20 APPENDICES TO THE PBRER

Appendix 1 Reference Safety Information

CCDS v13.0 dated 03 Jun 2022

Moderna COVID-19 Vaccine
COMPANY CORE DATA SHEET
CCDS0001/3 June 2022/Version 13.0

IMPORTANT NOTE: Grey highlight text is mandatory for all regional Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

SPIKEVAX
Pharmaceutical form: 0.20 mg/mL dispersion for injection
INN: elasomeran
Common name assigned by EU: COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) of the primary series contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

One dose (0.25 mL) of the booster contains 50 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 embedded in the SM-102 lipid nanoparticles [composed of the lipids, Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (SM-102)].

Moderna COVID-19 Vaccine does not contain any preservatives, antibiotics, adjuvants, or human- or animal-derived materials. The vial stopper does not contain natural rubber latex.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
White to off white dispersion (pH: 7.0 – 8.0).

Alternate description of pharmaceutical form is "Suspension for injection". The pharmaceutical form on the prescribing information should align with the description on the carton.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Moderna COVID-19 Vaccine is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older.[1]

4.2 Posology and method of administration

Posology

Primary series
Individuals 12 years of age and older
Moderna COVID-19 Vaccine (100 micrograms, 0.5 mL) is a two-dose regimen.

Individuals 6 through 11 years of age
Moderna COVID-19 Vaccine is administered as a course of 2 (two) 50 microgram doses (0.25 mL each).[2]

The second dose should be administered one month after the first dose (see sections 4.4 and 5.1).

Immunocompromised individuals
A third dose of the Moderna COVID-19 Vaccine (0.5 mL) administered at least 28 days following the first two doses of this vaccine is authorised for administration to individuals at least 18 years of age who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Booster dose
Individuals 12 years of age and older
Moderna COVID-19 Vaccine is administered intramuscularly as a single dose (0.25 mL) at least 3 months after completing a primary series.[3] Local health authority recommendations for booster interval should be followed.

Interchangeability
Primary series
The interchangeability of Moderna COVID-19 Vaccine with other COVID-19 vaccines to complete the primary vaccination course has not been established.

Individuals who have received one dose of Moderna COVID-19 Vaccine (0.5 mL, 100 micrograms) should receive a second dose of Moderna COVID-19 Vaccine (0.5 mL, 100 micrograms) to complete the primary vaccination course.

Children aged 6 through 11 years who have received one dose of Moderna COVID-19 Vaccine (0.25 mL, 50 micrograms) should

receive a second dose of Moderna COVID-19 Vaccine (0.25 mL, 50 micrograms) to complete the primary vaccination course.

Booster dose in individuals 12 years of age and older
A single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered as a heterologous booster dose following completion of primary vaccination with another authorised or approved COVID-19 vaccine. The eligible population(s) and dosing interval for the

heterologous booster dose are the same as those authorised for a booster dose of the Moderna COVID-19 Vaccine.

Paediatric population
The safety and efficacy of Moderna COVID-19 Vaccine in children and adolescents less than 6 years of age have not yet been established. No data are available.

Elderly population
Clinical studies of Moderna COVID-19 Vaccine included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In the ongoing adult study of primary series dosing (0.5 mL), 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,399) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 86.4% (95% CI 61.4, 95.2) compared to 95.6% (95% CI 90.6, 97.9) in participants 18 to <65 years of age. Overall, there were no notable differences in the safety profiles observed in participants 65 years of age and older and younger participants.

In the ongoing clinical study of a single booster dose (0.25 mL), 22.2% (n=38) of participants were 65 years of age and older. This study did not include sufficient numbers of participants 65 years of age and older to determine whether they respond differently than younger participants. Some local and systemic adverse reactions were reported in a lower proportion of participants 65 years of age and older compared to participants 18 through 64 years of age.

Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications

Moderna COVID-19 Vaccine is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or to a previous dose of Moderna COVID-19 Vaccine. See excipients listed in 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported in individuals who have received the Moderna COVID-19 Vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation is recommended following vaccination as follows:

- 30 minutes:
  - People with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy.
  - People with a history of anaphylaxis due to any cause.
- 15 minutes:
  - All other persons.

A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Moderna COVID-19 Vaccine.

Myocarditis and pericarditis

There have been very rare reports of myocarditis and pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. The majority of the cases have been reported in young males, and shortly after the second primary dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Moderna COVID-19 Vaccine has not yet been characterised.

Altered immunocompetence

If Moderna COVID-19 Vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response to the vaccine may be diminished.

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), safety and effectiveness of a third dose of the Moderna COVID-19 Vaccine have been evaluated in participants who received solid organ transplants. The administration of a third vaccine dose (0.5 mL) appears to be only moderately effective in increasing antibody titers. Patients should be counselled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated as appropriate for their health status.

Persons at risk of bleeding

As with other intramuscular injections, Moderna COVID-19 Vaccine 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.

Acute illness

Consideration should be given to postponing immunisation 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.

Limitations of vaccine effectiveness

Vaccination with Moderna COVID-19 Vaccine may not protect all recipients.

Excipients with known effect

Sodium
This vaccine contains 0.033 mg of sodium per 0.5 mL dose and is considered 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Other vaccines

There are no data to assess the concomitant administration of Moderna COVID-19 Vaccine with other vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate and well-controlled studies of Moderna COVID-19 Vaccine use in pregnant women have been conducted. Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 mcg) and other ingredients included in a single human dose of Moderna COVID-19 Vaccine 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, foetal development or postnatal development were reported in the study.

Breast-feeding

Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion. Pregnant or breastfeeding mothers are advised to discuss their options with their healthcare providers.

Fertility

No data are available on fertility in humans with use of Moderna COVID-19 Vaccine.

4.7 Effects on ability to drive and use machines

No studies on the effects of the Moderna COVID-19 Vaccine on the ability to drive and use machines have been performed.

Some of the effects mentioned under section 4.8 "Undesirable Effects" may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Participants 18 years of age and older

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,351 participants[4] ≥ 18 years of age.

Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants. The most frequently reported adverse reactions after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70.1% any grade; 10.1% grade ≥ 3), headache (64.9% any grade; 5.8% grade ≥ 3), myalgia (61.6% any grade; 9.1% grade ≥ 3) arthralgia (46.5%; 5.4% grade ≥ 3), and chills (45.5% any grade; 1.4% grade ≥ 3). 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 adverse reactions in adults aged 18 to < 65 years than in those aged 65 years and above.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. In the participants who received the vaccine, solicited systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1. Grade 3 systemic adverse reactions were reported more frequently after Dose 2 than after Dose 1.

Immunocompromised participants 18 years of age and older

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third*

Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med) in 60 participants who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported.

Adolescents 12 through 17 years of age

Safety data for Moderna COVID-19 Vaccine in adolescents were collected in an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind clinical trial (Study 2, NCT04649151) conducted in the United States involving 3,726[5] participants 12 through 17 years of age who received at least one dose of Moderna COVID-19 Vaccine (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.[6] Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.

In a clinical study, the most frequent adverse reactions in participants 12 through 17 years of age were pain at the injection site (97.2%), headache (78.4%), fatigue (75.2%), myalgia (54.3%), chills (49.1%), arthralgia (34.6%), axillary swelling/tenderness (34.6%), nausea/vomiting (29.3%), swelling at the injection site (27.7%), erythema at the injection site (25.8%), and fever (13.7%).[7]

Children 6 through 11 years of age

Safety data for Moderna COVID-19 Vaccine in children were collected in an ongoing Phase 2/3 two-part randomised, observer-blind clinical trial conducted in the United States and Canada (NCT04796896).[8] 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) of Moderna COVID-19 Vaccine.[9] Part 2 is the placebo-controlled phase for safety and included 4,002 participants 6 through 11 years of age who received at least one dose (0.25 mL) of Moderna COVID-19 Vaccine (n=3,007) or placebo (n=995).[10] No participants in Part 1 participated in Part 2.[11] Demographic characteristics were similar among participants who received Moderna COVID-19 Vaccine and those who received placebo.[12]

The most frequent adverse reactions in children 6 through 11 years of age following administration of the primary series were injection site pain (98.4%), fatigue (73%), headache (62%), myalgia (35.2%), chills (34.6%), nausea/vomiting (29.2%), axillary swelling/tenderness (26.9%), fever (25.9%), injection site erythema (24.3%), injection site swelling (22.5%), and arthralgia (21.2%).[13]

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 6 years of age and older

The safety profile presented below is based on data generated in a placebo-controlled clinical study on 30,346 adults ≥ 18 years of age, another placebo-controlled clinical study with

3,726 participants 12 through 17 years of age, another clinical study with 4,002 participants 6 through 11 years of age, and post-marketing experience.

Adverse reactions reported are listed according to the following frequency convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (Table 1).

Table 1: Adverse reactions from Moderna COVID-19 Vaccine clinical trials and post authorisation experience in individuals 6 years of age and older

MedDRA system organ class	Frequency	Adverse reaction(s)
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known†	Anaphylaxis Hypersensitivity (includes urticaria‡)
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
	Rare	Acute peripheral facial paralysis§ Hypoaesthesia/ paraesthesia[14]
Cardiac disorders	Very rare	Myocarditis Pericarditis
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling Injection site erythema
	Common	Injection site urticaria Injection site rash

		Delayed injection site reaction[¶]
	Uncommon	Injection site pruritus
	Rare	Facial swelling[#]

*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases.
†These terms are based on reports in the post-marketing authorisation period. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.
‡The frequency category for urticaria was rare.
[§] Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the vaccine 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.
[¶] Median time to onset was 9 days after the first injection, and 11 days after the second injection. Median duration was 4 days after the first injection, and 4 days after the second injection.
[#] 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 1 and 2 days, respectively, after vaccination.

Booster dose participants

Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076).[15] In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series.[16] In an open-label phase of this study, 167 of those participants received a single booster dose (0.25 mL) at least 6 months after receiving the second dose of the primary series.[17] The solicited adverse reaction profile for the booster dose was similar to that after the second dose in the primary series.[18]

Booster dose following primary vaccination with another authorised or approved COVID-19 vaccine

The safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from the safety of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series (homologous booster dose) and from data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2- dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARSCoV-2 infection were randomised 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine (0.5 mL), Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster

dose. An overall review of adverse reactions reported following the Moderna COVID-19 Vaccine heterologous booster dose (0.5 mL) did not identify any new safety concerns, as compared with adverse reactions reported following Moderna COVID-19 Vaccine primary series doses or homologous booster dose (0.25 mL).

Post-authorisation experience
Anaphylaxis, myocarditis, and pericarditis have been reported following Moderna COVID-19 Vaccine administration (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccine, COVID-19 Vaccine, ATC code: J07BX03

Mechanism of action

Moderna COVID-19 Vaccine encodes for the pre-fusion stabilised Spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. 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 expressed Spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Clinical studies

Efficacy in adults 18 years of age and older

Study 1 was randomised, placebo-controlled, observer-blind clinical study conducted in participants 18 years of age and older who were at increased risk of COVID-19 disease (NCT04470427). In addition, pre-specified cohorts of participants who were either ≥65 years of age or 18 to < 65 years of age with comorbid medical conditions were included. A total of 30,351 participants[19] were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease.

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 participants who received a 2-dose regimen (at 0 and 1 month) of either Moderna

COVID-19 Vaccine (n=14,134) or placebo (n=14,073), had a negative baseline SARS-CoV-2 status, and did not develop confirmed COVID-19 within 14 days after the second dose (Table 2). The PPS study population included 47.4% female, 52.6% male, 79.5% White, 19.7% Hispanic or Latino, and 9.7% African American, 4.6% Asian, and 6.2% other. The median age of participants was 53 years (range 18-95). Of the study participants, 22.6% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, or HIV infection). A dosing window of –7 to +14 days for administration of the second dose (scheduled at day 29) was allowed for inclusion in the PPS.

COVID-19 cases were confirmed by polymerase chain reaction (PCR) and by a clinical adjudication committee.

Table 2: Primary efficacy analysis: confirmed COVID-19[#] regardless of severity starting 14 days after the 2nd dose – per-protocol set[20]

Age group (years)	Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)*
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	
Overall (≥18)	14,134	11	3.328	14,073	185	56.510	94.1 (89.3, 96.8)
18 to <65	10,551	7	2.875	10,521	156	64.625	95.6 (90.6, 97.9)
≥65	3,583	4	4.595	3,552	29	33.728	86.4 (61.4, 95.2)

[#] COVID-19: symptomatic COVID-19 requiring positive RT-PCR (reverse transcription-polymerase chain reaction) result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose.
*VE and 95% CI from the stratified Cox proportional hazard model

Efficacy against severe COVID-19

Among all participants in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 cases reported in the placebo group (incidence rate 9.138 per 1,000 persons/years). Vaccine efficacy against severe COVID-19 was 100% (Table 3).

Table 3: Secondary efficacy analysis: confirmed severe COVID-19[#] cases starting 14 days after the 2nd dose – per-protocol set[21]

Endpoint	Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)*
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	
Severe* cases 14	14,134	0	NA	14,073	30	9.138	100%

days after Dose 2							

#Severe COVID-19 cases are defined as a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:
-Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
-Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
-Significant acute renal, hepatic or neurologic dysfunction, OR
-Admission to an intensive care unit or death.
* VE and 95% CI from the stratified Cox proportional hazard model

Additional efficacy analyses

Subgroup analyses of vaccine efficacy 14 days after Dose 2 can be found in Table 4.

Table 4: Subgroup analyses of vaccine efficacy - COVID-19 14 days after Dose 2 per adjudication committee assessments (primary efficacy analysis set) – per-protocol set[22]

Subgroup	Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)**
	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	Participants N	COVID-19 cases n	Incidence rate of COVID-19 per 1,000 person-years	
Overall High risk*	3,206	4	5.227	3,167	43	57.202	90.9 (74.7, 96.7)
High risk 18 to <65	2,155	2	3.947	2,118	35	70.716	94.4 (76.9, 98.7)
Not High risk 18 to <65	8,396	5	2.594	8,403	121	63.054	95.9 (90.0,98.3)
Females	6,768	7	4.364	6,611	98	62.870	93.1 (85.2,96.8)
Males	7,366	4	2.352	7,462	87	50.730	95.4 (87.4,98.3)

* Participants at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age
** VE and 95% CI from the stratified Cox proportional hazard model

Immunogenicity in immunocompromised recipients

From an independent report (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med*), a separate randomised controlled study has been conducted in 120 participants who had undergone various solid organ

transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years). A third dose (0.5 mL) of Moderna COVID-19 Vaccine was administered to 60 participants approximately 2 months after they had received a second dose; saline placebo was given to 60 individuals for comparison (NCT04885907). Significant increases in levels of SARS-CoV-2 antibodies occurred four weeks after the third dose in 55.0% of participants in the Moderna COVID-19 Vaccine group (33 of 60) and 17.5% of participants in the placebo group (10 of 57).

Efficacy in adolescents 12 through 17 years of age

Study 2 is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in adolescents ages 12 to 17 years in the United States (NCT04649151).[23] Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732[1] participants were randomised 2:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart.[24] Participants will be followed for efficacy and safety until 1 year after the second dose.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Moderna COVID-19 Vaccine (n=2,163) or placebo (n=1,073), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set).[25] In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races.[26] Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription-polymerase chain reaction). Listed symptoms were fever (temperature > 38°C/≥ 100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea.

There were 2 COVID-19 cases in the Moderna COVID-19 Vaccine group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% confidence interval of 67.8% to 99.2%) (Table 5).[27]

Table 5: Efficacy analysis: COVID-19* in participants 12 to 17 years of age starting 14 days after Dose 1 – modified intent-to-treat set[28]

Moderna COVID-19 Vaccine	Placebo	

[1] 3,726 participants were randomised and received the first injection, with 1,240 on placebo and 2,486 on the Moderna COVID-19 Vaccine.

Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	% Vaccine efficacy (95% CI)†
2,163	2	3.828	1,073	13	52.473	92.7 (67.8, 99.2)

* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.
† Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Immunogenicity in adolescents 12 through 17 years of age[29]

In Study 2 (NCT04649151), an analysis was conducted of SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in Study 2 and in participants aged 18 through 25 in Study 1 who had no immunologic or virologic evidence of prior COVID-19 at baseline. Noninferior immune responses and seroresponse rates were demonstrated in a comparison of adolescents aged 12 through 17 years to participants aged 18 through 25 (Table 6).

Table 6: Summary of geometric mean titer and seroresponse rate – comparison of adolescents aged 12 through 17 to participants aged 18 through 25 – per-protocol immunogenicity subset[30]

Assay	Time point	Moderna COVID-19 Vaccine		12 through 17 years/ 18 through 25 years	
		12 through 17 years n=340	18 through 25 years n=305		
		GLSM (95% CI)*	GLSM (95% CI)*	GMR (95% CI)†	Met noninferiority objective (Y/N)‡
SARS-CoV-2 neutralisation assay – ID50 (titer)§	28 days after Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	1.08 (0.94, 1.24)	Y
		Seroresponse % (95% CI)¶	**Seroresponse % (95% CI)¶**	**Difference in seroresponse rate % (95% CI)#**	
		98.8 (97.0, 99.7)	98.6 (96.6, 99.6)	0.2 (-1.8, 2.4)	

GLSM = Geometric least squares mean
GMR = Geometric mean ratio
n = Number of subjects with non-missing data at the corresponding timepoint
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
† The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in Study 2 and young adults in Study 1) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
‡ Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.
§ SARS-CoV-2 50% inhibitory dose (ID50) neutralisation titers were determined using a SARS-CoV-2 Spike-Pseudotyped Virus Neutralisation Assay. Quantification of SARS-CoV-2 neutralising antibodies utilises lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Neutralisation is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.
¶ Seroresponse due to vaccination specific to pseudovirus neutralising antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
# Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Efficacy in children 6 through 11 years of age

The paediatric study is an ongoing Phase 2/3 randomised, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in children ages 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomised 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until 1 year after the second dose.[31]

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of October 6, 2021 was performed in 3,556 participants who received two doses (0.25 mL at 0 and 1 month) of either the Moderna COVID-19 Vaccine (n=2,678) or placebo (n=878), and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-

Treat Set [mITT]). Between participants who received the Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics.[32]

The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 7.

Table 7: Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1 – modified intent-to-treat set

	Moderna COVID-19 Vaccine N=2,672		Placebo N=877		% Vaccine Efficacy (95% CI)*
	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
COVID-19 Cases - Definition 1[a]	0	0	13	152.027	100.0 (89.3, NE)
COVID-19 Cases - Definition 2[b]	3	11.399	14	163.810	93.0 (75.1, 98.7)
SARS-CoV-2 Infections (regardless of symptoms)[c]	16	60.958	26	306.853	80.1 (61.5, 90.0)
Asymptomatic SARS-CoV-2 Infections[d]	13	49.529	12	141.625	65.0 (16.1, 85.3)

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.
NE = Not estimable
* Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
[a] Participant must have experienced at least two of the following systemic symptoms: fever (≥38°C / ≥100.4°F), 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.
[b] Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.
[c] A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.
[d] Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Immunogenicity in children 6 through 11 years of age[33]
An analysis evaluating SARS-CoV-2 50% neutralising titers and seroresponse rates 28 days after Dose 2 was conducted in subset of children aged 6 through 11 (n=134) in the paediatric study and in participants aged 18 through 25 (n=296) in the adult study (NCT04796896). 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 through 11 years of age compared to the 18- to 25-year-olds was 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). 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.

Immunogenicity in booster dose participants
Study 3 is an ongoing Phase 2, randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076).[34] In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series.[35] In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL) at least 6 months after receiving the second dose in the primary series.[36] A single booster dose (0.25 mL) was shown to be immunogenic at Day 29 post-booster dose and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in Study 1.[37]

Immunogenicity of a booster dose following primary vaccination with another authorised or approved COVID-19 vaccine in adults 18 years of age and older
Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

Immunogenicity in adult participants against the B.1.617.2 (Delta) variant[38]
Serum samples were obtained from participants in Study 3 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralisation assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of the Moderna COVID-19 Vaccine booster (50 mcg) induced an 18-fold rise in neutralising titers against the Delta variant compared with pre-booster

levels (Geometric mean fold rise (GMFR) = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall Study 3 (Part B) group (n = 293), the pre-booster neutralising antibodies (nAb) Geometric mean titre (GMT) for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n = 293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50 µg mRNA-1273 prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyses of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Moderna COVID-19 Vaccine booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Moderna COVID-19 Vaccine booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89]), it also was able to broaden and increase nAb levels against Delta variant.

Immunogenicity in children against the B.1.617.2 (Delta) variant[39]
Additional data on the immunogenicity of the Moderna COVID-19 Vaccine against the Delta variant comes from paediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per-protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 mcg of the Moderna COVID-19 Vaccine, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Carcinogenesis, mutagenesis, impairment of fertility

Conventional studies of repeat dose toxicity and reproductive and developmental toxicity in animals and *in vitro* did not reveal any risks for humans.

General toxicity
Intramuscular administration of mRNA to rats (up to 4 doses exceeding the human dose once every 2 weeks, resulting in higher doses in rats due to body weight differences) revealed some injection erythema and oedema and transient changes in haematology (neutrophils, eosinophils, lymphocytes, activated partial thromboplastin time, fibrinogen), chemistry (albumin and globulin), and increased cellularity and/or inflammation of lymphoid organs consistent with an inflammatory response, as well as vacuolation or hypertrophy in hepatocytes or Kupffer cells, without evidence of liver injury. All effects were reversible.

Genotoxicity/carcinogenicity
In vitro and in vivo genotoxicity studies were conducted with the novel lipid components of the vaccine. Results suggest the genotoxicity potential to humans is low. Carcinogenicity studies were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate (Lipid SM-102)
Cholesterol
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG)
Trometamol
Trometamol hydrochloride
Acetic acid
Sodium acetate trihydrate
Sucrose
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6.3 Shelf life

9 months at -50°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days.

Once thawed the vaccine should not be re-frozen.

The vial may be stored at 8°C to 25°C for a total of 24 hours after removal from refrigerated conditions.

Vials may be held for up to 12 hours at 2°C to 25°C after initial puncture.

6.4 Special precautions for storage

Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50° to -15°C (-58° to 5°F).

Any freezer that reliably maintains an average temperature between -50° and -15°C (-58° to 5°F) and has a separate sealed freezer door is acceptable for storing Moderna COVID-19 Vaccine.

Moderna COVID-19 Vaccine can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured). Do not refreeze.

The total storage time of a vial after removal from refrigerated conditions should not exceed 24 hours at 8° to 25°C (46° to 77°F). Do not refreeze.

Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 12 hours. Do not refreeze.

Protect from light.

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 minimised. 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.[40]

6.5 Nature and contents of container

5 mL dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminum seal).
Each vial contains 5 mL.
Pack size: 10 multidose vials

6.6 Special precautions for disposal and other handling

Moderna COVID-19 Vaccine vials are for multiple use. Ten (10) doses of 0.5 mL volume each or a maximum of twenty (20) doses of 0.25 mL volume can be withdrawn from each multiple-dose vial.
Moderna COVID-19 Vaccine multiple-dose vials are stored frozen between -50°C to -15°C.

Moderna COVID-19 Vaccine can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days if not entered (needle-punctured).

Thaw each vial before use:

- Thaw in refrigerated conditions between 2°C to 8°C for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.
- Alternatively, thaw at room temperature between 15°C to 25°C for 1 hour.
- Do not re-freeze vials after thawing.

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

Moderna COVID-19 Vaccine is a white to off-white dispersion. It may contain white or translucent product-related particulates.

Inspect Moderna COVID-19 Vaccine vials visually for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.

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 to prevent transmission of infectious agents from one person to another. Pierce the stopper, preferably at a different site each time. Do not puncture the vial more than 20 times.[41] The dose in the syringe should be used promptly.

This product is preservative free. Once the vial has been entered (needle-punctured) to withdraw the initial dose, the product should be used immediately and be discarded after 12 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.

International birth date: December 18, 2020

10. DATE OF REVISION OF THE TEXT

Approved = all concepts endorsed by GLT/ELC and ready for formal signatures
Effective = last signature received and ready for dispatch and issuance (dates not available before version 3.0)

Date	Version	Summary of changes
November 28th 2020 (Approved)	1.1	QC corrections
December 8rd 2020 (Approved)	1.2	Correction to Undesirable Effects summary text; correction/addition of footnotes to adverse reactions

		and efficacy tables; updates to shelf life, excipients, and container description Correction of instructions for handling after first puncture
December 16th 2020 (Approved)	2.0	Modified Pregnancy/lactation section to reflect availability of DART study Updated phase 3 data with data from Nov 25 snapshot
December 18th 2020 (Approved)	2.1	Minor updates to align with Company Core Safety Information and editorial corrections
December 29th 2020 (Approved) 22 Jan 2021 (Effective)	3.0	Updates to align with CCSI V3.0 to include information on anaphylaxis and editorial corrections. Additional n/c data added to support SmPC
February 1st 2021 (Approved) 3 February 2021 (Effective)	3.1	Updates to include adverse reaction frequency table, minor updates to add/change text to support SmPC and US PI, technical updates to ingredient descriptions, addition of International Birth Date
May 6th 2021 (Approved) 10 May 2021 (Effective)	4.0	Addition of 30-minute observation recommendation for anaphylaxis in Warnings. Addition of delayed injection site reaction data to Undesirable Effects. Updates to and addition of storage and handling conditions; removal of grey shading as noted to sections 4.2, 4.6 and 4.7. Typographical edits as noted in the annotated version.
June 1st 2021 (Approved and Effective)	5.0	Addition of Adolescent EUA data (sections 4.8, and 5.2). Addition of brand name. Typographical edits as noted in the annotated version.

June 25 2021 (Approved) 27 June 2021 (Effective)	6.0	Addition of myocarditis and pericarditis Warnings (section 4.4) and post authorisation experience (section 4.8).
August 13 2021 (Approved) 17 August 2021 (Effective)	7.0	Addition of immunocompromised booster data (sections 4.2, 4.4, 4.8, and 5.1).
August 30 2021 (Approved) 3 September 2021 (Effective)	8.0	Addition of elasomeran INN (section 1); addition of booster data in sections 2, 4.2, 4.8 and 5.2. Clarifications to immunocompromised text in sections 4.4, 4.8 and 5.2. Edits to accommodate booster in sections 6.5 and 6.6.
November 3 2021 (Approved) 7 November 2021 (Effective)	9.0	Addition of paediatric data (6-11 yr olds) and related edits in sections 4.1, 4.2, 4.8 and 5.2. Addition of heterologous boosting data in sections 4.2, 4.8 and 5.2.
November 17 2021 (Approved) 20 November 2021 (Effective)	10.0	Extension in shelf life to 9 months and deletion of dry ice statements.
December 10 2021 (Approved) 14 December 2021 (Effective)	11.0	**Section 4.4:** Myocarditis/pericarditis: redline edits were discussed and agreed upon at SRB on 10 Dec 2021. **Section 4.6:** Breastfeeding: aligned text with US Fact Sheets. **Section 4.8:** removed US-based ADR content and re-organized and simplified to establish Table 1 as the most current and cumulative reflection of ADRs. Minor updates to align with the IB. **Table 1:** addition of paraesthesia per PBRER outcome. Myocarditis and pericarditis frequency

		reclassified from Not Known to Very Rare to reflect latest available data. **Section 5.2:** Addition of Adults and Peds Delta data.
9 February 2022 (Approved) 21 February 2022 (Effective)	12.0	**Section 4.2:** Posology: lower booster age from 18 to 12 years and lower booster interval from 6 to 3 months. **Table 1:** footnote 3 was added back after accidentally getting deleted in version 11.0.
3 June 2022 (Approved) 15 June 2022 (Effective)	13.0	**Section 4.8, Table 1:** added urticaria as an ADR to the term of Hypersensitivity, including two new footnotes. Category 3 (local submissions no later than 22 October 2022).

REFERENCES

[1] Module 2.5.2.2
[2] Module 2.5.7.5
[3] Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
[4] PPD_Re-QC_IND 19745_Shell Templates_CBER_DSS 2_15Dec2020_Version1-1_For Sponsor Review and Incorporation_16Dec2020_safety tables.doc Table 9 (sum of vaccine + placebo P301)
[5] Table 1.4 Summary of Study Duration by Age Group Safety Set (Number of Subjects, n (%) Received First Injection)
[6] Module 2.5, Table 3 Subject Demographics and Baseline Characteristics by Age Group Safety Set (Overall)
[7] Table 3.1.1.3 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade Solicited Safety Set (N1)
[8] 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age; Module 2.5.5.1.3
[9] Table 14.1.3.1.1 Subject Demographics and Baseline Characteristics by Age Group and Dose Level in Part 1 Safety Set
[10] 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age; Table 14.1.3.2 Subject Demographics and Baseline Characteristics by Age Group Safety Set
[11] 2.5.2.5 Overview of Clinical Development of mRNA-1273 for Children 6 Months to < 12 Years of Age
[12] 2.5.5.1.2 Demographics and Baseline Characteristics
[13] Table 14.3.1.1.3.2.1 Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade Solicited Safety Set
[14] Based on the analysis of available safety data presented as of 30 June 2021 in PBRER #1.
P301: 14 cases in the mRNA-1273 arm [n=15,184] = 0.0922%
[15] Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
[16] IND 19745 SN0176 Executive Summary P201 Part B (100 mcg Prime Part A D57)
[17] Module 2.5, section 2.5.4.1.1.2 Disposition and section 2.5.4.1.1 Analysis Sets (Solicited Safety Set)
[18] Module 2.5, section 2.5.5 Overview of Safety

[19] PPD_Re-QC_IND 19745_Shell Templates_CBER_DSS 2_15Dec2020_Version1-1_For Sponsor Review and Incorporation_16Dec2020_safety tables.doc Table 3
[20] PPD_Re-QC_IND 19745_Shell Templates_CBER_DSS 2_15Dec2020_Version1-1_For Sponsor Review and Incorporation_16Dec2020_safety tables.doc Table 4
[21] PPD_Re-QC_IND 19745_Shell Templates_CBER_DSS 2_15Dec2020_Version1-1_For Sponsor Review and Incorporation_16Dec2020_safety tables.doc Table 6
[22] PPD_Re-QC_IND 19745_Shell Templates_CBER_DSS 2_15Dec2020_Version1-1_For Sponsor Review and Incorporation_16Dec2020_safety tables.doc Table 7
[23] Emergency Use Authorisation (EUA) Request, Section 6.2.1.1.1 Disposition
[24] Emergency Use Authorisation (EUA) Request, Section 6.2.1.1.1 Disposition
[25] Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
[26] Table 1.3.3, Subject Demographics and Baseline Characteristics by Age Group mITT1 Set
[27] Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
[28] Table 2.8.2.1 Analysis of Incidence Rate of Secondary Definition of COVID-19 Starting 14 Days After First Injection mITT1 Set
[29] Table 2.1.1.3.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers -ANCOVA Model Per-Protocol Immunogenicity Subset
[30] Table 2.1.2.3.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers — Seroresponse Rate Per-Protocol Immunogenicity Subset
[31] Module 2.5.2.5, 2.5.5.2.2.3.1; Table 14.1.1.1.2
[32] Module 2.5.5.1.1, 2.5.5.1.2, 2.5.5.2.2.3.3; Table 14.1.2.1.2
[33] 2.5.5.2.1 Statistical Methods Used for P204; 2.5.5.2.2.2 Immunogenicity; Table 14.2.1.1.3.4.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group and Dose Level in Part 1 Expansion Per-Protocol Immunogenicity Subset; Table 14.2.1.2.3.4.1 Analysis of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group and Dose Level in Part 1 Expansion —Seroresponse Rate Per-Protocol Immunogenicity Subset
[34] Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
[35] Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201
[36] Module 2.5, section 2.5.1.4.1 Study mRNA-1273-P201 and section 2.5.4.1.1 Analysis Sets (Per-Protocol Set)
[37] Module 2.5, section 2.5.4.2.2 Results
[38] Module 2.5, section 2.5.5.2.2.1.1
[39] Module 2.5, section 2.5.1
[40] Module P.2.2 (Stability during shipping); WHO dossier
[41] EUA 27073 SN0083 3.2.P.2.4 Attachment PD-MEM-0517 USP<381> up to 20 punctures

Appendix 2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Blood and lymphatic system disorders	**6**	**40**		**46**
Anaemia	1	16		17
Autoimmune haemolytic anaemia		1		1
Blood loss anaemia		5		5
Febrile neutropenia	1	4		5
Hypercoagulation		1		1
Immune thrombocytopenia		1		1
Iron deficiency anaemia	1	3		4
Leukocytosis		3		3
Lymphadenopathy		2		2
Myelosuppression	1			1
Neutropenia		1		1
Normocytic anaemia		1		1
Pancytopenia		1		1
Splenic infarction		1		1
Thrombocytopenia	2			2
Cardiac disorders	**30**	**381**	**1**	**412**
Acute coronary syndrome	1	7		8
Acute left ventricular failure	1	8		9
Acute myocardial infarction	1	39		40
Angina pectoris	1	21		22
Angina unstable		10		10
Aortic valve incompetence		3		3
Aortic valve stenosis		4		4
Arrhythmia		3		3
Arteriosclerosis coronary artery		1		1
Arteriospasm coronary		1		1
Atrial fibrillation	3	51	1	55
Atrial flutter	1	16		17
Atrial tachycardia		2		2
Atrioventricular block complete		6		6
Atrioventricular block first degree		1		1
Bradycardia	2	8		10
Bundle branch block left		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Bundle branch block right		1		1
Cardiac arrest	1	13		14
Cardiac failure		6		6
Cardiac failure acute		6		6
Cardiac failure chronic		2		2
Cardiac failure congestive	3	32		35
Cardiac flutter		1		1
Cardiogenic shock		3		3
Cardiomyopathy		4		4
Cardio-respiratory arrest	3	2		5
Chronic left ventricular failure		1		1
Coronary artery disease	2	41		43
Coronary artery insufficiency		1		1
Coronary artery occlusion		6		6
Coronary artery stenosis		1		1
Ischaemic cardiomyopathy		1		1
Left ventricular failure		2		2
Microvascular coronary artery disease		1		1
Mitral valve incompetence		3		3
Myocardial infarction	9	35		44
Myocardial ischaemia		1		1
Myocarditis		3		3
Palpitations		2		2
Paroxysmal atrioventricular block		1		1
Pericardial effusion		2		2
Pericarditis	1	4		5
Pulseless electrical activity	1	2		3
Sinoatrial block		1		1
Sinus node dysfunction		1		1
Sinus tachycardia		1		1
Stress cardiomyopathy		3		3
Supraventricular tachycardia		5		5
Tachycardia		1		1
Ventricular extrasystoles		3		3

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Ventricular fibrillation		1		1
Ventricular tachycardia		6		6
Congenital, familial and genetic disorders	**3**	**4**		**7**
Arnold-Chiari malformation		2		2
Congenital hydronephrosis		1		1
Diverticulitis Meckel's		1		1
Pectus excavatum	1			1
Syringomyelia	2			2
Ear and labyrinth disorders		**8**		**8**
Vertigo		7		7
Vertigo positional		1		1
Endocrine disorders		**7**		**7**
Autoimmune thyroiditis		1		1
Basedow's disease		1		1
Goitre		1		1
Hyperthyroidism		3		3
Inappropriate antidiuretic hormone secretion		1		1
Eye disorders	**2**	**12**	**1**	**15**
Blindness transient		1		1
Central serous chorioretinopathy		1		1
Diplopia		2		2
Eye pain			1	1
Optic disc drusen		1		1
Optic ischaemic neuropathy		1		1
Retinal artery occlusion		2		2
Retinal detachment	1	3		4
Retinal tear	1	1		2
Gastrointestinal disorders	**29**	**234**	**2**	**265**
Abdominal discomfort	1	1		2
Abdominal hernia		2		2
Abdominal mass		1		1
Abdominal pain	4	11	1	16
Abdominal pain upper		3		3
Abdominal rigidity		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Ascites		2		2
Chronic gastritis		1		1
Colitis	2	7		9
Colitis ischaemic		5		5
Constipation	1	2		3
Crohn's disease		1		1
Dental caries		1		1
Diarrhoea	3	4		7
Dieulafoy's vascular malformation		1		1
Diverticular perforation		4		4
Diverticulum		2		2
Duodenal ulcer		3		3
Duodenal ulcer haemorrhage	1	1		2
Duodenal ulcer perforation	1	2		3
Dysphagia		6		6
Enteritis		3		3
Enterocolitis		1		1
Enterovesical fistula		2		2
Food poisoning		2		2
Gastric fistula		2		2
Gastric perforation	1			1
Gastric ulcer		3		3
Gastric ulcer haemorrhage	1			1
Gastritis		1		1
Gastrointestinal haemorrhage	1	13		14
Gastrointestinal motility disorder		1		1
Gastrooesophageal reflux disease	1	9		10
Haematemesis		2		2
Haematochezia		1		1
Haemoperitoneum		1		1
Haemorrhoids thrombosed		1		1
Hiatus hernia	1	3		4
Ileal perforation		1		1
Ileus		6		6

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Impaired gastric emptying		2		2
Inguinal hernia	1	2		3
Internal hernia		1		1
Intestinal ischaemia		1		1
Intestinal obstruction		15		15
Intestinal perforation		2		2
Intestinal pseudo-obstruction		1		1
Intra-abdominal fluid collection	1			1
Intra-abdominal haemorrhage		2		2
Intussusception		2		2
Large intestinal haemorrhage		2		2
Large intestinal obstruction		1		1
Large intestinal stenosis		1		1
Large intestine perforation		5		5
Lower gastrointestinal haemorrhage		1		1
Lumbar hernia		1		1
Nausea	1	7		8
Obstructive pancreatitis		1		1
Oesophageal achalasia		1		1
Oesophageal rupture		2		2
Oesophageal spasm		1		1
Oesophageal varices haemorrhage		1		1
Pancreatitis	1	9		10
Pancreatitis acute	1	9		10
Pancreatitis chronic		1		1
Pancreatitis haemorrhagic		1		1
Pancreatitis relapsing		2		2
Peptic ulcer perforation		1		1
Rectal fissure		1		1
Rectal haemorrhage		2		2
Rectal prolapse		2		2
Rectal ulcer		1		1
Retroperitoneal haematoma		1		1
Retroperitoneal haemorrhage		3		3

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Small intestinal obstruction	3	21		24
Terminal ileitis		1		1
Umbilical hernia		1	1	2
Upper gastrointestinal haemorrhage		3		3
Varices oesophageal		1		1
Volvulus		2		2
Vomiting	3	7		10
General disorders and administration site conditions	**10**	**64**		**74**
Asthenia		1		1
Chest pain		16		16
Condition aggravated		3		3
Death	3	10		13
Drug withdrawal syndrome		1		1
Fatigue		1		1
Feeling hot	1			1
Generalised oedema	1			1
Impaired healing		1		1
Incarcerated hernia	1	1		2
Multiple organ dysfunction syndrome	1			1
Necrosis		1		1
Non-cardiac chest pain	2	15		17
Oedema peripheral		2		2
Pain		1		1
Peripheral swelling		1		1
Procedural failure		1		1
Pyrexia		3		3
Sudden cardiac death		1		1
Swelling face	1	2		3
Systemic inflammatory response syndrome		2		2
Vascular stent stenosis		1		1
Hepatobiliary disorders	**5**	**51**		**56**
Bile duct stone	1	2		3
Biliary colic		2		2
Biliary obstruction		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Cholecystitis	2	19		21
Cholecystitis acute		8		8
Cholecystitis chronic		1		1
Cholelithiasis		9		9
Cholelithiasis obstructive		1		1
Cholestasis of pregnancy		1		1
Drug-induced liver injury	1			1
Hepatic cirrhosis		2		2
Hepatic cyst		1		1
Hepatic failure		2		2
Hepatitis acute	1			1
Hepatorenal syndrome		1		1
Hypertransaminasaemia		1		1
Immune system disorders	**1**	**17**		**18**
Allergy to arthropod sting		1		1
Anaphylactic reaction		6		6
Anaphylactic shock		2		2
Cytokine storm	1			1
Drug hypersensitivity		4		4
Liver transplant rejection		2		2
Transplant rejection		2		2
Infections and infestations	**77**	**460**	**2**	**539**
Abdominal abscess	1	3		4
Abdominal wall abscess	1			1
Abscess		1		1
Abscess limb		2		2
Adenovirus infection	3	1		4
Anal abscess		1		1
Appendiceal abscess		1		1
Appendicitis	7	37		44
Appendicitis perforated		10		10
Arthritis bacterial		6		6
Arthritis gonococcal		1		1
Arthritis infective		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Atypical pneumonia		1		1
Bacteraemia		2		2
Bacterial sepsis		2		2
Biliary sepsis		1		1
Breast cellulitis		2		2
Bronchiolitis	6			6
Bronchitis	1	5		6
Bronchitis viral	1			1
Campylobacter gastroenteritis		1		1
Campylobacter sepsis		1		1
Cellulitis	1	24		25
Cellulitis orbital	1			1
Cholangitis infective		1		1
Cholecystitis infective		1		1
Clostridium bacteraemia		1		1
Clostridium difficile colitis		4		4
Clostridium difficile infection	1	1		2
Colonic abscess		3		3
COVID-19	6	26		32
COVID-19 pneumonia		5		5
Croup infectious	5			5
Cystitis		1		1
Cystitis klebsiella		1		1
Cytomegalovirus infection		1		1
Device related infection		3		3
Diabetic foot infection		4		4
Diverticulitis		22		22
Empyema		1		1
Enterobacter sepsis		1		1
Enterococcal bacteraemia	1	1		2
Epididymitis		1		1
Epstein-Barr virus infection	1			1
Escherichia infection		1		1
Escherichia urinary tract infection		4		4

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Extradural abscess		1		1
Fournier's gangrene		1		1
Gangrene		3		3
Gastroenteritis	1	3		4
Gastroenteritis norovirus		1		1
Gastroenteritis salmonella	1			1
Gastroenteritis viral	2	1		3
Gastrointestinal candidiasis		1		1
Gastrointestinal infection		1		1
Giardiasis		1		1
Groin abscess		1		1
Haematoma infection		1		1
Helicobacter infection		1		1
Hepatitis A		1		1
Herpes simplex meningitis		1		1
Implant site infection		1		1
Infected bite		1		1
Infection		1	1	2
Influenza		2		2
Joint abscess		1		1
Klebsiella bacteraemia		1		1
Klebsiella infection		1		1
Klebsiella sepsis		1		1
Liver abscess	1	3		4
Localised infection		2		2
Lung abscess		1		1
Mastoiditis	1	1		2
Medical device site infection		1		1
Meningitis		1		1
Meningitis aseptic	1	4		5
Metapneumovirus infection	3			3
Murine typhus	1			1
Nosocomial infection		1		1
Oesophageal candidiasis		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Orchitis		2		2
Osteomyelitis	1	11		12
Osteomyelitis bacterial		1		1
Osteomyelitis chronic		2		2
Otitis media acute		1		1
Parainfluenzae virus infection	1			1
Perineal abscess		1		1
Perirectal abscess		2		2
Peritoneal abscess		2		2
Peritonitis		2		2
Peritonitis bacterial		1		1
Pharyngitis		1		1
Pharyngitis streptococcal	1			1
Pneumonia	5	61	1	67
Pneumonia aspiration		3		3
Pneumonia bacterial	1	5		6
Pneumonia mycoplasmal		2		2
Pneumonia parainfluenzae viral		1		1
Pneumonia respiratory syncytial viral	1	1		2
Pneumonia staphylococcal		2		2
Pneumonia viral	1	1		2
Post procedural cellulitis		1		1
Post procedural infection		9		9
Post-acute COVID-19 syndrome	1			1
Postoperative abscess		2		2
Postoperative wound infection		5		5
Pyelonephritis	1	4		5
Pyelonephritis acute		2		2
Respiratory syncytial virus bronchiolitis	1			1
Respiratory syncytial virus infection	2			2
Rhinovirus infection	5	3		8
Salpingitis	1			1
Sepsis		35		35
Septic shock	1	11		12

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Shigella infection		1		1
Shigella sepsis		1		1
Sialoadenitis		1		1
Sinusitis		1		1
Skin infection		1		1
Spinal cord abscess		1		1
Staphylococcal bacteraemia		3		3
Staphylococcal infection		4		4
Staphylococcal sepsis		1		1
Streptococcal bacteraemia		1		1
Streptococcal endocarditis		1		1
Streptococcal infection		1		1
Suspected COVID-19		2		2
Tonsillitis		1		1
Tooth abscess		1		1
Toxic shock syndrome	1			1
Upper respiratory tract infection		2		2
Urinary tract infection	2	26		28
Urinary tract infection bacterial	1			1
Urinary tract infection pseudomonal		1		1
Urosepsis	2	5		7
Varicella zoster virus infection		1		1
Viral infection		1		1
Viral pharyngitis	1			1
Wound infection		1		1
Injury, poisoning and procedural complications	**29**	**241**	**3**	**273**
Abdominal wound dehiscence		1		1
Accidental overdose		3		3
Acetabulum fracture		2		2
Alcohol poisoning		1		1
Anaemia postoperative		3		3
Anastomotic ulcer		1		1
Animal bite		3		3
Ankle fracture	1	13		14

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Avulsion fracture		1		1
Back injury	1			1
Brain herniation		1		1
Cartilage injury	1			1
Central cord syndrome		1		1
Cervical vertebral fracture		7		7
Clavicle fracture		2		2
Concussion		4		4
Contusion		2		2
Craniocerebral injury		5	1	6
Cystitis radiation		1		1
Epiphyseal fracture		1		1
Exposure to toxic agent		1		1
Eye injury		1		1
Facial bones fracture		2		2
Fall	1	13		14
Femoral neck fracture	1	6		7
Femur fracture	1	12		13
Fibula fracture		5		5
Foot fracture		4		4
Foreign body in respiratory tract	1			1
Foreign body ingestion		2		2
Fracture displacement		1		1
Fractured sacrum		1		1
Gastrointestinal procedural complication		1		1
Greenstick fracture	1			1
Gun shot wound		2		2
Hand fracture		1		1
Head injury	1	4		5
Hip fracture	2	9		11
Humerus fracture	1	2		3
Incarcerated incisional hernia	1			1
Incision site pain	1			1
Incisional hernia		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Incisional hernia, obstructive		1		1
Injury		1		1
Joint dislocation		1		1
Joint injury		1		1
Ligament rupture		1		1
Limb injury		2		2
Lower limb fracture		5		5
Lumbar vertebral fracture		2		2
Meniscus injury		1		1
Multiple fractures		1		1
Muscle strain		1		1
Overdose		5		5
Patella fracture		2		2
Pelvic fracture		1		1
Post procedural complication		4		4
Post procedural fever	1	1		2
Post procedural haematoma	1	1		2
Post procedural haemorrhage	1	1		2
Post procedural hypotension		1		1
Post procedural urine leak		1		1
Procedural complication		2		2
Procedural haemorrhage		1		1
Procedural nausea		1		1
Procedural pain		5		5
Pulmonary contusion		1		1
Radius fracture		4		4
Rib fracture		8		8
Road traffic accident	2	11		13
Seroma		1		1
Skin laceration	1	6		7
Snake bite		1		1
Spinal compression fracture		1		1
Spinal fracture			1	1
Sternal fracture		3		3

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Struck by lightning		1		1
Subdural haematoma		7		7
Sunburn	1			1
Superficial injury of eye	1			1
Tendon rupture	1	5		6
Thoracic vertebral fracture		1		1
Tibia fracture	1	5		6
Toxicity to various agents	1	2		3
Tracheal haemorrhage	1			1
Traumatic fracture		2		2
Traumatic liver injury		2		2
Ulna fracture	1	2		3
Upper limb fracture		6	1	7
Vulvovaginal injury		1		1
Wound dehiscence		5		5
Wrist fracture	2	3		5
Investigations		**15**	**1**	**16**
Ammonia increased		1		1
Anticoagulation drug level above therapeutic		1		1
Blood pressure increased		1		1
Blood sodium decreased			1	1
Ejection fraction decreased		1		1
Heart rate decreased		1		1
Heart rate irregular		1		1
Hepatic enzyme increased		2		2
Liver function test increased		2		2
Myocardial necrosis marker increased		2		2
Platelet count decreased		1		1
Staphylococcus test positive		1		1
Weight increased		1		1
Metabolism and nutrition disorders	**8**	**95**		**103**
Dehydration	1	9		10
Diabetes mellitus		2		2
Diabetes mellitus inadequate control		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Diabetic complication	1			1
Diabetic ketoacidosis	1	12		13
Electrolyte imbalance	1	1		2
Euglycaemic diabetic ketoacidosis		1		1
Failure to thrive		1		1
Gout	1	5		6
Hypercalcaemia		1		1
Hypercholesterolaemia		1		1
Hyperglycaemia		3		3
Hyperglycaemic hyperosmolar nonketotic syndrome		2		2
Hyperkalaemia		9		9
Hypervolaemia		1		1
Hypochloraemia		1		1
Hypoglycaemia	1	2		3
Hypokalaemia		3		3
Hypomagnesaemia		1		1
Hyponatraemia		8		8
Hypovolaemia		1		1
Ketoacidosis		2		2
Lactic acidosis		3		3
Metabolic acidosis		4		4
Obesity	1	12		13
Pseudohyponatraemia		1		1
Type 1 diabetes mellitus	1	4		5
Type 2 diabetes mellitus		3		3
Vitamin B12 deficiency		1		1
Musculoskeletal and connective tissue disorders	**14**	**194**	**1**	**209**
Ankylosing spondylitis		1		1
Arthralgia		6		6
Arthritis		2		2
Back pain		10		10
Bursitis		1		1
Cervical spinal stenosis		6		6
Chondrocalcinosis pyrophosphate		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Connective tissue disorder		1		1
Costochondritis		1		1
Flank pain	1	5		6
Foot deformity		3		3
Fracture nonunion		1		1
Haemarthrosis		1		1
Intervertebral disc degeneration		8		8
Intervertebral disc disorder		2		2
Intervertebral disc protrusion		7		7
Joint swelling		1		1
Lumbar spinal stenosis		10		10
Muscle spasms		1		1
Muscular weakness	1	5		6
Musculoskeletal chest pain	1	3	1	5
Myositis		1		1
Neck pain	1	3		4
Osteoarthritis	1	80		81
Osteonecrosis		2		2
Pain in extremity	1	2		3
Pseudarthrosis		1		1
Rhabdomyolysis	1	4		5
Rheumatoid arthritis		1		1
Rotator cuff syndrome		2		2
Soft tissue disorder		1		1
Spinal instability		1		1
Spinal osteoarthritis	1	5		6
Spinal stenosis	4	3		7
Spinal synovial cyst		3		3
Spondylolisthesis		6		6
Synovitis	1			1
Tendon disorder		1		1
Tenosynovitis		2		2
Vertebral foraminal stenosis	1			1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5**	**215**	**1**	**221**

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Adenocarcinoma of colon		1		1
Adenocarcinoma pancreas		1		1
Anaplastic large-cell lymphoma		1		1
B-cell lymphoma		2		2
B-cell small lymphocytic lymphoma		1		1
Benign lung neoplasm		1		1
Benign neoplasm of thymus		1		1
Benign pancreatic neoplasm		1		1
Benign salivary gland neoplasm		1		1
Bladder cancer		1		1
Bladder cancer recurrent		1		1
Bone cancer metastatic		1		1
Bone neoplasm		1		1
Borderline mucinous tumour of ovary		1		1
Breast cancer		5		5
Breast cancer male		1		1
Breast cancer metastatic		1		1
Breast cancer stage I	1	2		3
Cancer pain		1		1
Carcinoid tumour pulmonary			1	1
Clear cell renal cell carcinoma		4		4
Colon cancer		7		7
Colon cancer metastatic		1		1
Colon cancer stage III	1			1
Colon cancer stage IV		1		1
Colorectal adenoma		1		1
Colorectal cancer		2		2
Cutaneous T-cell lymphoma		1		1
Diffuse large B-cell lymphoma stage IV		1		1
Endometrial cancer		2		2
Ewing's sarcoma		1		1
Follicular lymphoma		1		1
Gallbladder neoplasm		1		1
Gastric cancer	1	2		3

