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

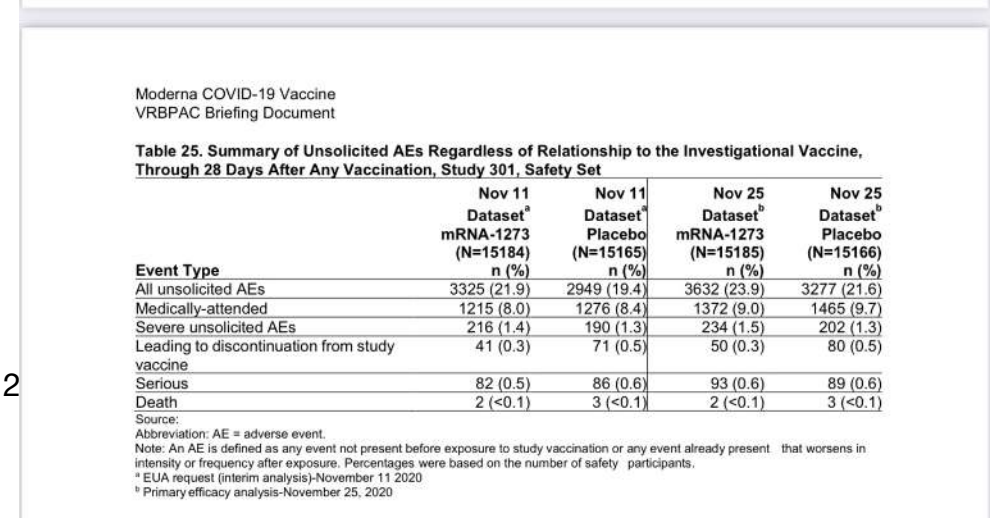
https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf

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.

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.

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.

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

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

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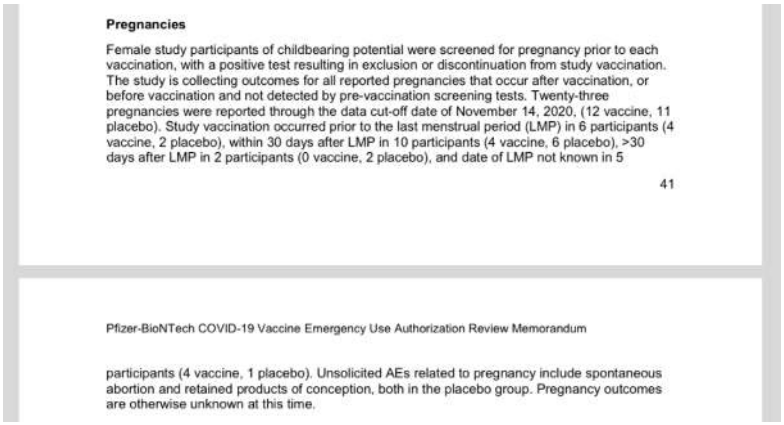
Each of the vaccines showed adverse reactions in the clinical trials, reactions that are now being seen in the general population as the vaccine roll-out continues.

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

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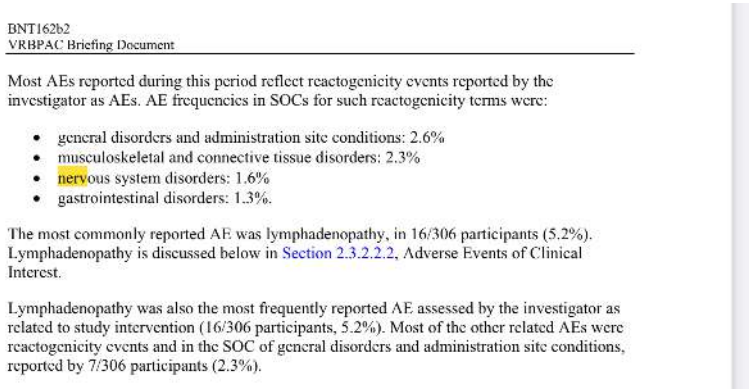
Pfizer-BioNTech COVID-19 Vaccine Emergency Use Authorization Review Memorandum

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
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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