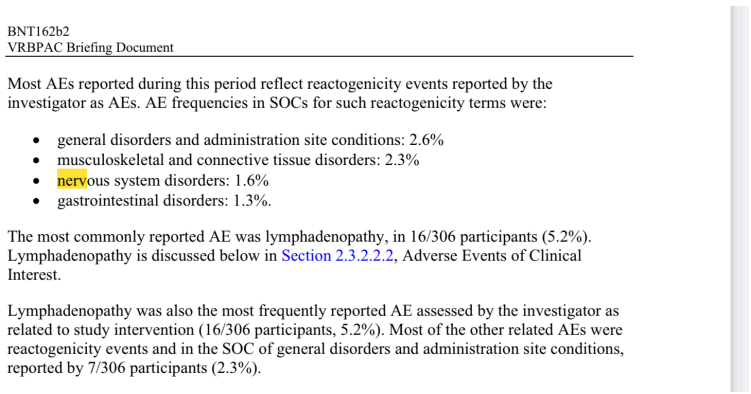
Female study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests. Twenty-three pregnancies were reported through the data cut-off date of November 14, 2020, (12 vaccine, 11 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 6 participants (4 vaccine, 2 placebo), within 30 days after LMP in 10 participants (4 vaccine, 6 placebo), >30 days after LMP in 2 participants (0 vaccine, 2 placebo), and date of LMP not known in 5

41

Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum

participants (4 vaccine, 1 placebo). Unsolicited AEs related to pregnancy include spontaneous abortion and retained products of conception, both in the placebo group. Pregnancy outcomes are otherwise unknown at this time.

Pfizer Clinical Trial Pfizer Booster Dose:



BNT162b2
VRBPAC Briefing Document

Most AEs reported during this period reflect reactogenicity events reported by the investigator as AEs. AE frequencies in SOCs for such reactogenicity terms were:

- general disorders and administration site conditions: 2.6%
- musculoskeletal and connective tissue disorders: 2.3%
- nervous system disorders: 1.6%
- gastrointestinal disorders: 1.3%.

The most commonly reported AE was lymphadenopathy, in 16/306 participants (5.2%). Lymphadenopathy is discussed below in Section 2.3.2.2.2, Adverse Events of Clinical Interest.

Lymphadenopathy was also the most frequently reported AE assessed by the investigator as related to study intervention (16/306 participants, 5.2%). Most of the other related AEs were reactogenicity events and in the SOC of general disorders and administration site conditions, reported by 7/306 participants (2.3%).

Unexplained “nervous system disorders” continue to be reported at rates exceeding 1/100 doses, no further information on symptoms or severity is provided by sponsors.

One notable difference for this Phase 3 booster adult population was the higher frequency of lymphadenopathy after Dose 3 (5.2%) compared to the frequency of lymphadenopathy associated with the first two doses: 0.4% in individuals ≥16 years of age and 0.8% in adolescents 12 to 15 years of age.

Lymphadenopathy

In the Phase 3 booster safety population, 16/306 participants (5.2%) had cases of lymphadenopathy reported from Dose 3 to 1 month after Dose 3, of which all were considered by the investigator as related to study intervention. All cases of lymphadenopathy had an onset within 1 to 4 days after BNT162b2 booster (Dose 3) administration, and most were reported as recovered/resolved as of the data cutoff date, most within ≤5 days after onset. These cases predominantly occurred in female participants and were located in axillary nodes. Only 1 participant who had lymphadenopathy after receiving Dose 3 had also previously experienced lymphadenopathy during the blinded placebo-controlled period (with onset on the fourth day after Dose 2). No participants in the booster safety population reported a past medical history of lymphadenopathy at baseline (before Dose 1).

All lymphadenopathy cases occurring after Dose 3 were Grade 1, with one exception. One case of lymphadenopathy was graded as severe and judged by the investigator as related to study intervention: left axillary lymphadenopathy was reported in a participant in their early 40s, with onset at 2 days post-Dose 3, lasting for 5 days, and reported as recovered/resolved. The investigator-judged severity was based on the participant reporting that the lymphadenopathy prevented use of the affected arm.

Lymphadenopathy has been identified as an adverse reaction causally associated with the vaccine and is thought to be related to the development of the immune response to the vaccine. As Dose 3 is a booster, it is not surprising that stimulation of a lymph node reaction by vaccination would be present in the setting of a significant increase in neutralizing antibodies observed after Dose 3. While related to vaccination, this ADR is generally mild and self-limited and is unlikely to impede a booster vaccination program.

Significant increase in lymphadenopathy (13 fold increase) across all ages with the increase rising to ~17 fold in younger groups