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Gastric cancer stage III		1		1
Gastrointestinal stromal tumour		1		1
Glioblastoma		2		2
Glioblastoma multiforme		1		1
Hepatocellular carcinoma	2	1		3
High-grade B-cell lymphoma		1		1
Hodgkin's disease		1		1
Hormone receptor positive breast cancer		1		1
Intraductal proliferative breast lesion		4		4
Invasive breast carcinoma		2		2
Invasive ductal breast carcinoma		8		8
Invasive lobular breast carcinoma		2		2
Langerhans' cell histiocytosis		1		1
Lentigo maligna		1		1
Liposarcoma		1		1
Lung adenocarcinoma		3		3
Lung adenocarcinoma stage IV		1		1
Lung cancer metastatic		2		2
Lung carcinoma cell type unspecified stage I		1		1
Lung carcinoma cell type unspecified stage III		1		1
Lung neoplasm malignant		4		4
Malignant ascites		1		1
Malignant melanoma		9		9
Malignant melanoma stage III		1		1
Malignant neoplasm of thymus		1		1
Malignant neoplasm progression		1		1
Meningioma		2		2
Metastases to central nervous system		2		2
Metastases to lung		2		2
Metastatic malignant melanoma		1		1
Myxofibrosarcoma		1		1
Neoplasm malignant		1		1
Neoplasm of orbit		1		1
Neurilemmoma benign		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Neuroendocrine carcinoma		1		1
Neuroendocrine carcinoma metastatic		1		1
Non-Hodgkin's lymphoma		1		1
Non-small cell lung cancer		1		1
Non-small cell lung cancer metastatic		1		1
Oesophageal adenocarcinoma		2		2
Oesophageal carcinoma		3		3
Osteoma		1		1
Ovarian cancer		2		2
Ovarian clear cell carcinoma		1		1
Pancreatic carcinoma		6		6
Pancreatic carcinoma metastatic		2		2
Pancreatic carcinoma stage IV		2		2
Papillary renal cell carcinoma		1		1
Papillary thyroid cancer		2		2
Paranasal sinus neoplasm		1		1
Pelvic neoplasm		1		1
Phaeochromocytoma		2		2
Pituitary tumour benign		1		1
Plasma cell myeloma		1		1
Pleomorphic malignant fibrous histiocytoma		1		1
Prolactin-producing pituitary tumour		1		1
Prostate cancer		26		26
Prostate cancer metastatic		2		2
Prostate cancer recurrent		1		1
Prostate cancer stage II		1		1
Renal cancer		1		1
Renal cancer metastatic		1		1
Renal cell carcinoma		3		3
Salivary gland cancer stage IV		1		1
Sarcoma		1		1
Small cell lung cancer		2		2
Small cell lung cancer metastatic		1		1
Splenic marginal zone lymphoma		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Squamous cell carcinoma		2		2
Squamous cell carcinoma of skin		4		4
Squamous cell carcinoma of the tongue		1		1
T-cell type acute leukaemia		1		1
Throat cancer		1		1
Thymoma malignant		1		1
Thyroid cancer		1		1
Thyroid cancer metastatic		1		1
Tongue neoplasm malignant stage unspecified		1		1
Tonsil cancer		1		1
Uterine cancer		2		2
Uterine leiomyoma		9		9
Nervous system disorders	**21**	**215**		**236**
Alcoholic seizure		1		1
Altered state of consciousness		1		1
Amnesia		2		2
Amyotrophic lateral sclerosis	1	1		2
Ataxia		1		1
Autonomic nervous system imbalance		1		1
Balance disorder		2		2
Bell's palsy		3		3
Brain stem haemorrhage		1		1
Brain stem infarction		1		1
Carotid artery occlusion		1		1
Carotid artery stenosis		5		5
Carotid artery thrombosis		2		2
Cauda equina syndrome	1			1
Cerebellar haemorrhage		2		2
Cerebral artery stenosis		1		1
Cerebral haemorrhage		1		1
Cerebral infarction		2		2
Cerebrospinal fluid leakage		2		2
Cerebrovascular accident	4	32		36
Cerebrovascular disorder		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Cervical cord compression		1		1
Cervical radiculopathy		1		1
Cognitive disorder		1		1
Coma		1		1
Dementia		1		1
Dizziness		2		2
Drug withdrawal convulsions		1		1
Embolic stroke		4		4
Encephalopathy		3		3
Epilepsy	1			1
Essential tremor		1		1
Febrile convulsion	2	2		4
Guillain-Barre syndrome		1		1
Haemorrhage intracranial		1		1
Haemorrhagic stroke		1		1
Headache		3		3
Hemiparesis	1	2		3
Hemiplegia		1		1
Hemiplegic migraine		1		1
Hydrocephalus		1		1
Hypoaesthesia		2		2
Hypoxic-ischaemic encephalopathy		1		1
Idiopathic generalised epilepsy	1			1
Idiopathic partial epilepsy		1		1
Incoherent		1		1
Intracranial aneurysm		2		2
Ischaemic cerebral infarction		1		1
Ischaemic stroke		3		3
Lacunar stroke		1		1
Loss of consciousness		1		1
Lumbar radiculopathy		5		5
Migraine	1	1		2
Multiple sclerosis		1		1
Myasthenia gravis		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Myelitis transverse		1		1
Myelopathy		6		6
Nerve compression		1		1
Nervous system cyst		1		1
Neuropathy peripheral		2		2
Optic neuritis		1		1
Paraesthesia	2	2		4
Paralysis		1		1
Petit mal epilepsy		1		1
Presyncope		4		4
Ruptured cerebral aneurysm		1		1
Sciatica		3		3
Seizure	4	9		13
Seizure like phenomena		1		1
Sensory disturbance		1		1
Speech disorder		1		1
Spinal claudication		1		1
Spinal cord compression		2		2
Subarachnoid haemorrhage	1	5		6
Syncope	2	34		36
Thalamic infarction		1		1
Toxic encephalopathy		2		2
Transient global amnesia		2		2
Transient ischaemic attack		16		16
Tremor		1		1
Trigeminal neuralgia		1		1
Unresponsive to stimuli		1		1
Pregnancy, puerperium and perinatal conditions	**4**	**41**		**45**
Abortion missed		2		2
Abortion spontaneous	3	18		21
Delivery		1		1
Ectopic pregnancy	1	2		3
Foetal death		1		1
Foetal hypokinesia		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Gestational diabetes		1		1
Gestational hypertension		2		2
Hyperemesis gravidarum		1		1
Morning sickness		2		2
Pre-eclampsia		6		6
Premature rupture of membranes		2		2
Premature separation of placenta		1		1
Prolonged pregnancy		1		1
Product issues	**1**	**5**		**6**
Device dislocation		1		1
Device electrical impedance issue		1		1
Device failure		2		2
Device loosening		1		1
Lead dislodgement	1			1
Psychiatric disorders	**28**	**77**		**105**
Acute stress disorder		1		1
Affective disorder	1			1
Alcohol abuse	1			1
Alcohol use disorder		2		2
Alcohol withdrawal syndrome	2	2		4
Anxiety		6		6
Anxiety disorder	1			1
Bipolar disorder		4		4
Bipolar I disorder		4		4
Completed suicide	1	2		3
Confusional state	1			1
Delirium		1		1
Depression	1	14		15
Depression suicidal	1	1		2
Disruptive mood dysregulation disorder		1		1
Generalised anxiety disorder		1		1
Immunisation stress-related response	1			1
Intentional self-injury	1	1		2
Major depression	4	5		9

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Mania		2		2
Mental status changes		3		3
Oppositional defiant disorder		1		1
Panic attack		1		1
Post-traumatic stress disorder		1		1
Psychotic disorder		1		1
Schizoaffective disorder	2	2		4
Schizophrenia	1			1
Substance use disorder		3		3
Substance-induced mood disorder		1		1
Substance-induced psychotic disorder	1			1
Suicidal ideation	4	15		19
Suicide attempt	5	2		7
Renal and urinary disorders	**6**	**110**		**116**
Acute kidney injury	1	36		37
Azotaemia		1		1
Bladder prolapse		3		3
Chronic kidney disease	1	3		4
Haematuria		4		4
Hydronephrosis		6		6
Nephritis		1		1
Nephrolithiasis	3	25		28
Nephropathy toxic		1		1
Obstructive nephropathy	1			1
Renal aneurysm		1		1
Renal artery stenosis		1		1
Renal cyst		2		2
Renal failure		5		5
Renal impairment		1		1
Renal mass		1		1
Ureteric obstruction		1		1
Ureterolithiasis		6		6
Urinary retention		9		9
Urinary tract obstruction		2		2

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Urogenital fistula		1		1
Reproductive system and breast disorders	**3**	**32**		**35**
Abnormal uterine bleeding		1		1
Adenomyosis		1		1
Adnexal torsion	1			1
Benign prostatic hyperplasia		8		8
Cervical dysplasia		2		2
Cervix haemorrhage uterine		1		1
Endometriosis		1		1
Erectile dysfunction		1		1
Haemorrhagic ovarian cyst		1		1
Heavy menstrual bleeding		4		4
Menometrorrhagia		1		1
Ovarian cyst		1		1
Ovarian cyst torsion		1		1
Pelvic organ prolapse	1	1		2
Pelvic pain		2		2
Prostatomegaly		3		3
Uterine haemorrhage	1	2		3
Uterine prolapse		1		1
Respiratory, thoracic and mediastinal disorders	**29**	**160**		**189**
Acquired diaphragmatic eventration		1		1
Acute pulmonary oedema		1		1
Acute respiratory distress syndrome	1			1
Acute respiratory failure	8	17		25
Asthma	4	8		12
Asthma-chronic obstructive pulmonary disease overlap syndrome		1		1
Atelectasis	1	1		2
Bronchial hyperreactivity	1			1
Bronchiectasis		1		1
Bronchopulmonary dysplasia	1			1
Bronchospasm	1			1
Chronic obstructive pulmonary disease	3	22		25
Dyspnoea	2	10		12

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Dyspnoea exertional		5		5
Emphysema	1			1
Haemothorax		2		2
Hiccups		1		1
Hypoxia	1	3		4
Pleural effusion		12		12
Pleuritic pain	1			1
Pneumothorax		7		7
Pneumothorax spontaneous		2		2
Pulmonary artery thrombosis		1		1
Pulmonary embolism	4	43		47
Pulmonary mass		3		3
Pulmonary oedema		7		7
Respiratory acidosis		1		1
Respiratory distress		2		2
Respiratory failure		7		7
Respiratory tract congestion		1		1
Tonsillar hypertrophy		1		1
Skin and subcutaneous tissue disorders	**1**	**8**		**9**
Angioedema		2		2
Decubitus ulcer		1		1
Drug eruption		1		1
Erythema multiforme	1			1
Erythema nodosum		1		1
Rash		1		1
Rash vesicular		1		1
Skin ulcer		1		1
Social circumstances		**1**		**1**
Physical assault		1		1
Surgical and medical procedures		**8**		**8**
Abdominoplasty		1		1
Abortion induced		1		1
Colectomy		2		2
Knee arthroplasty		1		1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Liposuction		1		1
Mammoplasty		1		1
Stent placement		1		1
Vascular disorders	**9**	**94**		**103**
Accelerated hypertension		1		1
Aortic aneurysm		2		2
Aortic dissection		1		1
Aortic stenosis		5		5
Arterial insufficiency		1		1
Arteriosclerosis		2		2
Axillary vein thrombosis		1		1
Deep vein thrombosis	1	17		18
Embolism		1		1
Embolism venous		2		2
Extremity necrosis		1		1
Haematoma	1	2		3
Hypertension	1	11		12
Hypertensive crisis		3		3
Hypertensive emergency	1			1
Hypertensive urgency		4		4
Hypotension		15		15
Intermittent claudication		1		1
Ischaemia		1		1
Jugular vein thrombosis		1		1
Kawasaki's disease	2			2
Orthostatic hypotension		6		6
Pelvic venous thrombosis		1		1
Peripheral arterial occlusive disease		4		4
Peripheral artery aneurysm	1	2		3
Peripheral artery occlusion		1		1
Peripheral artery thrombosis		1		1
Peripheral ischaemia		1		1
Peripheral vascular disorder		1		1
Polyarteritis nodosa	1			1

Event Counts	Exposure			
SOC - PT	mRNA-1273 vs Placebo	mRNA-1273	mRNA-1273 vs mRNA-1273.214	Grand Total
Shock	1	1		2
Shock haemorrhagic		1		1
Subclavian vein thrombosis		1		1
Thrombosis		1		1
Venous thrombosis limb		1		1
(blank)		**1**		**1**
(blank)		1		1
Grand Total	**321**	**2790**	**12**	**3123**

Appendix 3 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-marketing Data Sources

Cumulative and Interval Summary Tabulations of Serious and Non Serious Adverse Reactions from Post-marketing Data Sources (Through 18 June 2022)

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
Blood and lymphatic system disorders	*** SOC TOTAL ***	1268	5295	10610	26237	31532	0	0
	Abdominal lymphadenopathy	2	3	1	3	6	0	0
	Abnormal clotting factor	2	3	0	1	4	0	0
	Acquired Von Willebrand's disease	0	1	0	0	1	0	0
	Acquired haemophilia	6	19	0	0	19	0	0
	Acquired protein S deficiency	1	1	0	0	1	0	0
	Agranulocytosis	1	8	0	0	8	0	0
	Anaemia	39	243	33	153	396	0	0
	Anaemia folate deficiency	0	2	0	0	2	0	0
	Anaemia macrocytic	0	9	0	2	11	0	0
	Anaemia megaloblastic	1	2	0	0	2	0	0
	Anaemia of chronic disease	0	6	0	0	6	0	0
	Anaemia of pregnancy	0	0	0	1	1	0	0
	Anaemia vitamin B12 deficiency	1	1	0	1	2	0	0
	Anisocytosis	0	5	0	2	7	0	0
	Antiphospholipid syndrome	6	24	0	0	24	0	0
	Aplasia pure red cell	0	2	0	0	2	0	0
	Aplastic anaemia	7	22	0	0	22	0	0
	Atypical haemolytic uraemic syndrome	0	2	0	0	2	0	0
	Autoimmune anaemia	1	1	0	0	1	0	0
	Autoimmune haemolytic anaemia	14	48	0	0	48	0	0
	Autoimmune neutropenia	0	1	0	0	1	0	0
	Autoimmune pancytopenia	0	1	0	0	1	0	0
	Bandaemia	0	4	0	0	4	0	0
	Bicytopenia	0	6	0	0	6	0	0
	Blood disorder	5	19	2	17	36	0	0
	Blood loss anaemia	2	20	0	0	20	0	0
	Bone marrow disorder	0	3	0	2	5	0	0
	Bone marrow failure	2	7	0	0	7	0	0
	Bone marrow oedema	2	4	2	6	10	0	0
	Bone marrow oedema syndrome	0	1	0	0	1	0	0
	Bone marrow reticulin fibrosis	0	1	0	0	1	0	0
	Breakthrough haemolysis	2	3	1	1	4	0	0
	Coagulation factor deficiency	2	2	0	0	2	0	0
	Coagulopathy	21	65	16	46	111	0	0
	Cold type haemolytic anaemia	0	4	0	0	4	0	0
	Coombs negative haemolytic anaemia	1	2	0	0	2	0	0
	Coombs positive haemolytic anaemia	0	5	0	0	5	0	0
	Cytopenia	0	3	0	0	3	0	0
	Disseminated intravascular coagulation	6	38	0	0	38	0	0
	Eosinopenia	0	1	0	0	1	0	0
	Eosinophilia	5	28	3	18	46	0	0
	Erythropoiesis abnormal	0	1	0	0	1	0	0
	Evans syndrome	1	7	0	0	7	0	0
	Factor VIII inhibition	2	5	0	0	5	0	0
	Factor XIII inhibition	0	0	0	1	1	0	0
	Febrile neutropenia	3	14	0	0	14	0	0
	Granulocytopenia	0	1	0	0	1	0	0
	Granulomatous lymphadenitis	0	1	0	0	1	0	0
	Haemoconcentration	0	2	0	0	2	0	0
	Haemolysis	2	26	2	3	29	0	0
	Haemolytic anaemia	10	36	0	1	37	0	0
	Haemolytic uraemic syndrome	1	2	0	0	2	0	0
	Haemorrhagic diathesis	2	16	1	1	17	0	0
	Haemorrhagic disorder	0	4	0	0	4	0	0
	Heparin-induced thrombocytopenia	0	9	0	0	9	0	0
	Hilar lymphadenopathy	0	13	1	4	17	0	0
	Hyperchromic anaemia	0	1	0	0	1	0	0
	Hypercoagulation	2	16	1	9	25	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Hypereosinophilic syndrome	1	4	0	0	4	0	0
	Hyperfibrinogenaemia	0	2	0	0	2	0	0
	Hyperfibrinolysis	0	1	0	0	1	0	0
	Hypergammaglobulinaemia	1	2	0	1	3	0	0
	Hyperleukocytosis	0	5	1	2	7	0	0
	Hypochromic anaemia	1	4	0	0	4	0	0
	Hypofibrinogenaemia	0	2	0	0	2	0	0
	Hyposplenism	0	1	0	0	1	0	0
	Immune thrombocytopenia	68	312	1	7	319	0	0
	Increased tendency to bruise	7	25	15	50	75	0	0
	Iron deficiency anaemia	6	22	5	9	31	0	0
	Leukocytosis	6	124	12	40	164	0	0
	Leukopenia	9	69	3	8	77	0	0
	Lymph node calcification	0	2	0	1	3	0	0
	Lymph node haemorrhage	0	0	0	1	1	0	0
	Lymph node pain	58	271	610	2370	2641	0	0
	Lymph node rupture	1	1	0	1	2	0	0
	Lymph node ulcer	0	1	0	0	1	0	0
	Lymphadenitis	31	85	214	473	558	0	0
	Lymphadenopathy	690	2370	9609	22785	25155	0	0
	Lymphadenopathy mediastinal	1	32	1	5	37	0	0
	Lymphatic disorder	1	3	4	11	14	0	0
	Lymphatic insufficiency	1	1	1	1	2	0	0
	Lymphocytic infiltration	0	2	0	2	4	0	0
	Lymphocytosis	1	6	0	1	7	0	0
	Lymphoid tissue hyperplasia	0	0	1	2	2	0	0
	Lymphopenia	4	28	10	19	47	0	0
	Macrocytosis	0	4	0	0	4	0	0
	Mast cell activation syndrome	6	21	1	3	24	0	0
	Mastocytosis	0	1	3	3	4	0	0
	Microcytic anaemia	2	7	0	2	9	0	0
	Monoclonal B-cell lymphocytosis	0	3	0	0	3	0	0
	Monocytosis	2	5	0	1	6	0	0
	Myelosuppression	1	4	0	0	4	0	0
	Necrotic lymphadenopathy	0	3	0	0	3	0	0
	Neutropenia	10	54	2	3	57	0	0
	Neutropenia neonatal	0	1	0	0	1	0	0
	Neutrophilia	1	7	0	2	9	0	0
	Normochromic anaemia	1	1	0	1	2	0	0
	Normochromic normocytic anaemia	0	1	0	0	1	0	0
	Normocytic anaemia	4	16	0	2	18	0	0
	Nucleated red cells	0	10	0	0	10	0	0
	Pancytopenia	12	64	0	0	64	0	0
	Paratracheal lymphadenopathy	0	0	0	2	2	0	0
	Pernicious anaemia	0	1	2	2	3	0	0
	Placental transfusion syndrome	0	1	0	0	1	0	0
	Platelet destruction increased	1	1	0	0	1	0	0
	Platelet disorder	3	8	1	9	17	0	0
	Polychromasia	0	5	0	1	6	0	0
	Polycythaemia	1	6	2	7	13	0	0
	Pseudolymphoma	0	2	0	4	6	0	0
	Red blood cell abnormality	0	1	0	11	12	0	0
	Retroperitoneal lymphadenopathy	0	4	0	0	4	0	0
	Rouleaux formation	0	1	0	0	1	0	0
	Schistocytosis	0	1	0	0	1	0	0
	Sickle cell anaemia with crisis	0	11	0	0	11	0	0
	Spleen disorder	0	0	0	5	5	0	0
	Spleen ischaemia	1	2	0	0	2	0	0
	Splenic artery stenosis	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Splenic artery thrombosis	0	1	0	0	1	0	0
	Splenic calcification	0	1	0	1	2	0	0
	Splenic cyst	0	1	0	0	1	0	0
	Splenic granuloma	0	2	0	0	2	0	0
	Splenic haematoma	1	2	0	0	2	0	0
	Splenic haemorrhage	0	3	0	0	3	0	0
	Splenic infarction	4	31	0	0	31	0	0
	Splenic lesion	0	2	0	0	2	0	0
	Splenic thrombosis	0	7	0	0	7	0	0
	Splenic vein thrombosis	4	14	0	0	14	0	0
	Splenitis	0	0	2	2	2	0	0
	Splenomegaly	6	32	11	31	63	0	0
	Spontaneous haematoma	4	12	10	23	35	0	0
	Spontaneous haemorrhage	0	8	0	0	8	0	0
	Stress polycythaemia	1	1	0	0	1	0	0
	Subcapsular splenic haematoma	0	1	0	0	1	0	0
	Thrombocytopenia	132	660	18	34	694	0	0
	Thrombocytopenic purpura	4	16	0	1	17	0	0
	Thrombocytosis	7	18	S	12	30	0	0
	Thrombosis with thrombocytopenia syndrome	12	2S	0	0	2S	0	0
	Thrombotic microangiopathy	1	8	0	0	8	0	0
	Thrombotic thrombocytopenic purpura	S	38	1	1	39	0	0
	Thymus enlargement	1	3	0	0	3	0	0
	Warm autoimmune haemolytic anaemia	1	4	0	0	4	0	0
	White blood cell disorder	1	9	2	13	22	0	0
Cardiac disorders	*** SOC TOTAL ***	6S48	23316	6440	17OSS	40371	0	0
	Accelerated idioventricular rhythm	0	0	0	2	2	0	0
	Acute cardiac event	3	8	0	0	8	0	0
	Acute coronary syndrome	41	88	0	0	88	0	0
	Acute left ventricular failure	0	31	0	0	31	0	0
	Acute myocardial infarction	114	S59	1	1	S60	0	0
	Adams-Stokes syndrome	1	1	0	0	1	0	0
	Agonal rhythm	0	3	0	0	3	0	0
	Angina pectoris	293	692	148	207	899	0	0
	Angina unstable	S	23	1	1	24	0	0
	Aortic valve calcification	0	6	0	0	6	0	0
	Aortic valve disease	0	2	0	1	3	0	0
	Aortic valve incompetence	3	18	0	0	18	0	0
	Aortic valve sclerosis	0	4	0	1	S	0	0
	Aortic valve stenosis	0	9	1	1	10	0	0
	Aortic valve thickening	0	3	0	0	3	0	0
	Arrhythmia	805	1647	7S2	896	2S43	0	0
	Arrhythmia supraventricular	1	4	0	1	S	0	0
	Arrhythmic storm	0	1	0	0	1	0	0
	Arteriosclerosis coronary artery	1	37	0	6	43	0	0
	Arteriospasm coronary	1	10	1	1	11	0	0
	Arteritis coronary	1	2	0	0	2	0	0
	Atrial enlargement	0	8	1	S	13	0	0
	Atrial fibrillation	223	1S69	78	1S4	1723	0	0
	Atrial flutter	23	108	4	49	1S7	0	0
	Atrial tachycardia	S	16	4	17	33	0	0
	Atrial thrombosis	1	6	0	0	6	0	0
	Atrioventricular block	10	60	1	21	81	0	0
	Atrioventricular block complete	16	49	0	1	S0	0	0
	Atrioventricular block first degree	0	12	2	8	20	0	0
	Atrioventricular block second degree	2	18	3	8	26	0	0
	Autoimmune pericarditis	1	3	0	0	3	0	0
	Bifascicular block	0	3	0	0	3	0	0
	Bradyarrhythmia	1	1	1	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Bradycardia	37	410	23	62	472	0	0
	Bradycardia foetal	1	2	0	0	2	0	0
	Bradycardia neonatal	0	1	0	0	1	0	0
	Bundle branch block	0	3	0	5	8	0	0
	Bundle branch block bilateral	0	1	0	1	2	0	0
	Bundle branch block left	4	28	3	20	48	0	0
	Bundle branch block right	1	36	1	22	58	0	0
	Cardiac amyloidosis	0	1	0	0	1	0	0
	Cardiac aneurysm	1	5	0	0	5	0	0
	Cardiac arrest	114	670	0	1	671	0	0
	Cardiac discomfort	50	102	173	317	419	0	0
	Cardiac disorder	36	185	32	194	379	0	0
	Cardiac dysfunction	7	34	0	0	34	0	0
	Cardiac failure	98	402	8	10	412	0	0
	Cardiac failure acute	23	89	0	0	89	0	0
	Cardiac failure chronic	9	22	0	0	22	0	0
	Cardiac failure congestive	13	285	0	5	290	0	0
	Cardiac fibrillation	23	45	3	6	51	0	0
	Cardiac flutter	43	496	13	123	619	0	0
	Cardiac hypertrophy	2	9	2	2	11	0	0
	Cardiac perforation	1	1	0	0	1	0	0
	Cardiac perfusion defect	0	3	0	0	3	0	0
	Cardiac sarcoidosis	0	3	0	0	3	0	0
	Cardiac septal hypertrophy	0	2	1	2	4	0	0
	Cardiac steatosis	0	1	0	0	1	0	0
	Cardiac tamponade	5	39	0	0	39	0	0
	Cardiac valve disease	3	7	1	2	9	0	0
	Cardiac valve thickening	0	1	0	0	1	0	0
	Cardiac ventricular disorder	0	2	0	0	2	0	0
	Cardiac ventricular thrombosis	2	21	0	0	21	0	0
	Cardio-respiratory arrest	61	237	0	1	238	0	0
	Cardio-respiratory distress	0	3	0	0	3	0	0
	Cardiogenic shock	19	90	0	0	90	0	0
	Cardiomegaly	12	172	6	36	208	0	0
	Cardiomyopathy	16	104	1	4	108	0	0
	Cardiomyopathy acute	0	1	0	0	1	0	0
	Cardiopulmonary failure	3	11	0	0	11	0	0
	Cardiorenal syndrome	0	1	0	0	1	0	0
	Cardiovascular deconditioning	0	1	1	1	2	0	0
	Cardiovascular disorder	44	111	252	453	564	0	0
	Cardiovascular insufficiency	3	12	3	4	16	0	0
	Cardiovascular symptom	6	18	0	3	21	0	0
	Carditis	8	45	0	3	48	0	0
	Chordae tendinae rupture	1	3	0	0	3	0	0
	Chronic left ventricular failure	1	23	0	1	24	0	0
	Chronotropic incompetence	0	1	0	0	1	0	0
	Conduction disorder	0	3	2	4	7	0	0
	Congestive cardiomyopathy	15	42	0	2	44	0	0
	Cor pulmonale	0	4	0	0	4	0	0
	Cor pulmonale acute	2	9	0	0	9	0	0
	Coronary artery aneurysm	1	4	0	0	4	0	0
	Coronary artery dilatation	0	2	0	0	2	0	0
	Coronary artery disease	21	102	2	10	112	0	0
	Coronary artery dissection	4	27	0	0	27	0	0
	Coronary artery embolism	0	3	0	0	3	0	0
	Coronary artery insufficiency	1	1	0	0	1	0	0
	Coronary artery occlusion	6	84	0	0	84	0	0
	Coronary artery stenosis	6	35	0	0	35	0	0
	Coronary artery thrombosis	4	29	0	0	29	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Coronary ostial stenosis	0	2	0	0	2	0	0
	Defect conduction intraventricular	1	3	0	1	4	0	0
	Diabetic cardiomyopathy	0	1	0	0	1	0	0
	Diastolic dysfunction	0	26	0	2	28	0	0
	Dilatation ventricular	1	1	0	0	1	0	0
	Dressler's syndrome	0	1	0	0	1	0	0
	Endocarditis noninfective	0	1	0	0	1	0	0
	Eosinophilic myocarditis	1	4	0	0	4	0	0
	Extrasystoles	88	181	151	404	585	0	0
	Foetal arrhythmia	1	2	0	0	2	0	0
	Foetal heart rate disorder	0	2	0	0	2	0	0
	Giant cell myocarditis	0	1	0	0	1	0	0
	Heart alternation	0	1	0	4	5	0	0
	Heart valve calcification	0	0	0	1	1	0	0
	Heart valve incompetence	2	12	0	8	20	0	0
	Hyperdynamic left ventricle	0	4	0	0	4	0	0
	Hypersensitivity myocarditis	1	3	0	0	3	0	0
	Hypertensive cardiomegaly	0	1	0	0	1	0	0
	Hypertensive cardiomyopathy	0	1	0	0	1	0	0
	Hypertensive heart disease	1	11	1	1	12	0	0
	Immune-mediated myocarditis	3	4	0	0	4	0	0
	Intracardiac mass	0	2	0	0	2	0	0
	Intracardiac thrombus	4	56	0	0	56	0	0
	Ischaemic cardiomyopathy	1	8	0	0	8	0	0
	Left atrial dilatation	0	13	0	0	13	0	0
	Left atrial enlargement	0	11	0	7	18	0	0
	Left ventricular dilatation	1	10	0	0	10	0	0
	Left ventricular dysfunction	6	51	1	2	53	0	0
	Left ventricular enlargement	1	7	0	2	9	0	0
	Left ventricular failure	4	36	0	0	36	0	0
	Left ventricular hypertrophy	1	32	0	13	45	0	0
	Long QT syndrome	1	2	0	1	3	0	0
	Microvascular coronary artery disease	0	1	0	0	1	0	0
	Mitral valve calcification	0	4	0	0	4	0	0
	Mitral valve disease	0	2	0	0	2	0	0
	Mitral valve incompetence	9	68	2	5	73	0	0
	Mitral valve prolapse	2	10	1	7	17	0	0
	Mitral valve stenosis	0	3	0	0	3	0	0
	Mitral valve thickening	0	2	0	0	2	0	0
	Myocardial fibrosis	1	14	1	1	15	0	0
	Myocardial infarction	214	954	2	9	963	0	0
	Myocardial injury	1	28	0	0	28	0	0
	Myocardial ischaemia	5	53	0	0	53	0	0
	Myocardial necrosis	1	3	0	0	3	0	0
	Myocardial oedema	3	21	0	0	21	0	0
	Myocardial rupture	0	7	0	0	7	0	0
	Myocarditis	895	2955	46	96	3051	0	0
	Myopericarditis	209	758	6	7	765	0	0
	Myxomatous mitral valve degeneration	0	1	0	0	1	0	0
	Neonatal bradyarrhythmia	1	1	0	0	1	0	0
	Nodal arrhythmia	0	3	0	0	3	0	0
	Nodal rhythm	0	1	0	0	1	0	0
	Non-obstructive cardiomyopathy	1	1	0	0	1	0	0
	Palpitations	1145	3205	2057	7381	10586	0	0
	Paroxysmal arrhythmia	1	1	0	0	1	0	0
	Pericardial cyst	1	3	0	0	3	0	0
	Pericardial disease	2	3	2	2	5	0	0
	Pericardial effusion	95	391	12	19	410	0	0
	Pericardial fibrosis	0	9	0	1	10	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Pericardial haemorrhage	4	14	0	0	14	0	0
	Pericardial mass	0	1	0	0	1	0	0
	Pericardial rub	0	3	1	2	5	0	0
	Pericarditis	563	1869	72	137	2006	0	0
	Pericarditis constrictive	3	8	0	0	8	0	0
	Pleuropericarditis	11	23	1	1	24	0	0
	Postural orthostatic tachycardia syndrome	15	42	7	48	90	0	0
	Prinzmetal angina	2	9	1	1	10	0	0
	Pulmonary valve disease	0	1	0	0	1	0	0
	Pulmonary valve incompetence	0	4	0	0	4	0	0
	Pulmonary valve stenosis	2	4	0	0	4	0	0
	Pulmonary valve thickening	0	2	0	0	2	0	0
	Pulseless electrical activity	2	55	0	1	56	0	0
	Reperfusion arrhythmia	1	1	0	0	1	0	0
	Restrictive cardiomyopathy	0	2	0	0	2	0	0
	Rhythm idioventricular	0	1	0	0	1	0	0
	Right atrial dilatation	0	6	0	2	8	0	0
	Right atrial enlargement	0	2	0	3	5	0	0
	Right ventricular diastolic collapse	0	3	0	0	3	0	0
	Right ventricular dilatation	0	14	0	2	16	0	0
	Right ventricular dysfunction	0	20	0	1	21	0	0
	Right ventricular enlargement	0	7	0	1	8	0	0
	Right ventricular failure	4	21	0	0	21	0	0
	Right ventricular hypertrophy	0	5	0	1	6	0	0
	Sigmoid-shaped ventricular septum	0	1	0	0	1	0	0
	Silent myocardial infarction	0	1	0	0	1	0	0
	Sinoatrial block	1	2	0	0	2	0	0
	Sinus arrest	1	10	0	0	10	0	0
	Sinus arrhythmia	4	23	2	14	37	0	0
	Sinus bradycardia	2	24	2	31	55	0	0
	Sinus node dysfunction	2	13	0	0	13	0	0
	Sinus tachycardia	22	135	16	152	287	0	0
	Stress cardiomyopathy	11	48	1	5	53	0	0
	Supraventricular extrasystoles	12	32	18	91	123	0	0
	Supraventricular tachyarrhythmia	0	1	0	0	1	0	0
	Supraventricular tachycardia	18	134	12	106	240	0	0
	Systolic dysfunction	1	12	0	1	13	0	0
	Tachyarrhythmia	12	29	4	13	42	0	0
	Tachycardia	772	2095	2456	5454	7549	0	0
	Tachycardia foetal	0	4	1	1	5	0	0
	Tachycardia induced cardiomyopathy	1	1	0	0	1	0	0
	Tachycardia paroxysmal	4	9	3	7	16	0	0
	Thyrotoxic cardiomyopathy	1	1	0	0	1	0	0
	Torsade de pointes	2	4	0	0	4	0	0
	Toxic cardiomyopathy	1	1	0	0	1	0	0
	Tricuspid valve disease	0	2	0	0	2	0	0
	Tricuspid valve incompetence	3	45	0	1	46	0	0
	Tricuspid valve prolapse	0	0	0	1	1	0	0
	Ventricle rupture	0	2	0	0	2	0	0
	Ventricular arrhythmia	4	11	1	1	12	0	0
	Ventricular dysfunction	0	8	0	0	8	0	0
	Ventricular dyskinesia	0	1	0	0	1	0	0
	Ventricular dyssynchrony	0	2	0	0	2	0	0
	Ventricular enlargement	0	4	0	1	5	0	0
	Ventricular extrasystoles	38	128	32	314	442	0	0
	Ventricular failure	0	2	0	0	2	0	0
	Ventricular fibrillation	45	117	0	0	117	0	0
	Ventricular hypertrophy	0	5	0	2	7	0	0
	Ventricular hypokinesia	1	62	0	1	63	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Ventricular remodelling	1	1	0	0	1	0	0
	Ventricular tachyarrhythmia	1	3	0	0	3	0	0
	Ventricular tachycardia	18	146	3	7	153	0	0
	Wandering pacemaker	0	0	0	1	1	0	0
	Wolff-Parkinson-White syndrome	1	3	0	1	4	0	0
Congenital, familial and genetic disorders	*** SOC TOTAL ***	46	228	22	97	325	1	1
	Accessory spleen	0	1	0	1	2	0	0
	Alpha-1 antitrypsin deficiency	0	1	0	0	1	0	0
	Anencephaly	0	1	0	0	1	0	0
	Angelman's syndrome	0	0	0	1	1	0	0
	Ankyloglossia congenital	0	1	0	0	1	0	0
	Antithrombin III deficiency	0	1	0	0	1	0	0
	Aorticopulmonary septal defect	0	1	0	0	1	0	0
	Aplasia	1	2	0	0	2	0	0
	Arnold-Chiari malformation	1	5	0	0	5	0	0
	Arteriovenous malformation	0	3	0	0	3	0	0
	Atrial septal defect	1	16	0	3	19	0	0
	Bicuspid aortic valve	1	2	0	0	2	0	0
	Birth mark	0	0	1	6	6	0	0
	Block vertebra	1	1	0	0	1	0	0
	Branchial cyst	0	0	0	1	1	0	0
	Bronchogenic cyst	0	2	0	0	2	0	0
	Brugada syndrome	0	3	0	0	3	0	0
	Cardiac malposition	0	0	0	1	1	0	0
	Cardiac septal defect	0	1	0	0	1	0	0
	Cerebellar hypoplasia	0	2	0	0	2	0	0
	Cerebral cavernous malformation	0	5	0	0	5	0	0
	Cerebral palsy	0	5	0	0	5	0	0
	Cerebrovascular arteriovenous malformation	0	1	0	0	1	0	0
	Chronic granulomatous disease	0	1	0	0	1	0	0
	Cleft lip	0	1	0	1	2	0	0
	Cleft palate	0	2	0	0	2	0	0
	Cleft uvula	0	1	0	0	1	0	0
	Coloboma	0	1	0	0	1	0	0
	Colour blindness	2	4	2	5	9	0	0
	Combined immunodeficiency	0	2	0	0	2	0	0
	Congenital acrochordon	0	0	0	1	1	0	0
	Congenital anomaly	1	2	0	0	2	0	0
	Congenital brain damage	1	1	0	0	1	0	0
	Congenital cardiovascular anomaly	1	1	0	0	1	0	0
	Congenital central nervous system anomaly	2	3	0	0	3	0	0
	Congenital diaphragmatic hernia	0	1	0	0	1	0	0
	Congenital ectodermal dysplasia	0	1	0	0	1	0	0
	Congenital hydronephrosis	0	1	0	0	1	0	0
	Congenital hypercoagulation	0	1	0	0	1	0	0
	Congenital midline defect	1	1	0	0	1	0	0
	Congenital musculoskeletal disorder of limbs	1	3	0	0	3	0	0
	Congenital musculoskeletal disorder of spine	0	1	0	0	1	0	0
	Congenital nose malformation	0	1	0	0	1	0	0
	Congenital skin disorder	0	1	0	0	1	0	0
	Conjoined twins	0	2	0	0	2	0	0
	Corneal dystrophy	0	0	0	1	1	0	0
	Cryptorchism	0	1	0	0	1	0	0
	Cystic fibrosis	0	1	0	1	2	0	0
	Cytogenetic abnormality	0	2	0	1	3	0	0
	DNMT3A gene mutation	0	1	0	0	1	0	0
	Dermoid cyst	1	2	0	0	2	0	0
	Developmental hip dysplasia	0	0	0	0	0	1	1
	Dysmorphism	0	1	0	3	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Ehlers-Danlos syndrome	0	2	1	3	5	0	0
	Epidermal naevus	0	0	0	1	1	0	0
	Epidermal naevus syndrome	0	0	0	1	1	0	0
	Exomphalos	0	2	0	0	2	0	0
	Eyelid ptosis congenital	0	1	0	0	1	0	0
	Facioscapulohumeral muscular dystrophy	0	0	0	1	1	0	0
	Factor II mutation	0	3	0	0	3	0	0
	Factor IX deficiency	0	0	0	1	1	0	0
	Factor V Leiden mutation	0	4	0	3	7	0	0
	Factor V deficiency	0	1	0	0	1	0	0
	Factor VII deficiency	0	1	0	0	1	0	0
	Factor VIII deficiency	0	2	0	0	2	0	0
	Factor XI deficiency	1	1	0	0	1	0	0
	Fallot's tetralogy	0	1	0	0	1	0	0
	Familial mediterranean fever	0	0	0	1	1	0	0
	Familial periodic paralysis	1	1	0	0	1	0	0
	Foetal chromosome abnormality	1	3	0	0	3	0	0
	Foetal malformation	1	3	0	0	3	0	0
	Fragile X carrier	0	0	0	1	1	0	0
	Gastrointestinal malformation	0	1	0	0	1	0	0
	Gastroschisis	0	1	0	0	1	0	0
	Gene mutation	0	2	2	10	12	0	0
	Glucose-6-phosphate dehydrogenase deficiency	0	0	0	2	2	0	0
	Grey matter heterotopia	1	2	0	0	2	0	0
	Haemoglobinopathy	0	0	0	1	1	0	0
	Haemophilia	0	1	0	2	3	0	0
	Haemorrhagic arteriovenous malformation	0	1	0	0	1	0	0
	Heart disease congenital	1	5	1	1	6	0	0
	Hereditary angioedema	4	4	4	10	14	0	0
	Hereditary ataxia	0	1	0	0	1	0	0
	Hereditary haemolytic anaemia	0	1	0	0	1	0	0
	Hereditary motor and sensory neuropathy	0	0	1	1	1	0	0
	Hereditary optic atrophy	0	1	0	0	1	0	0
	Hereditary spastic paraplegia	0	0	1	1	1	0	0
	Heterotaxia	0	1	0	0	1	0	0
	Hydrocele	1	1	0	2	3	0	0
	Hyperexplexia	0	0	0	2	2	0	0
	Hypertrophic cardiomyopathy	1	7	0	0	7	0	0
	Hypoplastic left heart syndrome	0	1	0	0	1	0	0
	Hypospadias	1	1	1	1	2	0	0
	Intestinal atresia	1	1	0	0	1	0	0
	Janus kinase 2 mutation	0	2	0	0	2	0	0
	Keratosis follicular	0	0	1	1	1	0	0
	Kidney duplex	0	1	0	0	1	0	0
	Kidney malformation	0	1	0	0	1	0	0
	Klinefelter's syndrome	1	1	0	0	1	0	0
	Labial tie	1	1	0	0	1	0	0
	Laryngomalacia	0	3	0	0	3	0	0
	Macrocephaly	0	0	0	1	1	0	0
	Macroglossia	0	1	1	1	2	0	0
	Marcus Gunn syndrome	0	1	0	0	1	0	0
	Marfan's syndrome	0	0	0	1	1	0	0
	Methylenetetrahydrofolate reductase gene mutation	0	2	0	1	3	0	0
	Methylenetetrahydrofolate reductase polymorphism	0	0	1	1	1	0	0
	Methylmalonic aciduria	0	1	0	0	1	0	0
	Microcephaly	0	1	0	0	1	0	0
	Multiple congenital abnormalities	0	2	0	0	2	0	0
	Muscular dystrophy	0	1	0	6	7	0	0
	Myocardial bridging	0	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Myotonic dystrophy	0	0	1	1	1	0	0
	Naevus flammeus	0	0	0	1	1	0	0
	Neonatal alloimmune thrombocytopenia	0	0	1	1	1	0	0
	Non-compaction cardiomyopathy	0	1	0	0	1	0	0
	Oesophageal atresia	0	1	0	0	1	0	0
	Opitz trigonocephaly syndrome	1	1	0	0	1	0	0
	Optic disc pit	1	1	0	0	1	0	0
	Ornithine transcarbamoylase deficiency	0	1	0	0	1	0	0
	Paroxysmal extreme pain disorder	1	1	0	0	1	0	0
	Patent ductus arteriosus	0	2	0	0	2	0	0
	Persistent foetal circulation	1	1	0	0	1	0	0
	Pfeiffer syndrome	1	1	0	0	1	0	0
	Phimosis	1	2	0	2	4	0	0
	Platelet storage pool deficiency	0	0	1	1	1	0	0
	Porencephaly	0	1	0	0	1	0	0
	Porphyria	1	1	0	0	1	0	0
	Porphyria acute	0	1	0	0	1	0	0
	Protein C deficiency	0	1	0	0	1	0	0
	Protein S deficiency	0	1	0	0	1	0	0
	Renal aplasia	0	2	0	1	3	0	0
	Renal fusion anomaly	0	1	0	1	2	0	0
	Retinitis pigmentosa	1	1	0	0	1	0	0
	Right-to-left cardiac shunt	0	1	0	0	1	0	0
	Roberts syndrome	0	0	0	1	1	0	0
	Sclerotylosis	1	1	0	0	1	0	0
	Sickle cell anaemia	0	1	0	0	1	0	0
	Sickle cell disease	0	0	0	1	1	0	0
	Stiff skin syndrome	0	1	0	0	1	0	0
	Syringomyelia	0	1	0	0	1	0	0
	Teratogenicity	1	1	0	0	1	0	0
	Thyroglossal cyst	0	0	0	1	1	0	0
	Tourette's disorder	1	3	0	0	3	0	0
	Tracheo-oesophageal fistula	1	2	0	0	2	0	0
	Transposition of the great vessels	1	2	0	0	2	0	0
	Trisomy 21	1	1	0	0	1	0	0
	Trisomy 22	0	1	0	0	1	0	0
	Turner's syndrome	0	2	0	0	2	0	0
	Type IIa hyperlipidaemia	0	0	1	1	1	0	0
	Type V hyperlipidaemia	0	2	0	0	2	0	0
	VEXAS syndrome	1	1	0	0	1	0	0
	Vascular malformation	0	2	1	2	4	0	0
	Venous angioma of brain	0	4	0	0	4	0	0
	Ventricular septal defect	0	8	0	0	8	0	0
	Von Willebrand's disease	0	2	0	0	2	0	0
Ear and labyrinth disorders	*** SOC TOTAL ***	1184	4879	2977	12431	17310	0	0
	Acute vestibular syndrome	4	8	3	4	12	0	0
	Auditory disorder	7	13	24	47	60	0	0
	Auricular swelling	2	3	4	6	9	0	0
	Autoimmune inner ear disease	0	3	0	0	3	0	0
	Autophony	1	1	0	1	2	0	0
	Cerumen impaction	0	0	1	2	2	0	0
	Conductive deafness	0	4	0	0	4	0	0
	Deafness	68	S30	23	S7	S87	0	0
	Deafness bilateral	4	4S	3	3	48	0	0
	Deafness neurosensory	6	127	0	3	130	0	0
	Deafness permanent	0	S	0	0	S	0	0
	Deafness transitory	0	1S	3	4	19	0	0
	Deafness unilateral	38	422	1S	31	4S3	0	0
	Diplacusis	0	0	1	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Dysacusis	0	0	1	3	3	0	0
	Ear canal erythema	1	2	1	3	5	0	0
	Ear congestion	2	13	6	78	91	0	0
	Ear deformity acquired	0	0	0	1	1	0	0
	Ear discomfort	20	138	111	808	946	0	0
	Ear disorder	5	11	8	33	44	0	0
	Ear haemorrhage	3	4	6	23	27	0	0
	Ear inflammation	3	4	14	20	24	0	0
	Ear pain	101	415	335	1703	2118	0	0
	Ear pruritus	1	6	11	93	99	0	0
	Ear swelling	3	29	21	172	201	0	0
	Endolymphatic hydrops	0	1	0	0	1	0	0
	Eustachian tube disorder	0	0	0	6	6	0	0
	Eustachian tube dysfunction	0	2	0	13	15	0	0
	Eustachian tube obstruction	1	3	1	4	7	0	0
	Excessive cerumen production	0	2	1	10	12	0	0
	External ear disorder	0	0	1	2	2	0	0
	External ear inflammation	0	2	0	6	8	0	0
	External ear pain	0	3	2	18	21	0	0
	Haematotympanum	0	1	0	0	1	0	0
	Hyperacusis	13	56	47	216	272	0	0
	Hypoacusis	77	238	126	512	750	0	0
	Inner ear disorder	2	5	1	15	20	0	0
	Inner ear infarction	0	2	0	0	2	0	0
	Inner ear inflammation	5	9	3	19	28	0	0
	Mastoid disorder	0	3	0	3	6	0	0
	Mastoid effusion	0	0	0	1	1	0	0
	Meniere's disease	11	56	7	14	70	0	0
	Middle ear disorder	0	1	0	2	3	0	0
	Middle ear effusion	0	2	1	33	35	0	0
	Middle ear inflammation	1	3	8	15	18	0	0
	Misophonia	0	1	0	2	3	0	0
	Mixed deafness	0	1	0	0	1	0	0
	Motion sickness	1	20	2	48	68	0	0
	Neurosensory hypoacusis	3	4	1	2	6	0	0
	Noninfective myringitis	0	0	1	2	2	0	0
	Otolithiasis	0	1	2	3	4	0	0
	Otorrhoea	0	2	4	20	22	0	0
	Paracusis	1	1	0	0	1	0	0
	Paraesthesia ear	0	1	2	11	12	0	0
	Phobic postural vertigo	0	0	1	1	1	0	0
	Presbyacusis	0	1	0	1	2	0	0
	Red ear syndrome	0	0	0	2	2	0	0
	Sudden hearing loss	79	266	19	32	298	0	0
	Superior semicircular canal dehiscence	0	0	0	1	1	0	0
	Tinnitus	401	1281	1320	4563	5844	0	0
	Tympanic membrane disorder	0	1	1	5	6	0	0
	Tympanic membrane hyperaemia	0	0	0	1	1	0	0
	Tympanic membrane perforation	0	2	1	2	4	0	0
	Vertigo	299	1023	777	3574	4597	0	0
	Vertigo labyrinthine	0	1	0	1	2	0	0
	Vertigo positional	17	51	50	151	202	0	0
	Vestibular disorder	4	35	7	23	58	0	0
	Vestibular paroxysmia	0	0	0	1	1	0	0
Endocrine disorders	*** SOC TOTAL ***	198	614	159	422	1036	0	0
	Addison's disease	3	7	0	0	7	0	0
	Adrenal disorder	0	1	0	9	10	0	0
	Adrenal haemorrhage	0	1	0	0	1	0	0
	Adrenal insufficiency	1	11	1	1	12	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Adrenal mass	0	9	0	1	10	0	0
	Adrenocortical insufficiency acute	11	28	1	1	29	0	0
	Adrenocorticotropic hormone deficiency	0	1	0	0	1	0	0
	Anovulatory cycle	0	9	17	39	48	0	0
	Autoimmune hypothyroidism	0	1	1	1	2	0	0
	Autoimmune thyroid disorder	1	2	0	0	2	0	0
	Autoimmune thyroiditis	19	65	5	10	75	0	0
	Basedow's disease	41	89	12	17	106	0	0
	Carcinoid syndrome	0	1	0	0	1	0	0
	Central hypothyroidism	0	1	0	0	1	0	0
	Cushing's syndrome	1	2	0	0	2	0	0
	Cushingoid	0	0	0	1	1	0	0
	Delayed menarche	0	1	0	1	2	0	0
	Diabetes insipidus	0	3	1	1	4	0	0
	Endocrine disorder	0	1	3	5	6	0	0
	Endocrine pancreatic disorder	0	0	2	2	2	0	0
	Glucocorticoid deficiency	1	1	0	0	1	0	0
	Goitre	3	15	8	49	64	0	0
	Growth hormone deficiency	0	1	0	0	1	0	0
	Hyperadrenalism	1	2	0	1	3	0	0
	Hyperaldosteronism	0	1	0	0	1	0	0
	Hyperparathyroidism	1	3	1	1	4	0	0
	Hyperparathyroidism secondary	0	2	0	0	2	0	0
	Hyperprolactinaemia	2	2	1	2	4	0	0
	Hyperthyroidism	34	111	20	32	143	0	0
	Hypogonadism	0	0	0	1	1	0	0
	Hypoparathyroidism	1	1	0	0	1	0	0
	Hypophysitis	0	2	0	0	2	0	0
	Hypopituitarism	1	5	0	0	5	0	0
	Hypothalamo-pituitary disorder	0	4	0	0	4	0	0
	Hypothyroidism	23	85	11	21	106	0	0
	Immune-mediated hyperthyroidism	0	1	0	0	1	0	0
	Inappropriate antidiuretic hormone secretion	0	11	0	0	11	0	0
	Myxoedema	0	1	0	0	1	0	0
	Ovarian dysfunction	0	0	0	1	1	0	0
	Ovulation delayed	1	6	8	24	30	0	0
	Parathyroid disorder	0	0	0	1	1	0	0
	Parathyroid gland enlargement	2	2	0	1	3	0	0
	Pituitary haemorrhage	0	2	0	0	2	0	0
	Pituitary-dependent Cushing's syndrome	0	1	0	0	1	0	0
	Polyglandular autoimmune syndrome type II	1	1	0	0	1	0	0
	Polyglandular disorder	0	1	0	0	1	0	0
	Premature menarche	0	0	0	3	3	0	0
	Primary hyperaldosteronism	1	2	0	0	2	0	0
	Primary hyperthyroidism	2	2	0	0	2	0	0
	Secondary adrenocortical insufficiency	0	1	0	0	1	0	0
	Secondary hypogonadism	0	1	0	0	1	0	0
	Silent thyroiditis	1	2	1	2	4	0	0
	Steroid withdrawal syndrome	0	1	0	0	1	0	0
	Testicular failure	0	1	0	0	1	0	0
	Thyroid atrophy	0	1	0	1	2	0	0
	Thyroid calcification	0	0	0	2	2	0	0
	Thyroid cyst	0	5	1	4	9	0	0
	Thyroid disorder	7	13	17	50	63	0	0
	Thyroid mass	8	18	4	18	36	0	0
	Thyroid pain	3	5	8	19	24	0	0
	Thyroiditis	9	22	13	45	67	0	0
	Thyroiditis acute	3	9	0	0	9	0	0
	Thyroiditis chronic	0	0	1	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Thyroiditis subacute	14	31	22	53	84	0	0
	Thyrotoxic crisis	1	5	0	1	6	0	0
	Thyrotoxic periodic paralysis	1	1	0	0	1	0	0
Eye disorders	*** SOC TOTAL ***	1477	6213	2913	15185	21398	0	0
	Abnormal sensation in eye	1	7	8	82	89	0	0
	Accommodation disorder	3	6	6	13	19	0	0
	Acute macular neuroretinopathy	0	2	2	3	5	0	0
	Acute myopia	0	0	1	1	1	0	0
	Age-related macular degeneration	0	2	0	0	2	0	0
	Allergic keratitis	0	0	0	1	1	0	0
	Altered visual depth perception	0	5	0	9	14	0	0
	Amaurosis	2	6	2	2	8	0	0
	Amaurosis fugax	6	20	3	4	24	0	0
	Amblyopia	1	5	0	5	10	0	0
	Angle closure glaucoma	0	3	0	0	3	0	0
	Anisocoria	4	11	1	13	24	0	0
	Anterior chamber inflammation	0	1	0	0	1	0	0
	Asthenopia	13	38	23	183	221	0	0
	Astigmatism	0	2	0	2	4	0	0
	Autoimmune eye disorder	0	1	0	0	1	0	0
	Bell's phenomenon	1	1	0	0	1	0	0
	Binocular eye movement disorder	1	3	1	5	8	0	0
	Blepharal pigmentation	0	0	0	1	1	0	0
	Blepharitis	1	4	17	53	57	0	0
	Blepharospasm	6	41	57	244	285	0	0
	Blindness	56	401	5	28	429	0	0
	Blindness transient	14	77	6	15	92	0	0
	Blindness unilateral	18	171	0	5	176	0	0
	Cataract	15	46	5	8	54	0	0
	Central serous chorioretinopathy	2	9	0	0	9	0	0
	Central vision loss	0	2	0	0	2	0	0
	Chalazion	1	1	2	15	16	0	0
	Chloropsia	0	1	0	0	1	0	0
	Chorioretinal disorder	0	0	0	1	1	0	0
	Chorioretinopathy	1	4	0	0	4	0	0
	Choroidal neovascularisation	1	1	0	0	1	0	0
	Chromatopsia	1	1	0	12	13	0	0
	Ciliary body disorder	0	1	0	0	1	0	0
	Cogan's syndrome	0	1	0	0	1	0	0
	Colour blindness acquired	0	0	0	1	1	0	0
	Computer vision syndrome	0	0	1	1	1	0	0
	Conjunctival adhesion	1	1	0	0	1	0	0
	Conjunctival cyst	0	0	0	1	1	0	0
	Conjunctival discolouration	0	0	1	1	1	0	0
	Conjunctival disorder	0	0	0	1	1	0	0
	Conjunctival haemorrhage	9	91	21	35	126	0	0
	Conjunctival hyperaemia	3	12	3	20	32	0	0
	Conjunctival irritation	0	0	1	1	1	0	0
	Conjunctival oedema	1	4	2	5	9	0	0
	Conjunctivitis allergic	0	2	6	12	14	0	0
	Corneal defect	0	0	1	2	2	0	0
	Corneal disorder	0	2	0	3	5	0	0
	Corneal endothelilitis	2	3	0	0	3	0	0
	Corneal irritation	0	0	0	3	3	0	0
	Corneal lesion	1	3	0	0	3	0	0
	Corneal oedema	1	2	1	6	8	0	0
	Corneal opacity	0	5	0	0	5	0	0
	Corneal perforation	1	1	0	0	1	0	0
	Corneal pigmentation	0	0	1	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Corneal thinning	0	0	1	1	1	0	0
	Cyanopsia	0	1	0	3	4	0	0
	Cystoid macular oedema	5	10	0	0	10	0	0
	Dacryostenosis acquired	0	0	0	2	2	0	0
	Dark circles under eyes	0	2	3	22	24	0	0
	Deposit eye	0	0	0	1	1	0	0
	Dermatochalasis	1	1	1	11	12	0	0
	Detachment of macular retinal pigment epithelium	0	1	0	0	1	0	0
	Diabetic retinopathy	0	1	0	0	1	0	0
	Diplopia	82	287	78	356	643	0	0
	Dry age-related macular degeneration	1	1	0	0	1	0	0
	Dry eye	22	69	42	235	304	0	0
	Dyschromatopsia	2	10	2	15	25	0	0
	Eczema eyelids	1	1	3	9	10	0	0
	Endocrine ophthalmopathy	9	15	1	2	17	0	0
	Entropion	0	0	0	1	1	0	0
	Epiretinal membrane	0	2	1	1	3	0	0
	Episcleritis	2	5	3	13	18	0	0
	Erythema of eyelid	5	6	15	66	72	0	0
	Erythropsia	0	0	0	3	3	0	0
	Excessive eye blinking	0	3	0	12	15	0	0
	Exophthalmos	3	23	1	2	25	0	0
	Extraocular muscle disorder	0	1	0	2	3	0	0
	Exudative retinopathy	0	1	0	0	1	0	0
	Eye allergy	2	5	1	12	17	0	0
	Eye colour change	0	2	3	28	30	0	0
	Eye discharge	0	9	8	68	77	0	0
	Eye disorder	8	44	18	155	199	0	0
	Eye haematoma	1	7	5	6	13	0	0
	Eye haemorrhage	23	158	20	39	197	0	0
	Eye infarction	5	15	2	2	17	0	0
	Eye inflammation	6	20	50	130	150	0	0
	Eye irritation	16	62	91	546	608	0	0
	Eye movement disorder	6	57	6	211	268	0	0
	Eye muscle entrapment	0	1	0	0	1	0	0
	Eye oedema	6	15	18	43	58	0	0
	Eye opacity	0	0	0	1	1	0	0
	Eye pain	113	487	334	1582	2069	0	0
	Eye paraesthesia	0	4	2	6	10	0	0
	Eye pruritus	10	54	80	612	666	0	0
	Eye swelling	45	177	151	1174	1351	0	0
	Eye symptom	2	2	0	6	8	0	0
	Eye ulcer	1	1	1	3	4	0	0
	Eyelash discolouration	0	0	0	1	1	0	0
	Eyelid bleeding	0	1	1	3	4	0	0
	Eyelid cyst	0	2	0	1	3	0	0
	Eyelid disorder	2	11	4	41	52	0	0
	Eyelid exfoliation	0	0	0	1	1	0	0
	Eyelid function disorder	3	32	2	48	80	0	0
	Eyelid haematoma	0	0	2	12	12	0	0
	Eyelid irritation	2	4	10	39	43	0	0
	Eyelid margin crusting	0	0	1	23	23	0	0
	Eyelid myoclonus	0	0	1	1	1	0	0
	Eyelid myokymia	0	0	0	1	1	0	0
	Eyelid oedema	14	42	69	163	205	0	0
	Eyelid pain	0	1	7	40	41	0	0
	Eyelid ptosis	17	59	10	105	164	0	0
	Eyelid rash	2	7	4	24	31	0	0
	Eyelid retraction	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Eyelid sensory disorder	0	1	1	12	13	0	0
	Eyelid skin dryness	0	0	0	6	6	0	0
	Eyelid thickening	0	1	0	5	6	0	0
	Eyelids pruritus	2	6	8	51	57	0	0
	Foreign body sensation in eyes	1	7	9	29	36	0	0
	Gaze palsy	2	96	0	9	105	0	0
	Glare	0	0	4	5	5	0	0
	Glaucoma	5	27	1	3	30	0	0
	Glaucomatocyclitic crises	1	2	0	0	2	0	0
	Growth of eyelashes	0	0	0	2	2	0	0
	Halo vision	1	3	0	6	9	0	0
	Heterophoria	0	1	0	1	2	0	0
	Hippus	0	0	0	1	1	0	0
	Holmes-Adie pupil	0	2	1	1	3	0	0
	Hyalosis asteroid	0	0	0	1	1	0	0
	Hypermetropia	0	0	1	6	6	0	0
	Hypoaesthesia eye	1	10	3	52	62	0	0
	Idiopathic orbital inflammation	0	2	0	0	2	0	0
	Inflammation of lacrimal passage	1	1	0	0	1	0	0
	Iridocyclitis	15	32	3	5	37	0	0
	Iris adhesions	1	5	0	0	5	0	0
	Iris discolouration	0	0	1	2	2	0	0
	Iris disorder	0	0	1	1	1	0	0
	Iritis	5	15	6	30	45	0	0
	Keratitis	0	7	5	15	22	0	0
	Keratitis interstitial	0	1	0	0	1	0	0
	Lacrimal disorder	0	1	0	1	2	0	0
	Lacrimal haemorrhage	0	0	0	1	1	0	0
	Lacrimation decreased	0	0	1	3	3	0	0
	Lacrimation disorder	0	1	0	3	4	0	0
	Lacrimation increased	18	65	92	566	631	0	0
	Lagophthalmos	1	5	0	17	22	0	0
	Lens disorder	1	1	0	0	1	0	0
	Lenticular opacities	0	3	0	0	3	0	0
	Lid lag	0	0	0	2	2	0	0
	Lid sulcus deepened	0	3	1	5	8	0	0
	Limbal swelling	1	2	0	1	3	0	0
	Macular degeneration	4	15	1	2	17	0	0
	Macular detachment	0	3	0	0	3	0	0
	Macular hole	2	5	0	0	5	0	0
	Macular ischaemia	0	0	1	1	1	0	0
	Macular oedema	8	24	0	0	24	0	0
	Macular pseudohole	0	1	0	0	1	0	0
	Macular telangiectasia	0	1	1	1	2	0	0
	Maculopathy	0	4	1	3	7	0	0
	Meibomian gland discharge	0	0	0	1	1	0	0
	Meibomian gland dysfunction	0	0	0	1	1	0	0
	Metamorphopsia	2	15	1	49	64	0	0
	Miosis	0	7	1	20	27	0	0
	Mydriasis	5	28	4	68	96	0	0
	Myopia	2	4	2	7	11	0	0
	Necrotising retinitis	0	2	0	0	2	0	0
	Neovascular age-related macular degeneration	5	7	0	0	7	0	0
	Neurological eyelid disorder	0	0	0	1	1	0	0
	Night blindness	1	2	0	4	6	0	0
	Ocular discomfort	20	64	125	525	589	0	0
	Ocular hyperaemia	29	91	104	656	747	0	0
	Ocular hypertension	4	17	2	4	21	0	0
	Ocular ischaemic syndrome	1	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Ocular myasthenia	6	9	0	0	9	0	0
	Ocular rosacea	0	1	0	0	1	0	0
	Ocular vascular disorder	1	4	0	1	5	0	0
	Oculogyric crisis	0	3	0	0	3	0	0
	Ophthalmic artery occlusion	0	1	0	0	1	0	0
	Ophthalmic artery thrombosis	1	3	0	0	3	0	0
	Ophthalmic vein thrombosis	16	26	1	1	27	0	0
	Ophthalmoplegia	6	53	1	2	55	0	0
	Optic atrophy	2	4	0	0	4	0	0
	Optic disc disorder	0	0	1	1	1	0	0
	Optic disc hyperaemia	0	1	0	0	1	0	0
	Optic discs blurred	0	1	0	0	1	0	0
	Optic ischaemic neuropathy	14	46	0	0	46	0	0
	Optic nerve compression	0	1	0	0	1	0	0
	Optic nerve disorder	2	9	1	5	14	0	0
	Optic nerve infarction	1	3	0	0	3	0	0
	Optic nerve sheath haemorrhage	0	2	0	0	2	0	0
	Optic neuropathy	3	10	0	0	10	0	0
	Orbital apex syndrome	1	1	0	0	1	0	0
	Orbital haematoma	0	1	0	0	1	0	0
	Orbital myositis	1	3	0	0	3	0	0
	Orbital oedema	0	4	0	2	6	0	0
	Orbital swelling	0	0	1	6	6	0	0
	Oscillopsia	0	3	0	1	4	0	0
	Panophthalmitis	0	1	0	0	1	0	0
	Papilloedema	7	39	0	0	39	0	0
	Papillophlebitis	1	2	0	0	2	0	0
	Paralytic lagophthalmos	0	1	0	0	1	0	0
	Parinaud syndrome	1	1	0	0	1	0	0
	Parophthalmia	0	1	0	0	1	0	0
	Periorbital dermatitis	0	0	1	1	1	0	0
	Periorbital discomfort	0	0	0	2	2	0	0
	Periorbital inflammation	1	2	0	0	2	0	0
	Periorbital irritation	0	0	1	2	2	0	0
	Periorbital oedema	2	8	5	63	71	0	0
	Periorbital pain	1	4	3	9	13	0	0
	Periorbital swelling	10	40	46	294	334	0	0
	Photophobia	41	260	123	721	981	0	0
	Photopsia	13	54	55	179	233	0	0
	Pinguecula	0	0	0	1	1	0	0
	Polypoidal choroidal vasculopathy	0	1	0	0	1	0	0
	Presbyopia	0	1	1	3	4	0	0
	Punctate keratitis	0	5	0	0	5	0	0
	Pupil fixed	2	15	0	1	16	0	0
	Pupillary disorder	1	3	0	2	5	0	0
	Pupillary reflex impaired	1	5	0	1	6	0	0
	Purtscher retinopathy	0	1	0	0	1	0	0
	Refraction disorder	0	0	0	1	1	0	0
	Retinal artery embolism	2	3	0	0	3	0	0
	Retinal artery occlusion	13	61	0	0	61	0	0
	Retinal artery thrombosis	1	6	1	1	7	0	0
	Retinal degeneration	0	2	0	1	3	0	0
	Retinal deposits	0	0	0	1	1	0	0
	Retinal detachment	35	85	1	1	86	0	0
	Retinal disorder	0	5	1	7	12	0	0
	Retinal drusen	0	0	2	2	2	0	0
	Retinal exudates	1	6	0	0	6	0	0
	Retinal fovea disorder	0	0	1	1	1	0	0
	Retinal haemorrhage	5	35	0	0	35	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Retinal infarction	0	1	0	0	1	0	0
	Retinal ischaemia	3	6	1	1	7	0	0
	Retinal neovascularisation	1	1	0	0	1	0	0
	Retinal oedema	0	8	0	0	8	0	0
	Retinal scar	0	1	0	0	1	0	0
	Retinal tear	9	20	0	1	21	0	0
	Retinal vascular disorder	0	3	0	0	3	0	0
	Retinal vascular occlusion	3	5	0	0	5	0	0
	Retinal vascular thrombosis	3	15	0	2	17	0	0
	Retinal vasculitis	2	7	0	0	7	0	0
	Retinal vein occlusion	35	100	6	7	107	0	0
	Retinal vein thrombosis	9	30	0	1	31	0	0
	Retinal white dots syndrome	2	3	0	0	3	0	0
	Retinopathy	1	5	0	0	5	0	0
	Retinoschisis	1	1	0	0	1	0	0
	Rhegmatogenous retinal detachment	0	2	0	0	2	0	0
	5accadic eye movement	0	0	0	1	1	0	0
	Scintillating scotoma	3	9	6	16	25	0	0
	5cleral discolouration	0	2	0	1	3	0	0
	Scleral disorder	2	2	2	3	5	0	0
	5cleral haemorrhage	0	4	0	2	6	0	0
	Scleral hyperaemia	0	0	2	3	3	0	0
	5cleral oedema	0	1	0	0	1	0	0
	Scleritis	4	21	2	2	23	0	0
	5cleritis allergic	0	1	0	0	1	0	0
	Serous retinopathy	0	1	0	0	1	0	0
	5trabismus	1	11	4	22	33	0	0
	Subretinal fluid	0	2	0	0	2	0	0
	5udden visual loss	1	3	0	1	4	0	0
	Swelling of eyelid	11	53	76	447	500	0	0
	5wollen tear duct	0	0	0	1	1	0	0
	Tolosa-Hunt syndrome	3	3	0	0	3	0	0
	Ulcerative keratitis	2	9	0	0	9	0	0
	Uveitis	15	79	6	12	91	0	0
	Venous stasis retinopathy	1	1	0	0	1	0	0
	Vision blurred	185	782	350	2343	3125	0	0
	Visual acuity reduced	23	48	43	74	122	0	0
	Visual acuity reduced transiently	0	0	0	1	1	0	0
	Visual brightness	0	0	0	6	6	0	0
	Visual field defect	22	83	16	77	160	0	0
	Visual impairment	176	602	511	1798	2400	0	0
	Visual snow syndrome	0	0	3	5	5	0	0
	Vitreoretinal traction syndrome	0	1	0	0	1	0	0
	Vitreous adhesions	0	0	0	1	1	0	0
	Vitreous degeneration	0	2	0	0	2	0	0
	Vitreous detachment	14	48	5	8	56	0	0
	Vitreous disorder	0	0	1	2	2	0	0
	Vitreous floaters	15	54	19	156	210	0	0
	Vitreous haemorrhage	5	16	1	2	18	0	0
	Vitreous haze	2	2	0	0	2	0	0
	Vitreous opacities	2	3	3	4	7	0	0
	Vitritis	0	2	0	0	2	0	0
	Vogt-Koyanagi-Harada disease	3	8	0	0	8	0	0
	Xanthopsia	2	4	0	4	8	0	0
	Xerophthalmia	1	1	0	0	1	0	0
Gastrointestinal disorders	*** SOC TOTAL ***	5321	24945	25082	114924	139869	0	2
	Abdominal adhesions	0	2	0	0	2	0	0
	Abdominal discomfort	85	339	415	2798	3137	0	0
	Abdominal distension	44	174	144	689	863	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Abdominal hernia	0	4	0	2	6	0	0
	Abdominal mass	1	6	1	2	8	0	0
	Abdominal migraine	0	1	0	0	1	0	0
	Abdominal pain	270	1290	988	3886	5176	0	0
	Abdominal pain lower	35	156	228	524	680	0	0
	Abdominal pain upper	265	1279	649	3568	4847	0	0
	Abdominal rebound tenderness	0	3	0	0	3	0	0
	Abdominal rigidity	3	9	8	30	39	0	0
	Abdominal symptom	0	3	2	3	6	0	0
	Abdominal tenderness	4	17	7	37	54	0	0
	Abdominal wall haematoma	0	7	0	1	8	0	0
	Abdominal wall haemorrhage	0	1	0	0	1	0	0
	Abdominal wall mass	0	1	0	0	1	0	0
	Abdominal wall oedema	0	2	0	1	3	0	0
	Abnormal faeces	10	24	54	175	199	0	0
	Acetonaemic vomiting	0	0	6	9	9	0	0
	Achlorhydria	0	0	0	1	1	0	0
	Acquired oesophageal web	0	0	0	1	1	0	0
	Acute abdomen	2	9	0	0	9	0	0
	Acute haemorrhagic ulcerative colitis	0	1	0	0	1	0	0
	Aerophagia	0	0	0	1	1	0	0
	Anaesthesia oral	1	6	5	21	27	0	0
	Anal blister	0	0	0	1	1	0	0
	Anal eczema	0	0	1	1	1	0	0
	Anal erythema	0	1	1	3	4	0	0
	Anal fissure	0	0	1	1	1	0	0
	Anal fistula	0	1	0	0	1	0	0
	Anal haemorrhage	2	5	3	7	12	0	0
	Anal hypoaesthesia	0	1	0	0	1	0	0
	Anal incontinence	5	48	12	74	122	0	0
	Anal paraesthesia	0	0	1	1	1	0	0
	Anal pruritus	0	0	3	13	13	0	0
	Anal rash	1	1	1	1	2	0	0
	Anal spasm	0	0	1	1	1	0	0
	Anal sphincter atony	2	7	0	0	7	0	0
	Anal sphincter hypertonia	1	1	0	0	1	0	0
	Anal ulcer	0	1	0	0	1	0	0
	Angular cheilitis	0	1	4	10	11	0	0
	Anorectal discomfort	1	4	5	14	18	0	0
	Anorectal disorder	1	2	1	2	4	0	0
	Anorectal swelling	0	1	0	2	3	0	0
	Anorectal ulcer	1	1	0	0	1	0	0
	Aphthous ulcer	13	30	86	235	265	0	0
	Appendicolith	0	2	0	0	2	0	0
	Appendix disorder	1	3	0	2	5	0	0
	Aptyalism	1	2	1	16	18	0	0
	Ascites	10	64	0	0	64	0	0
	Atrophic glossitis	0	0	0	1	1	0	0
	Autoimmune pancreatitis	2	5	0	0	5	0	0
	Barrett's oesophagus	0	2	0	0	2	0	0
	Bile acid malabsorption	0	0	0	3	3	0	0
	Biliary ascites	0	1	0	0	1	0	0
	Bowel movement irregularity	0	2	6	76	78	0	0
	Breath odour	0	6	4	21	27	0	0
	Burning mouth syndrome	1	3	0	3	6	0	0
	Cardiospasm	2	4	1	6	10	0	0
	Change of bowel habit	1	2	4	12	14	0	0
	Chapped lips	3	4	11	76	80	0	0
	Cheilitis	4	12	13	97	109	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Chronic gastritis	2	4	2	3	7	0	0
	Coating in mouth	0	1	3	12	13	0	0
	Coeliac artery compression syndrome	0	1	0	0	1	0	0
	Coeliac artery stenosis	0	4	0	0	4	0	0
	Coeliac disease	2	10	0	0	10	0	0
	Colitis	20	93	19	61	154	0	0
	Colitis ischaemic	6	43	0	0	43	0	0
	Colitis microscopic	3	21	1	2	23	0	0
	Colitis ulcerative	42	137	12	21	158	0	0
	Colonic fistula	0	1	0	0	1	0	0
	Constipation	26	164	86	459	623	0	0
	Crohn's disease	24	77	11	21	98	0	0
	Cyclic vomiting syndrome	0	3	0	0	3	0	0
	Defaecation disorder	0	1	2	10	11	0	0
	Defaecation urgency	1	12	7	38	50	0	0
	Dental abfraction	0	0	1	1	1	0	0
	Dental caries	0	4	0	8	12	0	0
	Dental cyst	0	0	1	1	1	0	0
	Dental discomfort	1	3	3	44	47	0	0
	Dental dysaesthesia	1	1	0	0	1	0	0
	Dental paraesthesia	0	3	0	12	15	0	0
	Dental pulp disorder	0	0	0	1	1	0	0
	Diaphragmatic hernia	0	2	0	1	3	0	0
	Diarrhoea	545	2654	2572	13250	15904	0	0
	Diarrhoea haemorrhagic	6	85	4	14	99	0	0
	Diarrhoea neonatal	0	0	0	1	1	0	0
	Discoloured vomit	1	8	1	10	18	0	0
	Distal intestinal obstruction syndrome	0	1	0	0	1	0	0
	Diverticular perforation	0	5	0	0	5	0	0
	Diverticulum	1	13	0	7	20	0	0
	Diverticulum intestinal	0	13	2	5	18	0	0
	Diverticulum intestinal haemorrhagic	1	3	0	0	3	0	0
	Dry mouth	34	155	170	1010	1165	0	0
	Duodenal ulcer	2	5	0	0	5	0	0
	Duodenal ulcer haemorrhage	0	1	0	0	1	0	0
	Duodenitis	0	8	0	0	8	0	0
	Duodenogastric reflux	0	2	2	7	9	0	0
	Dysbiosis	0	2	2	3	5	0	0
	Dyschezia	2	5	6	19	24	0	0
	Dyskinesia oesophageal	0	0	1	1	1	0	0
	Dyspepsia	50	239	192	805	1044	0	0
	Dysphagia	72	440	168	1488	1928	0	0
	Enamel anomaly	0	0	0	1	1	0	0
	Enlarged uvula	1	6	9	53	59	0	0
	Enteric neuropathy	0	0	0	1	1	0	0
	Enteritis	2	19	2	13	32	0	0
	Enterocolitis	2	13	0	1	14	0	0
	Enterocolitis haemorrhagic	1	2	0	0	2	0	0
	Enterocutaneous fistula	0	1	0	1	2	0	0
	Enterovesical fistula	0	1	0	0	1	0	0
	Eosinophilic colitis	0	1	0	0	1	0	0
	Eosinophilic oesophagitis	0	1	1	4	5	0	0
	Epigastric discomfort	7	19	8	27	46	0	0
	Epiploic appendagitis	0	0	1	5	5	0	0
	Erosive oesophagitis	0	1	0	0	1	0	0
	Eructation	9	32	30	157	189	0	0
	Faecal vomiting	0	1	0	0	1	0	0
	Faecalith	0	1	0	0	1	0	0
	Faecaloma	1	11	1	1	12	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Faeces discoloured	5	50	10	130	180	0	0
	Faeces hard	0	2	4	11	13	0	0
	Faeces pale	1	2	1	15	17	0	0
	Faeces soft	0	5	10	55	60	0	0
	Flatulence	12	54	68	405	459	0	0
	Food poisoning	3	4	3	23	27	0	0
	Food protein-induced enterocolitis syndrome	0	1	0	0	1	0	0
	Frequent bowel movements	10	27	21	125	152	0	0
	Functional gastrointestinal disorder	1	9	9	29	38	0	0
	Gastric antral vascular ectasia	0	1	0	1	2	0	0
	Gastric dilatation	1	11	1	6	17	0	0
	Gastric disorder	1	9	3	36	45	0	0
	Gastric haemorrhage	1	10	0	0	10	0	0
	Gastric hypomotility	0	1	0	0	1	0	0
	Gastric mucosal lesion	0	1	0	1	2	0	0
	Gastric perforation	0	1	0	0	1	0	0
	Gastric polyps	0	1	0	1	2	0	0
	Gastric ulcer	3	19	1	3	22	0	0
	Gastric ulcer haemorrhage	2	6	0	0	6	0	0
	Gastric ulcer perforation	1	2	0	0	2	0	0
	Gastric varices	0	1	0	0	1	0	0
	Gastritis	27	67	38	123	190	0	0
	Gastritis erosive	1	5	0	0	5	0	0
	Gastritis haemorrhagic	0	1	0	0	1	0	0
	Gastrointestinal disorder	15	69	86	345	414	0	0
	Gastrointestinal erosion	0	0	1	1	1	0	0
	Gastrointestinal haemorrhage	19	134	1	3	137	0	0
	Gastrointestinal hypermotility	1	2	0	4	6	0	0
	Gastrointestinal hypomotility	1	2	0	0	2	0	0
	Gastrointestinal inflammation	3	24	5	20	44	0	0
	Gastrointestinal motility disorder	2	6	1	13	19	0	0
	Gastrointestinal mucosal disorder	0	0	0	1	1	0	0
	Gastrointestinal necrosis	0	6	0	0	6	0	0
	Gastrointestinal oedema	0	7	0	0	7	0	0
	Gastrointestinal pain	38	83	125	342	425	0	0
	Gastrointestinal perforation	0	1	0	0	1	0	0
	Gastrointestinal polyp	0	1	0	0	1	0	0
	Gastrointestinal sounds abnormal	0	5	8	34	39	0	0
	Gastrointestinal tract irritation	1	3	2	6	9	0	0
	Gastrointestinal ulcer	0	1	0	0	1	0	0
	Gastrointestinal wall thickening	1	13	0	2	15	0	0
	Gastrooesophageal reflux disease	23	99	49	296	395	0	0
	Gingival bleeding	8	40	29	120	160	0	0
	Gingival blister	0	0	0	16	16	0	0
	Gingival discolouration	0	2	1	11	13	0	0
	Gingival discomfort	0	1	6	31	32	0	0
	Gingival disorder	1	4	2	8	12	0	0
	Gingival erythema	0	2	2	14	16	0	0
	Gingival hypertrophy	0	0	1	1	1	0	0
	Gingival oedema	0	0	3	7	7	0	0
	Gingival pain	7	28	19	148	176	0	0
	Gingival pruritus	0	0	2	11	11	0	0
	Gingival recession	0	0	3	5	5	0	0
	Gingival swelling	3	14	12	98	112	0	0
	Gingival ulceration	0	0	0	4	4	0	0
	Glossitis	2	12	13	55	67	0	0
	Glossodynia	7	27	40	261	288	0	0
	Haematemesis	18	112	4	10	122	0	0
	Haematochezia	41	258	15	42	300	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Haemoperitoneum	1	9	0	0	9	0	0
	Haemorrhagic ascites	0	1	0	0	1	0	0
	Haemorrhoidal haemorrhage	0	0	1	14	14	0	0
	Haemorrhoids	9	22	27	91	113	0	0
	Haemorrhoids thrombosed	10	14	9	31	45	0	0
	Hiatus hernia	1	36	2	14	50	0	0
	Hyperaesthesia teeth	0	7	7	70	77	0	0
	Hyperchlorhydria	0	3	3	8	11	0	0
	Hypertrophy of tongue papillae	0	0	0	2	2	0	0
	Hypoaesthesia oral	41	218	130	1668	1886	0	0
	Hypoaesthesia teeth	0	4	1	2	6	0	0
	Ileal perforation	0	2	0	0	2	0	0
	Ileus	2	22	0	1	23	0	0
	Ileus paralytic	3	6	0	0	6	0	0
	Impaired gastric emptying	2	11	0	2	13	0	0
	Incarcerated umbilical hernia	0	2	0	0	2	0	0
	Infantile spitting up	0	0	2	2	2	0	0
	Infantile vomiting	0	0	1	5	5	0	0
	Inflammatory bowel disease	12	27	1	3	30	0	0
	Infrequent bowel movements	0	2	2	4	6	0	0
	Inguinal hernia	1	8	0	2	10	0	0
	Internal hernia	0	1	0	0	1	0	0
	Intestinal angina	0	1	0	0	1	0	0
	Intestinal angioedema	0	2	0	0	2	0	0
	Intestinal atony	0	0	0	1	1	0	0
	Intestinal barrier dysfunction	1	1	0	0	1	0	0
	Intestinal dilatation	0	3	0	0	3	0	0
	Intestinal haematoma	0	1	0	0	1	0	0
	Intestinal haemorrhage	6	15	0	0	15	0	0
	Intestinal infarction	5	6	0	0	6	0	0
	Intestinal ischaemia	8	29	0	0	29	0	0
	Intestinal mass	0	2	0	0	2	0	0
	Intestinal obstruction	6	44	1	4	48	0	0
	Intestinal perforation	1	12	0	0	12	0	0
	Intestinal pseudo-obstruction	2	5	0	0	5	0	0
	Intestinal ulcer	1	1	0	0	1	0	0
	Intra-abdominal calcification	0	1	0	0	1	0	0
	Intra-abdominal fluid collection	0	6	0	1	7	0	0
	Intra-abdominal haematoma	1	4	1	1	5	0	0
	Intra-abdominal haemorrhage	1	5	0	0	5	0	0
	Intussusception	0	1	13	13	14	0	0
	Irritable bowel syndrome	12	26	11	70	96	0	0
	Ischaemic enteritis	0	1	0	0	1	0	0
	Large intestinal haemorrhage	0	3	0	0	3	0	0
	Large intestinal obstruction	0	2	0	0	2	0	0
	Large intestinal stenosis	0	3	0	0	3	0	0
	Large intestinal ulcer	0	4	0	0	4	0	0
	Large intestinal ulcer haemorrhage	0	2	0	0	2	0	0
	Large intestine perforation	2	7	0	0	7	0	0
	Large intestine polyp	1	5	0	4	9	0	0
	Leukoplakia oral	0	4	0	3	7	0	0
	Levator syndrome	0	0	0	1	1	0	0
	Lip blister	1	3	11	114	117	0	0
	Lip discolouration	0	4	3	34	38	0	0
	Lip disorder	0	5	1	42	47	0	0
	Lip dry	2	6	20	100	106	0	0
	Lip erosion	0	0	0	1	1	0	0
	Lip erythema	0	2	5	50	52	0	0
	Lip exfoliation	1	1	1	15	16	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Lip haematoma	1	2	0	0	2	0	0
	Lip haemorrhage	0	3	1	13	16	0	0
	Lip oedema	16	51	40	117	168	0	0
	Lip pain	5	14	15	104	118	0	0
	Lip pruritus	0	12	10	119	131	0	0
	Lip scab	0	0	0	2	2	0	0
	Lip swelling	65	321	219	1992	2313	0	0
	Lip ulceration	1	4	2	11	15	0	0
	Loose tooth	0	2	2	12	14	0	0
	Lower gastrointestinal haemorrhage	0	3	0	0	3	0	0
	Lymphoid hyperplasia of intestine	2	2	0	0	2	0	0
	Malabsorption	1	1	0	5	6	0	0
	Mallory-Weiss syndrome	1	3	0	0	3	0	0
	Malocclusion	0	0	0	1	1	0	0
	Malpositioned teeth	0	0	1	1	1	0	0
	Melaena	2	53	1	1	54	0	0
	Mesenteric arterial occlusion	1	3	0	0	3	0	0
	Mesenteric artery thrombosis	1	8	0	0	8	0	0
	Mesenteric haemorrhage	0	1	0	0	1	0	0
	Mesenteric panniculitis	0	0	1	1	1	0	0
	Mesenteric vein thrombosis	12	50	0	0	50	0	0
	Mesenteric venous occlusion	0	1	0	0	1	0	0
	Mesenteritis	2	3	0	0	3	0	0
	Mouth cyst	0	1	0	0	1	0	0
	Mouth haemorrhage	6	41	8	50	91	0	0
	Mouth swelling	10	63	29	304	367	0	0
	Mouth ulceration	14	70	24	203	273	0	0
	Mucous stools	0	3	7	32	35	0	0
	Nausea	1920	8286	13700	53237	61523	0	1
	Noninfective gingivitis	4	10	23	58	68	0	0
	Noninfective sialoadenitis	0	1	5	9	10	0	0
	Obstruction gastric	0	2	0	0	2	0	0
	Obstructive defaecation	0	0	1	1	1	0	0
	Obstructive pancreatitis	0	5	0	0	5	0	0
	Odynophagia	11	37	45	173	210	0	0
	Oedema mouth	1	3	7	15	18	0	0
	Oedematous pancreatitis	0	2	0	0	2	0	0
	Oesophageal achalasia	0	2	1	4	6	0	0
	Oesophageal compression	0	1	0	0	1	0	0
	Oesophageal dilatation	0	2	0	0	2	0	0
	Oesophageal discomfort	2	4	4	15	19	0	0
	Oesophageal disorder	1	3	0	4	7	0	0
	Oesophageal food impaction	1	3	0	0	3	0	0
	Oesophageal haemorrhage	1	3	0	0	3	0	0
	Oesophageal irritation	1	1	1	6	7	0	0
	Oesophageal motility disorder	0	0	0	1	1	0	0
	Oesophageal obstruction	0	1	1	1	2	0	0
	Oesophageal oedema	0	1	1	1	2	0	0
	Oesophageal pain	2	9	9	23	32	0	0
	Oesophageal polyp	0	0	0	1	1	0	0
	Oesophageal rupture	1	4	0	0	4	0	0
	Oesophageal spasm	0	3	7	18	21	0	0
	Oesophageal stenosis	0	4	0	0	4	0	0
	Oesophageal ulcer	1	5	0	0	5	0	0
	Oesophageal varices haemorrhage	1	4	0	0	4	0	0
	Oesophagitis	3	13	9	25	38	0	0
	Omental haemorrhage	0	1	0	0	1	0	0
	Omental infarction	1	2	1	3	5	0	0
	Omental necrosis	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Oral blood blister	2	14	1	10	24	0	0
	Oral discharge	0	0	0	2	2	0	0
	Oral discomfort	8	38	54	362	400	0	0
	Oral disorder	1	15	7	52	67	0	0
	Oral dysaesthesia	0	1	3	15	16	0	0
	Oral hyperaesthesia	0	0	0	1	1	0	0
	Oral lichen planus	0	2	6	12	14	0	0
	Oral mucosa erosion	1	1	2	3	4	0	0
	Oral mucosa haematoma	0	1	0	3	4	0	0
	Oral mucosal blistering	4	24	30	170	194	0	0
	Oral mucosal discolouration	0	1	1	4	5	0	0
	Oral mucosal eruption	2	11	6	52	63	0	0
	Oral mucosal erythema	1	5	2	35	40	0	0
	Oral mucosal exfoliation	0	4	0	10	14	0	0
	Oral mucosal roughening	0	1	2	6	7	0	0
	Oral pain	20	48	36	337	385	0	0
	Oral pigmentation	0	0	0	1	1	0	0
	Oral pruritus	2	11	12	138	149	0	0
	Oral purpura	0	3	0	1	4	0	0
	Palatal disorder	1	1	1	6	7	0	0
	Palatal oedema	8	15	3	12	27	0	0
	Palatal swelling	2	7	9	34	41	0	0
	Palatal ulcer	1	1	1	1	2	0	0
	Pancreatic atrophy	0	6	0	0	6	0	0
	Pancreatic cyst	2	5	1	3	8	0	0
	Pancreatic disorder	0	2	1	4	6	0	0
	Pancreatic duct dilatation	0	4	0	0	4	0	0
	Pancreatic duct stenosis	0	1	0	0	1	0	0
	Pancreatic enlargement	1	2	0	0	2	0	0
	Pancreatic enzyme abnormality	0	1	0	0	1	0	0
	Pancreatic failure	2	6	0	0	6	0	0
	Pancreatic mass	0	3	0	0	3	0	0
	Pancreatic pseudocyst	0	2	0	0	2	0	0
	Pancreatic steatosis	1	1	0	0	1	0	0
	Pancreatitis	19	132	0	6	138	0	0
	Pancreatitis acute	17	102	1	2	104	0	0
	Pancreatitis chronic	0	3	0	0	3	0	0
	Pancreatitis necrotising	0	6	0	0	6	0	0
	Paraesthesia oral	35	236	202	2493	2729	0	0
	Paresis anal sphincter	0	0	1	1	1	0	0
	Parotid duct obstruction	0	0	0	1	1	0	0
	Parotid gland enlargement	0	3	6	20	23	0	0
	Pelvic floor dysfunction	0	2	0	1	3	0	0
	Peptic ulcer	2	7	0	0	7	0	0
	Peptic ulcer haemorrhage	0	3	0	2	5	0	0
	Periodontal disease	0	1	0	1	2	0	0
	Peritoneal disorder	0	0	0	1	1	0	0
	Peritoneal fibrosis	0	1	0	0	1	0	0
	Pigmentation lip	0	0	0	1	1	0	0
	Plicated tongue	0	0	1	5	5	0	0
	Pneumatosis intestinalis	0	1	0	0	1	0	0
	Pneumoperitoneum	1	3	0	0	3	0	0
	Portal hypertensive colopathy	0	1	0	0	1	0	0
	Post-tussive vomiting	0	1	0	1	2	0	0
	Pouchitis	0	0	0	1	1	0	0
	Proctalgia	5	14	8	28	42	0	0
	Proctitis	1	3	2	6	9	0	0
	Proctitis ulcerative	1	2	0	0	2	0	0
	Protein-losing gastroenteropathy	1	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Protrusion tongue	0	2	1	2	4	0	0
	Pseudodiverticular disease	0	1	0	0	1	0	0
	Rectal discharge	0	0	0	2	2	0	0
	Rectal fissure	0	0	0	1	1	0	0
	Rectal haemorrhage	17	134	9	20	154	0	0
	Rectal lesion	0	1	0	0	1	0	0
	Rectal tenesmus	0	1	0	5	6	0	0
	Reflux gastritis	0	0	3	15	15	0	0
	Regurgitation	0	6	1	15	21	0	0
	Retching	29	127	79	670	797	0	0
	Retroperitoneal effusion	0	1	0	0	1	0	0
	Retroperitoneal fibrosis	1	1	0	0	1	0	0
	Retroperitoneal haematoma	0	4	0	0	4	0	0
	Retroperitoneal haemorrhage	0	9	0	0	9	0	0
	Retroperitoneal mass	0	1	0	0	1	0	0
	Retroperitoneal oedema	0	1	0	0	1	0	0
	Saliva altered	3	5	2	12	17	0	0
	Saliva discolouration	0	1	0	2	3	0	0
	Salivary duct inflammation	0	0	2	2	2	0	0
	Salivary gland cyst	1	1	0	0	1	0	0
	Salivary gland disorder	0	0	0	2	2	0	0
	Salivary gland enlargement	0	0	5	20	20	0	0
	Salivary gland mass	0	0	0	1	1	0	0
	Salivary gland mucocoele	0	0	0	2	2	0	0
	Salivary gland pain	0	3	5	8	11	0	0
	Salivary hypersecretion	7	25	16	114	139	0	0
	Scalloped tongue	0	0	0	5	5	0	0
	Segmental diverticular colitis	1	1	0	0	1	0	0
	Short-bowel syndrome	0	1	0	0	1	0	0
	Small intestinal haemorrhage	0	3	0	0	3	0	0
	Small intestinal obstruction	0	34	0	0	34	0	0
	Small intestinal perforation	0	1	0	0	1	0	0
	Small intestinal ulcer haemorrhage	0	1	0	0	1	0	0
	Splenic artery aneurysm	0	1	0	0	1	0	0
	Stasis syndrome	0	0	0	1	1	0	0
	Stiff tongue	0	0	2	8	8	0	0
	Stomach mass	0	1	0	2	3	0	0
	Stomatitis	5	40	47	322	362	0	0
	Strawberry tongue	0	0	0	1	1	0	0
	Subacute pancreatitis	1	1	0	0	1	0	0
	Subileus	1	2	0	0	2	0	0
	Submaxillary gland enlargement	1	3	1	8	11	0	0
	Superior mesenteric artery dissection	2	2	0	0	2	0	0
	Superior mesenteric artery syndrome	0	1	0	0	1	0	0
	Swollen tongue	41	325	130	1452	1777	0	0
	Teeth brittle	0	0	0	2	2	0	0
	Teething	0	0	5	14	14	0	0
	Terminal ileitis	0	6	0	0	6	0	0
	Tongue atrophy	0	2	1	1	3	0	0
	Tongue blistering	2	7	8	70	77	0	0
	Tongue coated	1	4	7	27	31	0	0
	Tongue discolouration	2	9	12	84	93	0	0
	Tongue discomfort	6	22	35	257	279	0	0
	Tongue disorder	2	17	8	192	209	0	0
	Tongue dry	2	7	3	36	43	0	0
	Tongue eruption	0	1	2	26	27	0	0
	Tongue erythema	1	9	4	49	58	0	0
	Tongue exfoliation	1	2	1	8	10	0	0
	Tongue geographic	0	1	2	8	9	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Tongue haematoma	0	1	1	2	3	0	0
	Tongue haemorrhage	0	3	1	8	11	0	0
	Tongue induration	0	0	0	2	2	0	0
	Tongue movement disturbance	0	11	2	11	22	0	0
	Tongue oedema	7	31	14	64	95	0	0
	Tongue pigmentation	0	0	0	3	3	0	0
	Tongue pruritus	1	17	6	134	151	0	0
	Tongue rough	1	1	2	10	11	0	0
	Tongue spasm	0	2	0	8	10	0	0
	Tongue thrust	0	0	0	1	1	0	0
	Tongue ulceration	0	7	9	44	51	0	0
	Tooth discolouration	0	0	2	4	4	0	0
	Tooth disorder	0	3	5	28	31	0	0
	Tooth loss	0	1	3	15	16	0	0
	Tooth resorption	0	0	0	1	1	0	0
	Toothache	27	72	120	512	584	0	0
	Trichoglossia	0	0	0	6	6	0	0
	Truncus coeliacus thrombosis	0	2	0	0	2	0	0
	Ulcerative gastritis	0	0	0	1	1	0	0
	Umbilical hernia	0	6	0	2	8	0	0
	Upper gastrointestinal haemorrhage	5	27	0	0	27	0	0
	Uvulitis	1	1	0	3	4	0	0
	Varices oesophageal	1	4	0	1	5	0	0
	Vasculitis gastrointestinal	0	1	0	0	1	0	0
	Visceral venous thrombosis	0	1	1	1	2	0	0
	Volvulus	0	10	0	0	10	0	0
	Vomiting	876	4251	3106	14891	19142	0	1
	Vomiting projectile	13	36	6	46	82	0	0
General disorders and administration site conditions	*** SOC TOTAL ***	24267	90080	190089	808249	898329	0	7
	Abscess sterile	0	0	0	1	1	0	0
	Absence of immediate treatment response	0	3	0	0	3	0	0
	Acute phase reaction	0	2	0	0	2	0	0
	Adhesion	1	3	2	7	10	0	0
	Administration site acne	0	0	1	1	1	0	0
	Administration site bruise	0	1	3	19	20	0	0
	Administration site coldness	0	0	1	2	2	0	0
	Administration site discolouration	0	0	0	2	2	0	0
	Administration site discomfort	0	0	0	2	2	0	0
	Administration site dysaesthesia	0	0	1	2	2	0	0
	Administration site erythema	0	3	60	115	118	0	0
	Administration site extravasation	0	1	0	0	1	0	0
	Administration site haematoma	0	1	1	4	5	0	0
	Administration site hyperaesthesia	0	1	1	1	2	0	0
	Administration site hypersensitivity	0	0	0	1	1	0	0
	Administration site hypoaesthesia	0	0	0	1	1	0	0
	Administration site indentation	0	0	1	2	2	0	0
	Administration site induration	0	1	6	11	12	0	0
	Administration site inflammation	0	1	2	11	12	0	0
	Administration site irritation	0	0	0	3	3	0	0
	Administration site joint erythema	1	1	3	3	4	0	0
	Administration site joint movement impairment	1	1	0	3	4	0	0
	Administration site joint pain	1	1	0	1	2	0	0
	Administration site lymphadenopathy	1	2	41	51	53	0	0
	Administration site macule	0	0	0	3	3	0	0
	Administration site movement impairment	2	3	5	15	18	0	0
	Administration site nodule	0	0	0	1	1	0	0
	Administration site oedema	1	5	22	40	45	0	0
	Administration site pain	3	23	138	297	320	0	0
	Administration site papule	0	0	0	2	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Administration site paraesthesia	0	0	0	1	1	0	0
	Administration site plaque	0	0	0	1	1	0	0
	Administration site pruritus	0	1	10	25	26	0	0
	Administration site rash	0	1	8	25	26	0	0
	Administration site reaction	0	2	15	56	58	0	0
	Administration site swelling	1	4	28	50	54	0	0
	Administration site urticaria	0	0	1	2	2	0	0
	Administration site vesicles	0	0	1	1	1	0	0
	Administration site warmth	0	0	4	31	31	0	0
	Adverse drug reaction	68	107	86	244	351	0	0
	Adverse event	4	33	11	381	414	0	0
	Adverse food reaction	0	0	0	3	3	0	0
	Adverse reaction	7	34	88	504	538	0	0
	Agonal death struggle	0	2	0	0	2	0	0
	Alcohol interaction	0	1	1	1	2	0	0
	Application site acne	0	0	0	2	2	0	0
	Application site bruise	0	1	0	5	6	0	0
	Application site burn	0	1	1	1	2	0	0
	Application site coldness	0	0	0	1	1	0	0
	Application site discolouration	0	0	0	4	4	0	0
	Application site discomfort	0	0	2	2	2	0	0
	Application site eczema	0	0	0	2	2	0	0
	Application site erythema	3	13	53	524	537	0	0
	Application site fibrosis	0	0	0	1	1	0	0
	Application site haematoma	1	3	2	5	8	0	0
	Application site haemorrhage	0	0	3	3	3	0	0
	Application site hypersensitivity	0	1	0	8	9	0	0
	Application site hypoaesthesia	0	1	15	22	23	0	0
	Application site induration	0	0	2	15	15	0	0
	Application site inflammation	0	1	1	8	9	0	0
	Application site joint erythema	0	1	0	1	2	0	0
	Application site joint movement impairment	1	1	1	1	2	0	0
	Application site joint pain	0	0	0	4	4	0	0
	Application site joint swelling	0	1	1	4	5	0	0
	Application site lymphadenopathy	0	0	7	14	14	0	0
	Application site movement impairment	0	0	7	18	18	0	0
	Application site necrosis	0	1	0	0	1	0	0
	Application site nerve damage	0	0	0	1	1	0	0
	Application site oedema	0	0	0	3	3	0	0
	Application site pain	7	14	215	1262	1276	0	0
	Application site papules	0	0	1	2	2	0	0
	Application site paraesthesia	0	1	1	2	3	0	0
	Application site plaque	0	0	0	2	2	0	0
	Application site pruritus	0	3	6	117	120	0	0
	Application site rash	0	0	2	19	19	0	0
	Application site reaction	2	3	33	259	262	0	0
	Application site scar	0	0	0	1	1	0	0
	Application site swelling	3	8	59	444	452	0	0
	Application site urticaria	0	0	0	2	2	0	0
	Application site vasculitis	0	1	0	0	1	0	0
	Application site vesicles	0	0	1	8	8	0	0
	Application site warmth	0	0	5	44	44	0	0
	Asthenia	763	3957	3210	15733	19690	0	0
	Atrophy	1	11	0	4	15	0	0
	Axillary pain	166	743	1085	3949	4692	0	0
	Brain death	1	16	0	0	16	0	0
	Breakthrough pain	0	2	0	0	2	0	0
	Calcinosis	0	1	1	4	5	0	0
	Capsular contracture associated with breast implant	0	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Cardiac complication associated with device	0	0	0	1	1	0	0
	Cardiac death	8	17	0	0	17	0	0
	Catheter site haemorrhage	0	2	0	0	2	0	0
	Catheter site related reaction	1	1	0	0	1	0	0
	Challenge site reaction	0	0	1	4	4	0	0
	Chest discomfort	474	1862	1225	5561	7423	0	0
	Chest pain	1421	5392	2326	7593	12985	0	0
	Chills	1899	7869	22143	78576	86445	0	1
	Chronic disease	1	5	1	1	6	0	0
	Chronic fatigue syndrome	19	37	22	42	79	0	0
	Clinical death	0	1	0	0	1	0	0
	Complication associated with device	2	12	0	6	18	0	0
	Complication of device insertion	0	1	0	0	1	0	0
	Complication of device removal	0	0	0	1	1	0	0
	Concomitant disease aggravated	12	21	26	42	63	0	0
	Concomitant disease progression	1	1	0	0	1	0	0
	Condition aggravated	175	1698	362	2707	4405	0	0
	Contrast media deposition	0	0	0	1	1	0	0
	Crepitations	0	12	1	14	26	0	0
	Critical illness	0	8	0	0	8	0	0
	Crying	14	59	30	267	326	0	0
	Cyst	5	20	14	81	101	0	0
	Cyst rupture	0	0	0	1	1	0	0
	Death	206	2914	0	0	2914	0	0
	Death neonatal	1	3	0	0	3	0	0
	Decreased activity	3	18	13	66	84	0	0
	Decreased gait velocity	0	0	0	1	1	0	0
	Deformity	0	2	2	8	10	0	0
	Dehiscence	0	1	0	0	1	0	0
	Developmental delay	0	1	0	2	3	0	0
	Device embolisation	0	1	0	0	1	0	0
	Device intolerance	0	0	0	1	1	0	0
	Diet failure	0	0	0	1	1	0	0
	Discharge	1	7	4	38	45	0	0
	Discomfort	46	299	451	2073	2372	0	0
	Disease prodromal stage	0	0	0	2	2	0	0
	Disease progression	3	15	0	0	15	0	0
	Disease propensity	0	0	1	1	1	0	0
	Disease recurrence	31	66	32	65	131	0	0
	Disease susceptibility	0	0	2	3	3	0	0
	Drowning	5	6	0	0	6	0	0
	Drug ineffective	90	193	185	1485	1678	0	0
	Drug interaction	5	20	24	79	99	0	0
	Drug intolerance	0	4	1	3	7	0	0
	Drug tolerance	0	1	0	0	1	0	0
	Drug tolerance decreased	0	0	2	3	3	0	0
	Drug tolerance increased	0	0	1	1	1	0	0
	Drug withdrawal syndrome	0	1	0	0	1	0	0
	Drug withdrawal syndrome neonatal	1	1	0	0	1	0	0
	Drug-device interaction	1	1	1	1	2	0	0
	Dysplasia	0	1	0	0	1	0	0
	Early satiety	0	1	1	3	4	0	0
	Effusion	1	14	6	12	26	0	0
	Embolia cutis medicamentosa	0	1	0	0	1	0	0
	Enanthema	1	2	1	3	5	0	0
	Encapsulation reaction	0	0	2	3	3	0	0
	Energy increased	0	3	8	73	76	0	0
	Exercise tolerance decreased	44	111	165	291	402	0	0
	Extensive swelling of vaccinated limb	232	441	1252	2909	3350	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Extravasation	0	1	0	1	2	0	0
	Face oedema	33	96	100	285	381	0	0
	Facial discomfort	4	11	7	128	139	0	0
	Facial pain	17	99	70	530	629	0	0
	Fat necrosis	0	0	1	2	2	0	0
	Fat tissue decreased	0	1	1	1	2	0	0
	Fat tissue increased	0	0	1	1	1	0	0
	Fatigue	3527	12312	27196	95285	107597	0	3
	Feeling abnormal	153	1206	824	12299	13505	0	0
	Feeling cold	201	618	781	4579	5197	0	0
	Feeling drunk	4	28	19	125	153	0	0
	Feeling hot	117	606	2285	8353	8959	0	0
	Feeling jittery	2	26	22	213	239	0	0
	Feeling of body temperature change	56	206	93	652	858	0	0
	Feeling of relaxation	0	0	1	32	32	0	0
	Fever neonatal	0	1	0	0	1	0	0
	Fibrosis	1	8	1	5	13	0	0
	Foaming at mouth	0	25	1	21	46	0	0
	Food interaction	0	0	0	1	1	0	0
	Foreign body reaction	0	0	1	3	3	0	0
	Gait deviation	0	2	2	3	5	0	0
	Gait disturbance	159	894	333	2576	3470	0	0
	Gait inability	41	414	57	580	994	0	0
	General physical health deterioration	47	323	184	387	710	0	0
	General symptom	0	8	2	24	32	0	0
	Generalised oedema	12	33	16	42	75	0	0
	Glassy eyes	1	4	1	39	43	0	0
	Granuloma	0	9	5	11	20	0	0
	Gravitational oedema	1	3	0	1	4	0	0
	Haemorrhagic cyst	0	0	2	2	2	0	0
	Hangover	1	22	11	45	67	0	0
	Hernia	1	7	3	11	18	0	0
	Hernia pain	0	4	3	3	7	0	0
	High-pitched crying	0	0	0	1	1	0	0
	Hunger	4	19	18	115	134	0	0
	Hyperplasia	2	3	0	1	4	0	0
	Hyperpyrexia	148	615	192	280	895	0	0
	Hyperthermia	6	34	25	79	113	0	0
	Hyperthermia malignant	1	2	0	0	2	0	0
	Hypertrophy	1	3	0	0	3	0	0
	Hypothermia	12	86	16	35	121	0	0
	Idiopathic environmental intolerance	0	0	1	1	1	0	0
	Idiosyncratic drug reaction	0	2	1	3	5	0	0
	Ill-defined disorder	2	11	8	33	44	0	0
	Illness	172	809	426	3115	3924	0	0
	Immediate post-injection reaction	0	144	1	1114	1258	0	0
	Impaired healing	3	12	18	45	57	0	0
	Impaired self-care	0	18	0	5	23	0	0
	Implant site hyperaesthesia	0	0	0	1	1	0	0
	Implant site hypersensitivity	0	0	0	1	1	0	0
	Implant site hypoaesthesia	1	1	0	0	1	0	0
	Implant site induration	0	0	1	2	2	0	0
	Implant site inflammation	0	0	1	2	2	0	0
	Implant site pain	0	0	2	5	5	0	0
	Implant site paraesthesia	0	0	0	2	2	0	0
	Implant site pruritus	0	0	1	1	1	0	0
	Implant site swelling	0	0	4	10	10	0	0
	Implant site warmth	0	2	1	2	4	0	0
	Inadequate analgesia	0	2	0	1	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Induration	4	27	80	1355	1382	0	0
	Inflammation	81	409	459	1556	1965	0	0
	Inflammatory pain	7	13	17	25	38	0	0
	Influenza like illness	371	1570	2743	11340	12910	0	0
	Infusion site bruising	0	0	0	1	1	0	0
	Infusion site erythema	2	2	2	9	11	0	0
	Infusion site haemorrhage	2	2	0	0	2	0	0
	Infusion site hypoaesthesia	0	0	2	2	2	0	0
	Infusion site joint erythema	0	0	0	1	1	0	0
	Infusion site joint inflammation	0	0	1	2	2	0	0
	Infusion site joint movement impairment	0	0	0	1	1	0	0
	Infusion site joint pain	0	0	0	1	1	0	0
	Infusion site joint swelling	0	0	0	4	4	0	0
	Infusion site mobility decreased	0	0	3	7	7	0	0
	Infusion site oedema	0	0	1	2	2	0	0
	Infusion site pain	0	3	1	6	9	0	0
	Infusion site pruritus	2	4	0	6	10	0	0
	Infusion site rash	0	0	0	1	1	0	0
	Infusion site reaction	0	0	0	2	2	0	0
	Infusion site swelling	0	0	1	1	1	0	0
	Infusion site urticaria	0	1	2	5	6	0	0
	Infusion site warmth	2	2	1	6	8	0	0
	Inhibitory drug interaction	0	0	0	6	6	0	0
	Injected limb mobility decreased	33	170	177	946	1116	0	0
	Injection site atrophy	1	1	0	3	4	0	0
	Injection site bruising	5	26	29	711	737	0	0
	Injection site coldness	0	0	6	12	12	0	0
	Injection site cyst	0	1	0	9	10	0	0
	Injection site deformation	0	0	1	1	1	0	0
	Injection site dermatitis	0	2	1	4	6	0	0
	Injection site discharge	0	0	2	10	10	0	0
	Injection site discolouration	1	2	17	294	296	0	0
	Injection site discomfort	2	7	126	676	683	0	0
	Injection site dryness	0	0	1	10	10	0	0
	Injection site dysaesthesia	0	0	0	1	1	0	0
	Injection site eczema	0	0	5	6	6	0	0
	Injection site erosion	0	0	0	2	2	0	0
	Injection site erythema	86	406	5472	31010	31416	0	0
	Injection site exfoliation	0	0	0	9	9	0	0
	Injection site extravasation	1	2	5	55	57	0	0
	Injection site fibrosis	0	0	0	1	1	0	0
	Injection site granuloma	0	0	2	3	3	0	0
	Injection site haematoma	4	12	785	2023	2035	0	0
	Injection site haemorrhage	3	12	10	169	181	0	0
	Injection site hyperaesthesia	0	0	1	3	3	0	0
	Injection site hypersensitivity	3	7	46	263	270	0	0
	Injection site hypertrophy	0	0	0	1	1	0	0
	Injection site hypoaesthesia	3	24	29	2522	2546	0	0
	Injection site indentation	1	3	2	66	69	0	0
	Injection site induration	15	46	279	5041	5087	0	0
	Injection site inflammation	8	23	4533	14011	14034	0	0
	Injection site injury	0	0	4	19	19	0	0
	Injection site irritation	2	4	10	174	178	0	0
	Injection site joint discomfort	1	1	2	4	5	0	0
	Injection site joint erythema	1	4	6	27	31	0	0
	Injection site joint inflammation	1	2	0	0	2	0	0
	Injection site joint movement impairment	1	3	9	43	46	0	0
	Injection site joint pain	1	7	18	79	86	0	0
	Injection site joint swelling	1	2	23	54	56	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Injection site joint warmth	0	0	2	13	13	0	0
	Injection site laceration	0	0	0	1	1	0	0
	Injection site lymphadenopathy	9	14	28	103	117	0	0
	Injection site macule	0	0	5	19	19	0	0
	Injection site mass	12	113	22	1402	1515	0	0
	Injection site movement impairment	13	22	37	129	151	0	0
	Injection site muscle atrophy	0	2	0	1	3	0	0
	Injection site muscle weakness	4	7	14	52	59	0	0
	Injection site necrosis	1	5	2	2	7	0	0
	Injection site nerve damage	0	0	0	3	3	0	0
	Injection site nodule	1	9	9	460	469	0	0
	Injection site oedema	6	19	104	479	498	0	0
	Injection site pain	427	1571	21142	58789	60360	0	0
	Injection site pallor	0	0	0	12	12	0	0
	Injection site panniculitis	0	0	0	1	1	0	0
	Injection site papule	0	0	6	48	48	0	0
	Injection site paraesthesia	7	20	53	280	300	0	0
	Injection site phlebitis	0	0	1	2	2	0	0
	Injection site photosensitivity reaction	0	0	1	1	1	0	0
	Injection site plaque	0	4	2	13	17	0	0
	Injection site pruritus	31	143	1703	17143	17286	0	0
	Injection site rash	18	136	138	6499	6635	0	0
	Injection site reaction	596	1276	1210	4876	6152	0	0
	Injection site scab	0	0	0	17	17	0	0
	Injection site scar	0	1	0	9	10	0	0
	Injection site streaking	0	0	1	28	28	0	0
	Injection site swelling	90	354	8004	29175	29529	0	0
	Injection site telangiectasia	0	0	0	1	1	0	0
	Injection site thrombosis	2	3	0	0	3	0	0
	Injection site ulcer	0	0	2	13	13	0	0
	Injection site urticaria	1	21	54	1041	1062	0	0
	Injection site vasculitis	0	0	0	2	2	0	0
	Injection site vesicles	1	10	10	146	156	0	0
	Injection site warmth	20	122	3935	19116	19238	0	0
	Injury associated with device	0	1	1	18	19	0	0
	Instillation site erythema	0	0	0	2	2	0	0
	Instillation site induration	0	0	0	1	1	0	0
	Instillation site pain	0	0	1	1	1	0	0
	Instillation site paraesthesia	0	0	0	1	1	0	0
	Instillation site warmth	1	1	5	7	8	0	0
	Irritability postvaccinal	0	0	0	2	2	0	0
	Lithiasis	2	2	0	0	2	0	0
	Local reaction	9	30	224	985	1015	0	0
	Localised oedema	15	59	72	168	227	0	0
	Loss of control of legs	1	34	4	6	40	0	0
	Macrosomia	0	1	0	0	1	0	0
	Malaise	1330	4311	19206	52528	56839	0	1
	Mass	5	37	29	504	541	0	0
	Medical device discomfort	0	1	0	0	1	0	0
	Medical device pain	0	0	0	1	1	0	0
	Medical device site haemorrhage	0	1	0	0	1	0	0
	Medical device site joint inflammation	0	0	1	2	2	0	0
	Medical device site joint movement impairment	0	0	1	1	1	0	0
	Medical device site joint pain	0	0	0	1	1	0	0
	Medical device site phlebitis	0	0	0	1	1	0	0
	Medical device site thrombosis	0	1	0	0	1	0	0
	Metaplasia	2	3	0	0	3	0	0
	Meteoropathy	0	1	1	2	3	0	0
	Moaning	2	13	2	33	46	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Mucosa vesicle	1	1	0	2	3	0	0
	Mucosal discolouration	1	1	0	3	4	0	0
	Mucosal disorder	0	2	2	6	8	0	0
	Mucosal dryness	2	4	6	15	19	0	0
	Mucosal erosion	0	1	0	0	1	0	0
	Mucosal haemorrhage	0	4	0	0	4	0	0
	Mucosal hypertrophy	0	7	0	2	9	0	0
	Mucosal inflammation	2	8	4	19	27	0	0
	Mucosal necrosis	1	1	0	0	1	0	0
	Mucosal pain	1	2	2	4	6	0	0
	Mucosal ulceration	0	3	1	1	4	0	0
	Multi-organ disorder	3	8	1	1	9	0	0
	Multimorbidity	0	4	0	0	4	0	0
	Multiple organ dysfunction syndrome	17	95	0	0	95	0	0
	Necrosis	5	15	0	0	15	0	0
	No adverse event	2	3	585	1663	1666	0	0
	No reaction on previous exposure to drug	0	0	2	14	14	0	0
	Nodule	8	38	36	491	529	0	0
	Non-cardiac chest pain	2	9	15	41	50	0	0
	Non-pitting oedema	0	0	1	5	5	0	0
	Nonspecific reaction	0	0	0	14	14	0	0
	Obstruction	0	3	0	1	4	0	0
	Oedema	43	173	162	541	714	0	0
	Oedema due to cardiac disease	0	1	0	0	1	0	0
	Oedema mucosal	0	2	6	17	19	0	0
	Oedema peripheral	87	354	297	950	1304	0	0
	Oral administration complication	0	0	0	1	1	0	0
	Organ failure	1	22	0	0	22	0	0
	Pacemaker generated arrhythmia	0	2	0	0	2	0	0
	Pain	834	4569	3763	33997	38566	0	0
	Papillitis	0	2	0	1	3	0	0
	Paradoxical drug reaction	0	0	0	3	3	0	0
	Pelvic mass	0	1	0	0	1	0	0
	Perforation	0	5	0	0	5	0	0
	Performance status decreased	17	22	43	68	90	0	0
	Peripheral swelling	345	2087	1111	10243	12330	0	0
	Physical deconditioning	4	26	36	104	130	0	0
	Pneumatosis	0	1	0	0	1	0	0
	Polyp	4	6	1	4	10	0	0
	Polyserositis	3	5	0	0	5	0	0
	Positive dose response relationship	0	0	0	1	1	0	0
	Potentiating drug interaction	0	0	0	2	2	0	0
	Pre-existing condition improved	0	0	6	38	38	0	0
	Pre-existing disease	0	0	15	15	15	0	0
	Precancerous condition	0	1	0	0	1	0	0
	Premature ageing	0	0	2	6	6	0	0
	Premature baby death	2	2	0	0	2	0	0
	Procedural failure	0	1	0	0	1	0	0
	Product intolerance	1	1	1	1	2	0	0
	Prosthetic cardiac valve thrombosis	0	1	0	0	1	0	0
	Pseudoallergic reaction	0	2	1	1	3	0	0
	Pseudocyst	0	2	0	0	2	0	0
	Pseudohernia	0	1	0	0	1	0	0
	Pseudopolyp	0	0	1	1	1	0	0
	Puncture site bruise	2	6	1	4	10	0	0
	Puncture site erythema	0	0	6	15	15	0	0
	Puncture site haematoma	0	0	1	1	1	0	0
	Puncture site haemorrhage	0	0	0	1	1	0	0
	Puncture site induration	0	0	4	15	15	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Puncture site injury	0	0	0	1	1	0	0
	Puncture site oedema	0	2	3	23	25	0	0
	Puncture site pain	0	3	51	108	111	0	0
	Puncture site pruritus	0	0	3	13	13	0	0
	Puncture site reaction	1	1	13	26	27	0	0
	Puncture site swelling	0	2	4	11	13	0	0
	Pyrexia	3496	14945	27637	105233	120178	0	2
	Rebound effect	1	2	1	2	4	0	0
	Retention cyst	0	1	0	2	3	0	0
	Scar inflammation	1	3	0	3	6	0	0
	Screaming	4	14	2	31	45	0	0
	Secretion discharge	4	32	20	164	196	0	0
	Sensation of blood flow	1	7	6	21	28	0	0
	Sensation of foreign body	10	57	52	400	457	0	0
	Sense of oppression	14	35	39	74	109	0	0
	Sensitivity to weather change	0	0	1	7	7	0	0
	Serositis	1	3	0	0	3	0	0
	Shoulder injury related to vaccine administration	14	47	12	79	126	0	0
	Similar reaction on previous exposure to drug	0	2	0	9	11	0	0
	Sluggishness	0	18	30	340	358	0	0
	Soft tissue inflammation	1	1	0	3	4	0	0
	Stenosis	1	6	0	8	14	0	0
	Stent-graft endoleak	1	1	0	0	1	0	0
	Sudden cardiac death	9	32	0	0	32	0	0
	Sudden death	49	165	0	0	165	0	0
	Supraclavicular fossa pain	0	0	3	3	3	0	0
	Suprapubic pain	1	2	0	6	8	0	0
	Surgical failure	0	0	0	1	1	0	0
	Swelling	184	962	845	7345	8307	0	0
	Swelling face	91	473	400	2889	3362	0	0
	Symptom masked	0	0	0	2	2	0	0
	Symptom recurrence	3	11	5	44	55	0	0
	Systemic inflammatory response syndrome	5	90	1	3	93	0	0
	Temperature intolerance	4	28	3	68	96	0	0
	Temperature regulation disorder	0	7	82	274	281	0	0
	Tenderness	30	191	209	2474	2665	0	0
	Terminal state	1	7	0	1	8	0	0
	Therapeutic product effect decreased	1	4	12	20	24	0	0
	Therapeutic product effect delayed	0	0	1	2	2	0	0
	Therapeutic product effect incomplete	0	0	3	6	6	0	0
	Therapeutic product effect increased	0	0	0	1	1	0	0
	Therapeutic product effect variable	1	1	0	0	1	0	0
	Therapeutic product ineffective	0	1	0	9	10	0	0
	Therapeutic response changed	1	2	0	1	3	0	0
	Therapeutic response decreased	0	0	4	9	9	0	0
	Therapeutic response shortened	0	0	7	15	15	0	0
	Therapeutic response unexpected	0	1	124	472	473	0	0
	Therapy non-responder	0	5	2	4	9	0	0
	Therapy partial responder	0	0	31	31	31	0	0
	Thirst	23	144	145	709	853	0	0
	Thirst decreased	1	3	0	22	25	0	0
	Tissue discolouration	0	0	2	3	3	0	0
	Tissue infiltration	1	4	1	1	5	0	0
	Tissue irritation	0	0	0	1	1	0	0
	Tissue rupture	0	0	0	1	1	0	0
	Treatment failure	0	4	0	1	5	0	0
	Treatment noncompliance	0	8	0	8	16	0	0
	Ulcer	4	16	4	27	43	0	0
	Ulcer haemorrhage	0	11	0	0	11	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Unevaluable event	2	473	94	719	1192	0	0
	Unmasking of previously unidentified disease	0	0	1	1	1	0	0
	Vaccination failure	4456	5392	143	314	5706	0	0
	Vaccination site abscess sterile	0	0	4	4	4	0	0
	Vaccination site anaesthesia	0	3	3	39	42	0	0
	Vaccination site atrophy	0	0	0	2	2	0	0
	Vaccination site bruising	8	27	51	600	627	0	0
	Vaccination site calcification	0	0	1	3	3	0	0
	Vaccination site coldness	0	2	3	23	25	0	0
	Vaccination site cyst	0	0	0	3	3	0	0
	Vaccination site dermatitis	0	1	4	16	17	0	0
	Vaccination site discharge	0	1	4	64	65	0	0
	Vaccination site discolouration	1	8	50	514	522	0	0
	Vaccination site discomfort	2	6	74	689	695	0	0
	Vaccination site dryness	1	1	2	12	13	0	0
	Vaccination site dysaesthesia	0	2	8	54	56	0	0
	Vaccination site eczema	0	1	9	42	43	0	0
	Vaccination site erosion	0	0	0	5	5	0	0
	Vaccination site erythema	87	464	1799	17340	17804	0	0
	Vaccination site exfoliation	0	1	1	11	12	0	0
	Vaccination site extravasation	0	0	2	9	9	0	0
	Vaccination site fibrosis	0	0	1	2	2	0	0
	Vaccination site granuloma	0	0	0	7	7	0	0
	Vaccination site haematoma	6	18	72	249	267	0	0
	Vaccination site haemorrhage	3	12	24	236	248	0	0
	Vaccination site hyperaesthesia	2	6	18	28	34	0	0
	Vaccination site hypersensitivity	1	1	16	77	78	0	0
	Vaccination site hypertrophy	0	0	0	1	1	0	0
	Vaccination site hypoaesthesia	6	15	10	89	104	0	0
	Vaccination site induration	7	56	209	3442	3498	0	0
	Vaccination site inflammation	20	75	483	2206	2281	0	0
	Vaccination site injury	0	1	2	7	8	0	0
	Vaccination site irritation	3	5	24	113	118	0	0
	Vaccination site joint discomfort	0	0	5	10	10	0	0
	Vaccination site joint effusion	1	1	0	1	2	0	0
	Vaccination site joint erythema	1	8	27	177	185	0	0
	Vaccination site joint inflammation	0	1	2	11	12	0	0
	Vaccination site joint movement impairment	9	15	17	63	78	0	0
	Vaccination site joint pain	10	17	44	126	143	0	0
	Vaccination site joint swelling	2	8	38	116	124	0	0
	Vaccination site joint warmth	1	2	4	16	18	0	0
	Vaccination site laceration	0	0	0	1	1	0	0
	Vaccination site lymphadenopathy	19	49	1406	2023	2072	0	0
	Vaccination site macule	1	7	14	34	41	0	0
	Vaccination site mass	8	47	72	1265	1312	0	0
	Vaccination site movement impairment	28	85	287	990	1075	0	0
	Vaccination site necrosis	0	4	0	0	4	0	0
	Vaccination site nerve damage	0	1	1	4	5	0	0
	Vaccination site nodule	2	6	9	149	155	0	0
	Vaccination site oedema	25	119	314	984	1103	0	0
	Vaccination site pain	296	1115	5685	34385	35500	0	0
	Vaccination site pallor	0	0	2	6	6	0	0
	Vaccination site papule	0	3	1	35	38	0	0
	Vaccination site paraesthesia	3	14	46	198	212	0	0
	Vaccination site phlebitis	0	0	0	2	2	0	0
	Vaccination site photosensitivity reaction	0	0	1	2	2	0	0
	Vaccination site plaque	1	5	19	84	89	0	0
	Vaccination site pruritus	23	176	937	10198	10374	0	0
	Vaccination site rash	10	113	423	4731	4844	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Vaccination site reaction	47	187	2138	7265	7452	0	0
	Vaccination site recall reaction	0	1	4	10	11	0	0
	Vaccination site scab	0	0	1	26	26	0	0
	Vaccination site scar	0	2	4	37	39	0	0
	Vaccination site streaking	1	3	0	17	20	0	0
	Vaccination site swelling	79	382	1673	14786	15168	0	0
	Vaccination site thrombosis	0	1	0	1	2	0	0
	Vaccination site ulcer	0	0	0	3	3	0	0
	Vaccination site urticaria	0	20	77	758	778	0	0
	Vaccination site vasculitis	0	3	0	0	3	0	0
	Vaccination site vesicles	1	5	15	124	129	0	0
	Vaccination site warmth	21	173	589	8814	8987	0	0
	Vaccine positive rechallenge	0	10	0	242	252	0	0
	Vascular stent stenosis	0	0	1	1	1	0	0
	Vascular stent thrombosis	2	6	0	0	6	0	0
	Vessel puncture site bruise	1	2	0	1	3	0	0
	Vessel puncture site erythema	0	0	0	1	1	0	0
	Vessel puncture site haematoma	0	1	0	0	1	0	0
	Vessel puncture site inflammation	0	0	0	1	1	0	0
	Vessel puncture site pain	0	0	2	2	2	0	0
	Vessel puncture site rash	0	0	1	1	1	0	0
	Vessel puncture site swelling	0	0	0	1	1	0	0
	Visceral pain	0	3	1	7	10	0	0
	Withdrawal syndrome	0	7	1	7	14	0	0
	Xerosis	0	0	1	2	2	0	0
Hepatobiliary disorders	*** SOC TOTAL ***	190	1022	103	320	1342	0	0
	Acute fatty liver of pregnancy	0	1	0	0	1	0	0
	Acute hepatic failure	3	20	0	0	20	0	0
	Acute on chronic liver failure	1	1	0	0	1	0	0
	Alcoholic liver disease	0	1	0	0	1	0	0
	Autoimmune cholangitis	0	1	0	0	1	0	0
	Autoimmune hepatitis	16	63	3	5	68	0	0
	Bile duct stenosis	1	2	0	0	2	0	0
	Bile duct stone	0	4	0	1	5	0	0
	Biliary colic	4	15	6	24	39	0	0
	Biliary dilatation	0	4	0	0	4	0	0
	Biliary dyskinesia	0	1	0	0	1	0	0
	Biliary obstruction	0	5	0	0	5	0	0
	Biliary tract disorder	0	3	0	0	3	0	0
	Budd-Chiari syndrome	0	1	0	0	1	0	0
	Cholangitis	4	13	0	2	15	0	0
	Cholangitis acute	1	3	0	0	3	0	0
	Cholangitis sclerosing	0	1	0	0	1	0	0
	Cholecystitis	5	38	2	2	40	0	0
	Cholecystitis acute	3	27	0	0	27	0	0
	Cholelithiasis	4	57	2	21	78	0	0
	Cholestasis	1	9	0	0	9	0	0
	Cholestasis of pregnancy	0	4	0	0	4	0	0
	Cholestatic liver injury	1	3	0	0	3	0	0
	Chronic hepatic failure	0	1	0	0	1	0	0
	Chronic hepatitis	0	1	0	0	1	0	0
	Cirrhosis alcoholic	0	1	0	0	1	0	0
	Congestive hepatopathy	2	8	0	0	8	0	0
	Dilatation intrahepatic duct acquired	0	1	0	0	1	0	0
	Drug-induced liver injury	2	11	0	0	11	0	0
	Gallbladder disorder	1	22	2	14	36	0	0
	Gallbladder enlargement	1	15	0	0	15	0	0
	Gallbladder hypofunction	0	3	0	0	3	0	0
	Gallbladder necrosis	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Gallbladder oedema	0	5	0	1	6	0	0
	Gallbladder polyp	0	2	0	0	2	0	0
	Gallbladder rupture	0	4	0	0	4	0	0
	Granulomatous liver disease	0	1	0	0	1	0	0
	Haemobilia	0	2	0	0	2	0	0
	Hepatic artery thrombosis	0	1	0	0	1	0	0
	Hepatic atrophy	0	2	0	0	2	0	0
	Hepatic cirrhosis	3	29	0	1	30	0	0
	Hepatic cyst	0	6	3	5	11	0	0
	Hepatic cytolysis	5	26	4	4	30	0	0
	Hepatic failure	3	36	0	0	36	0	0
	Hepatic fibrosis	0	2	0	0	2	0	0
	Hepatic function abnormal	10	36	13	27	63	0	0
	Hepatic haematoma	0	1	0	0	1	0	0
	Hepatic infarction	1	4	0	0	4	0	0
	Hepatic ischaemia	0	1	0	0	1	0	0
	Hepatic lesion	0	12	0	5	17	0	0
	Hepatic lymphocytic infiltration	0	1	0	0	1	0	0
	Hepatic mass	2	7	1	4	11	0	0
	Hepatic necrosis	0	2	0	0	2	0	0
	Hepatic pain	5	22	28	68	90	0	0
	Hepatic perfusion disorder	0	1	0	1	2	0	0
	Hepatic steatosis	2	24	4	15	39	0	0
	Hepatic vascular thrombosis	1	2	0	0	2	0	0
	Hepatic vein thrombosis	1	10	0	0	10	0	0
	Hepatitis	31	74	8	11	85	0	0
	Hepatitis acute	7	27	0	0	27	0	0
	Hepatitis cholestatic	0	4	0	0	4	0	0
	Hepatitis fulminant	2	4	0	0	4	0	0
	Hepatocellular injury	2	13	0	0	13	0	0
	Hepatomegaly	2	19	4	20	39	0	0
	Hepatorenal syndrome	0	2	1	1	3	0	0
	Hepatosplenomegaly	1	7	1	1	8	0	0
	Hepatotoxicity	1	4	0	0	4	0	0
	Hydrocholecystis	0	3	0	0	3	0	0
	Hyperbilirubinaemia	4	15	0	1	16	0	0
	Hyperbilirubinaemia neonatal	0	2	0	0	2	0	0
	Hyperplastic cholecystopathy	0	0	1	1	1	0	0
	Hypertransaminasaemia	2	12	2	5	17	0	0
	Immune-mediated cholestasis	1	1	0	0	1	0	0
	Immune-mediated hepatic disorder	0	1	0	0	1	0	0
	Immune-mediated hepatitis	0	2	0	0	2	0	0
	Ischaemic hepatitis	0	8	0	0	8	0	0
	Jaundice	14	57	3	27	84	0	0
	Jaundice cholestatic	0	4	0	0	4	0	0
	Liver disorder	12	46	13	41	87	0	0
	Liver injury	8	36	0	0	36	0	0
	Liver tenderness	1	3	1	4	7	0	0
	Mixed liver injury	1	5	0	0	5	0	0
	Non-alcoholic fatty liver	0	1	0	0	1	0	0
	Non-alcoholic steatohepatitis	0	2	0	0	2	0	0
	Ocular icterus	2	7	1	7	14	0	0
	Perforation bile duct	0	2	0	0	2	0	0
	Perihepatic discomfort	0	0	0	1	1	0	0
	Periportal oedema	0	5	0	0	5	0	0
	Pneumobilia	0	1	0	0	1	0	0
	Portal fibrosis	0	1	0	0	1	0	0
	Portal hypertension	1	5	0	0	5	0	0
	Portal shunt	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Portal vein embolism	0	1	0	0	1	0	0
	Portal vein occlusion	0	2	0	0	2	0	0
	Portal vein thrombosis	14	60	0	0	60	0	0
	Portosplenomesenteric venous thrombosis	0	2	0	0	2	0	0
	Primary biliary cholangitis	0	1	0	0	1	0	0
	Steatohepatitis	1	1	0	0	1	0	0
	Venoocclusive liver disease	0	1	0	0	1	0	0
Immune system disorders	*** SOC TOTAL ***	804	3924	3513	10887	14811	0	0
	Allergic oedema	0	3	0	6	9	0	0
	Allergic reaction to excipient	0	0	1	4	4	0	0
	Allergy to animal	0	1	3	8	9	0	0
	Allergy to arthropod bite	0	0	0	6	6	0	0
	Allergy to arthropod sting	0	4	2	6	10	0	0
	Allergy to chemicals	0	2	3	12	14	0	0
	Allergy to metals	0	1	4	10	11	0	0
	Allergy to plants	0	0	0	3	3	0	0
	Allergy to surgical sutures	0	0	0	1	1	0	0
	Allergy to vaccine	9	50	34	332	382	0	0
	Allergy to venom	0	0	0	1	1	0	0
	Amyloidosis	1	8	0	0	8	0	0
	Anamnestic reaction	0	1	0	0	1	0	0
	Anaphylactic reaction	157	1604	15	34	1638	0	0
	Anaphylactic shock	45	227	1	2	229	0	0
	Anaphylactoid reaction	18	82	3	5	87	0	0
	Anaphylactoid shock	0	1	0	0	1	0	0
	Anti-neutrophil cytoplasmic antibody positive vasculitis	4	11	0	0	11	0	0
	Atopy	0	0	0	4	4	0	0
	Autoimmune disorder	34	173	2	19	192	0	0
	Autoinflammatory disease	2	5	0	2	7	0	0
	Bacille Calmette-Guerin scar reactivation	1	21	11	74	95	0	0
	Caffeine allergy	0	1	0	2	3	0	0
	Cell-mediated immune deficiency	0	1	0	0	1	0	0
	Chronic allograft nephropathy	0	1	0	0	1	0	0
	Chronic graft versus host disease	0	1	0	0	1	0	0
	Contrast media allergy	0	3	1	3	6	0	0
	Contrast media reaction	0	2	0	0	2	0	0
	Corneal graft rejection	4	13	0	0	13	0	0
	Cross sensitivity reaction	0	0	0	2	2	0	0
	Cytokine release syndrome	0	3	0	0	3	0	0
	Cytokine storm	2	19	0	0	19	0	0
	Decreased immune responsiveness	5	8	9	26	34	0	0
	Drug hypersensitivity	12	40	19	71	111	0	0
	Dust allergy	0	0	4	5	5	0	0
	Eosinophilic granulomatosis with polyangiitis	3	7	0	0	7	0	0
	Food allergy	9	22	23	52	74	0	0
	Graft versus host disease	0	1	0	0	1	0	0
	Haemophagocytic lymphohistiocytosis	4	30	0	0	30	0	0
	Hypersensitivity	228	865	599	2746	3611	0	0
	Hypogammaglobulinaemia	3	5	1	1	6	0	0
	Immune reconstitution inflammatory syndrome	0	1	0	0	1	0	0
	Immune system disorder	12	38	33	106	144	0	0
	Immune-mediated adverse reaction	0	9	1	13	22	0	0
	Immunisation reaction	178	411	2670	6888	7299	0	0
	Immunodeficiency	18	49	4	8	57	0	0
	Immunodeficiency common variable	0	1	0	1	2	0	0
	Immunosuppression	0	16	1	1	17	0	0
	Infusion related hypersensitivity reaction	1	2	2	15	17	0	0
	Insulin autoimmune syndrome	1	1	0	0	1	0	0
	Iodine allergy	0	0	0	3	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Kidney transplant rejection	0	1	0	0	1	0	0
	Liver transplant rejection	0	2	0	0	2	0	0
	Loefgren syndrome	3	5	2	2	7	0	0
	Lung transplant rejection	0	1	0	0	1	0	0
	Milk allergy	1	3	1	2	5	0	0
	Mite allergy	0	2	2	5	7	0	0
	Multiple allergies	2	5	0	12	17	0	0
	Multisystem inflammatory syndrome	9	10	1	2	12	0	0
	Multisystem inflammatory syndrome in adults	4	9	0	1	10	0	0
	Multisystem inflammatory syndrome in children	2	7	0	0	7	0	0
	Mycotic allergy	0	0	1	1	1	0	0
	Overlap syndrome	1	2	0	1	3	0	0
	Perfume sensitivity	1	2	0	2	4	0	0
	Polymers allergy	0	3	4	4	7	0	0
	Reaction to colouring	1	1	0	0	1	0	0
	Reaction to excipient	0	1	0	4	5	0	0
	Reaction to food additive	1	1	0	1	2	0	0
	Reaction to preservatives	1	3	0	15	18	0	0
	Rubber sensitivity	0	0	1	5	5	0	0
	Sarcoidosis	6	21	0	1	22	0	0
	Seasonal allergy	0	13	30	110	123	0	0
	Secondary immunodeficiency	2	2	0	0	2	0	0
	Sensitisation	0	4	2	18	22	0	0
	Serum sickness	0	5	0	12	17	0	0
	Serum sickness-like reaction	1	2	1	5	7	0	0
	Sunscreen sensitivity	0	0	1	2	2	0	0
	Systemic immune activation	1	3	0	0	3	0	0
	Transplant rejection	1	7	0	0	7	0	0
	Type I hypersensitivity	8	31	2	5	36	0	0
	Type II hypersensitivity	0	1	0	0	1	0	0
	Type III immune complex mediated reaction	1	14	1	4	18	0	0
	Type IV hypersensitivity reaction	4	12	17	200	212	0	0
	Vaccine associated enhanced disease	0	4	0	0	4	0	0
	Vaccine associated enhanced respiratory disease	3	3	1	1	4	0	0
Infections and infestations	*** SOC TOTAL ***	6881	21722	10257	29647	51369	0	1
	Abdominal abscess	3	10	0	0	10	0	0
	Abdominal infection	0	10	1	1	11	0	0
	Abdominal wall abscess	0	2	0	0	2	0	0
	Abortion infected	0	1	0	0	1	0	0
	Abscess	19	40	26	65	105	0	0
	Abscess bacterial	0	0	1	1	1	0	0
	Abscess intestinal	0	3	0	0	3	0	0
	Abscess jaw	1	2	1	2	4	0	0
	Abscess limb	2	12	5	14	26	0	0
	Abscess neck	0	3	0	2	5	0	0
	Abscess of external auditory meatus	0	0	1	1	1	0	0
	Abscess of eyelid	0	0	0	1	1	0	0
	Abscess oral	0	1	0	1	2	0	0
	Abscess rupture	0	2	0	0	2	0	0
	Acarodermatitis	0	1	0	3	4	0	0
	Acid fast bacilli infection	0	1	0	0	1	0	0
	Acinetobacter bacteraemia	0	1	0	0	1	0	0
	Acne pustular	1	2	1	6	8	0	0
	Acquired immunodeficiency syndrome	1	1	0	0	1	0	0
	Acute hepatitis 8	0	3	0	0	3	0	0
	Acute sinusitis	2	4	5	15	19	0	0
	Adenoviral meningitis	0	1	0	0	1	0	0
	Adenovirus infection	0	1	0	1	2	0	0
	Administration site abscess	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Administration site cellulitis	0	1	3	4	5	0	0
	Administration site infection	0	0	1	1	1	0	0
	Aerococcus urinae infection	0	2	0	0	2	0	0
	Amniotic cavity infection	0	1	0	0	1	0	0
	Amoebic dysentery	1	1	1	1	2	0	0
	Anal abscess	2	6	1	1	7	0	0
	Anal candidiasis	0	0	0	1	1	0	0
	Anal fungal infection	0	0	0	1	1	0	0
	Appendiceal abscess	0	2	0	0	2	0	0
	Appendicitis	30	268	2	5	273	0	0
	Appendicitis perforated	4	33	0	0	33	0	0
	Application site cellulitis	0	0	0	1	1	0	0
	Application site infection	0	2	0	1	3	0	0
	Application site pustules	0	0	3	8	8	0	0
	Arthritis bacterial	1	10	0	0	10	0	0
	Arthritis infective	1	6	0	0	6	0	0
	Arthritis viral	1	1	0	0	1	0	0
	Arthropod-borne disease	0	0	0	1	1	0	0
	Aspergillus infection	0	1	0	0	1	0	0
	Asymptomatic COVID-19	7	110	25	171	281	0	0
	Asymptomatic bacteriuria	0	3	0	1	4	0	0
	Atypical pneumonia	2	45	0	1	46	0	0
	BK virus infection	0	0	0	1	1	0	0
	Babesiosis	0	2	0	0	2	0	0
	Bacteraemia	2	27	0	1	28	0	0
	Bacterial abdominal infection	0	1	0	0	1	0	0
	Bacterial disease carrier	0	2	0	0	2	0	0
	Bacterial gingivitis	0	0	1	1	1	0	0
	Bacterial infection	4	31	8	38	69	0	0
	Bacterial prostatitis	0	1	0	0	1	0	0
	Bacterial rhinitis	0	0	1	1	1	0	0
	Bacterial sepsis	0	1	0	0	1	0	0
	Bacterial vaginosis	0	1	5	10	11	0	0
	Bacteriuria	0	2	0	0	2	0	0
	Bacteroides bacteraemia	0	2	0	0	2	0	0
	Bartholin's abscess	0	1	0	0	1	0	0
	Bartholinitis	0	0	0	2	2	0	0
	Bed bug infestation	1	1	0	0	1	0	0
	Beta haemolytic streptococcal infection	1	8	0	0	8	0	0
	Biliary sepsis	0	1	0	0	1	0	0
	Biliary tract infection	0	1	0	0	1	0	0
	Blastomycosis	0	1	0	0	1	0	0
	Blister infected	0	0	1	4	4	0	0
	Body tinea	0	1	2	7	8	0	0
	Bone tuberculosis	0	2	0	1	3	0	0
	Borrelia infection	0	5	0	0	5	0	0
	Brain abscess	0	3	0	0	3	0	0
	Breakthrough COVID-19	5	5	44	44	49	0	0
	Breast abscess	1	2	2	6	8	0	0
	Breast cellulitis	0	2	0	1	3	0	0
	Bronchiolitis	1	8	2	2	10	0	0
	Bronchitis	18	86	44	187	273	0	0
	Bronchitis bacterial	0	1	1	2	3	0	0
	Bronchitis viral	0	0	0	2	2	0	0
	Bronchopulmonary aspergillosis	0	2	0	0	2	0	0
	Bronchopulmonary aspergillosis allergic	0	1	0	0	1	0	0
	Bullous erysipelas	1	1	0	1	2	0	0
	Burn infection	0	0	1	1	1	0	0
	COVID-19	4907	9901	1709	7655	17556	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	COVID-19 pneumonia	60	907	1	5	912	0	0
	Campylobacter colitis	0	1	0	0	1	0	0
	Campylobacter gastroenteritis	0	1	0	0	1	0	0
	Campylobacter infection	0	1	0	0	1	0	0
	Candida infection	3	14	7	47	61	0	0
	Carbuncle	0	1	1	2	3	0	0
	Cardiac infection	1	7	0	0	7	0	0
	Cardiac valve vegetation	0	3	0	0	3	0	0
	Cat scratch disease	0	0	0	1	1	0	0
	Cavernous sinus thrombosis	0	5	0	0	5	0	0
	Cellulitis	54	1142	24	116	1258	0	0
	Cellulitis orbital	1	4	0	0	4	0	0
	Cellulitis staphylococcal	0	2	0	0	2	0	0
	Central nervous system infection	0	2	0	0	2	0	0
	Central nervous system viral infection	0	1	0	0	1	0	0
	Cervicitis	0	0	0	1	1	0	0
	Chest wall abscess	1	2	0	0	2	0	0
	Chikungunya virus infection	0	0	0	1	1	0	0
	Chlamydial infection	1	2	2	2	4	0	0
	Cholangitis infective	0	1	0	0	1	0	0
	Cholecystitis infective	0	11	0	0	11	0	0
	Chorioretinitis	2	5	0	0	5	0	0
	Chronic active Epstein-Barr virus infection	0	1	1	2	3	0	0
	Chronic hepatitis B	1	1	0	0	1	0	0
	Chronic hepatitis C	0	2	0	0	2	0	0
	Chronic sinusitis	1	7	2	4	11	0	0
	Clostridial infection	0	1	0	0	1	0	0
	Clostridium difficile colitis	1	27	0	0	27	0	0
	Clostridium difficile infection	3	23	0	0	23	0	0
	Coccidioidomycosis	0	1	0	0	1	0	0
	Coinfection	0	0	0	1	1	0	0
	Colonic abscess	0	1	0	0	1	0	0
	Colostomy infection	0	1	0	0	1	0	0
	Community acquired infection	0	0	0	1	1	0	0
	Complicated appendicitis	0	1	0	0	1	0	0
	Conjunctivitis	5	33	50	158	191	0	0
	Conjunctivitis bacterial	0	3	2	3	6	0	0
	Conjunctivitis viral	1	2	3	5	7	0	0
	Corneal infection	0	1	0	0	1	0	0
	Coronavirus infection	1	6	7	15	21	0	0
	Coronavirus pneumonia	0	1	0	0	1	0	0
	Coxsackie viral infection	0	0	0	2	2	0	0
	Cranial nerve infection	0	1	0	0	1	0	0
	Creutzfeldt-Jakob disease	5	10	0	0	10	0	0
	Croup infectious	0	1	0	0	1	0	0
	Cutaneous larva migrans	0	0	1	1	1	0	0
	Cutaneous mucormycosis	0	1	0	0	1	0	0
	Cystitis	22	62	69	171	233	0	0
	Cystitis bacterial	1	1	1	1	2	0	0
	Cystitis viral	0	1	0	0	1	0	0
	Cytomegalovirus hepatitis	2	3	0	0	3	0	0
	Cytomegalovirus infection	3	10	0	3	13	0	0
	Cytomegalovirus infection reactivation	0	3	1	1	4	0	0
	Cytomegalovirus viraemia	0	1	0	0	1	0	0
	Dacryocanaliculitis	0	0	0	1	1	0	0
	Dacryocystitis	0	1	0	0	1	0	0
	Dengue fever	0	2	2	3	5	0	0
	Dermatitis infected	1	2	0	4	6	0	0
	Dermatophytosis	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Dermo-hypodermitis	1	15	2	4	19	0	0
	Device related bacteraemia	0	1	0	0	1	0	0
	Device related infection	2	7	0	0	7	0	0
	Device related sepsis	1	1	0	0	1	0	0
	Diabetic foot infection	0	1	0	0	1	0	0
	Diarrhoea infectious	0	1	0	1	2	0	0
	Disseminated Bacillus Calmette-Guerin infection	0	0	1	1	1	0	0
	Disseminated mycobacterium avium complex infection	0	1	0	0	1	0	0
	Disseminated tuberculosis	0	1	0	0	1	0	0
	Disseminated varicella zoster virus infection	1	4	0	0	4	0	0
	Diverticulitis	24	113	2	9	122	0	0
	Diverticulitis intestinal perforated	0	1	0	0	1	0	0
	Dysentery	9	40	19	32	72	0	0
	Ear infection	8	31	19	153	184	0	0
	Ear infection bacterial	0	1	0	0	1	0	0
	Ear infection viral	0	1	0	2	3	0	0
	Ear, nose and throat infection	1	1	0	0	1	0	0
	Echinococciasis	1	1	0	0	1	0	0
	Eczema herpeticum	0	8	1	1	9	0	0
	Eczema impetiginous	0	1	0	0	1	0	0
	Eczema infected	0	3	1	1	4	0	0
	Embolic pneumonia	0	1	0	0	1	0	0
	Empyema	3	9	0	0	9	0	0
	Encephalitis	47	121	1	2	123	0	1
	Encephalitis Japanese B	0	1	0	0	1	0	0
	Encephalitis brain stem	2	4	0	0	4	0	0
	Encephalitis viral	1	4	0	0	4	0	0
	Encephalomyelitis	10	20	0	0	20	0	0
	Endocarditis	12	29	0	0	29	0	0
	Endocarditis bacterial	1	2	0	0	2	0	0
	Endocarditis staphylococcal	0	1	0	0	1	0	0
	Endometritis	1	2	0	0	2	0	0
	Endophthalmitis	0	2	0	0	2	0	0
	Enteritis infectious	0	1	0	0	1	0	0
	Enterobacter infection	0	1	0	0	1	0	0
	Enterobiasis	0	0	0	1	1	0	0
	Enterococcal bacteraemia	0	1	0	0	1	0	0
	Enterococcal infection	1	4	0	0	4	0	0
	Enterocolitis infectious	0	1	0	0	1	0	0
	Enterovirus infection	0	2	0	0	2	0	0
	Epidemic polyarthritis	0	0	0	1	1	0	0
	Epididymitis	4	28	0	2	30	0	0
	Epiglottitis	1	9	0	0	9	0	0
	Epiglottitis obstructive	0	1	0	0	1	0	0
	Epstein-Barr viraemia	1	4	0	1	5	0	0
	Epstein-Barr virus infection	3	10	8	21	31	0	0
	Epstein-Barr virus infection reactivation	7	24	5	8	32	0	0
	Eruptive pseudoangiomatosis	0	0	1	1	1	0	0
	Erysipelas	30	199	22	44	243	0	0
	Erysipeloid	0	0	0	2	2	0	0
	Erythema induratum	0	8	2	3	11	0	0
	Erythema infectiosum	0	0	1	2	2	0	0
	Erythema migrans	1	1	3	15	16	0	0
	Erythrasma	0	0	0	1	1	0	0
	Escherichia bacteraemia	1	11	0	0	11	0	0
	Escherichia infection	1	14	0	0	14	0	0
	Escherichia pyelonephritis	0	2	0	0	2	0	0
	Escherichia sepsis	0	2	0	0	2	0	0
	Escherichia urinary tract infection	0	7	0	0	7	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Extradural abscess	0	1	0	0	1	0	0
	Eye abscess	1	2	0	0	2	0	0
	Eye infection	4	17	6	45	62	0	0
	Eye infection bacterial	0	5	0	0	5	0	0
	Eye infection chlamydial	1	1	0	0	1	0	0
	Eye infection viral	0	0	2	3	3	0	0
	Eyelid boil	0	1	0	0	1	0	0
	Eyelid infection	1	2	5	14	16	0	0
	Febrile infection	0	2	0	2	4	0	0
	Folliculitis	4	5	4	25	30	0	0
	Foot and mouth disease	0	0	1	1	1	0	0
	Fournier's gangrene	0	1	0	0	1	0	0
	Fungaemia	0	1	0	0	1	0	0
	Fungal foot infection	0	1	3	4	5	0	0
	Fungal infection	5	14	14	66	80	0	0
	Fungal skin infection	1	4	3	18	22	0	0
	Furuncle	2	12	12	46	58	0	0
	Gangrene	2	9	0	1	10	0	0
	Gastric infection	1	3	1	3	6	0	0
	Gastroenteritis	9	34	28	46	80	0	0
	Gastroenteritis Escherichia coli	0	4	0	0	4	0	0
	Gastroenteritis norovirus	1	2	0	0	2	0	0
	Gastroenteritis rotavirus	0	0	0	1	1	0	0
	Gastroenteritis viral	3	10	2	28	38	0	0
	Gastrointestinal bacterial infection	0	2	0	0	2	0	0
	Gastrointestinal bacterial overgrowth	0	1	1	1	2	0	0
	Gastrointestinal candidiasis	1	1	0	0	1	0	0
	Gastrointestinal infection	1	6	3	12	18	0	0
	Gastrointestinal viral infection	0	0	1	3	3	0	0
	Genital abscess	2	4	0	0	4	0	0
	Genital herpes	10	28	37	96	124	0	0
	Genital herpes simplex	0	1	3	6	7	0	0
	Genital herpes zoster	0	2	4	6	8	0	0
	Genital infection	0	0	2	2	2	0	0
	Genital infection bacterial	0	1	1	2	3	0	0
	Genital infection female	0	0	0	2	2	0	0
	Genital infection fungal	0	0	3	4	4	0	0
	Genital ulcer syndrome	2	2	0	0	2	0	0
	Genitourinary tract infection	0	1	0	1	2	0	0
	Giardiasis	0	0	1	2	2	0	0
	Gingival abscess	0	1	0	4	5	0	0
	Gingivitis	3	9	28	76	85	0	0
	Gonorrhoea	0	2	0	0	2	0	0
	Groin abscess	2	5	0	0	5	0	0
	Groin infection	1	2	1	1	3	0	0
	H1N1 influenza	0	0	0	2	2	0	0
	HCoV-OC43 infection	0	1	0	0	1	0	0
	Haematoma infection	0	2	0	1	3	0	0
	Haemophilus infection	0	2	0	0	2	0	0
	Haemorrhagic pneumonia	0	1	0	0	1	0	0
	Hand-foot-and-mouth disease	0	3	0	5	8	0	0
	Helicobacter gastritis	0	1	0	2	3	0	0
	Helicobacter infection	1	10	2	4	14	0	0
	Helminthic infection	0	1	0	0	1	0	0
	Hepatic infection	0	1	0	0	1	0	0
	Hepatitis A	1	1	0	0	1	0	0
	Hepatitis B	0	2	0	0	2	0	0
	Hepatitis B reactivation	1	2	0	0	2	0	0
	Hepatitis C	0	6	0	0	6	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Hepatitis E	2	4	0	0	4	0	0
	Hepatitis infectious mononucleosis	0	3	0	0	3	0	0
	Hepatitis viral	0	1	0	0	1	0	0
	Herpangina	0	0	0	1	1	0	0
	Herpes dermatitis	0	1	1	7	8	0	0
	Herpes oesophagitis	0	1	0	0	1	0	0
	Herpes ophthalmic	20	54	6	8	62	0	0
	Herpes simplex	5	21	72	175	196	0	0
	Herpes simplex encephalitis	2	4	0	0	4	0	0
	Herpes simplex meningitis	0	3	0	0	3	0	0
	Herpes simplex oesophagitis	0	1	0	0	1	0	0
	Herpes simplex reactivation	3	6	7	26	32	0	0
	Herpes virus infection	13	28	75	161	189	0	0
	Herpes zoster	267	775	1345	3945	4720	0	0
	Herpes zoster cutaneous disseminated	3	10	2	2	12	0	0
	Herpes zoster disseminated	4	5	0	0	5	0	0
	Herpes zoster infection neurological	1	2	1	1	3	0	0
	Herpes zoster meningitis	0	7	0	0	7	0	0
	Herpes zoster meningoencephalitis	1	6	0	0	6	0	0
	Herpes zoster meningomyelitis	1	1	0	0	1	0	0
	Herpes zoster meningoradiculitis	0	1	0	0	1	0	0
	Herpes zoster oticus	13	45	1	3	48	0	0
	Herpes zoster reactivation	11	19	19	41	60	0	0
	Herpetic radiculopathy	0	1	0	0	1	0	0
	Histoplasmosis	0	1	0	0	1	0	0
	Hordeolum	1	7	10	69	76	0	0
	Human anaplasmosis	0	1	0	0	1	0	0
	Human ehrlichiosis	0	0	0	1	1	0	0
	Human herpesvirus 6 infection	0	1	0	0	1	0	0
	Human herpesvirus 6 infection reactivation	0	0	0	1	1	0	0
	Hypopyon	0	1	0	0	1	0	0
	Impetigo	2	7	3	17	24	0	0
	Implant site abscess	0	0	1	1	1	0	0
	Implant site pustules	0	0	0	1	1	0	0
	Infected bite	1	1	1	2	3	0	0
	Infected bunion	0	1	0	0	1	0	0
	Infected cyst	1	3	1	2	5	0	0
	Infected dermal cyst	0	1	2	3	4	0	0
	Infected fistula	0	0	0	1	1	0	0
	Infected skin ulcer	0	2	0	0	2	0	0
	Infection	30	221	26	283	504	0	0
	Infection in an immunocompromised host	0	1	0	0	1	0	0
	Infection parasitic	0	1	0	0	1	0	0
	Infection reactivation	0	1	2	4	5	0	0
	Infection susceptibility increased	5	6	19	20	26	0	0
	Infection transmission via personal contact	0	0	0	1	1	0	0
	Infection via vaccinee	0	0	0	1	1	0	0
	Infectious disease carrier	0	0	0	1	1	0	0
	Infectious iridocyclitis	0	0	1	1	1	0	0
	Infectious mononucleosis	2	9	8	34	43	0	0
	Infectious pleural effusion	0	3	0	0	3	0	0
	Infectious thyroiditis	0	0	2	2	2	0	0
	Infective corneal ulcer	0	2	0	0	2	0	0
	Infective glossitis	0	0	0	1	1	0	0
	Infective spondylitis	1	1	0	0	1	0	0
	Infective thrombosis	0	2	0	0	2	0	0
	Influenza	177	734	4331	7137	7871	0	0
	Injection site abscess	1	2	3	43	45	0	0
	Injection site cellulitis	2	27	1	226	253	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Injection site infection	0	4	7	81	85	0	0
	Injection site pustule	0	1	3	29	30	0	0
	Intervertebral discitis	1	1	1	1	2	0	0
	Intestinal sepsis	0	1	0	0	1	0	0
	Joint abscess	1	2	0	0	2	0	0
	Keratitis viral	2	3	0	0	3	0	0
	Kidney infection	7	58	2	7	65	0	0
	Klebsiella bacteraemia	0	1	0	0	1	0	0
	Klebsiella infection	0	5	0	0	5	0	0
	Klebsiella sepsis	1	1	0	0	1	0	0
	Labyrinthitis	9	29	7	33	62	0	0
	Large intestine infection	1	3	1	1	4	0	0
	Laryngitis	3	14	14	58	72	0	0
	Laryngopharyngitis	0	0	1	1	1	0	0
	Latent tuberculosis	0	1	2	2	3	0	0
	Lice infestation	0	1	0	1	2	0	0
	Lip infection	0	0	0	3	3	0	0
	Listeriosis	0	1	0	0	1	0	0
	Liver abscess	2	5	0	0	5	0	0
	Localised infection	5	38	10	61	99	0	0
	Lower respiratory tract infection	31	119	16	30	149	0	0
	Lung abscess	1	5	0	0	5	0	0
	Lyme disease	2	39	1	6	45	0	0
	Lymph gland infection	1	3	1	4	7	0	0
	Lymph node abscess	1	5	3	4	9	0	0
	Lymph node tuberculosis	0	1	0	0	1	0	0
	Lymphangitis	4	44	12	22	66	0	0
	Malaria relapse	1	1	0	0	1	0	0
	Mastitis	14	60	20	29	89	0	0
	Mastitis postpartum	0	0	1	1	1	0	0
	Mastoiditis	0	2	0	1	3	0	0
	Measles	0	2	0	2	4	0	0
	Mediastinitis	0	1	0	0	1	0	0
	Medical device site joint infection	0	1	0	0	1	0	0
	Meningitis	17	60	0	0	60	0	0
	Meningitis aseptic	4	49	0	0	49	0	0
	Meningitis bacterial	1	4	0	0	4	0	0
	Meningitis coxsackie viral	0	1	0	0	1	0	0
	Meningitis herpes	0	1	0	0	1	0	0
	Meningitis pneumococcal	1	1	0	0	1	0	0
	Meningitis viral	3	22	0	0	22	0	0
	Meningoencephalitis bacterial	0	1	0	0	1	0	0
	Meningoencephalitis herpetic	3	5	0	0	5	0	0
	Meningoencephalitis viral	0	2	0	0	2	0	0
	Molluscum contagiosum	0	1	1	4	5	0	0
	Mononucleosis syndrome	1	1	0	0	1	0	0
	Mucormycosis	0	1	0	0	1	0	0
	Mucosal infection	0	2	0	0	2	0	0
	Mumps	0	2	1	5	7	0	0
	Muscle abscess	0	1	0	0	1	0	0
	Mycobacterium avium complex infection	0	1	0	0	1	0	0
	Mycobacterium chelonae infection	1	1	0	0	1	0	0
	Myelitis	27	72	2	2	74	0	0
	Myocarditis infectious	0	1	0	0	1	0	0
	Myringitis	0	2	1	3	5	0	0
	Nail infection	0	1	0	1	2	0	0
	Nasal abscess	1	3	0	0	3	0	0
	Nasal herpes	3	6	17	33	39	0	0
	Nasal vestibulitis	1	1	3	8	9	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Nasopharyngitis	91	381	823	2972	3353	0	0
	Necrotising fasciitis	0	3	0	0	3	0	0
	Necrotising ulcerative gingivostomatitis	0	2	0	0	2	0	0
	Neuroborreliosis	0	2	0	0	2	0	0
	Neurological infection	0	1	0	0	1	0	0
	Neutropenic sepsis	0	2	0	0	2	0	0
	Nipple infection	0	0	0	1	1	0	0
	Norovirus infection	0	0	1	2	2	0	0
	Nosocomial infection	0	1	0	1	2	0	0
	Oesophageal candidiasis	0	1	0	0	1	0	0
	Omphalitis	0	1	0	0	1	0	0
	Onychomycosis	0	0	3	4	4	0	0
	Oophoritis	0	0	1	2	2	0	0
	Ophthalmic herpes simplex	2	9	2	3	12	0	0
	Ophthalmic herpes zoster	46	134	23	29	163	0	0
	Oral candidiasis	5	13	4	37	50	0	0
	Oral fungal infection	0	2	4	10	12	0	0
	Oral herpes	39	128	248	943	1071	0	0
	Oral infection	1	4	1	1	5	0	0
	Oral pustule	0	1	0	8	9	0	0
	Orbital infection	0	1	0	0	1	0	0
	Orchitis	2	7	1	6	13	0	0
	Oropharyngeal candidiasis	0	0	1	2	2	0	0
	Osteomyelitis	4	20	0	1	21	0	0
	Osteomyelitis acute	0	1	0	0	1	0	0
	Otitis externa	0	2	4	17	19	0	0
	Otitis externa fungal	1	1	0	0	1	0	0
	Otitis media	2	5	9	26	31	0	0
	Otitis media acute	0	2	1	5	7	0	0
	Otitis media chronic	0	0	0	1	1	0	0
	Otosalpingitis	0	0	1	4	4	0	0
	Overgrowth bacterial	0	1	0	0	1	0	0
	Overgrowth fungal	0	1	0	1	2	0	0
	Pancreas infection	1	2	0	0	2	0	0
	Pancreatic abscess	1	1	0	0	1	0	0
	Pancreatitis viral	0	1	0	0	1	0	0
	Papilloma viral infection	0	0	4	6	6	0	0
	Papular pruritic eruption of HIV	0	0	0	1	1	0	0
	Parainfluenzae virus infection	0	1	0	0	1	0	0
	Parasitic gastroenteritis	1	2	1	1	3	0	0
	Paronychia	0	0	2	7	7	0	0
	Parotitis	4	8	6	16	24	0	0
	Parvovirus B19 infection	1	1	0	0	1	0	0
	Parvovirus infection	0	0	0	2	2	0	0
	Pathogen resistance	0	2	0	0	2	0	0
	Pelvic abscess	0	2	0	0	2	0	0
	Pelvic inflammatory disease	2	10	0	0	10	0	0
	Peptostreptococcus infection	0	1	0	0	1	0	0
	Peri-implantitis	1	1	1	1	2	0	0
	Perichondritis	0	2	0	0	2	0	0
	Pericoronitis	0	0	0	1	1	0	0
	Perineal abscess	0	1	0	0	1	0	0
	Perinephritis	0	1	0	0	1	0	0
	Periodontitis	0	1	2	4	5	0	0
	Periorbital cellulitis	1	4	0	1	5	0	0
	Perirectal abscess	0	2	0	0	2	0	0
	Peritonitis	3	12	0	1	13	0	0
	Peritonitis bacterial	0	3	0	0	3	0	0
	Peritonsillar abscess	0	8	1	2	10	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Peritonsillitis	0	1	0	0	1	0	0
	Pertussis	0	4	0	0	4	0	0
	Pharyngeal abscess	0	1	0	0	1	0	0
	Pharyngeal pustule	0	0	0	2	2	0	0
	Pharyngitis	5	19	42	82	101	0	0
	Pharyngitis bacterial	0	1	0	1	2	0	0
	Pharyngitis streptococcal	0	4	1	25	29	0	0
	Pharyngotonsillitis	0	1	1	2	3	0	0
	Pilonidal disease	0	2	0	0	2	0	0
	Plague	0	1	0	0	1	0	0
	Pleural infection	0	2	0	0	2	0	0
	Pleurisy viral	0	1	0	0	1	0	0
	Pneumococcal sepsis	1	2	0	0	2	0	0
	Pneumocystis jirovecii pneumonia	1	6	0	0	6	0	0
	Pneumonia	141	1376	29	50	1426	0	0
	Pneumonia aspiration	9	68	0	1	69	0	0
	Pneumonia bacterial	3	63	1	4	67	0	0
	Pneumonia cytomegaloviral	1	1	0	0	1	0	0
	Pneumonia escherichia	0	0	0	1	1	0	0
	Pneumonia fungal	0	4	0	0	4	0	0
	Pneumonia haemophilus	1	1	0	0	1	0	0
	Pneumonia klebsiella	0	2	0	0	2	0	0
	Pneumonia legionella	1	2	0	0	2	0	0
	Pneumonia mycoplasmal	0	2	0	0	2	0	0
	Pneumonia necrotising	0	2	0	0	2	0	0
	Pneumonia pneumococcal	1	4	0	0	4	0	0
	Pneumonia pseudomonal	0	2	0	0	2	0	0
	Pneumonia staphylococcal	1	6	0	0	6	0	0
	Pneumonia streptococcal	0	2	0	0	2	0	0
	Pneumonia viral	2	38	0	2	40	0	0
	Poliomyelitis	1	2	0	0	2	0	0
	Post procedural infection	0	2	0	1	3	0	0
	Post procedural pneumonia	0	1	0	0	1	0	0
	Post treatment Lyme disease syndrome	1	1	0	0	1	0	0
	Post viral fatigue syndrome	8	19	7	21	40	0	0
	Post-acute COVID-19 syndrome	15	35	29	175	210	0	0
	Postoperative abscess	1	3	0	0	3	0	0
	Postoperative wound infection	0	7	0	1	8	0	0
	Prion disease	1	1	0	0	1	0	0
	Proctitis herpes	0	0	0	1	1	0	0
	Prostate infection	0	3	0	1	4	0	0
	Proteus infection	0	1	0	0	1	0	0
	Pseudomembranous colitis	0	1	0	0	1	0	0
	Pseudomonal bacteraemia	0	1	0	0	1	0	0
	Pseudomonas infection	1	7	0	0	7	0	0
	Psoas abscess	1	1	0	0	1	0	0
	Pulmonary sepsis	1	1	0	0	1	0	0
	Pulmonary tuberculosis	0	1	1	1	2	0	0
	Pulpitis dental	0	2	12	26	28	0	0
	Purulence	0	2	5	8	10	0	0
	Purulent discharge	0	3	0	6	9	0	0
	Purulent pericarditis	1	2	0	0	2	0	0
	Pustule	9	19	35	111	130	0	0
	Pyelitis	1	2	0	0	2	0	0
	Pyelonephritis	11	36	2	3	39	0	0
	Pyelonephritis acute	3	10	2	2	12	0	0
	Pyoderma	0	2	0	0	2	0	0
	Pyuria	1	8	0	4	12	0	0
	Q fever	2	12	1	2	14	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Rabies	0	1	1	1	2	0	0
	Rash pustular	1	11	20	90	101	0	0
	Recurrent subareolar breast abscess	0	1	0	0	1	0	0
	Relapsing fever	1	2	0	0	2	0	0
	Renal abscess	0	1	0	0	1	0	0
	Respiratory moniliasis	0	1	0	0	1	0	0
	Respiratory syncytial virus infection	0	7	1	5	12	0	0
	Respiratory tract infection	5	27	12	18	45	0	0
	Respiratory tract infection bacterial	1	1	0	0	1	0	0
	Respiratory tract infection viral	0	3	0	1	4	0	0
	Retinitis viral	0	1	0	0	1	0	0
	Rhinitis	14	36	80	186	222	0	0
	Rhinovirus infection	0	2	0	2	4	0	0
	Rickettsiosis	0	1	0	0	1	0	0
	Rocky mountain spotted fever	0	5	0	0	5	0	0
	Root canal infection	0	0	1	5	5	0	0
	Roseola	0	0	1	2	2	0	0
	Rotavirus infection	0	1	0	0	1	0	0
	Rubella	0	2	0	2	4	0	0
	SARS-CoV-2 carrier	0	1	0	1	2	0	0
	SARS-CoV-2 sepsis	0	3	0	0	3	0	0
	Salmonellosis	0	2	0	0	2	0	0
	Salpingitis	0	1	0	0	1	0	0
	Salpingo-oophoritis	0	1	0	0	1	0	0
	Scarlet fever	0	0	0	2	2	0	0
	Scedosporium infection	0	1	0	0	1	0	0
	Schistosomiasis cutaneous	0	0	0	1	1	0	0
	Scrotal cellulitis	0	1	0	0	1	0	0
	Sebaceous gland infection	0	1	1	1	2	0	0
	Secondary transmission	0	1	0	2	3	0	0
	Sepsis	41	450	4	10	460	0	0
	Septic cerebral embolism	1	1	0	0	1	0	0
	Septic embolus	0	1	0	0	1	0	0
	Septic encephalopathy	1	2	0	0	2	0	0
	Septic shock	15	135	0	0	135	0	0
	Serratia bacteraemia	0	1	0	0	1	0	0
	Serratia infection	0	1	0	0	1	0	0
	Severe acute respiratory syndrome	2	6	3	3	9	0	0
	Sexually transmitted disease	0	0	0	3	3	0	0
	Sialoadenitis	1	12	1	2	14	0	0
	Sinobronchitis	0	1	0	0	1	0	0
	Sinusitis	24	88	83	537	625	0	0
	Sinusitis bacterial	1	2	0	0	2	0	0
	Skin bacterial infection	0	4	0	8	12	0	0
	Skin candida	0	0	1	2	2	0	0
	Skin infection	5	18	7	80	98	0	0
	Smallpox	0	0	0	1	1	0	0
	Soft tissue infection	1	4	1	1	5	0	0
	Spinal cord infection	2	5	0	0	5	0	0
	Spontaneous bacterial peritonitis	0	1	0	0	1	0	0
	Sporotrichosis	1	1	0	0	1	0	0
	Sputum purulent	0	2	0	0	2	0	0
	Staphylococcal bacteraemia	1	12	0	0	12	0	0
	Staphylococcal infection	3	58	4	12	70	0	0
	Staphylococcal pharyngitis	0	0	0	1	1	0	0
	Staphylococcal sepsis	5	15	1	1	16	0	0
	Staphylococcal skin infection	0	2	0	2	4	0	0
	Streptococcal bacteraemia	1	7	0	0	7	0	0
	Streptococcal infection	0	8	0	5	13	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Subcutaneous abscess	2	7	3	17	24	0	0
	Superinfection	0	20	0	0	20	0	0
	Superinfection bacterial	0	3	0	0	3	0	0
	Suspected COVID-19	23	46	33	221	267	0	0
	Sweat gland infection	0	1	0	0	1	0	0
	Sweating fever	11	61	2	9	70	0	0
	Syphilis	0	4	0	0	4	0	0
	Systemic candida	0	2	0	0	2	0	0
	Systemic infection	0	4	0	0	4	0	0
	Systemic mycosis	1	1	0	0	1	0	0
	Tetanus	0	2	0	0	2	0	0
	Tinea capitis	1	1	0	0	1	0	0
	Tinea cruris	1	1	0	1	2	0	0
	Tinea infection	0	0	0	3	3	0	0
	Tinea pedis	0	0	2	5	5	0	0
	Tinea versicolour	0	0	0	3	3	0	0
	Tongue abscess	0	2	0	0	2	0	0
	Tonsillitis	9	32	35	82	114	0	0
	Tonsillitis bacterial	0	2	0	1	3	0	0
	Tonsillitis streptococcal	0	1	0	0	1	0	0
	Tooth abscess	0	3	5	29	32	0	0
	Tooth infection	0	5	1	38	43	0	0
	Toxic shock syndrome	0	1	0	0	1	0	0
	Toxocariasis	0	1	0	0	1	0	0
	Toxoplasmosis	2	2	0	1	3	0	0
	Tracheitis	1	3	6	6	9	0	0
	Tracheobronchitis	0	1	0	0	1	0	0
	Trachoma	0	0	0	1	1	0	0
	Trichomoniasis	0	0	0	2	2	0	0
	Tuberculosis	0	4	0	0	4	0	0
	Tubo-ovarian abscess	0	2	0	0	2	0	0
	Tularaemia	0	1	0	0	1	0	0
	Upper respiratory tract infection	3	25	69	126	151	0	0
	Upper respiratory tract infection bacterial	0	1	0	0	1	0	0
	Urethritis	0	1	1	1	2	0	0
	Urinary tract infection	41	396	70	459	855	0	0
	Urinary tract infection bacterial	1	2	0	2	4	0	0
	Urinary tract infection enterococcal	0	1	0	0	1	0	0
	Urinary tract infection staphylococcal	1	2	0	0	2	0	0
	Urosepsis	4	17	0	0	17	0	0
	Uterine infection	0	1	0	0	1	0	0
	Vaccination site abscess	0	2	7	24	26	0	0
	Vaccination site cellulitis	10	41	2	121	162	0	0
	Vaccination site infection	0	10	13	114	124	0	0
	Vaccination site joint infection	0	1	0	0	1	0	0
	Vaccination site pustule	0	0	1	25	25	0	0
	Vaccine breakthrough infection	15	486	4	106	592	0	0
	Vaccine virus shedding	0	0	0	1	1	0	0
	Vaccinia virus infection	0	0	1	1	1	0	0
	Vaginal infection	2	6	5	20	26	0	0
	Vaginitis gardnerella	0	0	1	1	1	0	0
	Varicella	1	10	11	33	43	0	0
	Varicella post vaccine	0	0	0	2	2	0	0
	Varicella zoster virus infection	1	6	3	12	18	0	0
	Vascular device infection	0	1	0	0	1	0	0
	Vertical infection transmission	0	0	0	1	1	0	0
	Vestibular neuronitis	32	101	10	45	146	0	0
	Vestibulitis	0	1	1	3	4	0	0
	Viraemia	0	3	0	1	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Viral cardiomyopathy	0	5	0	0	5	0	0
	Viral infection	6	47	9	65	112	0	0
	Viral labyrinthitis	0	3	0	2	5	0	0
	Viral myelitis	1	1	0	0	1	0	0
	Viral myocarditis	1	5	0	0	5	0	0
	Viral myositis	0	0	0	1	1	0	0
	Viral parotitis	0	0	0	1	1	0	0
	Viral pericarditis	1	7	0	0	7	0	0
	Viral pharyngitis	1	4	0	2	6	0	0
	Viral rash	1	7	3	15	22	0	0
	Viral sinusitis	0	1	0	0	1	0	0
	Viral skin infection	1	2	0	0	2	0	0
	Viral tonsillitis	0	0	0	1	1	0	0
	Viral upper respiratory tract infection	0	2	0	4	6	0	0
	Viral uveitis	1	3	0	0	3	0	0
	Virologic failure	0	0	1	1	1	0	0
	Vitritis infective	0	1	0	0	1	0	0
	Vulval abscess	0	1	0	1	2	0	0
	Vulval cellulitis	0	1	0	0	1	0	0
	Vulvitis	0	1	0	0	1	0	0
	Vulvovaginal candidiasis	2	5	8	22	27	0	0
	Vulvovaginal mycotic infection	0	2	19	42	44	0	0
	Vulvovaginitis	0	1	0	0	1	0	0
	Wound abscess	0	2	0	0	2	0	0
	Wound infection	1	7	0	2	9	0	0
	Wound infection bacterial	0	1	0	0	1	0	0
	Wound sepsis	0	0	1	1	1	0	0
	Yellow fever	0	0	1	1	1	0	0
	Zika virus infection	0	0	0	1	1	0	0
Injury, poisoning and procedural complications	*** SOC TOTAL ***	855	4911	17305	58576	63487	0	0
	Abdomen crushing	0	1	0	0	1	0	0
	Accident	1	6	3	15	21	0	0
	Accident at home	0	0	0	1	1	0	0
	Accident at work	0	2	0	3	5	0	0
	Accidental exposure to product	1	2	2	36	38	0	0
	Accidental overdose	0	7	277	778	785	0	0
	Accidental underdose	0	0	217	572	572	0	0
	Acetabulum fracture	0	1	0	0	1	0	0
	Administration related reaction	0	0	0	1	1	0	0
	Adverse event following immunisation	16	17	2	31	48	0	0
	Airway burns	0	1	0	1	2	0	0
	Airway complication of anaesthesia	0	1	0	0	1	0	0
	Alcohol poisoning	1	5	0	0	5	0	0
	Anaesthetic complication	0	2	0	0	2	0	0
	Animal bite	1	2	3	14	16	0	0
	Animal scratch	1	1	0	2	3	0	0
	Ankle fracture	1	15	3	11	26	0	0
	Arterial injury	0	3	0	0	3	0	0
	Arteriovenous fistula site haemorrhage	0	1	0	0	1	0	0
	Arteriovenous fistula thrombosis	0	1	0	0	1	0	0
	Arthropod bite	1	6	9	46	52	0	0
	Arthropod sting	0	1	4	25	26	0	0
	Avulsion fracture	0	0	0	1	1	0	0
	Axillary nerve injury	1	2	0	0	2	0	0
	Axillary web syndrome	0	1	0	2	3	0	0
	Back injury	1	9	1	29	38	0	0
	Barotitis media	0	0	0	1	1	0	0
	Barotrauma	0	0	0	2	2	0	0
	Bite	0	1	2	12	13	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Bladder injury	0	2	0	0	2	0	0
	Blindness traumatic	1	1	0	0	1	0	0
	Bone contusion	0	2	0	3	5	0	0
	Bone fissure	0	0	0	1	1	0	0
	Bone fragmentation	0	1	0	1	2	0	0
	Booster dose missed	0	1	0	1	2	0	0
	Brachial plexus injury	0	3	0	1	4	0	0
	Brain contusion	2	4	0	0	4	0	0
	Brain herniation	2	19	0	0	19	0	0
	Burn oesophageal	0	1	2	6	7	0	0
	Burn of internal organs	0	0	1	1	1	0	0
	Burn oral cavity	0	4	1	3	7	0	0
	Burns first degree	0	1	1	2	3	0	0
	Burns second degree	1	5	0	6	11	0	0
	Burns third degree	0	5	0	0	5	0	0
	Bursa injury	0	0	0	3	3	0	0
	Buttock injury	0	1	0	0	1	0	0
	Carbon monoxide poisoning	0	1	0	0	1	0	0
	Cardiac procedure complication	0	2	0	0	2	0	0
	Cardiac septal defect residual shunt	0	1	0	0	1	0	0
	Cardiac vein dissection	1	3	0	0	3	0	0
	Cartilage injury	0	3	1	3	6	0	0
	Central nervous system injury	0	1	0	0	1	0	0
	Cerebral ventricle collapse	0	1	0	0	1	0	0
	Cervical vertebral fracture	0	5	0	0	5	0	0
	Chemical burn	0	0	0	4	4	0	0
	Chemical burn of skin	0	0	1	1	1	0	0
	Chemical poisoning	0	1	0	0	1	0	0
	Chest crushing	1	6	0	2	B	0	0
	Chest injury	3	19	0	0	19	0	0
	Child maltreatment syndrome	0	5	0	0	5	0	0
	Chillblains	6	15	28	79	94	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 erro	0	0	19	28	28	0	0
	Clavicle fracture	1	10	0	6	16	0	0
	Cold burn	0	1	1	3	4	0	0
	Cold exposure injury	1	1	0	0	1	0	0
	Colon injury	0	0	1	3	3	0	0
	Complicated fracture	0	0	0	1	1	0	0
	Complications of transplant surgery	0	2	0	0	2	0	0
	Complications of transplanted kidney	0	1	0	0	1	0	0
	Complications of transplanted lung	0	1	0	0	1	0	0
	Compression fracture	1	5	0	2	7	0	0
	Concussion	3	43	7	67	110	0	0
	Conjunctival scar	0	0	0	2	2	0	0
	Contraindicated product administered	0	0	0	3	3	0	0
	Contraindicated product prescribed	0	2	0	1	3	0	0
	Contusion	80	440	208	1806	2246	0	0
	Corneal abrasion	0	2	0	5	7	0	0
	Corneal laceration	0	0	0	1	1	0	0
	Coronary artery reocclusion	0	1	0	0	1	0	0
	Coronary vascular graft occlusion	0	1	0	0	1	0	0
	Corrosive gastritis	1	1	0	0	1	0	0
	Counterfeit product administered	0	0	1	6	6	0	0
	Cranial nerve injury	1	3	0	0	3	0	0
	Craniocerebral injury	8	24	0	2	26	0	0
	Craniofacial fracture	1	1	0	0	1	0	0
	Dental leakage	0	0	0	1	1	0	0
	Dermal filler overcorrection	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Dermal filler reaction	0	0	4	4	4	0	0
	Device difficult to use	0	0	0	1	1	0	0
	Device dispensing error	0	0	0	1	1	0	0
	Device use confusion	0	0	0	2	2	0	0
	Device use error	0	0	0	2	2	0	0
	Device use issue	0	0	0	5	5	0	0
	Dialysis related complication	0	1	0	0	1	0	0
	Dislocation of vertebra	1	2	0	1	3	0	0
	Documented hypersensitivity to administered product	0	0	0	1	1	0	0
	Dose calculation error	0	0	0	5	5	0	0
	Drain site complication	0	0	0	1	1	0	0
	Drug administered in wrong device	0	0	0	1	1	0	0
	Drug dispensed to wrong patient	0	0	0	4	4	0	0
	Drug dose omission by device	0	1	0	0	1	0	0
	Duplicate therapy error	0	0	0	1	1	0	0
	Ear injury	0	0	0	3	3	0	0
	Electric shock	0	5	1	7	12	0	0
	Electrical burn	0	0	1	1	1	0	0
	Endotracheal intubation complication	0	2	0	0	2	0	0
	Epicondylitis	7	13	5	27	40	0	0
	Eschar	1	2	0	3	5	0	0
	Expired device used	0	0	1	2	2	0	0
	Expired product administered	0	3	5930	12155	12158	0	0
	Exposure during pregnancy	16	154	19	1292	1446	0	0
	Exposure to 5ARS-CoV-2	0	101	15	273	374	0	0
	Exposure to communicable disease	0	3	1	2	5	0	0
	Exposure to contaminated air	0	2	0	0	2	0	0
	Exposure to contaminated device	0	1	0	0	1	0	0
	Exposure to extreme temperature	0	3	0	3	6	0	0
	Exposure to noise	0	0	0	1	1	0	0
	Exposure to tobacco	0	0	0	1	1	0	0
	Exposure to toxic agent	0	1	1	2	3	0	0
	Exposure to unspecified agent	0	0	1	1	1	0	0
	Exposure to vaccinated person	0	1	0	1	2	0	0
	Exposure via body fluid	0	1	0	0	1	0	0
	Exposure via breast milk	2	48	25	519	567	0	0
	Exposure via contaminated device	0	0	0	1	1	0	0
	Exposure via direct contact	1	3	0	1	4	0	0
	Exposure via eye contact	0	0	0	4	4	0	0
	Exposure via partner	0	0	1	1	1	0	0
	Exposure via skin contact	0	1	0	98	99	0	0
	Exposure via unknown route	0	1	0	0	1	0	0
	Extra dose administered	0	40	227	798	838	0	0
	Extradural haematoma	1	2	0	0	2	0	0
	Extraskeletal ossification	0	1	0	0	1	0	0
	Eye contusion	0	6	3	43	49	0	0
	Eye injury	5	13	2	14	27	0	0
	Eyelid abrasion	0	0	1	1	1	0	0
	Eyelid contusion	0	0	0	3	3	0	0
	Eyelid injury	0	1	0	0	1	0	0
	Face injury	1	15	3	80	95	0	0
	Facial bones fracture	3	21	0	2	23	0	0
	Fall	124	1062	161	1902	2964	0	0
	Fallopian tube perforation	0	1	0	0	1	0	0
	Femoral neck fracture	1	8	0	0	8	0	0
	Femoral nerve injury	0	1	0	0	1	0	0
	Femur fracture	0	15	1	1	16	0	0
	Fibula fracture	0	3	0	2	5	0	0
	Flatback syndrome	1	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Foetal exposure during pregnancy	15	21	8	21	42	0	0
	Foot fracture	4	15	2	14	29	0	0
	Forearm fracture	0	0	1	2	2	0	0
	Foreign body	0	0	0	1	1	0	0
	Foreign body in ear	0	0	0	1	1	0	0
	Foreign body in eye	0	0	0	2	2	0	0
	Foreign body in gastrointestinal tract	0	1	0	1	2	0	0
	Foreign body in skin or subcutaneous tissue	0	0	0	2	2	0	0
	Foreign body in throat	0	5	0	2	7	0	0
	Foreign body ingestion	0	1	0	0	1	0	0
	Fracture	4	18	4	13	31	0	0
	Fracture displacement	1	3	0	0	3	0	0
	Fractured coccyx	0	3	0	0	3	0	0
	Fractured sacrum	0	1	1	3	4	0	0
	Frostbite	1	2	0	2	4	0	0
	Gastrointestinal anastomotic leak	0	1	0	0	1	0	0
	Gastrointestinal injury	0	2	0	2	4	0	0
	Gastrointestinal stoma complication	1	2	0	1	3	0	0
	Genital contusion	0	0	1	1	1	0	0
	Gingival injury	0	0	1	2	2	0	0
	Graft haemorrhage	0	1	0	0	1	0	0
	Graft thrombosis	1	3	0	0	3	0	0
	Gun shot wound	1	3	0	1	4	0	0
	Hair injury	0	0	0	4	4	0	0
	Hand fracture	0	5	1	5	10	0	0
	Head injury	15	164	12	448	612	0	0
	Heat exhaustion	1	2	0	6	8	0	0
	Heat illness	1	3	0	6	9	0	0
	Heat oedema	2	3	1	10	13	0	0
	Heat stroke	1	9	5	10	19	0	0
	Heavy exposure to ultraviolet light	0	0	0	2	2	0	0
	Hepatic rupture	1	1	0	0	1	0	0
	Hip fracture	3	36	0	1	37	0	0
	Humerus fracture	1	7	2	2	9	0	0
	Hypobarism	0	0	0	1	1	0	0
	Iliotibial band syndrome	0	0	1	1	1	0	0
	Inadequate aseptic technique in use of product	0	0	0	5	5	0	0
	Inappropriate schedule of product administration	3	96	1189	5911	6007	0	0
	Inappropriate schedule of product discontinuation	0	0	0	4	4	0	0
	Incarcerated incisional hernia	0	1	0	0	1	0	0
	Incision site complication	0	1	1	2	3	0	0
	Incision site discharge	0	1	0	0	1	0	0
	Incision site erythema	0	2	0	1	3	0	0
	Incision site haemorrhage	0	1	0	0	1	0	0
	Incision site impaired healing	0	1	0	0	1	0	0
	Incision site inflammation	0	0	0	1	1	0	0
	Incision site pain	0	1	0	3	4	0	0
	Incision site rash	0	1	1	3	4	0	0
	Incision site swelling	0	1	4	10	11	0	0
	Incisional hernia	0	1	0	0	1	0	0
	Incomplete course of vaccination	0	33	5	165	198	0	0
	Incorrect disposal of product	0	0	0	1	1	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

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Incorrect product formulation administered	0	0	1	62	62	0	0
	Incorrect route of product administration	1	19	36	840	859	0	0
	Induced abortion failed	0	1	0	0	1	0	0
	Inflammation of wound	0	2	1	3	5	0	0
	Infusion related reaction	0	1	1	9	10	0	0
	Injection related reaction	13	34	8	24	58	0	0
	Injury	7	44	19	70	114	0	0
	Injury corneal	0	0	0	1	1	0	0
	Intentional dose omission	0	0	4	164	164	0	0
	Intentional medical device removal by patient	0	0	1	1	1	0	0
	Intentional overdose	1	4	0	2	6	0	0
	Intentional product misuse	0	0	0	8	8	0	0
	Intentional product use issue	2	4	4	217	221	0	0
	Intentional removal of drug delivery system by patient	0	1	0	0	1	0	0
	Intentional underdose	1	1	1	7	8	0	0
	Intercepted medication error	0	0	2	2	2	0	0
	Intercepted product administration error	0	0	1	3	3	0	0
	Intercepted product prescribing error	0	0	0	1	1	0	0
	Intercepted product storage error	0	0	0	1	1	0	0
	Intervertebral disc injury	0	0	0	1	1	0	0
	Jaw fracture	0	5	0	0	5	0	0
	Joint dislocation	0	13	5	27	40	0	0
	Joint injury	1	26	8	73	99	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
	Lack of injection site rotation	0	0	0	1	1	0	0
	Ligament rupture	2	4	3	10	14	0	0
	Ligament sprain	3	8	5	48	56	0	0
	Limb crushing injury	0	1	0	0	1	0	0
	Limb injury	28	90	18	136	226	0	0
	Lip injury	1	11	1	24	35	0	0
	Lower limb fracture	0	11	1	4	15	0	0
	Lumbar vertebral fracture	0	6	0	0	6	0	0
	Lymphatic duct injury	0	0	1	1	1	0	0
	Maternal exposure before pregnancy	2	10	15	73	83	0	0
	Maternal exposure during breast feeding	78	295	228	833	1128	0	0
	Maternal exposure during delivery	0	0	0	3	3	0	0
	Maternal exposure during pregnancy	88	380	179	1832	2212	0	0
	Maternal exposure timing unspecified	0	2	1	25	27	0	0
	Medical device monitoring error	0	0	1	1	1	0	0
	Medication error	28	37	329	411	448	0	0
	Meningitis chemical	0	1	0	0	1	0	0
	Meniscus cyst	0	0	0	1	1	0	0
	Meniscus injury	3	6	2	6	12	0	0
	Metal poisoning	0	2	0	1	3	0	0
	Mouth injury	0	7	0	13	20	0	0
	Multiple fractures	2	8	0	0	8	0	0
	Multiple injuries	1	2	0	3	5	0	0
	Multiple use of single-use product	0	0	0	3	3	0	0
	Muscle contusion	0	0	0	1	1	0	0
	Muscle injury	4	15	6	16	31	0	0
	Muscle rupture	4	9	5	6	15	0	0
	Muscle strain	8	30	15	91	121	0	0
	Musculoskeletal injury	0	2	0	1	3	0	0
	Nail injury	0	1	0	2	3	0	0
	Nasal injury	1	6	2	16	22	0	0
	Near drowning	5	5	0	0	5	0	0
	Neck crushing	0	1	0	0	1	0	0
	Neck injury	1	4	0	14	18	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Nerve injury	14	72	12	85	157	0	0
	Nerve root injury	0	2	0	0	2	0	0
	Nerve root injury lumbar	1	1	0	0	1	0	0
	Nervous system injury	0	1	0	1	2	0	0
	Occupational exposure to SARS-CoV-2	0	1	0	12	13	0	0
	Occupational exposure to product	0	0	2	20	20	0	0
	Ocular procedural complication	0	1	0	0	1	0	0
	Oesophageal injury	0	2	0	0	2	0	0
	Off label use	38	49	172	728	777	0	0
	Open fracture	1	1	0	0	1	0	0
	Open globe injury	0	1	1	1	2	0	0
	Optic nerve injury	2	9	0	0	9	0	0
	Oral contusion	0	3	0	8	11	0	0
	Oral mucosal scar	0	0	0	1	1	0	0
	Oropharyngeal stenosis	0	1	0	0	1	0	0
	Osteochondral fracture	0	0	0	1	1	0	0
	Overdose	0	12	320	412	424	0	0
	Palate injury	0	0	3	6	6	0	0
	Patella fracture	0	2	0	0	2	0	0
	Paternal exposure before pregnancy	0	1	0	1	2	0	0
	Pelvic fracture	1	9	0	0	9	0	0
	Perineal injury	0	2	0	0	2	0	0
	Periorbital haematoma	0	2	2	2	4	0	0
	Periorbital haemorrhage	0	0	0	7	7	0	0
	Peripancreatic fluid collection	0	2	0	0	2	0	0
	Peripheral artery restenosis	1	1	0	0	1	0	0
	Peripheral nerve injury	1	5	0	0	5	0	0
	Periprosthetic fracture	0	1	0	0	1	0	0
	Peroneal nerve injury	0	0	2	2	2	0	0
	Phrenic nerve injury	0	1	0	0	1	0	0
	Pneumocephalus	0	2	0	0	2	0	0
	Pneumoconiosis	0	2	0	0	2	0	0
	Poisoning	1	5	0	1	6	0	0
	Poor quality product administered	1	1	3240	5009	5010	0	0
	Post concussion syndrome	0	2	0	3	5	0	0
	Post lumbar puncture syndrome	0	0	0	2	2	0	0
	Post procedural bile leak	1	1	0	0	1	0	0
	Post procedural complication	1	7	0	6	13	0	0
	Post procedural diarrhoea	0	0	2	2	2	0	0
	Post procedural discharge	0	0	0	1	1	0	0
	Post procedural discomfort	0	0	0	1	1	0	0
	Post procedural erythema	0	0	0	1	1	0	0
	Post procedural fever	0	1	0	0	1	0	0
	Post procedural haemorrhage	0	4	1	2	6	0	0
	Post procedural hypothyroidism	0	1	0	0	1	0	0
	Post procedural myocardial infarction	1	1	0	0	1	0	0
	Post procedural pulmonary embolism	1	1	0	0	1	0	0
	Post procedural swelling	0	0	0	1	1	0	0
	Post procedural urine leak	0	1	0	0	1	0	0
	Post vaccination syndrome	2	5	4	5	10	0	0
	Post-traumatic neck syndrome	0	1	0	4	5	0	0
	Post-traumatic pain	0	1	6	15	16	0	0
	Postoperative ileus	0	2	0	0	2	0	0
	Postoperative thrombosis	0	1	0	0	1	0	0
	Postoperative wound complication	0	2	0	0	2	0	0
	Prescribed overdose	0	0	1	1	1	0	0
	Procedural complication	0	1	0	2	3	0	0
	Procedural dizziness	0	2	3	6	8	0	0
	Procedural haemorrhage	0	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Procedural pain	0	2	6	21	23	0	0
	Procedural site reaction	0	0	0	1	1	0	0
	Procedural vomiting	0	1	0	0	1	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	4S6S	4S73	0	0
	Product administration error	2	S	37	403	408	0	0
	Product administration interrupted	0	0	1	6S	6S	0	0
	Product communication issue	1	1	0	0	1	0	0
	Product dispensing error	0	0	16	20	20	0	0
	Product dispensing issue	0	0	0	11	11	0	0
	Product dosage form confusion	0	0	0	1	1	0	0
	Product dose omission in error	0	0	0	18	18	0	0
	Product dose omission issue	1	14	4S	3180	3194	0	0
	Product label confusion	0	0	12	S6	S6	0	0
	Product monitoring error	0	0	0	2	2	0	0
	Product packaging confusion	0	0	0	1	1	0	0
	Product preparation error	0	0	1S	40	40	0	0
	Product preparation issue	0	1	2	S0	S1	0	0
	Product prescribing error	1	1	0	0	1	0	0
	Product prescribing issue	0	0	1	2	2	0	0
	Product selection error	0	0	7	11	11	0	0
	Product storage error	0	2	3039	5972	5974	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	S	S	0	0
	Product use issue	1	S	14	29	34	0	0
	Pulmonary contusion	0	3	0	0	3	0	0
	Radial head dislocation	0	1	0	0	1	0	0
	Radial nerve injury	0	3	1	3	6	0	0
	Radiation associated pain	0	1	0	1	2	0	0
	Radiation injury	0	0	0	1	1	0	0
	Radius fracture	0	S	0	0	S	0	0
	Reaction to previous exposure to any vaccine	1	1	0	28	29	0	0
	Recall phenomenon	0	0	2	2	2	0	0
	Recalled product administered	0	0	0	1	1	0	0
	Rectal injury	0	1	0	0	1	0	0
	Repetitive strain injury	1	1	0	0	1	0	0
	Retinal injury	1	3	0	0	3	0	0
	Rib fracture	3	28	2	23	S1	0	0
	Road traffic accident	10	49	7	27	76	0	0
	Sacroiliac fracture	0	0	0	1	1	0	0
	Scapula fracture	0	1	0	0	1	0	0
	Scar	4	18	1S	90	108	0	0
	Sciatic nerve injury	0	0	0	3	3	0	0
	Scratch	4	6	19	103	109	0	0
	Seroma	1	4	0	1	S	0	0
	Shunt malfunction	0	1	0	0	1	0	0
	Skeletal injury	0	1	1	1	2	0	0
	Skin abrasion	2	12	14	99	111	0	0
	Skin injury	1	3	1	16	19	0	0
	Skin laceration	1	43	6	68	111	0	0
	Skin pressure mark	0	0	1	1	1	0	0
	Skin wound	1	3	3	13	16	0	0
	Skull fracture	2	11	0	1	12	0	0
	Soft tissue injury	0	1	0	2	3	0	0
	Spinal column injury	0	3	0	1	4	0	0
	Spinal compression fracture	3	24	0	0	24	0	0
	Spinal cord injury	1	6	1	1	7	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Spinal cord injury cervical	0	7	0	0	7	0	0
	Spinal cord injury thoracic	0	6	0	0	6	0	0
	Spinal fracture	1	12	0	0	12	0	0
	Splenic injury	0	3	0	0	3	0	0
	Splenic rupture	3	7	0	0	7	0	0
	Splenosis	0	1	0	0	1	0	0
	Splinter	0	0	0	1	1	0	0
	Stab wound	1	2	0	1	3	0	0
	Sternal fracture	2	3	0	1	4	0	0
	Stoma site discomfort	0	1	0	0	1	0	0
	Stoma site hypergranulation	0	0	0	1	1	0	0
	Stoma site irritation	1	1	0	0	1	0	0
	Stoma site oedema	0	0	0	1	1	0	0
	Stoma site pain	0	0	0	1	1	0	0
	Stoma site rash	0	0	0	1	1	0	0
	Stress fracture	0	1	1	1	2	0	0
	Struck by lightning	1	1	0	0	1	0	0
	Subarachnoid haematoma	0	1	0	0	1	0	0
	Subcutaneous haematoma	0	6	S	12	18	0	0
	Subdural haematoma	3	SS	0	0	SS	0	0
	Subdural haemorrhage	2	11	0	0	11	0	0
	Sunburn	1	7	6	71	78	0	0
	Surgical procedure repeated	0	1	0	0	1	0	0
	Suture rupture	0	1	0	0	1	0	0
	Synovial rupture	0	0	1	3	3	0	0
	Systemic toxicity	0	1	0	0	1	0	0
	Tendon dislocation	0	0	0	1	1	0	0
	Tendon injury	1	6	3	11	17	0	0
	Tendon rupture	S	16	1	11	27	0	0
	Tensor fasciae latae syndrome	0	1	0	0	1	0	0
	Thermal burn	2	10	9	S7	67	0	0
	Thermal burns of eye	3	12	0	3	15	0	0
	Thoracic vertebral fracture	0	2	0	0	2	0	0
	Tibia fracture	4	12	0	1	13	0	0
	Tissue injury	0	0	0	6	6	0	0
	Tongue injury	0	4	3	9	13	0	0
	Tooth avulsion	0	0	0	1	1	0	0
	Tooth fracture	1	S	2	29	34	0	0
	Tooth injury	0	3	2	19	22	0	0
	Toxicity to various agents	2	7	0	4	11	0	0
	Tracheal deviation	0	1	0	0	1	0	0
	Tracheal haemorrhage	0	1	0	0	1	0	0
	Tracheal injury	0	2	0	0	2	0	0
	Tracheal obstruction	0	2	0	0	2	0	0
	Transcription medication error	0	0	1	3	3	0	0
	Transplant dysfunction	0	1	0	0	1	0	0
	Traumatic arthropathy	0	0	0	1	1	0	0
	Traumatic fracture	0	0	0	1	1	0	0
	Traumatic haematoma	1	S	0	S	10	0	0
	Traumatic haemorrhage	0	3	0	2	S	0	0
	Traumatic haemothorax	0	1	0	0	1	0	0
	Traumatic intracranial haemorrhage	1	3	0	0	3	0	0
	Traumatic lumbar puncture	0	1	0	0	1	0	0
	Traumatic lung injury	0	S	2	2	7	0	0
	Traumatic renal injury	0	1	0	0	1	0	0
	Trunk injury	0	1	0	0	1	0	0
	Ulna fracture	0	1	0	0	1	0	0
	Ulnar nerve injury	1	2	0	2	4	0	0
	Underdose	0	2	129	1208	1210	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Upper limb fracture	1	11	2	7	18	0	0
	Uterine cervical laceration	0	0	0	1	1	0	0
	VIIIth nerve injury	0	1	0	2	3	0	0
	VIIth nerve injury	1	1	1	1	2	0	0
	VIth nerve injury	1	1	0	0	1	0	0
	Vaccination complication	28	168	359	885	1053	0	0
	Vaccination error	0	1	20	142	143	0	0
	Vascular access site bruising	0	1	0	1	2	0	0
	Vascular access site swelling	0	0	0	2	2	0	0
	Vascular access site thrombosis	0	1	0	0	1	0	0
	Vascular graft occlusion	0	2	0	0	2	0	0
	Vascular graft thrombosis	1	3	0	0	3	0	0
	Vascular injury	1	7	0	8	15	0	0
	Vascular pseudoaneurysm	0	3	0	0	3	0	0
	Vascular pseudoaneurysm ruptured	1	1	0	0	1	0	0
	Vasoplegia syndrome	1	2	0	0	2	0	0
	Venous injury	0	2	1	1	3	0	0
	Vulvovaginal injury	1	3	1	1	4	0	0
	Weaning failure	0	2	0	0	2	0	0
	Wound	10	41	19	77	118	0	0
	Wound complication	0	7	1	9	16	0	0
	Wound dehiscence	0	1	0	1	2	0	0
	Wound haematoma	0	0	0	1	1	0	0
	Wound haemorrhage	1	5	1	20	25	0	0
	Wound necrosis	0	1	0	0	1	0	0
	Wound secretion	1	4	1	8	12	0	0
	Wrist fracture	4	7	0	8	15	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 patient received product	0	0	0	7	7	0	0
	Wrong product administered	0	3	17	298	301	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
Investigations	*** SOC TOTAL ***	1462	14850	5534	21323	36173	0	0
	ADAMTS13 activity decreased	1	1	0	0	1	0	0
	AST/ALT ratio	0	1	0	0	1	0	0
	AST/ALT ratio abnormal	0	0	1	1	1	0	0
	Abdominal X-ray	0	4	0	0	4	0	0
	Acoustic stimulation tests	0	9	0	3	12	0	0
	Acoustic stimulation tests abnormal	0	13	0	1	14	0	0
	Acoustic stimulation tests normal	0	1	0	0	1	0	0
	Activated partial thromboplastin time	0	6	0	4	10	0	0
	Activated partial thromboplastin time abnormal	2	2	0	1	3	0	0
	Activated partial thromboplastin time normal	0	1	0	0	1	0	0
	Activated partial thromboplastin time prolonged	1	5	2	5	10	0	0
	Activated partial thromboplastin time shortened	0	4	0	1	5	0	0
	Adenovirus test	0	11	0	1	12	0	0
	Adenovirus test positive	0	2	0	0	2	0	0
	Alanine aminotransferase	0	3	0	1	4	0	0
	Alanine aminotransferase decreased	0	0	0	2	2	0	0
	Alanine aminotransferase increased	3	42	4	26	68	0	0
	Alanine aminotransferase normal	0	29	0	1	30	0	0
	Albumin CSF decreased	0	1	0	0	1	0	0
	Albumin globulin ratio	0	3	0	0	3	0	0
	Albumin globulin ratio normal	0	1	0	1	2	0	0
	Albumin urine present	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Alcohol test negative	0	0	0	1	1	0	0
	Aldolase	0	0	0	1	1	0	0
	Allergy alert test	1	1	0	0	1	0	0
	Allergy alert test positive	1	1	0	0	1	0	0
	Allergy test	0	1	0	4	5	0	0
	Allergy test negative	0	2	0	1	3	0	0
	Allergy test positive	0	3	0	0	3	0	0
	Amino acid level normal	0	1	0	0	1	0	0
	Ammonia	0	1	0	0	1	0	0
	Ammonia decreased	0	1	0	0	1	0	0
	Ammonia increased	0	2	0	1	3	0	0
	Ammonia normal	0	2	0	0	2	0	0
	Amniotic fluid index decreased	0	4	0	0	4	0	0
	Amniotic fluid volume increased	0	1	0	0	1	0	0
	Amniotic membrane rupture test positive	0	1	0	0	1	0	0
	Amphetamines negative	0	1	0	0	1	0	0
	Amylase	0	0	0	1	1	0	0
	Amylase increased	1	2	1	4	6	0	0
	Analgesic drug level	0	2	0	0	2	0	0
	Analgesic drug level increased	0	1	0	0	1	0	0
	Androgens increased	0	0	1	1	1	0	0
	Angiocardiogram	0	3	0	0	3	0	0
	Angiogram	0	30	0	10	40	0	0
	Angiogram abnormal	0	10	0	1	11	0	0
	Angiogram cerebral	0	9	0	0	9	0	0
	Angiogram cerebral abnormal	0	9	0	0	9	0	0
	Angiogram cerebral normal	0	8	0	0	8	0	0
	Angiogram normal	0	11	0	0	11	0	0
	Angiogram peripheral abnormal	0	1	0	0	1	0	0
	Angiogram pulmonary	0	3	0	0	3	0	0
	Angiogram pulmonary abnormal	0	50	0	1	51	0	0
	Angiogram pulmonary normal	0	12	0	0	12	0	0
	Angiotensin converting enzyme	0	0	0	1	1	0	0
	Anion gap	0	30	0	2	32	0	0
	Anion gap decreased	0	6	0	2	8	0	0
	Anion gap increased	0	4	0	0	4	0	0
	Anion gap normal	0	9	0	1	10	0	0
	Ankle brachial index abnormal	0	1	0	0	1	0	0
	Ankle brachial index decreased	0	1	0	0	1	0	0
	Anti factor VIII antibody positive	1	2	0	0	2	0	0
	Anti-GAD antibody positive	0	1	0	0	1	0	0
	Anti-Muellerian hormone level decreased	0	0	1	1	1	0	0
	Anti-RNA polymerase III antibody	0	0	0	1	1	0	0
	Anti-cyclic citrullinated peptide antibody	0	1	0	1	2	0	0
	Anti-cyclic citrullinated peptide antibody negative	0	0	0	1	1	0	0
	Anti-cyclic citrullinated peptide antibody positive	0	2	1	1	3	0	0
	Anti-platelet antibody positive	2	3	0	0	3	0	0
	Anti-thrombin antibody	0	1	0	0	1	0	0
	Anti-thyroid antibody	0	0	1	2	2	0	0
	Anti-thyroid antibody decreased	0	1	0	0	1	0	0
	Anti-thyroid antibody increased	0	1	1	1	2	0	0
	Anti-thyroid antibody positive	0	4	2	3	7	0	0
	Anti-transglutaminase antibody	0	1	0	0	1	0	0
	Anti-transglutaminase antibody increased	0	0	1	1	1	0	0
	Antiacetylcholine receptor antibody	0	1	0	1	2	0	0
	Antiacetylcholine receptor antibody positive	0	1	0	1	2	0	0
	Antibiotic level	0	0	0	1	1	0	0
	Antibody test	0	3	0	4	7	0	0
	Antibody test abnormal	0	0	26	35	35	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Antibody test negative	0	0	2	47	47	0	0
	Antibody test normal	0	0	0	1	1	0	0
	Antibody test positive	1	1	0	1	2	0	0
	Anticoagulation drug level above therapeutic	0	2	0	0	2	0	0
	Anticoagulation drug level below therapeutic	0	0	0	1	1	0	0
	Anticoagulation drug level therapeutic	0	1	0	0	1	0	0
	Anticonvulsant drug level	0	0	0	1	1	0	0
	Anticonvulsant drug level decreased	1	1	0	0	1	0	0
	Antidepressant drug level decreased	0	0	1	1	1	0	0
	Antimicrobial susceptibility test	0	2	0	0	2	0	0
	Antimitochondrial antibody	0	1	0	0	1	0	0
	Antimitochondrial antibody positive	0	1	0	0	1	0	0
	Antineutrophil cytoplasmic antibody	0	0	0	1	1	0	0
	Antineutrophil cytoplasmic antibody increased	2	2	1	1	3	0	0
	Antineutrophil cytoplasmic antibody positive	0	1	0	0	1	0	0
	Antinuclear antibody	1	7	0	5	12	0	0
	Antinuclear antibody increased	1	1	0	2	3	0	0
	Antinuclear antibody negative	0	9	0	2	11	0	0
	Antinuclear antibody positive	3	9	4	10	19	0	0
	Antiphospholipid antibodies	0	4	1	1	5	0	0
	Antiphospholipid antibodies negative	0	2	0	0	2	0	0
	Antiphospholipid antibodies positive	0	2	2	3	5	0	0
	Antipsychotic drug level below therapeutic	0	0	0	1	1	0	0
	Antipsychotic drug level decreased	0	0	1	1	1	0	0
	Antipsychotic drug level increased	1	1	0	0	1	0	0
	Antithrombin III	0	1	0	0	1	0	0
	Antral follicle count low	0	1	0	0	1	0	0
	Arteriogram carotid	0	10	0	1	11	0	0
	Arteriogram carotid abnormal	0	6	0	0	6	0	0
	Arteriogram carotid normal	0	5	0	0	5	0	0
	Arteriogram coronary abnormal	0	8	0	0	8	0	0
	Arteriogram coronary normal	0	3	0	1	4	0	0
	Arthroscopy	0	0	1	1	1	0	0
	Aspartate aminotransferase	0	2	0	1	3	0	0
	Aspartate aminotransferase decreased	0	2	0	1	3	0	0
	Aspartate aminotransferase increased	2	43	3	17	60	0	0
	Aspartate aminotransferase normal	0	21	0	2	23	0	0
	Aspergillus test	0	2	0	0	2	0	0
	Aspergillus test positive	0	1	0	0	1	0	0
	Aspiration bursa	0	1	0	0	1	0	0
	Aspiration bursa abnormal	0	0	1	1	1	0	0
	Aspiration joint	1	3	0	1	4	0	0
	Aspiration pleural cavity	0	6	0	1	7	0	0
	Astrovirus test	0	1	0	0	1	0	0
	Atrial natriuretic peptide normal	0	1	0	0	1	0	0
	Atrial pressure increased	0	0	0	1	1	0	0
	Audiogram	0	2	0	3	5	0	0
	Audiogram abnormal	1	10	0	2	12	0	0
	Audiogram normal	0	0	0	1	1	0	0
	Auscultation	0	2	0	0	2	0	0
	Autoantibody positive	6	6	6	9	15	0	0
	Autoantibody test	0	1	0	0	1	0	0
	Autopsy	0	8	0	0	8	0	0
	B-lymphocyte count decreased	0	0	1	3	3	0	0
	Babinski reflex test	0	1	0	0	1	0	0
	Bacterial test	0	7	0	3	10	0	0
	Bacterial test negative	0	4	0	1	5	0	0
	Bacterial test positive	1	6	0	3	9	0	0
	Bacteroides test positive	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Balance test	0	2	0	0	2	0	0
	Band neutrophil count	0	1	0	0	1	0	0
	Band neutrophil percentage	0	1	0	0	1	0	0
	Band neutrophil percentage increased	0	1	0	1	2	0	0
	Barbiturates negative	0	1	0	0	1	0	0
	Barium swallow	0	1	0	0	1	0	0
	Barium swallow normal	0	0	0	1	1	0	0
	Base excess	0	2	0	0	2	0	0
	Base excess increased	0	2	0	0	2	0	0
	Basophil count	0	3	0	0	3	0	0
	Basophil count abnormal	0	0	0	1	1	0	0
	Basophil count decreased	0	8	0	0	8	0	0
	Basophil count normal	0	6	0	0	6	0	0
	Basophil percentage	0	10	0	1	11	0	0
	Basophil percentage decreased	0	22	0	0	22	0	0
	Basophil percentage increased	0	2	0	0	2	0	0
	Beta 2 microglobulin decreased	0	0	1	1	1	0	0
	Beta-2 glycoprotein antibody	0	1	0	0	1	0	0
	Beta-2 glycoprotein antibody negative	0	2	0	0	2	0	0
	Beta-2 glycoprotein antibody positive	2	3	0	0	3	0	0
	Bile output	2	3	0	0	3	0	0
	Bile output abnormal	0	0	0	1	1	0	0
	Bilirubin conjugated	0	1	0	0	1	0	0
	Bilirubin conjugated increased	0	3	0	1	4	0	0
	Bilirubin urine	0	5	0	0	5	0	0
	Biopsy	0	6	0	6	12	0	0
	Biopsy artery	0	1	0	0	1	0	0
	Biopsy artery abnormal	0	1	0	0	1	0	0
	Biopsy artery normal	0	1	0	0	1	0	0
	Biopsy bone marrow	0	1	0	0	1	0	0
	Biopsy bone marrow abnormal	0	2	0	0	2	0	0
	Biopsy brain	0	1	0	0	1	0	0
	Biopsy breast	0	1	0	0	1	0	0
	Biopsy breast abnormal	0	0	0	1	1	0	0
	Biopsy chorionic villous abnormal	0	1	0	0	1	0	0
	Biopsy endometrium normal	0	1	0	0	1	0	0
	Biopsy intestine normal	0	1	0	0	1	0	0
	Biopsy kidney	1	3	0	0	3	0	0
	Biopsy kidney abnormal	0	1	0	0	1	0	0
	Biopsy liver	0	2	0	0	2	0	0
	Biopsy liver abnormal	0	2	0	0	2	0	0
	Biopsy lung	0	1	0	0	1	0	0
	Biopsy lung abnormal	0	2	0	0	2	0	0
	Biopsy lymph gland	0	3	0	2	5	0	0
	Biopsy muscle	0	2	0	0	2	0	0
	Biopsy muscle normal	0	1	0	0	1	0	0
	Biopsy oesophagus abnormal	0	1	0	0	1	0	0
	Biopsy peripheral nerve	0	1	0	0	1	0	0
	Biopsy salivary gland abnormal	0	1	0	0	1	0	0
	Biopsy skin	0	5	0	2	7	0	0
	Biopsy skin abnormal	0	6	0	3	9	0	0
	Biopsy skin normal	0	0	0	2	2	0	0
	Biopsy soft tissue	0	1	0	0	1	0	0
	Biopsy stomach	0	1	0	0	1	0	0
	Bladder scan	0	2	0	0	2	0	0
	Blast cells present	0	1	0	0	1	0	0
	Bleeding time	0	1	0	1	2	0	0
	Bleeding time abnormal	0	1	1	2	3	0	0
	Bleeding time prolonged	1	1	3	5	6	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Bleeding time shortened	0	0	1	1	1	0	0
	Blood albumin	0	2	0	0	2	0	0
	Blood albumin decreased	0	26	0	2	28	0	0
	Blood albumin increased	0	2	1	2	4	0	0
	Blood albumin normal	0	11	0	2	13	0	0
	Blood alcohol increased	0	2	0	0	2	0	0
	Blood aldosterone decreased	0	0	0	1	1	0	0
	Blood alkaline phosphatase	0	1	0	0	1	0	0
	Blood alkaline phosphatase decreased	0	1	0	0	1	0	0
	Blood alkaline phosphatase increased	1	20	0	5	25	0	0
	Blood alkaline phosphatase normal	0	28	0	2	30	0	0
	Blood beta-D-glucan abnormal	0	1	0	0	1	0	0
	Blood bicarbonate	0	3	0	0	3	0	0
	Blood bicarbonate decreased	0	10	0	0	10	0	0
	Blood bicarbonate increased	0	5	0	0	5	0	0
	Blood bicarbonate normal	0	12	0	0	12	0	0
	Blood bilirubin	0	2	0	1	3	0	0
	Blood bilirubin decreased	0	3	0	0	3	0	0
	Blood bilirubin increased	0	19	5	9	28	0	0
	Blood bilirubin normal	0	32	0	3	35	0	0
	Blood calcitonin increased	0	1	1	1	2	0	0
	Blood calcium	0	3	0	0	3	0	0
	Blood calcium decreased	0	29	1	5	34	0	0
	Blood calcium increased	2	4	0	1	5	0	0
	Blood calcium normal	0	17	0	2	19	0	0
	Blood catecholamines	0	1	0	0	1	0	0
	Blood chloride	0	1	0	0	1	0	0
	Blood chloride decreased	0	17	0	2	19	0	0
	Blood chloride increased	0	16	0	2	18	0	0
	Blood chloride normal	0	28	0	3	31	0	0
	Blood cholesterol abnormal	0	0	0	1	1	0	0
	Blood cholesterol decreased	0	0	0	1	1	0	0
	Blood cholesterol increased	2	9	6	28	37	0	0
	Blood cholesterol normal	0	3	0	3	6	0	0
	Blood copper normal	0	1	0	0	1	0	0
	Blood corticotrophin normal	0	1	0	0	1	0	0
	Blood creatine	0	0	0	1	1	0	0
	Blood creatine increased	0	3	0	1	4	0	0
	Blood creatine normal	0	1	0	0	1	0	0
	Blood creatine phosphokinase	0	5	0	3	8	0	0
	Blood creatine phosphokinase MB	0	4	0	1	5	0	0
	Blood creatine phosphokinase MB increased	0	2	0	0	2	0	0
	Blood creatine phosphokinase abnormal	0	1	0	0	1	0	0
	Blood creatine phosphokinase decreased	0	1	0	1	2	0	0
	Blood creatine phosphokinase increased	7	32	B	19	51	0	0
	Blood creatine phosphokinase normal	0	9	0	2	11	0	0
	Blood creatinine	0	3	0	0	3	0	0
	Blood creatinine abnormal	0	1	0	1	2	0	0
	Blood creatinine decreased	0	2	0	1	3	0	0
	Blood creatinine increased	2	92	3	15	107	0	0
	Blood creatinine normal	0	36	0	6	42	0	0
	Blood culture	0	27	0	2	29	0	0
	Blood culture negative	0	24	0	0	24	0	0
	Blood culture positive	0	19	0	0	19	0	0
	Blood elastase decreased	0	0	2	2	2	0	0
	Blood electrolytes	0	3	0	0	3	0	0
	Blood electrolytes abnormal	0	2	0	0	2	0	0
	Blood electrolytes decreased	0	0	0	2	2	0	0
	Blood electrolytes normal	0	9	0	1	10	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Blood erythropoietin increased	0	1	0	0	1	0	0
	Blood erythropoietin normal	0	1	0	0	1	0	0
	Blood fibrinogen	1	3	0	0	3	0	0
	Blood fibrinogen increased	2	11	3	4	15	0	0
	Blood fibrinogen normal	0	1	0	0	1	0	0
	Blood folate	0	1	0	1	2	0	0
	Blood folate decreased	0	0	1	2	2	0	0
	Blood folate normal	0	2	0	0	2	0	0
	Blood follicle stimulating hormone	0	0	0	1	1	0	0
	Blood follicle stimulating hormone increased	0	1	3	3	4	0	0
	Blood gases	0	14	0	2	16	0	0
	Blood gases abnormal	0	4	0	1	5	0	0
	Blood gases normal	0	3	0	1	4	0	0
	Blood glucose	0	6	0	14	20	0	0
	Blood glucose abnormal	2	6	5	26	32	0	0
	Blood glucose decreased	4	25	8	93	118	0	0
	Blood glucose fluctuation	0	4	10	35	39	0	0
	Blood glucose increased	14	99	60	346	445	0	0
	Blood glucose normal	0	53	0	14	67	0	0
	Blood homocysteine increased	0	0	0	2	2	0	0
	Blood immunoglobulin E	0	0	0	1	1	0	0
	Blood immunoglobulin E increased	0	0	3	3	3	0	0
	Blood immunoglobulin G	0	3	0	0	3	0	0
	Blood immunoglobulin G abnormal	0	1	0	0	1	0	0
	Blood immunoglobulin G decreased	0	1	2	4	5	0	0
	Blood immunoglobulin G increased	0	1	1	3	4	0	0
	Blood immunoglobulin G normal	0	2	0	0	2	0	0
	Blood immunoglobulin M	0	4	0	0	4	0	0
	Blood immunoglobulin M abnormal	0	1	0	0	1	0	0
	Blood immunoglobulin M decreased	0	0	1	1	1	0	0
	Blood immunoglobulin M increased	0	1	1	1	2	0	0
	Blood immunoglobulin M normal	0	1	0	0	1	0	0
	Blood insulin abnormal	0	0	1	2	2	0	0
	Blood insulin decreased	2	2	0	0	2	0	0
	Blood insulin increased	2	2	0	3	5	0	0
	Blood iron	1	2	0	0	2	0	0
	Blood iron decreased	3	7	3	14	21	0	0
	Blood iron increased	0	0	1	3	3	0	0
	Blood iron normal	0	2	0	0	2	0	0
	Blood ketone body	0	2	0	1	3	0	0
	Blood lactate dehydrogenase	0	3	0	0	3	0	0
	Blood lactate dehydrogenase decreased	0	1	0	0	1	0	0
	Blood lactate dehydrogenase increased	1	22	2	3	25	0	0
	Blood lactate dehydrogenase normal	0	3	0	0	3	0	0
	Blood lactic acid	0	34	1	4	38	0	0
	Blood lactic acid decreased	0	5	0	0	5	0	0
	Blood lactic acid increased	0	17	0	0	17	0	0
	Blood lactic acid normal	0	9	0	0	9	0	0
	Blood luteinising hormone increased	0	0	1	1	1	0	0
	Blood magnesium	0	13	0	6	19	0	0
	Blood magnesium decreased	0	4	0	5	9	0	0
	Blood magnesium increased	0	5	0	1	6	0	0
	Blood magnesium normal	0	14	0	2	16	0	0
	Blood methaemoglobin	0	3	0	0	3	0	0
	Blood oestrogen decreased	0	0	1	1	1	0	0
	Blood oestrogen increased	0	0	0	2	2	0	0
	Blood osmolarity decreased	0	3	0	1	4	0	0
	Blood osmolarity increased	0	1	0	0	1	0	0
	Blood osmolarity normal	0	3	0	0	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Blood pH decreased	0	8	0	0	B	0	0
	Blood pH normal	0	5	0	0	5	0	0
	Blood parathyroid hormone	0	3	0	0	3	0	0
	Blood parathyroid hormone abnormal	0	0	0	1	1	0	0
	Blood parathyroid hormone increased	0	0	1	1	1	0	0
	Blood phosphorus	0	4	0	1	5	0	0
	Blood phosphorus decreased	0	7	0	0	7	0	0
	Blood phosphorus increased	0	4	0	0	4	0	0
	Blood phosphorus normal	0	3	0	0	3	0	0
	Blood potassium	0	4	0	0	4	0	0
	Blood potassium abnormal	0	1	1	1	2	0	0
	Blood potassium decreased	3	43	1	20	63	0	0
	Blood potassium increased	0	19	0	5	24	0	0
	Blood potassium normal	0	42	0	4	46	0	0
	Blood pressure abnormal	11	43	29	107	150	0	0
	Blood pressure ambulatory decreased	0	1	0	0	1	0	0
	Blood pressure ambulatory increased	0	0	0	1	1	0	0
	Blood pressure decreased	51	165	165	505	670	0	0
	Blood pressure diastolic decreased	1	1	0	3	4	0	0
	Blood pressure diastolic increased	1	7	11	22	29	0	0
	Blood pressure immeasurable	2	4	1	3	7	0	0
	Blood pressure increased	162	484	709	2737	3221	0	0
	Blood pressure measurement	3	10	4	29	39	0	0
	Blood pressure normal	0	1	0	1	2	0	0
	Blood pressure orthostatic	0	1	0	4	5	0	0
	Blood pressure orthostatic abnormal	0	0	1	2	2	0	0
	Blood pressure orthostatic decreased	0	2	0	0	2	0	0
	Blood pressure systolic abnormal	0	0	0	3	3	0	0
	Blood pressure systolic decreased	0	1	0	7	B	0	0
	Blood pressure systolic increased	1	5	5	16	21	0	0
	Blood prolactin abnormal	0	0	1	1	1	0	0
	Blood prolactin increased	1	1	1	4	5	0	0
	Blood smear test	0	1	0	0	1	0	0
	Blood smear test abnormal	0	1	0	0	1	0	0
	Blood smear test normal	0	1	0	0	1	0	0
	Blood sodium	0	2	0	0	2	0	0
	Blood sodium abnormal	0	1	0	0	1	0	0
	Blood sodium decreased	2	49	1	11	60	0	0
	Blood sodium increased	0	5	0	1	6	0	0
	Blood sodium normal	0	40	0	4	44	0	0
	Blood test	0	196	1	14B	344	0	0
	Blood test abnormal	7	45	5	34	79	0	0
	Blood test normal	2	47	0	35	B2	0	0
	Blood testosterone abnormal	0	0	1	1	1	0	0
	Blood testosterone decreased	2	3	0	0	3	0	0
	Blood testosterone increased	0	0	2	3	3	0	0
	Blood testosterone normal	0	1	0	0	1	0	0
	Blood thrombin	1	1	0	0	1	0	0
	Blood thromboplastin decreased	0	1	0	0	1	0	0
	Blood thyroid stimulating hormone	0	10	0	12	22	0	0
	Blood thyroid stimulating hormone abnormal	0	1	2	6	7	0	0
	Blood thyroid stimulating hormone decreased	0	10	4	14	24	0	0
	Blood thyroid stimulating hormone increased	9	19	15	27	46	0	0
	Blood thyroid stimulating hormone normal	0	10	0	3	13	0	0
	Blood triglycerides	0	1	0	0	1	0	0
	Blood triglycerides decreased	0	0	0	1	1	0	0
	Blood triglycerides increased	0	2	1	3	5	0	0
	Blood triglycerides normal	0	2	0	2	4	0	0
	Blood urea	0	1	0	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Blood urea decreased	0	1	0	4	5	0	0
	Blood urea increased	0	52	0	1	53	0	0
	Blood urea nitrogen/creatinine ratio	0	6	0	2	B	0	0
	Blood urea nitrogen/creatinine ratio increased	0	5	0	0	5	0	0
	Blood urea normal	0	29	0	3	32	0	0
	Blood uric acid	0	0	0	2	2	0	0
	Blood uric acid increased	0	2	0	3	5	0	0
	Blood uric acid normal	0	0	0	1	1	0	0
	Blood urine	2	8	3	12	20	0	0
	Blood urine absent	0	4	0	0	4	0	0
	Blood urine present	15	49	32	163	212	0	0
	Blood viscosity increased	0	1	0	0	1	0	0
	Blood zinc abnormal	0	0	0	1	1	0	0
	Blood zinc decreased	0	1	0	0	1	0	0
	Body height	0	0	0	4	4	0	0
	Body mass index	0	0	0	1	1	0	0
	Body temperature	12	70	17	88	158	0	0
	Body temperature abnormal	4	14	102	156	170	0	0
	Body temperature decreased	9	29	51	151	180	0	0
	Body temperature fluctuation	6	27	20	90	117	0	0
	Body temperature increased	55	223	2080	4515	473B	0	0
	Body temperature normal	0	0	2	3	3	0	0
	Bone density decreased	0	0	0	1	1	0	0
	Bone scan	0	2	0	1	3	0	0
	Bone scan abnormal	1	1	0	0	1	0	0
	Bordetella test	0	0	0	1	1	0	0
	Bordetella test negative	0	10	0	1	11	0	0
	Borrelia test	0	2	0	1	3	0	0
	Borrelia test negative	0	3	0	1	4	0	0
	Borrelia test positive	0	5	0	0	5	0	0
	Brachial pulse decreased	0	0	0	1	1	0	0
	Brain natriuretic peptide	0	9	0	1	10	0	0
	Brain natriuretic peptide increased	1	38	2	9	47	0	0
	Brain natriuretic peptide normal	0	16	0	1	17	0	0
	Brain scan abnormal	0	1	0	0	1	0	0
	Brain scan normal	0	3	0	3	6	0	0
	Breath sounds	0	1	1	4	5	0	0
	Breath sounds abnormal	4	16	3	18	34	0	0
	Breath sounds absent	0	1	0	1	2	0	0
	Breath sounds normal	0	1	0	2	3	0	0
	Bronchoalveolar lavage	0	1	0	0	1	0	0
	Bronchoalveolar lavage abnormal	0	2	0	0	2	0	0
	Bronchoalveolar lavage normal	0	1	0	0	1	0	0
	Bronchoscopy	0	2	0	1	3	0	0
	Bronchoscopy abnormal	0	3	0	0	3	0	0
	Bronchoscopy normal	0	1	0	0	1	0	0
	C-reactive protein	0	26	0	13	39	0	0
	C-reactive protein abnormal	0	2	0	2	4	0	0
	C-reactive protein decreased	0	0	0	1	1	0	0
	C-reactive protein increased	28	153	31	88	241	0	0
	C-reactive protein normal	0	9	1	3	12	0	0
	CD4 lymphocytes decreased	0	0	0	1	1	0	0
	CD4 lymphocytes increased	0	0	1	1	1	0	0
	CHA2DS2-VASc-score	0	1	0	0	1	0	0
	CSF culture	0	1	0	0	1	0	0
	CSF culture negative	0	1	0	0	1	0	0
	CSF glucose decreased	0	2	0	0	2	0	0
	CSF glucose increased	0	1	0	0	1	0	0
	CSF glucose normal	0	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	CSF immunoglobulin G index	0	1	0	0	1	0	0
	CSF mononuclear cell count increased	0	1	0	0	1	0	0
	CSF oligoclonal band	1	1	0	0	1	0	0
	CSF oligoclonal band present	0	3	0	0	3	0	0
	CSF pressure increased	0	2	0	0	2	0	0
	CSF protein increased	2	12	1	2	14	0	0
	CSF red blood cell count	0	1	0	0	1	0	0
	CSF red blood cell count positive	0	1	0	0	1	0	0
	CSF test	0	2	0	0	2	0	0
	CSF test abnormal	2	4	0	1	5	0	0
	CSF volume	0	1	0	0	1	0	0
	CSF white blood cell count increased	0	2	0	0	2	0	0
	CSF white blood cell count negative	0	2	0	0	2	0	0
	Calcium ionised increased	0	1	0	0	1	0	0
	Campylobacter test	0	2	0	0	2	0	0
	Capillary fragility increased	0	0	2	2	2	0	0
	Capillary permeability increased	0	3	0	1	4	0	0
	Carbohydrate antigen 125 normal	0	0	0	1	1	0	0
	Carbohydrate antigen 15-3 increased	0	1	0	0	1	0	0
	Carbohydrate antigen 19-9 increased	0	0	1	3	3	0	0
	Carbohydrate antigen 27.29 increased	0	0	0	1	1	0	0
	Carbon dioxide	0	1	0	1	2	0	0
	Carbon dioxide decreased	0	10	0	1	11	0	0
	Carbon dioxide increased	0	5	0	0	5	0	0
	Carbon dioxide normal	0	21	0	3	24	0	0
	Carboxyhaemoglobin	0	1	0	0	1	0	0
	Carboxyhaemoglobin normal	0	1	0	0	1	0	0
	Carcinoembryonic antigen increased	1	2	0	1	3	0	0
	Cardiac function test	0	2	0	2	4	0	0
	Cardiac function test abnormal	0	2	0	0	2	0	0
	Cardiac function test normal	0	3	0	1	4	0	0
	Cardiac imaging procedure	0	3	0	0	3	0	0
	Cardiac imaging procedure abnormal	0	12	0	1	13	0	0
	Cardiac imaging procedure normal	0	2	0	0	2	0	0
	Cardiac index decreased	0	1	0	0	1	0	0
	Cardiac monitoring	0	22	0	28	50	0	0
	Cardiac monitoring abnormal	0	8	0	6	14	0	0
	Cardiac monitoring normal	0	3	0	0	3	0	0
	Cardiac murmur	2	20	2	21	41	0	0
	Cardiac output increased	0	1	0	0	1	0	0
	Cardiac pharmacologic stress test	0	1	0	0	1	0	0
	Cardiac stress test	0	27	0	23	50	0	0
	Cardiac stress test abnormal	0	6	0	2	8	0	0
	Cardiac stress test normal	0	3	0	6	9	0	0
	Cardiac telemetry	0	9	0	1	10	0	0
	Cardiac telemetry abnormal	0	3	0	0	3	0	0
	Cardiac telemetry normal	0	1	0	0	1	0	0
	Cardiac ventriculogram left	0	1	0	0	1	0	0
	Cardiolipin antibody	0	1	0	0	1	0	0
	Cardiolipin antibody negative	0	3	0	0	3	0	0
	Cardiolipin antibody positive	2	5	0	1	6	0	0
	Cardiovascular evaluation	0	7	0	2	9	0	0
	Cardiovascular function test abnormal	0	0	0	1	1	0	0
	Carotid pulse	0	0	0	1	1	0	0
	Carotid pulse abnormal	0	2	0	1	3	0	0
	Catheter culture positive	0	1	0	0	1	0	0
	Catheterisation cardiac	0	35	0	6	41	0	0
	Catheterisation cardiac abnormal	0	18	0	0	18	0	0
	Catheterisation cardiac normal	0	12	0	0	12	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Cell marker increased	1	1	0	0	1	0	0
	Central venous pressure abnormal	0	1	0	0	1	0	0
	Ceruloplasmin	0	1	0	0	1	0	0
	Chest X-ray	0	98	0	60	158	0	0
	Chest X-ray abnormal	0	246	2	18	264	0	0
	Chest X-ray normal	0	74	0	27	101	0	0
	Chest scan	0	2	0	0	2	0	0
	Chlamydia test negative	0	9	0	1	10	0	0
	Chlamydia test positive	1	1	0	1	2	0	0
	Clostridium test	0	3	0	0	3	0	0
	Clostridium test negative	0	2	0	0	2	0	0
	Clostridium test positive	0	3	0	0	3	0	0
	Coagulation factor	0	2	0	0	2	0	0
	Coagulation factor VIII level decreased	1	1	1	1	2	0	0
	Coagulation factor VIII level increased	0	0	1	1	1	0	0
	Coagulation test	0	5	0	1	6	0	0
	Coagulation test abnormal	3	5	1	1	6	0	0
	Coagulation test normal	0	5	0	0	5	0	0
	Coagulation time	0	0	0	1	1	0	0
	Coagulation time abnormal	0	0	0	1	1	0	0
	Coagulation time prolonged	1	2	1	1	3	0	0
	Coagulation time shortened	2	2	0	1	3	0	0
	Cognitive test	0	3	0	0	3	0	0
	Cold agglutinins	0	0	1	1	1	0	0
	Colonoscopy	0	4	0	3	7	0	0
	Colonoscopy abnormal	0	2	0	0	2	0	0
	Colonoscopy normal	0	6	0	1	7	0	0
	Coma scale	0	2	0	0	2	0	0
	Coma scale abnormal	0	2	0	0	2	0	0
	Complement factor	0	0	0	1	1	0	0
	Complement factor C3	0	2	0	1	3	0	0
	Complement factor C4	0	2	0	1	3	0	0
	Computerised tomogram	0	141	0	59	200	0	0
	Computerised tomogram abdomen	0	12	0	4	16	0	0
	Computerised tomogram abdomen abnormal	0	51	0	4	55	0	0
	Computerised tomogram abdomen normal	0	7	0	2	9	0	0
	Computerised tomogram abnormal	1	36	2	17	53	0	0
	Computerised tomogram coronary artery	0	1	0	0	1	0	0
	Computerised tomogram head	0	41	0	20	61	0	0
	Computerised tomogram head abnormal	0	42	0	0	42	0	0
	Computerised tomogram head normal	0	54	0	5	59	0	0
	Computerised tomogram neck	0	11	0	2	13	0	0
	Computerised tomogram normal	0	31	0	19	50	0	0
	Computerised tomogram pelvis	0	3	0	1	4	0	0
	Computerised tomogram pelvis abnormal	0	1	0	2	3	0	0
	Computerised tomogram spine	0	13	0	0	13	0	0
	Computerised tomogram thorax	0	36	0	4	40	0	0
	Computerised tomogram thorax abnormal	0	98	0	1	99	0	0
	Computerised tomogram thorax normal	0	18	0	4	22	0	0
	Continuous glucose monitoring	0	0	0	1	1	0	0
	Coombs direct test	0	1	0	0	1	0	0
	Corneal reflex decreased	0	4	1	13	17	0	0
	Coronavirus test negative	0	7	0	0	7	0	0
	Coronavirus test positive	1	10	4	16	26	0	0
	Cortisol free urine normal	0	1	0	0	1	0	0
	Cortisol increased	1	2	0	1	3	0	0
	Cortisol normal	0	2	0	0	2	0	0
	Coxsackie virus test	0	1	0	0	1	0	0
	Coxsackie virus test negative	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Creatinine renal clearance	0	3	0	0	3	0	0
	Creatinine renal clearance decreased	0	4	0	0	4	0	0
	Creatinine renal clearance increased	0	1	0	0	1	0	0
	Creatinine urine normal	0	1	0	0	1	0	0
	Cryoglobulins	0	0	0	1	1	0	0
	Cryoglobulins present	0	0	0	1	1	0	0
	Culture	0	3	0	3	6	0	0
	Culture negative	0	4	0	1	5	0	0
	Culture positive	0	5	0	0	5	0	0
	Culture stool	0	1	0	0	1	0	0
	Culture stool positive	0	1	0	0	1	0	0
	Culture urine	0	8	0	3	11	0	0
	Culture urine negative	0	9	0	0	9	0	0
	Culture urine positive	0	10	0	1	11	0	0
	Culture wound	0	1	0	2	3	0	0
	Culture wound negative	0	1	0	0	1	0	0
	Culture wound positive	0	1	0	0	1	0	0
	Cystogram	0	1	0	0	1	0	0
	Cystoscopy	0	4	0	1	5	0	0
	Cytogenetic analysis	0	3	0	0	3	0	0
	Cytokine increased	0	0	0	1	1	0	0
	Cytology normal	0	1	0	0	1	0	0
	Cytomegalovirus test negative	0	1	0	0	1	0	0
	Cytomegalovirus test positive	1	4	2	3	7	0	0
	Dental examination abnormal	0	0	0	1	1	0	0
	Dermatologic examination	0	0	0	1	1	0	0
	Diagnostic procedure	0	1	0	0	1	0	0
	Differential white blood cell count	0	43	0	12	55	0	0
	Differential white blood cell count abnormal	0	5	0	0	5	0	0
	Differential white blood cell count normal	0	3	0	2	5	0	0
	Digestive enzyme normal	0	0	0	1	1	0	0
	Discogram abnormal	0	0	0	1	1	0	0
	Double stranded DNA antibody	0	1	0	0	1	0	0
	Drug level abnormal	0	1	0	0	1	0	0
	Drug level changed	0	0	0	1	1	0	0
	Drug level decreased	0	0	0	2	2	0	0
	Drug screen	0	0	0	1	1	0	0
	Drug screen negative	0	1	0	0	1	0	0
	Drug screen positive	0	1	0	2	3	0	0
	Drug specific antibody	0	0	0	1	1	0	0
	Drug specific antibody absent	0	0	0	5	5	0	0
	ECG signs of myocardial ischaemia	0	1	0	0	1	0	0
	Ear, nose and throat examination	0	1	0	0	1	0	0
	Ear, nose and throat examination abnormal	0	1	1	2	3	0	0
	Ear, nose and throat examination normal	0	1	0	0	1	0	0
	Echocardiogram	0	139	0	55	194	0	0
	Echocardiogram abnormal	2	78	0	9	87	0	0
	Echocardiogram normal	0	35	0	9	44	0	0
	Ejection fraction	0	13	0	1	14	0	0
	Ejection fraction decreased	3	65	1	5	70	0	0
	Ejection fraction normal	0	20	0	0	20	0	0
	Electrocardiogram	0	114	1	159	273	0	0
	Electrocardiogram J wave abnormal	0	1	0	0	1	0	0
	Electrocardiogram PR interval	0	2	0	0	2	0	0
	Electrocardiogram PR prolongation	0	0	2	2	2	0	0
	Electrocardiogram PR segment depression	0	3	0	0	3	0	0
	Electrocardiogram PR segment elevation	0	0	0	1	1	0	0
	Electrocardiogram Q wave abnormal	0	1	0	0	1	0	0
	Electrocardiogram QRS complex	0	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Electrocardiogram QRS complex abnormal	0	3	0	2	5	0	0
	Electrocardiogram QRS complex normal	0	1	0	0	1	0	0
	Electrocardiogram QT interval	0	7	0	1	8	0	0
	Electrocardiogram QT prolonged	0	12	0	1	13	0	0
	Electrocardiogram ST segment abnormal	0	2	0	1	3	0	0
	Electrocardiogram ST segment depression	0	4	0	0	4	0	0
	Electrocardiogram ST segment elevation	2	38	0	2	40	0	0
	Electrocardiogram ST-T change	0	7	0	0	7	0	0
	Electrocardiogram ST-T segment abnormal	1	4	0	1	5	0	0
	Electrocardiogram T wave abnormal	0	4	0	4	8	0	0
	Electrocardiogram T wave inversion	1	10	0	1	11	0	0
	Electrocardiogram T wave normal	0	2	0	0	2	0	0
	Electrocardiogram T wave peaked	0	1	0	0	1	0	0
	Electrocardiogram abnormal	5	110	8	82	192	0	0
	Electrocardiogram ambulatory	1	14	0	29	43	0	0
	Electrocardiogram ambulatory abnormal	0	3	0	6	9	0	0
	Electrocardiogram ambulatory normal	0	4	0	1	5	0	0
	Electrocardiogram change	0	2	0	1	3	0	0
	Electrocardiogram delta waves abnormal	0	1	0	0	1	0	0
	Electrocardiogram normal	0	64	3	54	118	0	0
	Electrocardiogram repolarisation abnormality	1	2	1	1	3	0	0
	Electroencephalogram	0	23	0	7	30	0	0
	Electroencephalogram abnormal	0	7	0	4	11	0	0
	Electroencephalogram normal	0	9	0	1	10	0	0
	Electromyogram	0	13	0	3	16	0	0
	Electromyogram abnormal	1	9	0	1	10	0	0
	Electromyogram normal	0	3	0	1	4	0	0
	Electronystagmogram	0	1	0	0	1	0	0
	Electronystagmogram abnormal	0	1	0	0	1	0	0
	Electronystagmogram normal	0	2	0	0	2	0	0
	Electrophoresis	0	0	0	1	1	0	0
	Electrophoresis protein normal	0	1	0	0	1	0	0
	Emergency care examination	1	1	0	2	3	0	0
	Emergency care examination normal	0	0	0	1	1	0	0
	Endobronchial ultrasound	0	1	0	0	1	0	0
	Endocrine test normal	0	2	0	0	2	0	0
	Endoscopic retrograde cholangiopancreatography	0	2	0	0	2	0	0
	Endoscopic retrograde cholangiopancreatography abnormal	0	1	0	0	1	0	0
	Endoscopy	0	4	0	1	5	0	0
	Endoscopy gastrointestinal abnormal	0	1	0	0	1	0	0
	Endoscopy normal	0	3	0	1	4	0	0
	Endoscopy upper gastrointestinal tract	0	1	0	2	3	0	0
	Endoscopy upper gastrointestinal tract abnormal	0	1	0	0	1	0	0
	Endoscopy upper gastrointestinal tract normal	0	2	0	0	2	0	0
	Enterobacter test positive	0	1	0	0	1	0	0
	Enterococcus test positive	0	3	0	0	3	0	0
	Enterovirus test	0	1	0	0	1	0	0
	Enterovirus test negative	0	10	0	1	11	0	0
	Enterovirus test positive	0	1	0	0	1	0	0
	Enzyme level abnormal	0	2	0	0	2	0	0
	Enzyme level increased	0	2	0	2	4	0	0
	Enzyme level test	0	1	0	0	1	0	0
	Eosinophil count	0	2	0	0	2	0	0
	Eosinophil count decreased	0	12	1	2	14	0	0
	Eosinophil count increased	1	4	1	8	12	0	0
	Eosinophil count normal	0	5	0	3	8	0	0
	Eosinophil percentage	0	16	0	1	17	0	0
	Eosinophil percentage decreased	0	19	0	2	21	0	0
	Eosinophil percentage increased	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Epinephrine abnormal	0	0	2	2	2	0	0
	Epinephrine increased	0	0	1	4	4	0	0
	Epstein-Barr virus antibody	0	0	0	1	1	0	0
	Epstein-Barr virus antibody negative	0	1	0	0	1	0	0
	Epstein-Barr virus antibody positive	1	3	2	4	7	0	0
	Epstein-Barr virus test	0	1	0	0	1	0	0
	Epstein-Barr virus test positive	0	2	0	4	6	0	0
	Erythrocyte osmotic fragility test	0	1	0	0	1	0	0
	Escherichia test negative	0	1	0	0	1	0	0
	Escherichia test positive	0	4	0	1	5	0	0
	Exercise electrocardiogram	0	0	0	1	1	0	0
	Exercise test	0	1	0	0	1	0	0
	Face and mouth X-ray abnormal	1	1	0	0	1	0	0
	Face and mouth X-ray normal	0	0	0	1	1	0	0
	Faecal calprotectin	0	1	0	1	2	0	0
	Faecal calprotectin increased	0	0	1	2	2	0	0
	Faecal volume increased	0	0	4	5	5	0	0
	False negative pregnancy test	0	0	0	1	1	0	0
	False positive investigation result	0	0	1	1	1	0	0
	False positive radioisotope investigation result	0	0	0	1	1	0	0
	Fibrin D dimer	0	68	0	12	80	0	0
	Fibrin D dimer decreased	0	1	1	1	2	0	0
	Fibrin D dimer increased	73	200	38	89	289	0	0
	Fibrin D dimer normal	0	9	0	7	16	0	0
	Fibrin abnormal	0	1	0	0	1	0	0
	Fibrinolysis increased	0	0	1	1	1	0	0
	Flow cytometry	0	2	0	0	2	0	0
	Fluorescent in situ hybridisation	0	1	0	0	1	0	0
	Foetal heart rate abnormal	1	16	0	3	19	0	0
	Foetal heart rate decreased	1	4	0	0	4	0	0
	Foetal heart rate increased	0	2	0	0	2	0	0
	Foetal non-stress test normal	0	1	0	0	1	0	0
	Forced expiratory volume decreased	1	1	0	1	2	0	0
	Forced expiratory volume increased	2	2	0	0	2	0	0
	Full blood count	0	106	0	68	174	0	0
	Full blood count abnormal	2	27	3	23	50	0	0
	Full blood count decreased	0	0	1	2	2	0	0
	Full blood count normal	0	31	0	24	55	0	0
	Functional residual capacity decreased	0	1	0	0	1	0	0
	Fungal test	0	0	0	1	1	0	0
	Fungal test negative	0	1	0	0	1	0	0
	Fungal test positive	0	1	0	0	1	0	0
	Gamma-glutamyltransferase increased	3	11	11	15	26	0	0
	Gastric emptying study	0	1	0	0	1	0	0
	Gastric occult blood positive	0	1	0	0	1	0	0
	Gastric pH decreased	2	2	1	2	4	0	0
	Gastrointestinal pathogen panel	0	1	0	0	1	0	0
	Gastrointestinal stoma output increased	1	1	0	0	1	0	0
	Gene mutation identification test	0	3	0	0	3	0	0
	Gene mutation identification test negative	0	2	0	0	2	0	0
	Gene mutation identification test positive	0	1	0	0	1	0	0
	General physical condition	0	0	1	8	8	0	0
	General physical condition abnormal	1	14	3	13	27	0	0
	General physical condition normal	0	0	1	2	2	0	0
	Geriatric assessment	0	0	0	1	1	0	0
	Giardia test negative	0	1	0	0	1	0	0
	Globulin	0	1	0	0	1	0	0
	Globulins decreased	0	1	0	0	1	0	0
	Globulins increased	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Glomerular filtration rate	0	5	0	5	10	0	0
	Glomerular filtration rate decreased	0	37	3	9	46	0	0
	Glomerular filtration rate increased	0	2	0	2	4	0	0
	Glomerular filtration rate normal	0	17	0	1	18	0	0
	Glucose urine	0	1	0	0	1	0	0
	Glucose urine absent	0	4	0	0	4	0	0
	Glycosylated haemoglobin	0	10	0	0	10	0	0
	Glycosylated haemoglobin decreased	0	2	0	1	3	0	0
	Glycosylated haemoglobin increased	0	17	6	17	34	0	0
	Glycosylated haemoglobin normal	0	3	0	3	6	0	0
	Gram stain	0	3	0	0	3	0	0
	Gram stain negative	0	3	0	0	3	0	0
	Gram stain positive	0	8	0	0	8	0	0
	Granulocyte count decreased	0	0	0	1	1	0	0
	Granulocyte count increased	0	0	0	1	1	0	0
	Granulocyte percentage	0	1	0	0	1	0	0
	Grip strength	0	2	0	4	6	0	0
	Grip strength decreased	9	65	18	98	163	0	0
	Gynaecological examination	0	2	0	0	2	0	0
	Gynaecological examination abnormal	0	1	0	0	1	0	0
	Gynaecological examination normal	0	0	0	1	1	0	0
	HIV test	0	0	0	1	1	0	0
	HIV test false positive	0	0	1	4	4	0	0
	HIV test negative	0	7	0	0	7	0	0
	HIV test positive	1	1	0	0	1	0	0
	HLA-B*27 assay	0	1	0	0	1	0	0
	HLA-B*27 positive	0	0	0	1	1	0	0
	Haematocrit	0	2	0	0	2	0	0
	Haematocrit decreased	0	34	1	9	43	0	0
	Haematocrit increased	0	8	2	3	11	0	0
	Haematocrit normal	0	21	0	2	23	0	0
	Haematology test	0	3	0	1	4	0	0
	Haemodynamic test	0	1	0	0	1	0	0
	Haemodynamic test normal	0	1	0	0	1	0	0
	Haemoglobin	0	1	0	0	1	0	0
	Haemoglobin E	0	1	0	0	1	0	0
	Haemoglobin abnormal	0	1	0	2	3	0	0
	Haemoglobin decreased	10	119	7	26	145	0	0
	Haemoglobin increased	0	3	1	4	7	0	0
	Haemoglobin normal	0	34	0	3	37	0	0
	Haemoglobin urine present	1	1	0	0	1	0	0
	Haemophilus test positive	0	1	0	0	1	0	0
	Haptoglobin decreased	0	2	0	0	2	0	0
	Haptoglobin normal	0	1	0	0	1	0	0
	Head lag	1	4	0	1	5	0	0
	Head lag abnormal	0	1	0	1	2	0	0
	Heart rate	64	177	13	60	237	0	0
	Heart rate abnormal	11	43	20	114	157	0	0
	Heart rate decreased	12	73	32	180	253	0	0
	Heart rate increased	237	877	675	3364	4241	0	0
	Heart rate irregular	63	207	117	551	758	0	0
	Heart rate normal	0	0	0	1	1	0	0
	Heart rate variability decreased	0	1	0	0	1	0	0
	Heart rate variability increased	0	2	0	4	6	0	0
	Heart sounds	1	3	0	2	5	0	0
	Heart sounds abnormal	0	4	1	6	10	0	0
	Heavy metal normal	0	1	0	0	1	0	0
	Heavy metal test	0	0	0	1	1	0	0
	Heparin-induced thrombocytopenia test	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Heparin-induced thrombocytopenia test positive	0	1	0	0	1	0	0
	Hepatic enzyme	0	3	0	1	4	0	0
	Hepatic enzyme abnormal	1	5	2	11	16	0	0
	Hepatic enzyme increased	8	40	9	51	91	0	0
	Hepatitis A antibody	0	1	0	0	1	0	0
	Hepatitis A antibody positive	0	1	1	1	2	0	0
	Hepatitis A virus test	0	1	0	0	1	0	0
	Hepatitis B core antibody	0	1	0	0	1	0	0
	Hepatitis B core antibody positive	0	1	0	0	1	0	0
	Hepatitis B surface antigen	0	1	0	0	1	0	0
	Hepatitis C RNA	0	0	0	1	1	0	0
	Hepatitis C RNA positive	0	1	0	0	1	0	0
	Hepatitis C antibody negative	0	0	0	1	1	0	0
	Hepatitis C antibody positive	0	0	0	1	1	0	0
	Hepatitis C test negative	0	1	0	0	1	0	0
	Hepatitis C virus test	0	0	0	1	1	0	0
	Hepatitis E antibody positive	0	0	0	1	1	0	0
	Hepatitis viral test	0	2	0	0	2	0	0
	Hepatitis viral test negative	0	2	0	0	2	0	0
	Hepatobiliary scan	0	1	0	0	1	0	0
	Hepatobiliary scan abnormal	0	1	0	0	1	0	0
	Hepatobiliary scan normal	0	1	0	0	1	0	0
	Herpes simplex test negative	0	3	0	0	3	0	0
	Herpes simplex test positive	0	1	0	0	1	0	0
	High density lipoprotein decreased	0	2	1	2	4	0	0
	High density lipoprotein increased	0	0	0	2	2	0	0
	High density lipoprotein normal	0	2	0	0	2	0	0
	Histamine abnormal	1	1	1	3	4	0	0
	Histamine level	0	0	0	1	1	0	0
	Histamine level increased	0	2	0	1	3	0	0
	Hormone level abnormal	13	30	50	88	118	0	0
	Human chorionic gonadotropin	0	4	0	2	6	0	0
	Human chorionic gonadotropin decreased	0	0	0	1	1	0	0
	Human chorionic gonadotropin increased	0	1	0	0	1	0	0
	Human chorionic gonadotropin normal	0	0	0	2	2	0	0
	Human herpes virus 6 serology negative	0	1	0	0	1	0	0
	Human herpes virus 6 serology positive	0	1	0	0	1	0	0
	Human metapneumovirus test	0	10	0	1	11	0	0
	Human rhinovirus test	0	11	0	1	12	0	0
	Human rhinovirus test positive	0	1	0	0	1	0	0
	Hysteroscopy	0	1	1	2	3	0	0
	Imaging procedure	0	7	0	1	8	0	0
	Imaging procedure abnormal	0	7	0	1	8	0	0
	Immature granulocyte count	0	16	0	0	16	0	0
	Immature granulocyte count increased	0	0	0	1	1	0	0
	Immature granulocyte percentage increased	0	2	0	0	2	0	0
	Immunoglobulins decreased	1	1	0	1	2	0	0
	Immunoglobulins normal	0	1	0	0	1	0	0
	Immunology test	1	5	0	3	8	0	0
	Immunology test abnormal	0	1	0	1	2	0	0
	Immunology test normal	0	1	0	0	1	0	0
	Indeterminate investigation result	0	1	0	0	1	0	0
	Inflammatory marker decreased	0	1	0	0	1	0	0
	Inflammatory marker increased	11	37	13	22	59	0	0
	Inflammatory marker test	0	13	0	0	13	0	0
	Influenza A virus test	0	6	0	1	7	0	0
	Influenza A virus test negative	0	20	0	8	28	0	0
	Influenza B virus test	0	25	0	6	31	0	0
	Influenza B virus test positive	0	1	0	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Influenza virus test	0	6	0	5	11	0	0
	Influenza virus test negative	0	22	0	15	37	0	0
	Influenza virus test positive	0	2	0	1	3	0	0
	Inspiratory capacity decreased	0	1	0	0	1	0	0
	Interleukin level increased	0	0	0	1	1	0	0
	International normalised ratio	0	8	0	3	11	0	0
	International normalised ratio abnormal	0	0	0	4	4	0	0
	International normalised ratio decreased	1	1	2	11	12	0	0
	International normalised ratio fluctuation	0	0	2	5	5	0	0
	International normalised ratio increased	2	35	6	34	69	0	0
	International normalised ratio normal	0	4	0	3	7	0	0
	Intestinal transit time abnormal	0	2	0	0	2	0	0
	Intraocular pressure increased	5	12	7	12	24	0	0
	Intraocular pressure test	0	1	1	2	3	0	0
	Intraocular pressure test abnormal	0	0	3	3	3	0	0
	Investigation	0	1	0	0	1	0	0
	Investigation abnormal	0	0	0	1	1	0	0
	Iron binding capacity total decreased	0	1	0	0	1	0	0
	Iron binding capacity total normal	0	2	0	0	2	0	0
	JC polyomavirus test positive	0	1	0	0	1	0	0
	Joint position sense decreased	0	0	0	1	1	0	0
	Klebsiella test positive	0	7	0	0	7	0	0
	Laboratory test	0	170	2	64	234	0	0
	Laboratory test abnormal	0	41	0	11	52	0	0
	Laboratory test normal	0	42	1	10	52	0	0
	Laparoscopy	0	1	0	0	1	0	0
	Laryngoscopy	0	0	0	1	1	0	0
	Left ventricular end-diastolic pressure	0	1	0	0	1	0	0
	Left ventricular end-diastolic pressure increased	0	2	0	0	2	0	0
	Left-handedness	0	0	1	1	1	0	0
	Legionella test	0	14	0	0	14	0	0
	Light chain analysis abnormal	0	1	0	1	2	0	0
	Light chain analysis increased	0	0	0	3	3	0	0
	Light chain analysis normal	0	1	0	0	1	0	0
	Limb girth decreased	0	0	0	1	1	0	0
	Lipase	0	3	0	2	5	0	0
	Lipase decreased	0	1	0	0	1	0	0
	Lipase increased	1	13	4	11	24	0	0
	Lipase normal	0	7	0	1	8	0	0
	Lipids	0	6	0	4	10	0	0
	Lipids increased	0	0	0	1	1	0	0
	Lipids normal	0	0	0	1	1	0	0
	Lipoprotein increased	0	1	0	0	1	0	0
	Liver function test	0	5	0	3	8	0	0
	Liver function test abnormal	10	21	8	21	42	0	0
	Liver function test decreased	0	1	0	1	2	0	0
	Liver function test increased	1	17	7	20	37	0	0
	Liver function test normal	0	4	0	3	7	0	0
	Liver iron concentration increased	0	1	0	0	1	0	0
	Liver scan	0	1	0	0	1	0	0
	Low density lipoprotein decreased	0	0	2	2	2	0	0
	Low density lipoprotein increased	1	5	2	6	11	0	0
	Low density lipoprotein normal	0	4	0	1	5	0	0
	Lumbar puncture	0	32	0	1	33	0	0
	Lumbar puncture abnormal	0	13	0	1	14	0	0
	Lumbar puncture normal	0	5	0	1	6	0	0
	Lymph node palpable	1	7	7	42	49	0	0
	Lymph nodes scan abnormal	0	0	0	1	1	0	0
	Lymph nodes scan normal	0	0	1	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Lymphocyte count	0	13	0	1	14	0	0
	Lymphocyte count abnormal	0	0	1	2	2	0	0
	Lymphocyte count decreased	1	18	1	4	22	0	0
	Lymphocyte count increased	2	4	0	4	8	0	0
	Lymphocyte count normal	0	4	0	2	6	0	0
	Lymphocyte morphology abnormal	1	2	0	0	2	0	0
	Lymphocyte percentage	0	9	0	1	10	0	0
	Lymphocyte percentage decreased	0	29	0	1	30	0	0
	Lymphocyte percentage increased	0	1	0	2	3	0	0
	Magnetic resonance imaging	1	112	0	49	161	0	0
	Magnetic resonance imaging abdominal	0	1	0	1	2	0	0
	Magnetic resonance imaging abdominal abnormal	0	1	0	0	1	0	0
	Magnetic resonance imaging abdominal normal	0	1	0	1	2	0	0
	Magnetic resonance imaging abnormal	1	28	0	14	42	0	0
	Magnetic resonance imaging head	0	39	0	13	52	0	0
	Magnetic resonance imaging head abnormal	1	56	0	5	61	0	0
	Magnetic resonance imaging head normal	0	25	0	1	26	0	0
	Magnetic resonance imaging heart	0	15	0	6	21	0	0
	Magnetic resonance imaging hepatobiliary	0	0	0	1	1	0	0
	Magnetic resonance imaging joint	0	2	0	0	2	0	0
	Magnetic resonance imaging neck	0	9	0	2	11	0	0
	Magnetic resonance imaging normal	0	25	0	8	33	0	0
	Magnetic resonance imaging spinal	0	9	0	0	9	0	0
	Magnetic resonance imaging spinal abnormal	0	13	0	1	14	0	0
	Magnetic resonance imaging spinal normal	0	3	0	0	3	0	0
	Magnetic resonance imaging thoracic	0	3	0	1	4	0	0
	Magnetic resonance imaging thoracic abnormal	0	2	0	0	2	0	0
	Magnetic resonance imaging thoracic normal	0	1	0	0	1	0	0
	Mammogram	0	3	0	1	4	0	0
	Mammogram abnormal	0	2	0	3	5	0	0
	Mammogram normal	0	1	0	3	4	0	0
	Maximal voluntary ventilation increased	0	0	1	1	1	0	0
	Maximum heart rate	1	1	0	0	1	0	0
	Maximum heart rate decreased	0	0	1	1	1	0	0
	Maximum heart rate increased	0	1	0	0	1	0	0
	Mean arterial pressure decreased	1	1	0	0	1	0	0
	Mean cell haemoglobin	0	2	0	1	3	0	0
	Mean cell haemoglobin concentration	0	1	0	1	2	0	0
	Mean cell haemoglobin concentration decreased	0	8	1	2	10	0	0
	Mean cell haemoglobin concentration increased	0	1	0	0	1	0	0
	Mean cell haemoglobin concentration normal	0	29	0	1	30	0	0
	Mean cell haemoglobin decreased	0	2	0	1	3	0	0
	Mean cell haemoglobin increased	0	15	0	1	16	0	0
	Mean cell haemoglobin normal	0	21	0	2	23	0	0
	Mean cell volume	0	1	0	0	1	0	0
	Mean cell volume decreased	0	2	0	0	2	0	0
	Mean cell volume increased	0	15	0	0	15	0	0
	Mean cell volume normal	0	33	0	3	36	0	0
	Mean platelet volume	0	1	0	0	1	0	0
	Mean platelet volume decreased	0	4	0	1	5	0	0
	Mean platelet volume increased	0	10	0	1	11	0	0
	Mean platelet volume normal	0	16	0	1	17	0	0
	Mediastinoscopy	0	1	0	0	1	0	0
	Medical observation	0	0	0	6	6	0	0
	Megakaryocytes normal	0	1	0	0	1	0	0
	Menstruation normal	0	0	8	19	19	0	0
	Metabolic function test	0	89	0	54	143	0	0
	Metabolic function test abnormal	0	18	0	1	19	0	0
	Metabolic function test normal	0	16	0	6	22	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Metamyelocyte percentage	0	1	0	0	1	0	0
	Microscopy	0	2	0	0	2	0	0
	Model for end stage liver disease score	0	1	0	0	1	0	0
	Monoclonal immunoglobulin increased	0	0	0	1	1	0	0
	Monoclonal immunoglobulin present	0	0	0	1	1	0	0
	Monocyte count	0	19	0	0	19	0	0
	Monocyte count decreased	0	1	0	1	2	0	0
	Monocyte count increased	0	6	2	7	13	0	0
	Monocyte count normal	0	9	0	1	10	0	0
	Monocyte percentage	0	20	0	2	22	0	0
	Monocyte percentage decreased	0	1	0	0	1	0	0
	Monocyte percentage increased	0	14	0	0	14	0	0
	Mononucleosis heterophile test	0	0	0	1	1	0	0
	Montreal cognitive assessment	0	1	0	0	1	0	0
	Moraxella test positive	0	1	0	0	1	0	0
	Multipathogen PCR test	0	2	0	1	3	0	0
	Mumps antibody test	0	0	0	1	1	0	0
	Murphy's sign test	0	1	0	0	1	0	0
	Muscle strength abnormal	6	10	8	22	32	0	0
	Mycobacterium tuberculosis complex test	0	1	0	0	1	0	0
	Mycobacterium tuberculosis complex test positive	0	0	1	2	2	0	0
	Mycoplasma test negative	0	9	0	1	10	0	0
	Mycoplasma test positive	0	0	2	3	3	0	0
	Myelocyte count increased	0	0	1	1	1	0	0
	Myocardial necrosis marker	0	5	0	2	7	0	0
	Myocardial necrosis marker increased	4	23	0	0	23	0	0
	Myocardial necrosis marker normal	0	3	0	2	5	0	0
	Myocardial strain imaging	0	22	0	3	25	0	0
	Myocardial strain imaging abnormal	0	2	0	0	2	0	0
	Myoglobin blood	0	0	0	1	1	0	0
	Myoglobin blood decreased	0	0	1	1	1	0	0
	Myoglobin blood increased	0	0	1	1	1	0	0
	N-telopeptide	0	1	0	0	1	0	0
	N-terminal prohormone brain natriuretic peptide	0	1	0	1	2	0	0
	N-terminal prohormone brain natriuretic peptide abnormal	0	1	0	0	1	0	0
	N-terminal prohormone brain natriuretic peptide increased	1	12	1	5	17	0	0
	NIH stroke scale	0	2	0	2	4	0	0
	NIH stroke scale score increased	0	1	0	0	1	0	0
	Natural killer T cell count decreased	1	1	0	0	1	0	0
	Nerve conduction studies	0	9	0	2	11	0	0
	Nerve conduction studies abnormal	0	5	0	1	6	0	0
	Nerve conduction studies normal	0	3	0	0	3	0	0
	Nerve stimulation test	0	2	0	0	2	0	0
	Nerve stimulation test abnormal	0	0	0	1	1	0	0
	Nerve stimulation test normal	0	1	0	0	1	0	0
	Neurological examination	0	9	0	3	12	0	0
	Neurological examination abnormal	0	3	1	4	7	0	0
	Neurological examination normal	0	3	0	1	4	0	0
	Neurone-specific enolase increased	0	0	1	1	1	0	0
	Neurotransmitter level altered	0	0	1	1	1	0	0
	Neutralising antibodies negative	0	0	2	3	3	0	0
	Neutrophil count	0	20	0	2	22	0	0
	Neutrophil count abnormal	0	1	0	1	2	0	0
	Neutrophil count decreased	2	9	1	7	16	0	0
	Neutrophil count increased	0	9	0	5	14	0	0
	Neutrophil count normal	0	8	0	1	9	0	0
	Neutrophil percentage	0	6	0	2	8	0	0
	Neutrophil percentage decreased	0	4	0	0	4	0	0
	Neutrophil percentage increased	0	28	0	1	29	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Neutrophil toxic granulation present	0	1	0	0	1	0	0
	Nitrite urine	0	0	0	1	1	0	0
	Nitrite urine absent	0	8	0	0	8	0	0
	Nitrite urine present	0	1	0	1	2	0	0
	Non-high-density lipoprotein cholesterol	0	1	0	1	2	0	0
	Norepinephrine increased	0	1	0	1	2	0	0
	Norovirus test	0	2	0	0	2	0	0
	Nucleic acid test	0	8	0	3	11	0	0
	Nutritional condition abnormal	1	1	0	1	2	0	0
	Occult blood	0	1	0	1	2	0	0
	Occult blood negative	0	1	0	0	1	0	0
	Occult blood positive	0	4	0	0	4	0	0
	Oesophagogastroduodenoscopy	0	1	0	0	1	0	0
	Oesophagogastroduodenoscopy abnormal	0	1	0	0	1	0	0
	Oesophagogastroduodenoscopy normal	0	2	0	0	2	0	0
	Ophthalmic scan	0	1	0	0	1	0	0
	Ophthalmological examination	1	7	1	6	13	0	0
	Ophthalmological examination abnormal	0	6	0	0	6	0	0
	Ophthalmological examination normal	0	2	0	1	3	0	0
	Opiates positive	0	0	0	1	1	0	0
	Optical coherence tomography	0	0	0	1	1	0	0
	Oral soft tissue biopsy	0	1	0	0	1	0	0
	Orthostatic heart rate response increased	0	0	0	1	1	0	0
	Oxygen consumption	0	1	0	0	1	0	0
	Oxygen consumption decreased	1	1	0	6	7	0	0
	Oxygen consumption increased	0	4	1	1	5	0	0
	Oxygen saturation	2	5	0	11	16	0	0
	Oxygen saturation abnormal	0	7	2	16	23	0	0
	Oxygen saturation decreased	41	274	40	181	455	0	0
	Oxygen saturation increased	0	0	1	3	3	0	0
	PCO2 decreased	0	1	0	0	1	0	0
	PCO2 increased	0	9	0	0	9	0	0
	PCO2 normal	0	1	0	0	1	0	0
	PO2 decreased	0	11	0	0	11	0	0
	PO2 increased	0	2	0	0	2	0	0
	Pain assessment	0	0	0	2	2	0	0
	Palpatory finding abnormal	1	2	0	0	2	0	0
	Pancreatic enzymes increased	2	3	1	4	7	0	0
	Panel-reactive antibody	0	0	0	1	1	0	0
	Paracentesis eye	0	1	0	0	1	0	0
	Parvovirus B19 test	0	2	0	0	2	0	0
	Pathology test	0	6	0	0	6	0	0
	Peak expiratory flow rate	0	0	0	1	1	0	0
	Pedal pulse decreased	0	0	1	1	1	0	0
	Perfusion brain scan normal	0	1	0	0	1	0	0
	Pericardial drainage test abnormal	0	1	0	0	1	0	0
	Peritoneal cancer index	1	1	0	0	1	0	0
	Philadelphia chromosome positive	0	1	0	0	1	0	0
	Physical examination	0	0	0	7	7	0	0
	Platelet aggregation abnormal	0	0	2	3	3	0	0
	Platelet count	0	1	0	1	2	0	0
	Platelet count abnormal	0	2	0	2	4	0	0
	Platelet count decreased	16	132	15	104	236	0	0
	Platelet count increased	5	23	3	21	44	0	0
	Platelet count normal	1	44	1	7	51	0	0
	Platelet morphology abnormal	0	1	0	0	1	0	0
	Platelet morphology normal	0	0	0	1	1	0	0
	Pleural fluid analysis abnormal	0	1	0	0	1	0	0
	Polymerase chain reaction	0	11	2	6	17	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Polymerase chain reaction positive	1	2	2	5	7	0	0
	Popliteal pulse decreased	0	1	0	0	1	0	0
	Portogram	0	2	0	0	2	0	0
	Positron emission tomogram	0	6	0	1	7	0	0
	Positron emission tomogram abnormal	1	4	0	0	4	0	0
	Positron emission tomogram normal	0	2	0	0	2	0	0
	Prealbumin decreased	0	2	0	0	2	0	0
	Precancerous cells present	0	1	0	1	2	0	0
	Pregnancy test	0	1	0	1	2	0	0
	Pregnancy test false positive	1	1	0	0	1	0	0
	Pregnancy test negative	0	2	2	5	7	0	0
	Pregnancy test positive	0	0	0	2	2	0	0
	Pregnancy test urine negative	0	1	0	0	1	0	0
	Prenatal screening test	0	2	0	0	2	0	0
	Prenatal screening test abnormal	0	2	0	0	2	0	0
	Procalcitonin	0	34	0	2	36	0	0
	Procalcitonin decreased	0	1	0	0	1	0	0
	Procalcitonin increased	0	22	0	0	22	0	0
	Procalcitonin normal	0	6	0	0	6	0	0
	Proctoscopy	0	1	0	0	1	0	0
	Product residue present	0	0	0	1	1	0	0
	Progesterone	0	0	0	1	1	0	0
	Progesterone decreased	1	1	2	2	3	0	0
	Progesterone increased	0	0	1	1	1	0	0
	Prohormone brain natriuretic peptide increased	0	7	1	1	8	0	0
	Prostatic specific antigen	0	4	0	1	5	0	0
	Prostatic specific antigen decreased	0	0	1	3	3	0	0
	Prostatic specific antigen increased	0	2	4	15	17	0	0
	Prostatic specific antigen normal	0	1	0	0	1	0	0
	Protein C	0	3	0	0	3	0	0
	Protein C increased	4	7	1	3	10	0	0
	Protein S	0	1	0	0	1	0	0
	Protein S decreased	0	0	1	1	1	0	0
	Protein S normal	0	2	0	0	2	0	0
	Protein total	0	2	0	0	2	0	0
	Protein total abnormal	0	1	0	1	2	0	0
	Protein total decreased	0	11	0	1	12	0	0
	Protein total increased	0	3	0	2	5	0	0
	Protein total normal	0	21	0	2	23	0	0
	Protein urine	2	5	1	2	7	0	0
	Protein urine absent	0	4	0	1	5	0	0
	Protein urine present	0	4	1	2	6	0	0
	Prothrombin consumption time prolonged	0	0	0	1	1	0	0
	Prothrombin level	0	2	0	1	3	0	0
	Prothrombin level decreased	0	0	0	2	2	0	0
	Prothrombin level increased	0	1	0	0	1	0	0
	Prothrombin level normal	0	1	0	0	1	0	0
	Prothrombin time	0	10	0	1	11	0	0
	Prothrombin time abnormal	0	0	0	1	1	0	0
	Prothrombin time normal	0	2	0	1	3	0	0
	Prothrombin time prolonged	1	14	0	5	19	0	0
	Prothrombin time shortened	0	0	1	2	2	0	0
	Pseudomonas test positive	0	2	0	0	2	0	0
	Psychiatric evaluation	0	1	0	0	1	0	0
	Pulmonary arterial pressure increased	0	1	0	1	2	0	0
	Pulmonary arterial wedge pressure decreased	0	1	0	0	1	0	0
	Pulmonary arterial wedge pressure increased	1	1	0	0	1	0	0
	Pulmonary function test	0	5	0	3	8	0	0
	Pulmonary function test decreased	4	8	5	9	17	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Pulmonary function test normal	0	1	0	0	1	0	0
	Pulmonary imaging procedure	0	1	0	0	1	0	0
	Pulmonary imaging procedure abnormal	0	3	0	1	4	0	0
	Pulmonary physical examination	0	0	0	1	1	0	0
	Pulse abnormal	11	20	30	74	94	0	0
	Pulse absent	3	52	2	12	64	0	0
	Pulse pressure increased	0	0	0	1	1	0	0
	Pulse volume decreased	0	2	0	0	2	0	0
	Pulse waveform normal	0	1	0	0	1	0	0
	Pupil dilation procedure	0	4	0	0	4	0	0
	Pupillary light reflex tests abnormal	0	1	0	0	1	0	0
	Pus in stool	0	0	0	1	1	0	0
	QRS axis	0	2	0	0	2	0	0
	QRS axis abnormal	0	2	0	0	2	0	0
	Quality of life decreased	4	12	6	23	35	0	0
	Radial pulse	0	0	0	1	1	0	0
	Radial pulse abnormal	0	0	1	1	1	0	0
	Radioallergosorbent test negative	0	0	1	1	1	0	0
	Red blood cell count	0	1	0	0	1	0	0
	Red blood cell count abnormal	0	1	1	1	2	0	0
	Red blood cell count decreased	2	41	1	8	49	0	0
	Red blood cell count increased	0	4	0	2	6	0	0
	Red blood cell count normal	0	14	0	2	16	0	0
	Red blood cell microcytes present	0	1	0	0	1	0	0
	Red blood cell morphology abnormal	0	1	0	0	1	0	0
	Red blood cell morphology normal	0	1	0	1	2	0	0
	Red blood cell nucleated morphology	0	13	0	0	13	0	0
	Red blood cell nucleated morphology present	0	1	0	0	1	0	0
	Red blood cell scan	0	1	0	0	1	0	0
	Red blood cell schistocytes present	0	1	0	0	1	0	0
	Red blood cell sedimentation rate	0	7	0	6	13	0	0
	Red blood cell sedimentation rate increased	1	23	6	27	50	0	0
	Red blood cell sedimentation rate normal	0	7	0	8	15	0	0
	Red blood cells urine	0	1	1	3	4	0	0
	Red blood cells urine positive	0	6	0	1	7	0	0
	Red cell distribution width	0	2	0	0	2	0	0
	Red cell distribution width decreased	0	0	0	1	1	0	0
	Red cell distribution width increased	0	12	1	1	13	0	0
	Red cell distribution width normal	0	26	0	3	29	0	0
	Reflex test normal	0	2	0	0	2	0	0
	Renal function test	0	2	0	0	2	0	0
	Renal function test abnormal	0	4	0	2	6	0	0
	Renal function test normal	0	5	0	0	5	0	0
	Renin decreased	0	0	0	1	1	0	0
	Respiratory rate	0	1	1	2	3	0	0
	Respiratory rate decreased	1	8	5	14	22	0	0
	Respiratory rate increased	4	29	8	79	108	0	0
	Respiratory syncytial virus test	0	5	0	0	5	0	0
	Respiratory syncytial virus test negative	0	20	0	2	22	0	0
	Respiratory syncytial virus test positive	0	2	0	1	3	0	0
	Respiratory viral panel	0	14	0	4	18	0	0
	Reticulocyte count increased	2	2	0	1	3	0	0
	Retinogram abnormal	0	2	0	0	2	0	0
	Rhesus antibodies positive	0	0	0	1	1	0	0
	Rheumatoid factor	0	1	0	4	5	0	0
	Rheumatoid factor decreased	0	0	1	1	1	0	0
	Rheumatoid factor increased	3	6	1	3	9	0	0
	Rheumatoid factor negative	0	3	0	5	8	0	0
	Rheumatoid factor positive	0	1	0	2	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Rheumatological examination	0	2	0	0	2	0	0
	Right ventricular ejection fraction decreased	0	1	0	0	1	0	0
	Right ventricular systolic pressure	0	6	0	0	6	0	0
	Right ventricular systolic pressure decreased	0	1	0	0	1	0	0
	Right ventricular systolic pressure increased	0	2	0	0	2	0	0
	Romberg test	0	1	0	0	1	0	0
	Romberg test positive	0	1	0	0	1	0	0
	Rotavirus test negative	0	2	0	0	2	0	0
	Russell's viper venom time normal	0	1	0	0	1	0	0
	SARS-CoV-1 test negative	0	0	0	1	1	0	0
	SARS-CoV-1 test positive	0	1	0	4	S	0	0
	SARS-CoV-2 RNA	0	12	0	8	20	0	0
	SARS-CoV-2 RNA increased	0	1	0	1	2	0	0
	SARS-CoV-2 antibody test	0	4	10	24	28	0	0
	SARS-CoV-2 antibody test negative	0	4	122	162	166	0	0
	SARS-CoV-2 antibody test positive	1	8	1	30	38	0	0
	SARS-CoV-2 test	0	39	4	S1	90	0	0
	SARS-CoV-2 test false negative	0	0	0	1	1	0	0
	SARS-CoV-2 test false positive	0	1	0	S	6	0	0
	SARS-CoV-2 test negative	3	72	32	152	224	0	0
	SARS-CoV-2 test positive	S1	1208	230	1782	2990	0	0
	Saliva analysis	0	0	0	1	1	0	0
	Salmonella test negative	0	2	0	0	2	0	0
	Scan	0	6	0	4	10	0	0
	Scan abdomen abnormal	0	2	0	0	2	0	0
	Scan abnormal	0	2	0	1	3	0	0
	Scan brain	0	4	0	1	S	0	0
	Scan myocardial perfusion	0	S	0	0	S	0	0
	Scan normal	0	2	0	0	2	0	0
	Scan thyroid gland	0	0	1	1	1	0	0
	Scan with contrast	0	31	0	S	36	0	0
	Scan with contrast abnormal	0	37	0	4	41	0	0
	Scan with contrast normal	0	10	0	2	12	0	0
	Semen analysis abnormal	0	2	0	0	2	0	0
	Semen liquefaction	0	0	1	1	1	0	0
	Semen volume decreased	0	0	0	1	1	0	0
	Sensory level	0	1	0	1	2	0	0
	Sensory level abnormal	S	7	1S	33	40	0	0
	Sensory level normal	0	0	1	1	1	0	0
	Seroconversion test negative	0	0	0	3	3	0	0
	Serology normal	0	1	0	0	1	0	0
	Serratia test positive	0	1	0	0	1	0	0
	Serum ferritin	0	6	0	1	7	0	0
	Serum ferritin decreased	1	4	2	6	10	0	0
	Serum ferritin increased	1	18	6	9	27	0	0
	Serum ferritin normal	0	4	0	0	4	0	0
	Sexually transmitted disease test	0	0	0	2	2	0	0
	Shift to the left	0	0	0	1	1	0	0
	Sinus rhythm	3	10	0	12	22	0	0
	Skin temperature	3	13	2	11	24	0	0
	Skin test	0	1	1	3	4	0	0
	Skin test negative	0	1	0	0	1	0	0
	Skin test positive	0	1	0	3	4	0	0
	Skin turgor decreased	0	1	0	0	1	0	0
	Skull X-ray	0	1	0	0	1	0	0
	Sleep study	0	1	0	0	1	0	0
	Smear cervix	0	0	0	1	1	0	0
	Smear cervix abnormal	0	1	1	2	3	0	0
	Smear test	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Smear vaginal normal	0	1	0	0	1	0	0
	Smooth muscle antibody	0	1	0	0	1	0	0
	Smooth muscle antibody positive	0	0	0	1	1	0	0
	Specific gravity body fluid	0	0	0	1	1	0	0
	Specific gravity urine decreased	0	0	0	1	1	0	0
	Specific gravity urine normal	0	5	0	1	6	0	0
	Spinal X-ray abnormal	0	3	0	1	4	0	0
	Spinal X-ray normal	0	2	0	1	3	0	0
	Spirometry	0	2	0	0	2	0	0
	Sputum abnormal	0	1	2	6	7	0	0
	Sputum culture	0	8	0	0	8	0	0
	Sputum culture positive	0	5	0	0	5	0	0
	Staphylococcus test	0	3	0	0	3	0	0
	Staphylococcus test negative	0	7	0	0	7	0	0
	Staphylococcus test positive	0	13	0	0	13	0	0
	Steroid activity	0	0	0	1	1	0	0
	Stool analysis	0	1	0	2	3	0	0
	Stool analysis abnormal	0	1	0	0	1	0	0
	Stool analysis normal	0	2	0	0	2	0	0
	Streptococcus test	0	3	0	3	6	0	0
	Streptococcus test negative	0	11	0	4	15	0	0
	Streptococcus test positive	0	1	1	2	3	0	0
	Stress echocardiogram	0	2	0	7	9	0	0
	Stress echocardiogram abnormal	0	1	0	0	1	0	0
	Stroke volume	0	2	0	0	2	0	0
	Stroke volume decreased	0	1	0	0	1	0	0
	Stroke volume increased	0	0	1	1	1	0	0
	Swallow study	0	2	0	0	2	0	0
	Swollen joint count	0	0	0	2	2	0	0
	Synovial fluid analysis abnormal	0	0	0	1	1	0	0
	Synovial fluid crystal present	0	1	0	0	1	0	0
	Systemic lupus erythematosus disease activity index increased	0	0	0	1	1	0	0
	T-lymphocyte count abnormal	0	0	0	1	1	0	0
	T-lymphocyte count decreased	0	0	1	1	1	0	0
	T-lymphocyte count increased	0	0	3	3	3	0	0
	Temperature difference of extremities	2	6	1	7	13	0	0
	Temperature perception test abnormal	0	1	0	0	1	0	0
	Temperature perception test decreased	0	0	1	2	2	0	0
	Temperature perception test increased	0	0	4	4	4	0	0
	Tender joint count	0	1	0	0	1	0	0
	Thrombin time prolonged	0	1	0	0	1	0	0
	Thromboelastogram	0	1	0	0	1	0	0
	Thyroglobulin increased	0	0	1	2	2	0	0
	Thyroid function test	0	8	0	0	8	0	0
	Thyroid function test abnormal	0	1	2	5	6	0	0
	Thyroid function test normal	0	6	0	2	8	0	0
	Thyroid gland scan abnormal	0	0	0	1	1	0	0
	Thyroid hormones decreased	1	1	1	2	3	0	0
	Thyroid hormones increased	1	1	4	7	8	0	0
	Thyroid hormones test	0	1	0	0	1	0	0
	Thyroid stimulating immunoglobulin	0	0	1	1	1	0	0
	Thyroid stimulating immunoglobulin increased	0	0	0	1	1	0	0
	Thyroxine	0	0	0	1	1	0	0
	Thyroxine decreased	0	0	0	1	1	0	0
	Thyroxine free	0	3	0	0	3	0	0
	Thyroxine free decreased	0	2	0	0	2	0	0
	Thyroxine free increased	0	1	0	1	2	0	0
	Thyroxine free normal	0	1	0	1	2	0	0
	Thyroxine increased	1	2	0	2	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Tilt table test	0	2	0	1	3	0	0
	Tilt table test positive	0	0	0	2	2	0	0
	Topography corneal abnormal	0	1	0	0	1	0	0
	Total bile acids increased	0	2	0	0	2	0	0
	Total fluid output	0	1	0	0	1	0	0
	Total lung capacity decreased	2	8	2	6	14	0	0
	Toxicologic test	0	2	0	0	2	0	0
	Toxicologic test normal	0	1	0	1	2	0	0
	Toxoplasma serology negative	0	1	0	0	1	0	0
	Transaminases	0	1	0	1	2	0	0
	Transaminases abnormal	1	1	0	1	2	0	0
	Transaminases increased	9	32	13	23	55	0	0
	Transferrin decreased	0	1	0	0	1	0	0
	Transferrin saturation decreased	2	4	0	1	5	0	0
	Transvalvular pressure gradient	0	1	0	0	1	0	0
	Treponema test	0	2	0	1	3	0	0
	Treponema test positive	0	1	0	1	2	0	0
	Tri-iodothyronine	0	1	0	0	1	0	0
	Tri-iodothyronine abnormal	0	0	0	1	1	0	0
	Tri-iodothyronine decreased	0	1	0	0	1	0	0
	Tri-iodothyronine free increased	0	0	0	1	1	0	0
	Tri-iodothyronine increased	0	2	0	2	4	0	0
	Troponin	1	40	0	24	64	0	0
	Troponin I	0	7	0	4	11	0	0
	Troponin I abnormal	0	1	0	0	1	0	0
	Troponin I increased	2	27	0	2	29	0	0
	Troponin I normal	0	8	0	0	8	0	0
	Troponin T	0	2	0	1	3	0	0
	Troponin T increased	3	12	0	1	13	0	0
	Troponin T normal	0	1	1	2	3	0	0
	Troponin abnormal	2	2	0	0	2	0	0
	Troponin decreased	0	0	1	2	2	0	0
	Troponin increased	19	190	2	20	210	0	0
	Troponin normal	0	27	0	15	42	0	0
	Tryptase	0	1	0	4	5	0	0
	Tuberculin test	0	1	0	0	1	0	0
	Tumour marker increased	0	3	0	4	7	0	0
	Tympanometry	0	2	0	0	2	0	0
	Ultrasound Doppler	0	30	0	11	41	0	0
	Ultrasound Doppler abnormal	0	44	0	13	57	0	0
	Ultrasound Doppler normal	0	24	0	2	26	0	0
	Ultrasound abdomen	0	6	0	2	8	0	0
	Ultrasound abdomen abnormal	0	10	0	2	12	0	0
	Ultrasound abdomen normal	0	3	0	1	4	0	0
	Ultrasound antenatal screen	0	0	0	1	1	0	0
	Ultrasound antenatal screen abnormal	1	8	0	0	8	0	0
	Ultrasound antenatal screen normal	0	0	0	1	1	0	0
	Ultrasound biliary tract	0	0	0	1	1	0	0
	Ultrasound bladder	0	1	0	0	1	0	0
	Ultrasound bladder abnormal	0	1	0	0	1	0	0
	Ultrasound bladder normal	0	1	0	0	1	0	0
	Ultrasound breast	0	0	0	2	2	0	0
	Ultrasound breast abnormal	0	1	0	0	1	0	0
	Ultrasound chest	0	0	0	1	1	0	0
	Ultrasound foetal	0	2	0	0	2	0	0
	Ultrasound foetal abnormal	0	4	0	0	4	0	0
	Ultrasound head	0	2	0	1	3	0	0
	Ultrasound head normal	0	1	0	0	1	0	0
	Ultrasound kidney	0	3	0	0	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Ultrasound kidney abnormal	0	3	0	0	3	0	0
	Ultrasound kidney normal	0	1	0	0	1	0	0
	Ultrasound liver	0	2	0	0	2	0	0
	Ultrasound liver normal	0	1	0	0	1	0	0
	Ultrasound ovary abnormal	0	1	0	0	1	0	0
	Ultrasound pelvis abnormal	0	1	0	0	1	0	0
	Ultrasound pelvis normal	0	2	0	0	2	0	0
	Ultrasound scan	1	37	0	38	75	0	0
	Ultrasound scan abnormal	0	12	2	31	43	0	0
	Ultrasound scan normal	0	11	0	8	19	0	0
	Ultrasound scan vagina	1	2	0	0	2	0	0
	Ultrasound scan vagina abnormal	0	1	0	0	1	0	0
	Ultrasound scan vagina normal	0	1	0	0	1	0	0
	Ultrasound testes	0	0	0	1	1	0	0
	Ultrasound testes normal	0	1	0	0	1	0	0
	Ultrasound thyroid abnormal	0	0	0	1	1	0	0
	Ultrasound uterus abnormal	0	0	0	1	1	0	0
	Unevaluable investigation	0	0	1	1	1	0	0
	Ureteroscopy	0	1	0	0	1	0	0
	Urinary casts	0	1	0	1	2	0	0
	Urinary casts present	0	1	0	0	1	0	0
	Urinary sediment abnormal	0	0	1	1	1	0	0
	Urinary sediment present	0	6	0	1	7	0	0
	Urinary system X-ray	0	2	0	0	2	0	0
	Urine albumin/creatinine ratio	0	1	0	0	1	0	0
	Urine analysis	0	42	0	25	67	0	0
	Urine analysis abnormal	1	21	1	15	36	0	0
	Urine analysis normal	0	27	1	6	33	0	0
	Urine bilirubin decreased	0	0	0	1	1	0	0
	Urine copper	1	1	0	0	1	0	0
	Urine ketone body	0	1	0	0	1	0	0
	Urine ketone body absent	0	3	0	0	3	0	0
	Urine ketone body present	0	6	0	3	9	0	0
	Urine leukocyte esterase	0	7	0	3	10	0	0
	Urine leukocyte esterase positive	0	5	0	0	5	0	0
	Urine osmolarity	0	1	0	0	1	0	0
	Urine osmolarity increased	0	0	0	1	1	0	0
	Urine output	4	7	0	4	11	0	0
	Urine output decreased	1	17	3	17	34	0	0
	Urine output increased	1	2	2	15	17	0	0
	Urine protein/creatinine ratio	0	0	0	1	1	0	0
	Urine protein/creatinine ratio increased	1	1	0	0	1	0	0
	Urine sodium	0	1	0	0	1	0	0
	Urobilinogen urine	0	6	0	2	8	0	0
	Urobilinogen urine increased	0	1	0	0	1	0	0
	Urogram	0	1	0	0	1	0	0
	Urogram abnormal	0	1	0	0	1	0	0
	Urogram normal	0	1	0	0	1	0	0
	Vaccine induced antibody absent	0	0	2	2	2	0	0
	Varicella virus test	0	1	0	1	2	0	0
	Varicella virus test negative	0	1	0	0	1	0	0
	Varicella virus test positive	0	1	0	1	2	0	0
	Vascular imaging	0	1	0	0	1	0	0
	Vascular resistance systemic	0	0	0	1	1	0	0
	Vascular resistance systemic decreased	0	0	1	1	1	0	0
	Vascular test	0	1	0	0	1	0	0
	Venogram	0	4	0	1	5	0	0
	Venogram abnormal	0	1	0	0	1	0	0
	Venogram normal	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Venous oxygen partial pressure decreased	0	0	0	1	1	0	0
	Venous oxygen saturation decreased	0	1	0	0	1	0	0
	Venous pressure jugular	0	1	0	0	1	0	0
	Ventilation/perfusion scan	0	1	0	0	1	0	0
	Ventilation/perfusion scan abnormal	0	1	0	0	1	0	0
	Ventricular internal diameter abnormal	2	2	0	0	2	0	0
	Very low density lipoprotein	0	1	0	0	1	0	0
	Vestibular function test abnormal	0	1	0	1	2	0	0
	Vestibular function test normal	0	1	0	0	1	0	0
	Viral load increased	0	1	0	1	2	0	0
	Viral test	0	2	0	1	3	0	0
	Viral test negative	0	6	0	0	6	0	0
	Viral test positive	0	2	0	0	2	0	0
	Viral titre decreased	0	0	0	2	2	0	0
	Viral titre increased	0	1	0	0	1	0	0
	Visual field tests	0	1	0	0	1	0	0
	Visual field tests abnormal	0	2	0	0	2	0	0
	Visual tracking test	0	1	0	0	1	0	0
	Vital capacity decreased	0	0	1	1	1	0	0
	Vital functions abnormal	0	2	0	3	5	0	0
	Vital signs measurement	0	0	0	30	30	0	0
	Vitamin B12	0	4	0	3	7	0	0
	Vitamin B12 abnormal	0	1	0	1	2	0	0
	Vitamin B12 decreased	0	2	2	5	7	0	0
	Vitamin B12 increased	0	1	1	1	2	0	0
	Vitamin B12 normal	0	8	0	0	8	0	0
	Vitamin B6 normal	0	1	0	0	1	0	0
	Vitamin C decreased	0	1	0	0	1	0	0
	Vitamin D	0	2	0	5	7	0	0
	Vitamin D decreased	0	3	4	13	16	0	0
	Vitamin D increased	0	1	0	1	2	0	0
	Vitamin K decreased	0	1	0	0	1	0	0
	Volume blood decreased	0	2	0	0	2	0	0
	Waist circumference increased	0	0	0	1	1	0	0
	Walking distance test abnormal	0	1	0	0	1	0	0
	Wall motion score index abnormal	0	1	0	0	1	0	0
	Weight decreased	89	262	120	610	872	0	0
	Weight increased	12	62	58	173	235	0	0
	West Nile virus test negative	0	2	0	0	2	0	0
	White blood cell count	0	4	0	3	7	0	0
	White blood cell count abnormal	0	1	0	1	2	0	0
	White blood cell count decreased	3	29	2	32	61	0	0
	White blood cell count increased	7	111	5	55	166	0	0
	White blood cell count normal	0	58	0	4	62	0	0
	White blood cell morphology normal	0	2	0	1	3	0	0
	White blood cells urine	0	2	1	1	3	0	0
	White blood cells urine negative	0	3	0	1	4	0	0
	White blood cells urine positive	0	8	1	3	11	0	0
	Whole body scan	0	1	0	0	1	0	0
	X-ray	0	53	0	31	84	0	0
	X-ray abnormal	0	6	0	4	10	0	0
	X-ray dental	0	0	0	1	1	0	0
	X-ray dental abnormal	0	0	0	1	1	0	0
	X-ray limb	0	2	0	4	6	0	0
	X-ray limb abnormal	0	7	0	2	9	0	0
	X-ray limb normal	0	3	0	3	6	0	0
	X-ray normal	0	8	0	10	18	0	0
	X-ray of pelvis and hip	0	1	0	1	2	0	0
	X-ray of pelvis and hip normal	0	1	0	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	X-ray with contrast	0	1	0	0	1	0	0
	Xanthochromia	0	1	0	0	1	0	0
	Yersinia test negative	0	2	0	0	2	0	0
	pH body fluid abnormal	0	1	0	0	1	0	0
	pH urine	0	1	0	1	2	0	0
	pH urine increased	0	1	0	0	1	0	0
	pH urine normal	0	4	0	0	4	0	0
Metabolism and nutrition disorders	*** SOC TOTAL ***	566	3809	1210	8361	12170	0	0
	Abnormal loss of weight	12	36	8	41	77	0	0
	Abnormal weight gain	1	6	5	11	17	0	0
	Acidosis	1	24	1	5	29	0	0
	Adult failure to thrive	0	9	0	0	9	0	0
	Alcohol intolerance	1	3	8	17	20	0	0
	Alcoholic ketoacidosis	1	1	0	0	1	0	0
	Apoptosis	0	1	0	0	1	0	0
	Appetite disorder	1	7	8	58	65	0	0
	Body fat disorder	0	0	1	2	2	0	0
	Cachexia	2	11	1	1	12	0	0
	Carbohydrate intolerance	0	0	1	1	1	0	0
	Cell death	0	4	0	1	5	0	0
	Central obesity	0	1	0	0	1	0	0
	Cholesterosis	0	0	0	1	1	0	0
	Copper deficiency	0	0	0	1	1	0	0
	Dairy intolerance	0	0	1	3	3	0	0
	Dawn phenomenon	0	0	0	1	1	0	0
	Decreased appetite	267	1382	790	5860	7242	0	0
	Decreased insulin requirement	0	0	0	3	3	0	0
	Dehydration	46	448	49	673	1121	0	0
	Diabetes mellitus	19	117	11	21	138	0	0
	Diabetes mellitus inadequate control	9	53	27	32	85	0	0
	Diabetic complication	1	2	0	2	4	0	0
	Diabetic ketoacidosis	4	74	0	0	74	0	0
	Diabetic metabolic decompensation	1	7	1	1	8	0	0
	Diet refusal	0	4	0	5	9	0	0
	Dyslipidaemia	0	6	0	5	11	0	0
	Eating disorder symptom	1	2	1	12	14	0	0
	Electrolyte depletion	0	2	0	1	3	0	0
	Electrolyte imbalance	4	22	2	16	38	0	0
	Enzyme abnormality	1	2	1	2	4	0	0
	Failure to thrive	0	11	0	1	12	0	0
	Feeding disorder	20	166	59	518	684	0	0
	Feeding intolerance	0	1	0	1	2	0	0
	Fluid imbalance	0	3	0	1	4	0	0
	Fluid intake reduced	1	35	2	26	61	0	0
	Fluid retention	10	62	27	114	176	0	0
	Folate deficiency	2	4	1	2	6	0	0
	Food aversion	2	7	1	19	26	0	0
	Food craving	0	2	14	25	27	0	0
	Food intolerance	3	8	11	35	43	0	0
	Food refusal	1	12	0	11	23	0	0
	Fructose intolerance	0	0	0	1	1	0	0
	Glucose tolerance impaired	0	1	3	13	14	0	0
	Gluten sensitivity	0	2	1	4	6	0	0
	Gout	12	64	36	184	248	0	0
	Haemochromatosis	1	2	0	3	5	0	0
	Histamine intolerance	2	5	8	16	21	0	0
	Hyperammonaemia	0	5	0	0	5	0	0
	Hypercalcaemia	2	12	0	1	13	0	0
	Hyperchloraemia	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Hypercholesterolaemia	1	3	2	6	9	0	0
	Hypercreatininaemia	1	1	0	0	1	0	0
	Hyperferritinaemia	0	1	0	1	2	0	0
	Hyperglycaemia	12	91	22	111	202	0	0
	Hyperglycaemic hyperosmolar nonketotic syndrome	1	6	0	0	6	0	0
	Hyperhomocysteinaemia	1	1	1	1	2	0	0
	Hyperkalaemia	5	69	2	3	72	0	0
	Hyperlipasaemia	0	2	0	2	4	0	0
	Hyperlipidaemia	1	24	0	10	34	0	0
	Hypermagnesaemia	0	1	0	1	2	0	0
	Hypermetabolism	1	1	0	4	5	0	0
	Hypernatraemia	1	15	0	0	15	0	0
	Hyperphagia	0	6	1	6	12	0	0
	Hyperphosphataemia	1	1	0	1	2	0	0
	Hyperproteinaemia	0	3	0	0	3	0	0
	Hypertriglyceridaemia	1	8	0	2	10	0	0
	Hyperuricaemia	1	3	0	2	5	0	0
	Hypervolaemia	1	52	1	7	59	0	0
	Hypoalbuminaemia	2	11	2	5	16	0	0
	Hypocalcaemia	1	11	0	3	14	0	0
	Hypochloraemia	0	3	0	0	3	0	0
	Hypocholesterolaemia	0	0	1	1	1	0	0
	Hypoglycaemia	10	63	14	91	154	0	0
	Hypoglycaemia neonatal	0	1	0	0	1	0	0
	Hypokalaemia	9	113	1	7	120	0	0
	Hypokalaemic syndrome	0	0	0	1	1	0	0
	Hypomagnesaemia	1	23	0	1	24	0	0
	Hypometabolism	0	0	1	2	2	0	0
	Hyponatraemia	11	134	3	21	155	0	0
	Hypoosmolar state	0	8	0	0	8	0	0
	Hypophagia	4	147	8	48	195	0	0
	Hypophosphataemia	1	3	0	1	4	0	0
	Hypovitaminosis	0	3	0	4	7	0	0
	Hypovolaemia	5	20	1	6	26	0	0
	Increased appetite	2	9	8	55	64	0	0
	Increased insulin requirement	1	3	4	11	14	0	0
	Insulin resistance	0	3	1	4	7	0	0
	Insulin resistant diabetes	0	2	0	0	2	0	0
	Insulin-requiring type 2 diabetes mellitus	0	1	0	0	1	0	0
	Iron deficiency	1	4	8	14	18	0	0
	Iron metabolism disorder	0	0	0	1	1	0	0
	Ketoacidosis	2	11	0	0	11	0	0
	Lack of satiety	1	2	0	0	2	0	0
	Lactic acidosis	2	66	0	1	67	0	0
	Lactose intolerance	1	2	2	7	9	0	0
	Latent autoimmune diabetes in adults	1	2	2	4	6	0	0
	Lipoedema	4	5	2	2	7	0	0
	Lipomatosis	0	0	0	1	1	0	0
	Magnesium deficiency	0	1	0	0	1	0	0
	Malnutrition	1	19	1	5	24	0	0
	Metabolic acidosis	4	41	0	4	45	0	0
	Metabolic alkalosis	0	2	0	0	2	0	0
	Metabolic disorder	0	5	1	5	10	0	0
	Mineral deficiency	0	2	0	0	2	0	0
	Mitochondrial cytopathy	1	1	0	0	1	0	0
	Neonatal insufficient breast milk syndrome	1	5	1	3	8	0	0
	Obesity	0	23	2	9	32	0	0
	Oligodipsia	1	3	0	1	4	0	0
	Overweight	1	2	1	7	9	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Oxidative stress	0	1	0	0	1	0	0
	Periarthritis calcarea	0	0	2	3	3	0	0
	Polydipsia	3	9	7	31	40	0	0
	Poor feeding infant	1	2	3	10	12	0	0
	Postprandial hypoglycaemia	1	1	0	2	3	0	0
	Protein deficiency	0	0	0	2	2	0	0
	Pseudohyponatraemia	0	2	0	0	2	0	0
	Salt craving	0	1	0	7	8	0	0
	Shock hypoglycaemic	0	1	0	0	1	0	0
	Starvation	0	2	0	2	4	0	0
	Steroid diabetes	0	1	0	0	1	0	0
	Tetany	4	13	10	22	35	0	0
	Type 1 diabetes mellitus	20	47	3	5	52	0	0
	Type 2 diabetes mellitus	7	38	1	1	39	0	0
	Underweight	0	0	0	3	3	0	0
	Vitamin B complex deficiency	0	0	2	4	4	0	0
	Vitamin B12 deficiency	1	8	2	9	17	0	0
	Vitamin D deficiency	4	11	6	17	28	0	0
	Weight fluctuation	1	2	1	7	9	0	0
	Weight gain poor	0	1	0	1	2	0	0
	Weight loss poor	0	0	1	2	2	0	0
Musculoskeletal and connective tissue disorders	*** SOC TOTAL ***	7967	30302	54537	203762	234064	0	0
	Amplified musculoskeletal pain syndrome	0	0	1	4	4	0	0
	Amyotrophy	1	4	1	1	5	0	0
	Ankle deformity	0	1	0	0	1	0	0
	Ankle impingement	1	1	0	0	1	0	0
	Ankylosing spondylitis	14	35	11	13	48	0	0
	Arthralgia	1672	5550	12968	41680	47230	0	0
	Arthritis	52	196	156	894	1090	0	0
	Arthritis allergic	0	1	0	1	2	0	0
	Arthritis enteropathic	0	1	0	1	2	0	0
	Arthritis reactive	23	70	7	14	84	0	0
	Arthropathy	7	24	24	87	111	0	0
	Autoimmune arthritis	0	2	0	1	3	0	0
	Autoimmune myositis	7	9	0	0	9	0	0
	Axial spondyloarthritis	1	2	0	1	3	0	0
	Axillary mass	18	64	96	372	436	0	0
	Back disorder	1	5	2	18	23	0	0
	Back pain	348	1596	1377	6374	7970	0	0
	Bone atrophy	0	0	1	1	1	0	0
	Bone cyst	0	1	1	2	3	0	0
	Bone demineralisation	0	1	0	1	2	0	0
	Bone disorder	0	2	1	9	11	0	0
	Bone erosion	1	3	0	0	3	0	0
	Bone hypertrophy	0	1	0	0	1	0	0
	Bone infarction	0	1	0	0	1	0	0
	Bone lesion	1	4	0	1	5	0	0
	Bone pain	71	230	387	1597	1827	0	0
	Bone swelling	1	2	5	24	26	0	0
	Bursa disorder	0	2	3	10	12	0	0
	Bursal fluid accumulation	1	3	0	3	6	0	0
	Bursitis	18	73	54	198	271	0	0
	Camptocormia	0	0	0	1	1	0	0
	Cervical spinal stenosis	1	11	0	0	11	0	0
	Chest wall cyst	0	0	0	1	1	0	0
	Chest wall haematoma	1	2	0	0	2	0	0
	Chest wall mass	0	1	0	3	4	0	0
	Chondritis	1	1	1	2	3	0	0
	Chondrocalcinosis	0	2	0	3	5	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Chondrocalcinosis pyrophosphate	1	5	0	7	12	0	0
	Chondropathy	0	0	0	3	3	0	0
	Chronic kidney disease-mineral and bone disorder	0	1	0	0	1	0	0
	Clubbing	0	1	1	1	2	0	0
	Coccydynia	1	6	7	17	23	0	0
	Collagen disorder	1	3	0	0	3	0	0
	Collagen-vascular disease	0	0	0	1	1	0	0
	Compartment syndrome	1	8	0	0	8	0	0
	Connective tissue disorder	2	8	0	14	22	0	0
	Connective tissue inflammation	0	1	1	2	3	0	0
	Costochondritis	14	36	14	53	89	0	0
	Crystal arthropathy	0	0	1	1	1	0	0
	Dactylitis	1	1	2	4	5	0	0
	Decreased nasolabial fold	0	1	0	3	4	0	0
	Drooping shoulder syndrome	0	1	0	2	3	0	0
	Dupuytren's contracture	1	14	0	0	14	0	0
	Dysponesis	0	0	0	1	1	0	0
	Eagle's syndrome	0	0	0	1	1	0	0
	Elbow deformity	0	0	0	1	1	0	0
	Enthesopathy	2	5	5	7	12	0	0
	Exostosis	3	7	2	8	15	0	0
	Extremity contracture	0	4	4	15	19	0	0
	Facet joint syndrome	1	10	0	2	12	0	0
	Facial asymmetry	5	18	3	24	42	0	0
	Facial myokymia	2	2	1	1	3	0	0
	Fasciitis	4	8	0	1	9	0	0
	Femoroacetabular impingement	0	1	0	0	1	0	0
	Fibromyalgia	37	79	45	195	274	0	0
	Finger deformity	1	3	1	8	11	0	0
	Fistula	0	1	0	1	2	0	0
	Fistula discharge	0	2	0	0	2	0	0
	Flank pain	15	112	56	224	336	0	0
	Fluctuance	0	0	0	1	1	0	0
	Focal myositis	1	1	0	0	1	0	0
	Foot deformity	3	6	9	20	26	0	0
	Fracture pain	0	0	0	2	2	0	0
	Gouty arthritis	0	1	3	5	6	0	0
	Gouty tophus	0	0	0	1	1	0	0
	Greater trochanteric pain syndrome	1	3	0	2	5	0	0
	Groin pain	14	70	58	219	289	0	0
	Growing pains	0	17	0	16	33	0	0
	Growth accelerated	0	0	0	1	1	0	0
	Growth retardation	0	1	0	1	2	0	0
	Haemarthrosis	0	4	2	3	7	0	0
	Haematoma muscle	0	8	6	8	16	0	0
	Hand deformity	1	3	2	14	17	0	0
	Hip deformity	0	1	0	0	1	0	0
	Hypermobility syndrome	0	2	0	2	4	0	0
	Immune-mediated myositis	0	2	0	0	2	0	0
	Inclusion body myositis	1	1	0	0	1	0	0
	Inguinal mass	0	1	0	2	3	0	0
	Intervertebral disc annular tear	0	1	0	0	1	0	0
	Intervertebral disc compression	0	1	0	0	1	0	0
	Intervertebral disc degeneration	1	29	1	17	46	0	0
	Intervertebral disc disorder	1	8	3	10	18	0	0
	Intervertebral disc displacement	0	1	0	0	1	0	0
	Intervertebral disc protrusion	4	31	9	31	62	0	0
	Intervertebral disc space narrowing	0	6	0	3	9	0	0
	Jaw clicking	0	1	2	7	8	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Jaw cyst	0	0	0	1	1	0	0
	Jaw disorder	1	11	4	27	38	0	0
	Joint adhesion	0	0	0	1	1	0	0
	Joint ankylosis	1	3	1	4	7	0	0
	Joint contracture	0	7	3	10	17	0	0
	Joint destruction	0	1	0	0	1	0	0
	Joint effusion	3	23	9	29	52	0	0
	Joint hyperextension	0	0	0	4	4	0	0
	Joint impingement	1	1	0	0	1	0	0
	Joint instability	0	5	2	8	13	0	0
	Joint lock	6	20	7	38	58	0	0
	Joint noise	1	7	5	32	39	0	0
	Joint range of motion decreased	6	94	24	433	527	0	0
	Joint space narrowing	0	4	2	3	7	0	0
	Joint stiffness	30	144	77	470	614	0	0
	Joint swelling	78	297	224	1351	1648	0	0
	Joint vibration	1	2	2	6	8	0	0
	Joint warmth	5	11	4	29	40	0	0
	Juvenile idiopathic arthritis	1	4	0	1	5	0	0
	Knee deformity	0	0	0	5	5	0	0
	Kohler's disease	0	0	1	1	1	0	0
	Kyphoscoliosis	0	1	1	1	2	0	0
	Kyphosis	0	1	0	4	5	0	0
	Ligament disorder	0	0	2	2	2	0	0
	Ligament pain	0	0	4	13	13	0	0
	Ligamentitis	0	2	1	3	5	0	0
	Limb deformity	1	2	0	5	7	0	0
	Limb discomfort	192	663	5358	10529	11192	0	0
	Limb mass	3	15	10	110	125	0	0
	Locomotive syndrome	1	1	0	0	1	0	0
	Loose body in joint	0	0	0	1	1	0	0
	Lordosis	0	1	0	1	2	0	0
	Lumbar spinal stenosis	0	2	0	2	4	0	0
	Lupus-like syndrome	3	14	0	1	15	0	0
	Mandibular mass	0	0	0	1	1	0	0
	Mastication disorder	3	10	6	69	79	0	0
	Masticatory pain	0	1	0	1	2	0	0
	Medial tibial stress syndrome	1	2	2	9	11	0	0
	Metatarsalgia	1	1	0	3	4	0	0
	Mixed connective tissue disease	0	9	0	0	9	0	0
	Mobility decreased	53	615	284	3223	3838	0	0
	Morphoea	1	1	3	4	5	0	0
	Muscle atrophy	7	33	15	49	82	0	0
	Muscle contracture	2	17	9	33	50	0	0
	Muscle discomfort	4	10	38	156	166	0	0
	Muscle disorder	5	19	8	47	66	0	0
	Muscle fatigue	33	120	30	218	338	0	0
	Muscle haemorrhage	1	5	0	0	5	0	0
	Muscle hypertrophy	0	2	0	0	2	0	0
	Muscle hypoxia	0	0	1	1	1	0	0
	Muscle mass	0	1	1	7	8	0	0
	Muscle necrosis	1	1	0	0	1	0	0
	Muscle oedema	0	6	2	4	10	0	0
	Muscle rigidity	22	68	34	151	219	0	0
	Muscle spasms	238	879	624	3287	4166	0	0
	Muscle swelling	4	21	26	133	154	0	0
	Muscle tightness	20	97	108	774	871	0	0
	Muscle twitching	45	193	181	838	1031	0	0
	Muscular weakness	345	1384	582	3205	4589	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Musculoskeletal chest pain	33	163	127	507	670	0	0
	Musculoskeletal discomfort	29	90	154	699	789	0	0
	Musculoskeletal disorder	5	44	20	63	107	0	0
	Musculoskeletal pain	63	228	316	1108	1336	0	0
	Musculoskeletal stiffness	173	750	484	3165	3915	0	0
	Myalgia	2121	6996	21960	71223	78219	0	0
	Myalgia intercostal	1	1	3	6	7	0	0
	Myofascial pain syndrome	0	2	2	4	6	0	0
	Myofascitis	1	1	0	0	1	0	0
	Myokymia	2	2	3	8	10	0	0
	Myopathy	6	14	8	20	34	0	0
	Myosclerosis	5	31	5	11	42	0	0
	Myositis	20	61	33	107	168	0	0
	Neck deformity	1	1	1	1	2	0	0
	Neck mass	5	21	19	114	135	0	0
	Neck pain	200	868	776	4646	5514	0	0
	Necrotising myositis	2	2	0	0	2	0	0
	Neuropathic arthropathy	0	1	0	0	1	0	0
	Neuropathic muscular atrophy	1	4	0	0	4	0	0
	Nodal osteoarthritis	0	0	1	1	1	0	0
	Nose deformity	0	0	0	2	2	0	0
	Nuchal rigidity	2	12	37	83	95	0	0
	Oligoarthritis	3	3	1	2	5	0	0
	Osteitis	2	3	7	20	23	0	0
	Osteitis deformans	0	1	0	0	1	0	0
	Osteoarthritis	12	55	34	105	160	0	0
	Osteochondrosis	2	2	0	0	2	0	0
	Osteolysis	0	2	0	0	2	0	0
	Osteonecrosis	2	2	0	0	2	0	0
	Osteonecrosis of jaw	0	1	0	0	1	0	0
	Osteopenia	0	4	1	3	7	0	0
	Osteoporosis	1	6	2	8	14	0	0
	Osteosclerosis	0	0	0	1	1	0	0
	Pain in extremity	1303	5791	6801	41606	47397	0	0
	Pain in jaw	39	181	127	798	979	0	0
	Palindromic rheumatism	0	2	1	2	4	0	0
	Periarthritis	50	127	55	262	389	0	0
	Periarticular disorder	0	0	0	1	1	0	0
	Periostitis	1	1	1	2	3	0	0
	Peripheral spondyloarthritis	1	1	0	0	1	0	0
	Plantar fascial fibromatosis	0	0	0	2	2	0	0
	Plantar fasciitis	3	6	7	26	32	0	0
	Polyarthritis	26	64	10	14	78	0	0
	Polychondritis	1	6	0	0	6	0	0
	Polymyalgia rheumatica	47	188	25	36	224	0	0
	Polymyositis	0	7	0	2	9	0	0
	Posture abnormal	0	34	2	55	89	0	0
	Pseudarthrosis	0	0	0	1	1	0	0
	Psoriatic arthropathy	20	47	9	12	59	0	0
	Pubic pain	1	1	3	6	7	0	0
	Purple glove syndrome	0	1	0	0	1	0	0
	Resorption bone increased	0	0	0	2	2	0	0
	Reynold's syndrome	0	2	0	1	3	0	0
	Rhabdomyolysis	24	148	2	4	152	0	0
	Rheumatic disorder	15	20	26	46	66	0	0
	Rheumatic fever	2	2	0	0	2	0	0
	Rheumatoid arthritis	87	370	61	104	474	0	0
	Rheumatoid nodule	0	0	0	1	1	0	0
	Rotator cuff syndrome	15	36	24	79	115	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Sacral pain	0	1	7	15	16	0	0
	Sacroiliac joint dysfunction	0	1	1	1	2	0	0
	Sacroiliitis	2	3	4	6	9	0	0
	Sarcopenia	0	0	0	1	1	0	0
	Sclerodactylia	1	1	0	0	1	0	0
	Scleroderma	2	8	0	1	9	0	0
	Scoliosis	1	8	1	2	10	0	0
	Seronegative arthritis	1	5	0	0	5	0	0
	Shoulder deformity	0	1	1	3	4	0	0
	Shoulder girdle pain	0	0	1	1	1	0	0
	Sjogren's syndrome	8	25	4	7	32	0	0
	Soft tissue disorder	1	3	0	2	5	0	0
	Soft tissue haemorrhage	0	0	1	2	2	0	0
	Soft tissue mass	0	1	0	9	10	0	0
	Soft tissue necrosis	0	2	0	0	2	0	0
	Soft tissue swelling	0	8	3	16	24	0	0
	Somatic dysfunction	1	2	2	3	5	0	0
	Spinal deformity	0	5	0	1	6	0	0
	Spinal disorder	0	8	3	7	15	0	0
	Spinal flattening	0	1	0	0	1	0	0
	Spinal fusion acquired	0	0	0	1	1	0	0
	Spinal osteoarthritis	1	32	4	15	47	0	0
	Spinal pain	23	71	71	301	372	0	0
	Spinal retrolisthesis	0	4	0	1	5	0	0
	Spinal segmental dysfunction	0	0	1	1	1	0	0
	Spinal stenosis	1	18	0	7	25	0	0
	Spinal synovial cyst	0	0	1	2	2	0	0
	Spondylitis	4	12	5	24	36	0	0
	Spondyloarthropathy	0	1	1	2	3	0	0
	Spondylolisthesis	0	7	0	1	8	0	0
	Still's disease	5	10	1	2	12	0	0
	Symphysiolysis	1	2	0	0	2	0	0
	Synovial cyst	5	15	11	54	69	0	0
	Synovial disorder	0	0	1	2	2	0	0
	Synovitis	2	9	5	18	27	0	0
	Systemic lupus erythematosus	23	118	2	14	132	0	0
	Systemic scleroderma	1	4	0	0	4	0	0
	Temporomandibular joint syndrome	3	7	3	50	57	0	0
	Tendinous contracture	0	1	0	0	1	0	0
	Tendon calcification	0	0	0	1	1	0	0
	Tendon discomfort	1	2	4	16	18	0	0
	Tendon disorder	4	18	13	27	45	0	0
	Tendon laxity	0	0	0	1	1	0	0
	Tendon pain	11	26	33	86	112	0	0
	Tendon sheath disorder	0	0	6	8	8	0	0
	Tendonitis	16	44	45	151	195	0	0
	Tenosynovitis	7	9	7	12	21	0	0
	Tenosynovitis stenosans	0	0	1	3	3	0	0
	Toe walking	0	0	0	1	1	0	0
	Torticollis	7	18	19	44	62	0	0
	Trigger finger	2	11	6	34	45	0	0
	Trismus	12	34	13	99	133	0	0
	Undifferentiated connective tissue disease	0	1	0	1	2	0	0
	Vertebral end plate impression	0	0	1	1	1	0	0
	Vertebral end plate inflammation	0	0	0	1	1	0	0
	Vertebral foraminal stenosis	0	16	1	3	19	0	0
	Vertebral lesion	0	2	1	3	5	0	0
	Vertebral osteophyte	0	3	0	1	4	0	0
	Vertebral wedging	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Weight bearing difficulty	12	45	76	108	153	0	0
	Winged scapula	2	3	0	0	3	0	0
	Wrist deformity	0	0	0	3	3	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*** SOC TOTAL ***	233	905	61	230	1135	0	0
	Abdominal neoplasm	1	3	0	0	3	0	0
	Acanthoma	0	0	0	2	2	0	0
	Acoustic neuroma	1	3	0	0	3	0	0
	Acrochordon	1	2	1	4	6	0	0
	Acute leukaemia	4	9	0	0	9	0	0
	Acute lymphocytic leukaemia	2	7	0	0	7	0	0
	Acute monocytic leukaemia	0	2	0	0	2	0	0
	Acute myeloid leukaemia	2	22	0	0	22	0	0
	Acute myeloid leukaemia recurrent	0	1	0	0	1	0	0
	Acute myelomonocytic leukaemia	0	1	0	0	1	0	0
	Acute promyelocytic leukaemia	1	3	0	0	3	0	0
	Adenocarcinoma	0	2	0	0	2	0	0
	Adenocarcinoma gastric	0	1	0	0	1	0	0
	Adenocarcinoma metastatic	0	1	0	0	1	0	0
	Adenocarcinoma of colon	1	2	0	0	2	0	0
	Adenocarcinoma of the cervix	0	1	0	0	1	0	0
	Adenocarcinoma pancreas	0	1	0	0	1	0	0
	Adrenal adenoma	0	3	1	1	4	0	0
	Adrenal gland cancer	0	1	0	0	1	0	0
	Adrenal neoplasm	0	0	0	2	2	0	0
	Anal cancer	1	1	0	0	1	0	0
	Angioimmunoblastic T-cell lymphoma	0	1	0	0	1	0	0
	Angioimmunoblastic T-cell lymphoma stage III	0	1	0	0	1	0	0
	Angiolipoma	0	0	0	1	1	0	0
	Angiosarcoma	0	1	0	0	1	0	0
	Anogenital warts	2	3	4	6	9	0	0
	B-cell lymphoma	7	16	0	0	16	0	0
	B-cell lymphoma stage II	0	1	0	0	1	0	0
	B-cell lymphoma stage III	0	1	0	0	1	0	0
	B-cell small lymphocytic lymphoma	0	1	0	0	1	0	0
	B-cell type acute leukaemia	0	1	0	0	1	0	0
	Basal cell carcinoma	2	6	1	1	7	0	0
	Benign biliary neoplasm	0	1	0	0	1	0	0
	Benign breast neoplasm	2	2	0	2	4	0	0
	Benign hepatic neoplasm	0	0	0	1	1	0	0
	Benign hydatidiform mole	0	1	0	0	1	0	0
	Benign lung neoplasm	1	1	0	0	1	0	0
	Benign lymph node neoplasm	0	1	0	3	4	0	0
	Benign neoplasm	0	1	0	0	1	0	0
	Benign neoplasm of cervix uteri	0	1	0	0	1	0	0
	Benign neoplasm of thyroid gland	0	0	0	1	1	0	0
	Benign uterine neoplasm	0	1	0	1	2	0	0
	Bladder cancer	1	8	1	1	9	0	0
	Bladder cancer stage IV	0	1	0	0	1	0	0
	Bladder neoplasm	1	3	0	1	4	0	0
	Bladder transitional cell carcinoma	0	1	0	0	1	0	0
	Blast crisis in myelogenous leukaemia	0	1	0	0	1	0	0
	Bone cancer	2	7	0	0	7	0	0
	Bowen's disease	1	1	0	0	1	0	0
	Brain neoplasm	4	16	0	0	16	0	0
	Brain neoplasm benign	0	1	0	0	1	0	0
	Brain neoplasm malignant	1	1	0	0	1	0	0
	Breast adenoma	0	0	1	2	2	0	0
	Breast cancer	15	36	1	4	40	0	0
	Breast cancer female	6	24	0	1	25	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Breast cancer metastatic	2	5	0	0	5	0	0
	Breast cancer recurrent	1	3	0	0	3	0	0
	Breast neoplasm	1	1	0	0	1	0	0
	Brenner tumour	0	0	0	1	1	0	0
	Bronchial carcinoma	0	2	0	0	2	0	0
	Burkitt's lymphoma	1	2	0	0	2	0	0
	Castleman's disease	1	2	0	0	2	0	0
	Central nervous system lymphoma	1	3	0	0	3	0	0
	Cerebellar tumour	0	2	0	0	2	0	0
	Cerebral haemangioma	0	1	0	0	1	0	0
	Cervix carcinoma	0	3	0	0	3	0	0
	Cervix carcinoma stage 0	1	1	0	0	1	0	0
	Cholangiocarcinoma	0	1	0	0	1	0	0
	Chondroma	0	1	0	0	1	0	0
	Chronic eosinophilic leukaemia	0	1	0	0	1	0	0
	Chronic leukaemia	1	2	0	0	2	0	0
	Chronic lymphocytic leukaemia	3	16	0	0	16	0	0
	Chronic lymphocytic leukaemia recurrent	0	1	0	0	1	0	0
	Chronic myeloid leukaemia	2	6	1	1	7	0	0
	Chronic myeloid leukaemia recurrent	1	1	0	0	1	0	0
	Chronic myelomonocytic leukaemia	0	3	0	1	4	0	0
	Colon cancer	4	11	0	0	11	0	0
	Colon cancer metastatic	0	2	0	0	2	0	0
	Colon cancer stage IV	0	1	0	0	1	0	0
	Colon neoplasm	1	1	0	0	1	0	0
	Colorectal cancer	0	1	0	0	1	0	0
	Cutaneous T-cell lymphoma	2	3	0	0	3	0	0
	Cutaneous lymphoma	1	2	0	0	2	0	0
	Diffuse large B-cell lymphoma	4	8	0	0	8	0	0
	Diffuse large B-cell lymphoma recurrent	1	1	0	0	1	0	0
	Diffuse large B-cell lymphoma stage IV	0	2	0	0	2	0	0
	Endometrial adenocarcinoma	1	2	0	0	2	0	0
	Endometrial cancer	0	5	0	0	5	0	0
	Epstein-Barr virus associated lymphoproliferative disorder	1	1	0	0	1	0	0
	Essential thrombocythaemia	1	4	0	0	4	0	0
	Extradural neoplasm	0	1	0	0	1	0	0
	Extranodal marginal zone B-cell lymphoma (MALT type)	0	1	0	0	1	0	0
	Eye naevus	0	0	1	1	1	0	0
	Eyelid tumour	0	1	0	0	1	0	0
	Fallopian tube cancer	0	1	0	0	1	0	0
	Fibroadenoma of breast	2	2	2	4	6	0	0
	Follicular lymphoma	1	5	0	0	5	0	0
	Gallbladder adenoma	1	1	0	0	1	0	0
	Gastric cancer	0	1	0	0	1	0	0
	Gastric cancer stage I	0	1	0	0	1	0	0
	Gastric cancer stage IV	1	2	0	0	2	0	0
	Germ cell cancer	0	1	0	0	1	0	0
	Glioblastoma	3	8	0	0	8	0	0
	Glioblastoma multiforme	0	2	0	0	2	0	0
	Good syndrome	0	1	0	0	1	0	0
	Haemangioblastoma	0	1	0	0	1	0	0
	Haemangioma	3	4	4	17	21	0	0
	Haemangioma of bone	0	2	0	0	2	0	0
	Haemangioma of liver	1	5	0	1	6	0	0
	Haemangioma of skin	0	0	1	12	12	0	0
	Haematological malignancy	0	3	0	0	3	0	0
	Haematopoietic neoplasm	0	1	0	0	1	0	0
	Hepatic cancer	3	10	0	0	10	0	0
	Hepatic neoplasm	0	4	0	0	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Hepatocellular carcinoma	0	2	0	0	2	0	0
	High grade B-cell lymphoma Burkitt-like lymphoma	1	1	0	0	1	0	0
	Histiocytic necrotising lymphadenitis	1	1	0	0	1	0	0
	Hodgkin's disease	1	4	0	0	4	0	0
	Hodgkin's disease mixed cellularity stage unspecified	1	1	0	0	1	0	0
	Hodgkin's disease nodular sclerosis stage II	0	1	0	0	1	0	0
	Hormone receptor positive HER2 negative breast cancer	0	1	0	0	1	0	0
	Hypergammaglobulinaemia benign monoclonal	2	5	0	1	6	0	0
	Inflammatory carcinoma of the breast	1	1	0	0	1	0	0
	Inflammatory pseudotumour	1	1	0	0	1	0	0
	Intraductal papillary mucinous neoplasm	0	1	0	0	1	0	0
	Intraductal proliferative breast lesion	0	4	0	0	4	0	0
	Invasive breast carcinoma	0	3	0	0	3	0	0
	Invasive ductal breast carcinoma	1	5	0	0	5	0	0
	Kaposi's sarcoma	1	1	0	0	1	0	0
	Keratoacanthoma	2	5	1	1	6	0	0
	Knuckle pads	0	0	0	3	3	0	0
	Large intestine benign neoplasm	0	1	0	0	1	0	0
	Laryngeal neoplasm	0	0	0	1	1	0	0
	Laryngeal papilloma	0	0	0	1	1	0	0
	Leiomyoma	1	1	1	3	4	0	0
	Leiomyosarcoma	1	3	0	0	3	0	0
	Leukaemia	8	25	0	0	25	0	0
	Leukaemia in remission	0	1	0	0	1	0	0
	Leukaemia monocytic	0	2	0	0	2	0	0
	Leukaemia recurrent	0	1	0	0	1	0	0
	Leukaemic infiltration hepatic	0	1	0	0	1	0	0
	Lip and/or oral cavity cancer	0	1	0	0	1	0	0
	Lipoma	1	8	7	26	34	0	0
	Lung adenocarcinoma	0	1	0	0	1	0	0
	Lung adenocarcinoma stage IV	0	1	0	0	1	0	0
	Lung cancer metastatic	0	4	0	0	4	0	0
	Lung carcinoma cell type unspecified recurrent	0	1	0	0	1	0	0
	Lung carcinoma cell type unspecified stage IV	0	2	0	0	2	0	0
	Lung neoplasm	0	1	0	0	1	0	0
	Lung neoplasm malignant	7	27	0	0	27	0	0
	Lymphangioma	0	0	1	1	1	0	0
	Lymphatic system neoplasm	0	1	0	0	1	0	0
	Lymphocytic leukaemia	0	1	0	0	1	0	0
	Lymphoma	5	37	1	6	43	0	0
	Lymphoproliferative disorder	1	4	0	0	4	0	0
	Malignant ascites	0	3	0	0	3	0	0
	Malignant melanoma	1	3	0	0	3	0	0
	Malignant melanoma stage IV	0	1	0	0	1	0	0
	Malignant neoplasm of unknown primary site	0	1	0	0	1	0	0
	Malignant neoplasm progression	3	6	0	0	6	0	0
	Malignant pleural effusion	0	1	0	0	1	0	0
	Mantle cell lymphoma	1	2	0	0	2	0	0
	Marrow hyperplasia	0	1	0	0	1	0	0
	Melanocytic naevus	0	0	5	17	17	0	0
	Meningeal neoplasm	0	1	0	0	1	0	0
	Meningioma	1	8	0	0	8	0	0
	Meningioma benign	0	1	0	0	1	0	0
	Mesothelioma	1	1	0	0	1	0	0
	Metastases to bone	1	3	0	0	3	0	0
	Metastases to central nervous system	2	3	0	0	3	0	0
	Metastases to liver	0	4	0	0	4	0	0
	Metastases to lung	2	6	0	0	6	0	0
	Metastases to lymph nodes	1	8	1	1	9	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Metastases to meninges	0	1	0	0	1	0	0
	Metastases to oesophagus	0	1	0	0	1	0	0
	Metastases to peritoneum	0	4	0	0	4	0	0
	Metastases to reproductive organ	0	1	0	0	1	0	0
	Metastases to spine	0	1	0	0	1	0	0
	Metastases to spleen	0	1	0	0	1	0	0
	Metastases to trachea	0	1	0	0	1	0	0
	Metastasis	1	4	0	0	4	0	0
	Metastatic carcinoid tumour	0	1	0	0	1	0	0
	Metastatic lymphoma	1	3	0	0	3	0	0
	Metastatic neoplasm	1	13	1	1	14	0	0
	Metastatic squamous cell carcinoma	0	1	0	0	1	0	0
	Minimal residual disease	0	0	0	1	1	0	0
	Monoclonal gammopathy	1	3	0	1	4	0	0
	Myelodysplastic syndrome	2	10	0	0	10	0	0
	Myeloid leukaemia	0	5	0	0	5	0	0
	Myeloproliferative neoplasm	0	2	0	0	2	0	0
	Myxofibrosarcoma	0	1	0	1	2	0	0
	Neoplasm	0	11	3	21	32	0	0
	Neoplasm malignant	14	55	1	2	57	0	0
	Neoplasm progression	1	3	0	0	3	0	0
	Neoplasm recurrence	1	1	0	0	1	0	0
	Neoplasm skin	0	1	2	3	4	0	0
	Neuroendocrine carcinoma	0	1	0	0	1	0	0
	Neuroendocrine tumour	2	3	0	0	3	0	0
	Neuroma	0	0	1	2	2	0	0
	Nodular fasciitis	0	1	0	0	1	0	0
	Non-Hodgkin's lymphoma	6	13	0	0	13	0	0
	Non-small cell lung cancer	1	1	0	0	1	0	0
	Non-small cell lung cancer stage IV	0	1	0	0	1	0	0
	Oesophageal adenocarcinoma	0	1	0	0	1	0	0
	Oesophageal carcinoma	0	2	0	0	2	0	0
	Oral neoplasm	1	1	0	0	1	0	0
	Osteochondroma	0	0	0	2	2	0	0
	Osteoma	0	1	1	1	2	0	0
	Ovarian cancer	1	7	0	0	7	0	0
	Ovarian cancer metastatic	0	2	0	0	2	0	0
	Ovarian cancer stage IV	1	1	0	0	1	0	0
	Ovarian germ cell teratoma benign	1	1	0	0	1	0	0
	Ovarian neoplasm	0	1	0	0	1	0	0
	Pancreatic carcinoma	5	15	0	0	15	0	0
	Pancreatic carcinoma metastatic	0	1	0	0	1	0	0
	Pancreatic neoplasm	0	0	0	1	1	0	0
	Papillary thyroid cancer	2	2	0	0	2	0	0
	Papilloma	1	2	0	0	2	0	0
	Paraproteinaemia	0	0	0	1	1	0	0
	Peripheral T-cell lymphoma unspecified	0	1	0	0	1	0	0
	Phaeochromocytoma	0	1	0	0	1	0	0
	Philadelphia positive acute lymphocytic leukaemia	0	1	0	0	1	0	0
	Phyllodes tumour	1	1	0	0	1	0	0
	Pituitary tumour benign	1	3	0	1	4	0	0
	Plasma cell leukaemia	1	1	0	0	1	0	0
	Plasma cell myeloma	6	23	1	1	24	0	0
	Plasma cell myeloma recurrent	1	2	0	0	2	0	0
	Plasmacytoma	1	1	0	0	1	0	0
	Pleomorphic adenoma	0	2	0	0	2	0	0
	Pleomorphic malignant fibrous histiocytoma	1	1	0	0	1	0	0
	Polycythaemia vera	0	6	1	1	7	0	0
	Primary mediastinal large B-cell lymphoma	1	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Prostate cancer	2	10	0	1	11	0	0
	Prostate cancer metastatic	1	2	0	0	2	0	0
	Prostate cancer stage IV	0	1	0	0	1	0	0
	Pyogenic granuloma	0	0	0	1	1	0	0
	Rectal cancer	1	1	0	0	1	0	0
	Rectal cancer metastatic	0	1	0	0	1	0	0
	Renal cancer	2	6	0	0	6	0	0
	Renal cancer metastatic	1	1	0	0	1	0	0
	Renal neoplasm	1	2	0	0	2	0	0
	Retroperitoneal cancer	0	1	0	0	1	0	0
	Richter's syndrome	1	1	0	0	1	0	0
	Sarcoma	0	1	0	0	1	0	0
	Seborrhoeic keratosis	0	1	0	4	S	0	0
	Seminoma	0	1	0	0	1	0	0
	Skin cancer	0	3	0	0	3	0	0
	Skin papilloma	1	8	8	27	3S	0	0
	Small cell carcinoma	0	1	0	0	1	0	0
	Small cell lung cancer metastatic	0	1	0	0	1	0	0
	Small intestine adenocarcinoma	0	1	0	0	1	0	0
	Small intestine carcinoma	1	1	0	0	1	0	0
	Soft tissue sarcoma	1	1	0	0	1	0	0
	Spinal cord lipoma	0	1	0	0	1	0	0
	Splenic marginal zone lymphoma	1	1	0	0	1	0	0
	Squamous cell carcinoma	0	4	0	0	4	0	0
	Squamous cell carcinoma of lung	0	2	0	0	2	0	0
	Squamous cell carcinoma of skin	2	S	0	0	S	0	0
	Systemic mastocytosis	0	0	0	1	1	0	0
	T-cell lymphoma	0	1	0	0	1	0	0
	Testis cancer	1	4	0	0	4	0	0
	Thyroid adenoma	1	1	0	0	1	0	0
	Thyroid cancer	0	7	0	0	7	0	0
	Thyroid cancer metastatic	0	1	0	0	1	0	0
	Thyroid cancer recurrent	1	1	0	0	1	0	0
	Thyroid neoplasm	0	0	1	3	3	0	0
	Tonsil cancer	0	1	0	1	2	0	0
	Tracheal neoplasm	0	1	0	0	1	0	0
	Transitional cell carcinoma	1	S	0	0	S	0	0
	Transitional cell carcinoma metastatic	0	1	0	0	1	0	0
	Triple negative breast cancer	0	1	0	0	1	0	0
	Tubular breast carcinoma	0	1	0	0	1	0	0
	Tumour haemorrhage	0	1	0	0	1	0	0
	Tumour pain	0	1	0	0	1	0	0
	Uterine cancer	1	3	0	0	3	0	0
	Uterine leiomyoma	3	10	S	19	29	0	0
	Vascular neoplasm	0	1	0	0	1	0	0
Nervous system disorders	*** SOC TOTAL ***	14374	68773	S4276	217063	28S836	0	4
	Accessory nerve disorder	0	1	0	1	2	0	0
	Acquired epileptic aphasia	1	2	0	0	2	0	0
	Action tremor	0	3	0	1	4	0	0
	Acute disseminated encephalomyelitis	13	43	0	2	4S	0	0
	Acute motor axonal neuropathy	0	S	0	0	S	0	0
	Acute motor-sensory axonal neuropathy	1	6	0	0	6	0	0
	Acute polyneuropathy	2	11	0	0	11	0	0
	Ageusia	42	262	247	2278	2S40	0	0
	Agitation neonatal	0	1	0	0	1	0	0
	Agnosia	1	2	0	1	3	0	0
	Agraphia	0	1	0	0	1	0	0
	Akathisia	1	4	1	6	10	0	0
	Akinesia	2	11	0	0	11	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Allodynia	6	13	10	38	51	0	0
	Altered state of consciousness	64	272	7	21	293	0	0
	Amnesia	78	303	86	473	776	0	0
	Amnestic disorder	3	12	3	3	15	0	0
	Amputation stump pain	0	0	1	2	2	0	0
	Amyotrophic lateral sclerosis	6	17	0	0	17	0	0
	Anaesthesia	1	8	4	22	30	0	0
	Anosmia	23	176	183	1667	1843	0	0
	Anosognosia	0	1	0	1	2	0	0
	Anterior spinal artery syndrome	0	1	0	0	1	0	0
	Anterograde amnesia	0	4	0	0	4	0	0
	Apallic syndrome	1	8	0	0	8	0	0
	Aphasia	65	473	75	421	894	0	0
	Apraxia	4	16	2	6	22	0	0
	Aqueductal stenosis	1	1	0	0	1	0	0
	Arachnoid cyst	1	5	0	2	7	0	0
	Arachnoid web	0	0	0	1	1	0	0
	Arachnoiditis	0	1	0	1	2	0	0
	Areflexia	2	22	2	7	29	0	0
	Asterixis	2	3	0	0	3	0	0
	Ataxia	14	65	7	46	111	0	0
	Atonic seizures	2	2	2	4	6	0	0
	Auditory nerve disorder	0	0	0	1	1	0	0
	Aura	4	9	4	40	49	0	0
	Autoimmune demyelinating disease	0	3	0	0	3	0	0
	Autoimmune encephalopathy	1	4	0	0	4	0	0
	Autoimmune neuropathy	3	6	0	0	6	0	0
	Autonomic nervous system imbalance	9	24	12	34	58	0	0
	Autonomic neuropathy	1	9	1	2	11	0	0
	Axonal and demyelinating polyneuropathy	0	2	0	0	2	0	0
	Axonal neuropathy	1	3	1	2	5	0	0
	Balance disorder	117	528	296	1510	2038	0	0
	Ballismus	0	0	0	2	2	0	0
	Band sensation	2	6	0	3	9	0	0
	Basal ganglia haemorrhage	0	8	0	0	8	0	0
	Basal ganglia infarction	1	7	0	0	7	0	0
	Basal ganglia stroke	0	16	0	0	16	0	0
	Basilar artery aneurysm	1	2	0	0	2	0	0
	Basilar artery occlusion	2	4	0	0	4	0	0
	Basilar artery stenosis	0	1	0	0	1	0	0
	Basilar artery thrombosis	1	9	0	0	9	0	0
	Basilar migraine	0	0	0	1	1	0	0
	Bell's palsy	119	1655	28	152	1807	0	0
	Benign enlargement of the subarachnoid spaces	0	1	0	0	1	0	0
	Bickerstaff's encephalitis	0	2	0	0	2	0	0
	Blood brain barrier defect	1	2	0	0	2	0	0
	Brachial plexopathy	5	13	3	7	20	0	0
	Bradykinesia	1	12	6	64	76	0	0
	Brain compression	1	2	0	0	2	0	0
	Brain hypoxia	0	6	0	0	6	0	0
	Brain injury	8	41	0	0	41	0	0
	Brain oedema	11	74	0	4	78	0	0
	Brain stem embolism	1	2	0	0	2	0	0
	Brain stem haemorrhage	4	12	0	0	12	0	0
	Brain stem infarction	12	34	0	0	34	0	0
	Brain stem ischaemia	1	1	0	0	1	0	0
	Brain stem microhaemorrhage	1	1	0	0	1	0	0
	Brain stem stroke	2	16	0	0	16	0	0
	Brain stem syndrome	2	9	0	0	9	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Brain stem thrombosis	1	6	0	0	6	0	0
	Brown-Sequard syndrome	0	1	0	0	1	0	0
	Brudzinski's sign	0	0	0	1	1	0	0
	Bulbar palsy	0	3	0	0	3	0	0
	Burning feet syndrome	3	8	0	3	11	0	0
	Burning sensation	99	398	323	2658	3056	0	0
	Burning sensation mucosal	1	1	7	11	12	0	0
	Carotid arteriosclerosis	0	7	1	2	9	0	0
	Carotid artery aneurysm	1	4	0	0	4	0	0
	Carotid artery disease	1	6	0	0	6	0	0
	Carotid artery dissection	4	15	0	0	15	0	0
	Carotid artery occlusion	3	28	1	1	29	0	0
	Carotid artery stenosis	1	25	0	0	25	0	0
	Carotid artery thrombosis	3	17	0	0	17	0	0
	Carpal tunnel syndrome	5	18	9	42	60	0	0
	Cataplexy	0	8	0	0	8	0	0
	Cauda equina syndrome	0	5	0	0	5	0	0
	Central auditory processing disorder	1	1	0	0	1	0	0
	Central nervous system haemorrhage	0	1	0	0	1	0	0
	Central nervous system inflammation	0	6	0	0	6	0	0
	Central nervous system lesion	3	33	2	10	43	0	0
	Central nervous system vasculitis	0	5	0	0	5	0	0
	Central pain syndrome	0	3	4	9	12	0	0
	Cerebellar artery occlusion	0	1	0	0	1	0	0
	Cerebellar artery thrombosis	1	4	0	0	4	0	0
	Cerebellar ataxia	0	1	1	1	2	0	0
	Cerebellar atrophy	0	1	0	1	2	0	0
	Cerebellar haematoma	0	2	0	0	2	0	0
	Cerebellar haemorrhage	7	12	0	0	12	0	0
	Cerebellar infarction	11	32	2	2	34	0	0
	Cerebellar ischaemia	1	1	0	0	1	0	0
	Cerebellar stroke	3	40	0	1	41	0	0
	Cerebellar syndrome	1	2	0	0	2	0	0
	Cerebral amyloid angiopathy	1	3	0	0	3	0	0
	Cerebral aneurysm perforation	0	1	0	0	1	0	0
	Cerebral arteriosclerosis	1	4	0	0	4	0	0
	Cerebral artery embolism	1	10	0	0	10	0	0
	Cerebral artery occlusion	5	33	0	0	33	0	0
	Cerebral artery perforation	0	1	0	0	1	0	0
	Cerebral artery stenosis	0	14	0	0	14	0	0
	Cerebral artery thrombosis	2	9	0	0	9	0	0
	Cerebral ataxia	0	1	0	0	1	0	0
	Cerebral atrophy	1	29	0	0	29	0	0
	Cerebral calcification	0	2	0	3	5	0	0
	Cerebral congestion	1	3	0	6	9	0	0
	Cerebral cyst	0	2	0	3	5	0	0
	Cerebral disorder	3	15	3	29	44	0	0
	Cerebral haematoma	6	18	0	1	19	0	0
	Cerebral haemorrhage	90	341	1	2	343	0	0
	Cerebral haemorrhage foetal	1	2	0	0	2	0	0
	Cerebral haemorrhage neonatal	0	1	0	0	1	0	0
	Cerebral hypoperfusion	0	3	0	0	3	0	0
	Cerebral infarction	95	312	0	2	314	0	0
	Cerebral ischaemia	16	57	0	0	57	0	0
	Cerebral mass effect	0	18	0	0	18	0	0
	Cerebral microangiopathy	0	4	0	0	4	0	0
	Cerebral microembolism	0	1	0	0	1	0	0
	Cerebral microhaemorrhage	0	3	0	1	4	0	0
	Cerebral microinfarction	2	3	0	0	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Cerebral reperfusion injury	0	1	0	0	1	0	0
	Cerebral small vessel ischaemic disease	0	50	0	2	52	0	0
	Cerebral thrombosis	18	125	0	0	125	0	0
	Cerebral vascular occlusion	0	4	0	0	4	0	0
	Cerebral vasoconstriction	1	3	0	0	3	0	0
	Cerebral venous sinus thrombosis	44	157	2	3	160	0	0
	Cerebral venous thrombosis	16	53	0	0	53	0	0
	Cerebral ventricle dilatation	2	4	0	0	4	0	0
	Cerebral ventricular rupture	0	1	0	0	1	0	0
	Cerebrosclerosis	0	1	0	0	1	0	0
	Cerebrospinal fluid circulation disorder	0	1	0	0	1	0	0
	Cerebrospinal fluid leakage	0	2	0	0	2	0	0
	Cerebrovascular accident	311	1872	1	17	1889	0	0
	Cerebrovascular disorder	6	14	1	1	15	0	0
	Cerebrovascular insufficiency	1	1	0	0	1	0	0
	Cerebrovascular stenosis	0	1	0	0	1	0	0
	Cervical radiculopathy	3	8	10	17	25	0	0
	Cervicobrachial syndrome	7	11	11	18	29	0	0
	Cervicogenic headache	0	0	0	2	2	0	0
	Cervicogenic vertigo	0	0	1	1	1	0	0
	Change in seizure presentation	0	1	0	0	1	0	0
	Chorea	1	3	0	2	5	0	0
	Choreoathetosis	0	3	0	0	3	0	0
	Chronic inflammatory demyelinating polyradiculoneuropathy	22	44	2	4	48	0	0
	Circadian rhythm sleep disorder	0	0	2	7	7	0	0
	Claude's syndrome	1	1	0	0	1	0	0
	Clinically isolated syndrome	1	1	1	1	2	0	0
	Clonic convulsion	2	13	0	0	13	0	0
	Clonus	6	10	3	10	20	0	0
	Clumsiness	2	15	6	24	39	0	0
	Cluster headache	17	71	13	70	141	0	0
	Cognitive disorder	40	174	45	245	419	0	0
	Cognitive linguistic deficit	0	1	0	0	1	0	0
	Cogwheel rigidity	0	1	0	1	2	0	0
	Cold dysaesthesia	0	1	0	0	1	0	0
	Cold-stimulus headache	1	12	3	15	27	0	0
	Colloid brain cyst	0	2	0	0	2	0	0
	Coma	14	76	2	4	80	0	0
	Coma hepatic	1	1	0	0	1	0	0
	Complex regional pain syndrome	3	16	8	19	35	0	0
	Consciousness fluctuating	5	41	0	2	43	0	0
	Conus medullaris syndrome	0	2	0	0	2	0	0
	Convulsions local	1	3	0	0	3	0	0
	Coordination abnormal	13	76	22	129	205	0	0
	Cortical laminar necrosis	0	1	0	0	1	0	0
	Cramp-fasciculation syndrome	1	2	0	1	3	0	0
	Cranial nerve disorder	2	16	1	14	30	0	0
	Cranial nerve palsies multiple	1	4	0	0	4	0	0
	Cranial nerve paralysis	2	6	0	0	6	0	0
	Cubital tunnel syndrome	2	2	2	6	8	0	0
	Cytotoxic oedema	0	1	0	0	1	0	0
	Decerebrate posture	0	2	0	0	2	0	0
	Decreased vibratory sense	0	2	1	1	3	0	0
	Delayed sleep phase	0	1	0	1	2	0	0
	Dementia	22	114	2	10	124	0	0
	Dementia Alzheimer's type	6	23	1	2	25	0	0
	Dementia with Lewy bodies	0	0	1	1	1	0	0
	Demyelinating polyneuropathy	2	22	0	0	22	0	0
	Demyelination	8	41	0	1	42	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Depressed level of consciousness	62	363	24	44	407	0	0
	Diabetic coma	0	4	0	0	4	0	0
	Diabetic hyperosmolar coma	0	1	0	0	1	0	0
	Diabetic neuropathy	0	2	2	2	4	0	0
	Diplegia	21	78	6	12	90	0	0
	Disturbance in attention	139	380	526	1525	1905	0	0
	Dizziness	1508	6248	8099	34896	41144	0	1
	Dizziness exertional	11	26	16	34	60	0	0
	Dizziness postural	51	239	76	363	602	0	0
	Dreamy state	0	1	0	8	9	0	0
	Drooling	4	26	3	64	90	0	0
	Drop attacks	2	8	0	1	9	0	0
	Drug withdrawal headache	0	2	0	1	3	0	0
	Dural arteriovenous fistula	1	1	0	0	1	0	0
	Dysaesthesia	38	78	58	216	294	0	0
	Dysarthria	75	432	39	365	797	0	0
	Dyscalculia	0	0	0	2	2	0	0
	Dysdiadochokinesis	0	1	0	0	1	0	0
	Dysgeusia	46	225	281	1981	2206	0	0
	Dysgraphia	3	26	3	19	45	0	0
	Dyskinesia	19	121	28	358	479	0	0
	Dyslalia	1	4	0	2	6	0	0
	Dyslexia	0	2	0	5	7	0	0
	Dysmetria	3	6	0	1	7	0	0
	Dyspraxia	0	1	1	4	5	0	0
	Dysstasia	36	281	88	811	1092	0	0
	Dystonia	4	28	1	3	31	0	0
	Dystonic tremor	0	1	0	0	1	0	0
	Electric shock sensation	15	65	26	171	236	0	0
	Embolic cerebellar infarction	1	2	0	0	2	0	0
	Embolic cerebral infarction	2	13	0	0	13	0	0
	Embolic stroke	6	37	0	0	37	0	0
	Encephalitis allergic	1	3	0	0	3	0	0
	Encephalitis autoimmune	10	19	0	0	19	0	0
	Encephalitis post immunisation	2	3	0	0	3	0	0
	Encephalomalacia	0	5	0	1	6	0	0
	Encephalopathy	10	162	0	1	163	0	0
	Epilepsy	122	350	25	38	388	0	1
	Epileptic aura	1	1	1	2	3	0	0
	Essential tremor	0	8	0	6	14	0	0
	Exaggerated startle response	0	1	2	3	4	0	0
	Exertional headache	1	3	0	5	8	0	0
	Extensor plantar response	1	4	1	2	6	0	0
	External compression headache	0	0	0	2	2	0	0
	Extrapyramidal disorder	2	4	0	4	8	0	0
	Facial nerve disorder	4	9	0	10	19	0	0
	Facial paralysis	285	1562	69	162	1724	0	0
	Facial paresis	69	214	62	205	419	0	0
	Facial spasm	5	17	8	38	55	0	0
	Febrile convulsion	9	27	20	40	67	0	0
	Femoral nerve palsy	0	1	0	0	1	0	0
	Fine motor delay	0	1	0	0	1	0	0
	Fine motor skill dysfunction	3	32	6	31	63	0	0
	Focal dyscognitive seizures	3	9	0	0	9	0	0
	Foetal cerebrovascular disorder	0	1	0	0	1	0	0
	Foetal movement disorder	0	2	1	3	5	0	0
	Fontanelle bulging	1	1	0	0	1	0	0
	Formication	7	38	70	221	259	0	0
	Freezing phenomenon	2	13	1	36	49	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Fumbling	1	2	2	3	5	0	0
	Gait spastic	0	0	0	3	3	0	0
	Generalised onset non-motor seizure	0	1	0	0	1	0	0
	Generalised tonic-clonic seizure	26	223	1	12	235	0	0
	Geniculate ganglionitis	1	1	0	0	1	0	0
	Glial scar	0	0	1	1	1	0	0
	Gliosis	1	1	0	0	1	0	0
	Glossopharyngeal nerve disorder	0	1	0	0	1	0	0
	Glossopharyngeal neuralgia	1	2	0	3	5	0	0
	Grimacing	0	2	0	1	3	0	0
	Gross motor delay	0	2	0	0	2	0	0
	Guillain-Barre syndrome	141	529	3	7	536	0	0
	Gulf war syndrome	0	0	0	1	1	0	0
	Haemorrhage intracranial	7	36	0	1	37	0	0
	Haemorrhagic cerebral infarction	2	5	0	0	5	0	0
	Haemorrhagic stroke	14	74	0	0	74	0	0
	Haemorrhagic transformation stroke	0	12	0	0	12	0	0
	Hand-eye coordination impaired	0	2	1	1	3	0	0
	Hashimoto's encephalopathy	0	2	0	0	2	0	0
	Head discomfort	54	201	244	1352	1553	0	0
	Head titubation	0	8	1	27	35	0	0
	Headache	3827	14145	32205	111255	125400	0	2
	Hemianaesthesia	1	10	3	7	17	0	0
	Hemianopia	6	16	0	0	16	0	0
	Hemianopia homonymous	1	8	0	1	9	0	0
	Hemiasomatognosia	0	1	0	0	1	0	0
	Hemiataxia	1	2	1	1	3	0	0
	Hemidysaesthesia	1	6	1	1	7	0	0
	Hemihyperaesthesia	0	0	2	2	2	0	0
	Hemihypoaesthesia	14	39	7	7	46	0	0
	Hemiparaesthesia	17	61	9	18	79	0	0
	Hemiparesis	74	481	15	24	505	0	0
	Hemiplegia	29	202	4	9	211	0	0
	Hemiplegic migraine	7	16	1	8	24	0	0
	Hepatic encephalopathy	1	10	0	0	10	0	0
	Hoffmann's sign	0	1	0	1	2	0	0
	Horner's syndrome	2	8	0	1	9	0	0
	Hydrocephalus	3	17	0	0	17	0	0
	Hyperaesthesia	23	86	143	432	518	0	0
	Hyperammonaemic encephalopathy	0	1	0	0	1	0	0
	Hypergeusia	1	1	1	1	2	0	0
	Hyperglycaemic unconsciousness	1	1	0	0	1	0	0
	Hyperintensity in brain deep nuclei	0	4	0	0	4	0	0
	Hyperkinesia	1	2	0	0	2	0	0
	Hyperpathia	0	0	0	3	3	0	0
	Hyperreflexia	1	7	2	5	12	0	0
	Hyperresponsive to stimuli	1	1	0	0	1	0	0
	Hypersomnia	29	139	118	1278	1417	0	0
	Hypertensive cerebrovascular disease	1	1	0	0	1	0	0
	Hypertensive encephalopathy	0	2	0	0	2	0	0
	Hypertonia	4	12	2	17	29	0	0
	Hypoaesthesia	487	2238	1442	8455	10693	0	0
	Hypogeusia	2	17	31	89	106	0	0
	Hypoglossal nerve disorder	0	1	0	0	1	0	0
	Hypoglossal nerve paralysis	1	2	0	0	2	0	0
	Hypoglycaemic coma	1	2	0	0	2	0	0
	Hypoglycaemic seizure	0	1	0	0	1	0	0
	Hypoglycaemic unconsciousness	0	1	0	0	1	0	0
	Hypokinesia	24	93	117	630	723	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Hyporeflexia	3	19	4	12	31	0	0
	Hyporesponsive to stimuli	2	30	3	11	41	0	0
	Hyposmia	5	15	20	69	84	0	0
	Hypotonia	17	72	176	346	418	0	0
	Hypotonic-hyporesponsive episode	9	14	3	4	18	0	0
	Hypoxic-ischaemic encephalopathy	5	18	0	0	18	0	0
	IIIrd nerve disorder	2	2	0	0	2	0	0
	IIIrd nerve paralysis	5	28	0	0	28	0	0
	IIIrd nerve paresis	0	4	0	0	4	0	0
	IVth nerve paralysis	1	9	0	0	9	0	0
	IVth nerve paresis	2	4	0	0	4	0	0
	Idiopathic intracranial hypertension	4	13	0	0	13	0	0
	Immune-mediated encephalitis	0	1	0	0	1	0	0
	Immune-mediated neurological disorder	0	2	0	0	2	0	0
	Immune-mediated neuropathy	0	3	0	0	3	0	0
	Inability to crawl	0	1	0	3	4	0	0
	Incoherent	3	40	3	90	130	0	0
	Infant irritability	0	2	0	1	3	0	0
	Intellectual disability	1	6	0	0	6	0	0
	Intensive care unit acquired weakness	1	1	0	0	1	0	0
	Intention tremor	2	6	0	4	10	0	0
	Intercostal neuralgia	2	4	5	6	10	0	0
	Internal capsule infarction	0	3	0	0	3	0	0
	Internal carotid artery deformity	0	0	1	1	1	0	0
	Intracranial aneurysm	5	38	0	0	38	0	0
	Intracranial artery dissection	3	3	0	0	3	0	0
	Intracranial haematoma	0	3	0	0	3	0	0
	Intracranial hypotension	0	3	0	0	3	0	0
	Intracranial mass	0	5	0	1	6	0	0
	Intracranial pressure increased	6	32	1	1	33	0	0
	Intraventricular haemorrhage	5	22	0	0	22	0	0
	Intraventricular haemorrhage neonatal	0	1	0	0	1	0	0
	Irregular sleep phase	0	1	0	3	4	0	0
	Irregular sleep wake rhythm disorder	1	1	0	2	3	0	0
	Ischaemic cerebral infarction	23	51	0	0	51	0	0
	Ischaemic stroke	106	422	1	2	424	0	0
	Judgement impaired	0	1	1	3	4	0	0
	Juvenile myoclonic epilepsy	0	2	0	0	2	0	0
	Lacunar infarction	4	33	0	0	33	0	0
	Lacunar stroke	4	19	1	1	20	0	0
	Language disorder	23	45	28	49	94	0	0
	Laryngeal tremor	0	2	0	0	2	0	0
	Lateral medullary syndrome	0	2	0	0	2	0	0
	Lateropulsion	0	0	1	1	1	0	0
	Lethargy	125	752	140	2228	2980	0	0
	Leukoencephalopathy	0	2	0	0	2	0	0
	Lewis-Sumner syndrome	1	1	0	0	1	0	0
	Lhermitte's sign	0	2	2	5	7	0	0
	Limbic encephalitis	2	8	0	0	8	0	0
	Long thoracic nerve palsy	2	3	1	1	4	0	0
	Loss of consciousness	442	4365	197	625	4990	0	0
	Loss of proprioception	0	3	1	3	6	0	0
	Lumbar radiculopathy	2	4	1	3	7	0	0
	Lumbosacral plexopathy	0	1	0	0	1	0	0
	Lumbosacral radiculopathy	2	2	0	2	4	0	0
	Lumbosacral radiculoplexus neuropathy	0	0	1	1	1	0	0
	Medication overuse headache	0	0	3	4	4	0	0
	Memory impairment	75	316	217	787	1103	0	0
	Meningeal disorder	0	2	1	3	5	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Meningism	4	14	1	10	24	0	0
	Meningitis noninfective	0	1	0	0	1	0	0
	Meningoradiculitis	0	3	0	0	3	0	0
	Meningorrhagia	0	1	0	0	1	0	0
	Mental impairment	21	250	13	34	284	0	0
	Meralgia paraesthetica	0	0	2	5	5	0	0
	Metabolic encephalopathy	0	44	0	0	44	0	0
	Micrographia	1	1	0	0	1	0	0
	Microsleep	0	0	1	1	1	0	0
	Microvascular cranial nerve palsy	0	3	0	0	3	0	0
	Migraine	307	1245	763	3700	4945	0	0
	Migraine with aura	19	68	45	129	197	0	0
	Migraine without aura	1	4	1	4	8	0	0
	Migraine-triggered seizure	0	1	0	0	1	0	0
	Miller Fisher syndrome	5	21	0	0	21	0	0
	Mononeuritis	2	3	1	4	7	0	0
	Mononeuropathy	3	6	0	1	7	0	0
	Mononeuropathy multiplex	1	2	0	1	3	0	0
	Monoparesis	23	57	11	43	100	0	0
	Monoplegia	59	235	20	38	273	0	0
	Morton's neuralgia	0	0	1	3	3	0	0
	Motor dysfunction	15	71	25	105	176	0	0
	Motor neurone disease	2	8	0	0	8	0	0
	Movement disorder	35	171	152	640	811	0	0
	Multifocal motor neuropathy	1	3	0	0	3	0	0
	Multiple sclerosis	49	161	16	22	183	0	0
	Multiple sclerosis pseudo relapse	1	3	1	3	6	0	0
	Multiple sclerosis relapse	38	110	14	14	124	0	0
	Muscle contractions involuntary	19	49	51	159	208	0	0
	Muscle spasticity	3	20	8	34	54	0	0
	Muscle tension dysphonia	0	0	0	1	1	0	0
	Muscle tone disorder	0	0	4	5	5	0	0
	Myasthenia gravis	34	118	0	4	122	0	0
	Myasthenia gravis crisis	4	9	0	1	10	0	0
	Myasthenic syndrome	0	1	0	0	1	0	0
	Myelin oligodendrocyte glycoprotein antibody-associated disease	6	7	0	0	7	0	0
	Myelitis transverse	17	111	2	3	114	0	0
	Myelomalacia	0	2	0	1	3	0	0
	Myelopathy	7	14	0	0	14	0	0
	Myoclonic epilepsy	0	7	0	1	8	0	0
	Myoclonus	8	36	15	53	89	0	0
	Myotonia	0	1	0	1	2	0	0
	Myxoedema coma	0	1	0	0	1	0	0
	Narcolepsy	6	25	1	1	26	0	0
	Nerve compression	5	22	7	57	79	0	0
	Nerve degeneration	0	2	0	0	2	0	0
	Nervous system disorder	44	118	35	114	232	0	0
	Neuralgia	155	424	318	1105	1529	0	0
	Neuralgic amyotrophy	45	105	12	44	149	0	0
	Neuritis	14	25	32	66	91	0	0
	Neuritis cranial	2	2	1	1	3	0	0
	Neurodegenerative disorder	0	1	0	0	1	0	0
	Neuroleptic malignant syndrome	3	4	0	0	4	0	0
	Neurologic neglect syndrome	0	7	1	2	9	0	0
	Neurological decompensation	0	9	0	1	10	0	0
	Neurological symptom	13	180	13	108	288	0	0
	Neuromuscular blockade	0	0	0	1	1	0	0
	Neuromuscular pain	1	1	5	7	8	0	0
	Neuromyelitis optica spectrum disorder	3	15	0	0	15	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Neuromyopathy	0	6	0	1	7	0	0
	Neuropathy peripheral	78	533	39	86	619	0	0
	Neurotoxicity	0	1	0	0	1	0	0
	New daily persistent headache	10	18	2	18	36	0	0
	Non-24-hour sleep-wake disorder	2	4	1	2	6	0	0
	Noninfectious myelitis	1	3	0	0	3	0	0
	Noninfective encephalitis	4	15	0	1	16	0	0
	Normal pressure hydrocephalus	0	0	0	1	1	0	0
	Numb chin syndrome	0	7	0	0	7	0	0
	Nystagmus	3	32	9	44	76	0	0
	Occipital neuralgia	5	12	4	21	33	0	0
	Oculofacial paralysis	1	1	0	0	1	0	0
	Olfactory nerve disorder	0	3	0	7	10	0	0
	On and off phenomenon	0	0	2	7	7	0	0
	Ophthalmic migraine	2	13	13	48	61	0	0
	Ophthalmoplegic migraine	0	0	1	1	1	0	0
	Opisthotonus	0	1	1	3	4	0	0
	Optic neuritis	31	111	1	2	113	0	0
	Optic perineuritis	2	3	0	0	3	0	0
	Oromandibular dystonia	0	0	0	1	1	0	0
	Orthostatic intolerance	2	8	1	13	21	0	0
	Osmotic demyelination syndrome	0	2	0	0	2	0	0
	Pachymeningitis	0	1	0	0	1	0	0
	Paraesthesia	769	2546	3016	11855	14401	0	0
	Paraesthesia mucosal	0	0	5	8	8	0	0
	Paralysis	78	418	23	52	470	0	0
	Paralysis recurrent laryngeal nerve	1	4	0	0	4	0	0
	Paraparesis	14	23	1	3	26	0	0
	Paraplegia	6	20	0	0	20	0	0
	Paresis	13	35	18	40	75	0	0
	Paresis cranial nerve	1	1	0	0	1	0	0
	Parkinson's disease	9	43	2	5	48	0	0
	Parkinsonian gait	0	2	0	0	2	0	0
	Parkinsonian rest tremor	0	0	0	2	2	0	0
	Parkinsonism	4	6	2	5	11	0	0
	Parosmia	17	84	103	541	625	0	0
	Paroxysmal sympathetic hyperactivity	0	1	0	0	1	0	0
	Partial seizures	15	61	2	4	65	0	0
	Partial seizures with secondary generalisation	0	1	0	0	1	0	0
	Patient elopement	0	2	0	1	3	0	0
	Periodic limb movement disorder	0	1	1	2	3	0	0
	Peripheral motor neuropathy	1	6	1	2	8	0	0
	Peripheral nerve lesion	3	7	2	5	12	0	0
	Peripheral nerve palsy	0	2	0	1	3	0	0
	Peripheral nerve paresis	0	2	1	1	3	0	0
	Peripheral paralysis	5	15	0	0	15	0	0
	Peripheral sensorimotor neuropathy	3	7	0	0	7	0	0
	Peripheral sensory neuropathy	7	16	3	10	26	0	0
	Peroneal nerve palsy	2	23	4	16	39	0	0
	Persistent genital arousal disorder	0	1	0	0	1	0	0
	Persistent postural-perceptual dizziness	2	6	1	1	7	0	0
	Petit mal epilepsy	8	32	0	1	33	0	0
	Phantom limb syndrome	0	1	5	23	24	0	0
	Phrenic nerve paralysis	1	1	0	0	1	0	0
	Piriformis syndrome	0	1	0	2	3	0	0
	Pleocytosis	1	8	0	2	10	0	0
	Polyneuropathy	58	103	8	14	117	0	0
	Polyneuropathy chronic	0	1	0	1	2	0	0
	Polyneuropathy idiopathic progressive	1	2	0	0	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Post cardiac arrest syndrome	0	1	0	0	1	0	0
	Post herpetic neuralgia	5	21	15	41	62	0	0
	Post polio syndrome	0	1	0	0	1	0	0
	Post-traumatic headache	0	0	0	2	2	0	0
	Posterior interosseous syndrome	1	1	0	0	1	0	0
	Posterior reversible encephalopathy syndrome	3	15	0	0	15	0	0
	Postictal paralysis	0	4	0	0	4	0	0
	Postictal state	1	14	0	14	28	0	0
	Postural tremor	0	2	0	0	2	0	0
	Preictal state	0	0	0	1	1	0	0
	Presyncope	93	569	450	2974	3543	0	0
	Primary cough headache	0	0	0	2	2	0	0
	Primary headache associated with sexual activity	0	1	1	3	4	0	0
	Progressive multiple sclerosis	1	1	0	0	1	0	0
	Progressive supranuclear palsy	0	1	0	0	1	0	0
	Prosopagnosia	0	1	0	2	3	0	0
	Pseudoparalysis	0	0	0	1	1	0	0
	Pseudostroke	0	1	0	0	1	0	0
	Psychogenic seizure	0	2	0	4	6	0	0
	Psychomotor hyperactivity	6	11	4	48	59	0	0
	Psychomotor skills impaired	1	5	0	5	10	0	0
	Pudendal canal syndrome	0	2	0	1	3	0	0
	Putamen haemorrhage	2	5	0	0	5	0	0
	Pyramidal tract syndrome	1	4	0	0	4	0	0
	Quadrantanopia	0	1	0	0	1	0	0
	Quadriparesis	6	15	0	0	15	0	0
	Quadriplegia	4	10	0	0	10	0	0
	Radial nerve compression	0	0	0	1	1	0	0
	Radial nerve palsy	1	7	1	3	10	0	0
	Radicular pain	1	4	0	5	9	0	0
	Radiculitis brachial	4	14	1	15	29	0	0
	Radiculopathy	7	25	1	14	39	0	0
	Radiologically isolated syndrome	0	1	1	1	2	0	0
	Reduced facial expression	2	4	1	14	18	0	0
	Reflexes abnormal	1	4	0	3	7	0	0
	Relapsing multiple sclerosis	2	4	0	1	5	0	0
	Relapsing-remitting multiple sclerosis	3	9	0	0	9	0	0
	Repetitive speech	0	5	0	6	11	0	0
	Resting tremor	1	6	0	5	11	0	0
	Restless arm syndrome	0	1	2	7	8	0	0
	Restless legs syndrome	15	58	46	152	210	0	0
	Retinal migraine	2	7	1	15	22	0	0
	Retrograde amnesia	6	8	0	2	10	0	0
	Reversed hot-cold sensation	0	0	1	7	7	0	0
	Reversible cerebral vasoconstriction syndrome	3	11	0	0	11	0	0
	Reversible ischaemic neurological deficit	0	1	0	0	1	0	0
	Right hemisphere deficit syndrome	0	4	0	0	4	0	0
	Ruptured cerebral aneurysm	3	15	0	0	15	0	0
	Sciatic nerve neuropathy	1	3	0	0	3	0	0
	Sciatic nerve palsy	0	0	0	1	1	0	0
	Sciatica	23	58	40	176	234	0	0
	Secondary progressive multiple sclerosis	0	1	0	0	1	0	0
	Sedation	3	8	9	50	58	0	0
	Seizure	254	2175	47	200	2375	0	0
	Seizure anoxic	1	3	0	0	3	0	0
	Seizure cluster	3	11	0	0	11	0	0
	Seizure like phenomena	1	111	0	10	121	0	0
	Senile dementia	0	2	0	0	2	0	0
	Sensorimotor disorder	3	17	0	6	23	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Sensory disturbance	45	139	112	395	534	0	0
	Sensory integrative dysfunction	0	1	0	1	2	0	0
	Sensory loss	22	111	33	178	289	0	0
	Sensory overload	0	3	1	6	9	0	0
	Sensory processing disorder	0	2	0	1	3	0	0
	Serotonin syndrome	0	4	0	0	4	0	0
	Simple partial seizures	0	3	1	1	4	0	0
	Sinus headache	22	92	9	143	235	0	0
	Sleep deficit	1	20	11	69	89	0	0
	Sleep paralysis	2	9	2	23	32	0	0
	Slow response to stimuli	1	19	2	28	47	0	0
	Slow speech	0	30	1	35	65	0	0
	Small fibre neuropathy	6	23	4	14	37	0	0
	Somnolence	161	660	857	4416	5076	0	0
	Somnolence neonatal	0	0	0	1	1	0	0
	Spasmodic dysphonia	0	0	1	1	1	0	0
	Speech disorder	49	335	59	424	759	0	0
	Speech disorder developmental	0	3	0	6	9	0	0
	Spinal artery embolism	0	1	0	0	1	0	0
	Spinal cord compression	0	6	0	1	7	0	0
	Spinal cord disorder	2	11	0	1	12	0	0
	Spinal cord haemorrhage	0	2	0	0	2	0	0
	Spinal cord infarction	0	7	0	0	7	0	0
	Spinal cord ischaemia	3	6	0	0	6	0	0
	Spinal cord oedema	0	1	0	0	1	0	0
	Spinal epidural haematoma	0	0	0	1	1	0	0
	Spinal stroke	0	3	0	0	3	0	0
	Spinal subarachnoid haemorrhage	0	1	0	0	1	0	0
	Spinal subdural haematoma	0	1	0	0	1	0	0
	Spinal vascular disorder	0	1	0	0	1	0	0
	Spontaneous cerebrospinal fluid leak syndrome	0	1	0	0	1	0	0
	Status epilepticus	19	81	0	4	85	0	0
	Status migrainosus	3	8	0	3	11	0	0
	Stiff leg syndrome	0	3	0	0	3	0	0
	Stiff person syndrome	0	2	0	0	2	0	0
	Stroke in evolution	0	3	0	0	3	0	0
	Stupor	2	10	4	19	29	0	0
	Subacute combined cord degeneration	0	1	0	0	1	0	0
	Subacute inflammatory demyelinating polyneuropathy	0	1	0	1	2	0	0
	Subarachnoid haemorrhage	24	116	1	1	117	0	0
	Subdural effusion	0	1	0	0	1	0	0
	Subdural hygroma	0	1	0	0	1	0	0
	Sudden onset of sleep	9	16	5	7	23	0	0
	Superior sagittal sinus thrombosis	3	19	0	0	19	0	0
	Sympathicotonia	0	0	1	3	3	0	0
	Sympathomimetic effect	0	0	0	1	1	0	0
	Synaesthesia	0	1	0	0	1	0	0
	Syncope	912	6476	503	1291	7767	0	0
	Tardive dyskinesia	1	6	0	0	6	0	0
	Taste disorder	29	129	178	1053	1182	0	0
	Temporal lobe epilepsy	1	1	0	0	1	0	0
	Tension headache	34	172	45	230	402	0	0
	Thalamic infarction	5	25	0	0	25	0	0
	Thalamus haemorrhage	2	7	0	0	7	0	0
	Thecal sac compression	0	1	0	0	1	0	0
	Thermoanaesthesia	1	1	0	0	1	0	0
	Thermohyperaesthesia	0	0	1	1	1	0	0
	Thoracic outlet syndrome	0	0	0	2	2	0	0
	Thoracic radiculopathy	0	0	2	2	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Thrombotic cerebral infarction	3	7	0	0	7	0	0
	Thrombotic stroke	3	14	0	0	14	0	0
	Thunderclap headache	2	7	1	6	13	0	0
	Tinel's sign	0	0	0	1	1	0	0
	Tongue biting	3	18	0	28	46	0	0
	Tongue paralysis	5	29	1	5	34	0	0
	Tonic clonic movements	1	25	1	5	30	0	0
	Tonic convulsion	7	27	1	1	28	0	0
	Tonic posturing	0	3	0	0	3	0	0
	Toxic encephalopathy	0	18	0	0	18	0	0
	Transient aphasia	1	4	0	1	5	0	0
	Transient global amnesia	4	37	2	13	50	0	0
	Transient ischaemic attack	96	484	13	26	510	0	0
	Transverse sinus stenosis	1	2	0	0	2	0	0
	Transverse sinus thrombosis	3	24	0	1	25	0	0
	Tremor	313	1438	690	5213	6651	0	0
	Trigeminal nerve disorder	1	5	2	16	21	0	0
	Trigeminal nerve paresis	0	3	0	0	3	0	0
	Trigeminal neuralgia	26	72	63	159	231	0	0
	Trigeminal neuritis	0	2	1	6	8	0	0
	Trigeminal palsy	0	1	0	0	1	0	0
	Tunnel vision	7	104	2	28	132	0	0
	Typical aura without headache	1	3	0	2	5	0	0
	Uhthoff's phenomenon	0	1	1	2	3	0	0
	Ulnar nerve palsy	0	2	1	2	4	0	0
	Ulnar neuritis	0	3	0	0	3	0	0
	Unresponsive to stimuli	8	1003	2	95	1098	0	0
	Upper motor neurone lesion	0	8	0	0	8	0	0
	VIth nerve disorder	0	2	0	0	2	0	0
	VIth nerve paralysis	13	48	1	1	49	0	0
	VIth nerve paresis	2	2	0	1	3	0	0
	Vagus nerve disorder	2	6	0	2	8	0	0
	Vascular dementia	0	2	0	0	2	0	0
	Vascular encephalopathy	1	2	0	0	2	0	0
	Vascular headache	2	6	0	3	9	0	0
	Vasogenic cerebral oedema	0	4	0	0	4	0	0
	Vertebral artery aneurysm	1	1	0	0	1	0	0
	Vertebral artery dissection	2	12	0	0	12	0	0
	Vertebral artery occlusion	1	8	0	0	8	0	0
	Vertebral artery stenosis	0	4	0	0	4	0	0
	Vertebral artery thrombosis	0	1	0	0	1	0	0
	Vertebrobasilar insufficiency	1	5	0	0	5	0	0
	Vertebrobasilar stroke	0	3	0	0	3	0	0
	Vertigo CNS origin	1	3	1	4	7	0	0
	Vestibular migraine	3	11	2	12	23	0	0
	Vestibular nystagmus	0	0	0	1	1	0	0
	Vibration syndrome	0	1	0	1	2	0	0
	Vibratory sense increased	1	4	1	8	12	0	0
	Visual pathway disorder	0	0	1	1	1	0	0
	Visuospatial deficit	0	1	0	0	1	0	0
	Vocal cord paralysis	2	7	3	4	11	0	0
	Vocal cord paresis	0	2	0	3	5	0	0
	Wernicke's encephalopathy	0	2	0	0	2	0	0
	White matter lesion	0	40	0	4	44	0	0
Pregnancy, puerperium and perinatal conditions	*** SOC TOTAL ***	244	1254	78	302	1556	0	0
	Abnormal cord insertion	0	1	0	0	1	0	0
	Abnormal labour	0	0	0	1	1	0	0
	Abortion	11	20	0	0	20	0	0
	Abortion complete	1	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Abortion early	1	1	2	3	4	0	0
	Abortion incomplete	2	2	0	0	2	0	0
	Abortion late	1	2	0	0	2	0	0
	Abortion missed	7	26	0	0	26	0	0
	Abortion of ectopic pregnancy	0	1	0	0	1	0	0
	Abortion spontaneous	87	528	4	18	546	0	0
	Abortion spontaneous incomplete	1	2	0	0	2	0	0
	Abortion threatened	3	9	0	0	9	0	0
	Amniorrhexis	0	1	0	0	1	0	0
	Amniorrhoea	2	8	0	1	9	0	0
	Amniotic cavity disorder	0	1	0	0	1	0	0
	Anembryonic gestation	2	11	0	2	13	0	0
	Arrested labour	0	1	0	1	2	0	0
	Biochemical pregnancy	0	0	0	2	2	0	0
	Breech delivery	0	1	0	0	1	0	0
	Breech presentation	0	2	0	1	3	0	0
	Cervical dilatation	1	5	0	1	6	0	0
	Cervical incompetence	0	1	0	0	1	0	0
	Chorioamniotic separation	0	1	0	0	1	0	0
	Complication of pregnancy	0	2	0	0	2	0	0
	Decidual cast	0	1	0	0	1	0	0
	Delivery	0	17	0	5	22	0	0
	Eclampsia	0	1	0	0	1	0	0
	Ectopic pregnancy	6	17	1	1	18	0	0
	Ectopic pregnancy with contraceptive device	0	1	0	0	1	0	0
	Failed induction of labour	0	0	0	1	1	0	0
	First trimester pregnancy	0	0	0	6	6	0	0
	Foetal cardiac disorder	1	5	0	0	5	0	0
	Foetal death	9	72	1	1	73	0	0
	Foetal disorder	1	12	0	0	12	0	0
	Foetal distress syndrome	1	1	0	0	1	0	0
	Foetal growth abnormality	0	1	0	0	1	0	0
	Foetal growth restriction	4	22	1	1	23	0	0
	Foetal hypokinesia	3	26	1	1	27	0	0
	Foetal macrosomia	0	2	0	0	2	0	0
	Foetal malposition	0	1	0	0	1	0	0
	Foetal vascular malperfusion	2	3	0	0	3	0	0
	Gestational diabetes	2	11	1	2	13	0	0
	Gestational hypertension	1	7	0	2	9	0	0
	HELLP syndrome	0	1	0	0	1	0	0
	Haemorrhage in pregnancy	8	39	0	2	41	0	0
	High risk pregnancy	0	1	0	1	2	0	0
	Hydrops foetalis	0	3	0	0	3	0	0
	Hyperemesis gravidarum	0	0	1	1	1	0	0
	Induced labour	0	20	1	2	22	0	0
	Jaundice neonatal	0	1	0	1	2	0	0
	Labour complication	0	1	0	0	1	0	0
	Labour pain	19	19	23	24	43	0	0
	Large for dates baby	1	1	0	0	1	0	0
	Live birth	5	8	0	1	9	0	0
	Low birth weight baby	1	4	0	2	6	0	0
	Meconium in amniotic fluid	0	2	0	0	2	0	0
	Meconium stain	0	0	0	1	1	0	0
	Morning sickness	0	4	0	11	15	0	0
	Neonatal disorder	0	1	1	2	3	0	0
	Normal foetus	0	0	0	1	1	0	0
	Normal labour	0	1	0	0	1	0	0
	Normal newborn	2	7	2	7	14	0	0
	Oligohydramnios	2	4	0	0	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Pelvic girdle pain	1	1	1	4	5	0	0
	Peripartum cardiomyopathy	0	1	0	0	1	0	0
	Placenta accreta	0	0	0	1	1	0	0
	Placenta praevia	2	6	0	1	7	0	0
	Placenta praevia haemorrhage	0	1	0	0	1	0	0
	Placental calcification	0	1	0	0	1	0	0
	Placental disorder	1	5	0	1	6	0	0
	Placental infarction	0	1	0	0	1	0	0
	Placental insufficiency	0	1	0	0	1	0	0
	Polyhydramnios	0	7	0	0	7	0	0
	Poor weight gain neonatal	0	0	0	1	1	0	0
	Post abortion haemorrhage	0	1	0	0	1	0	0
	Postpartum disorder	0	1	0	1	2	0	0
	Postpartum haemorrhage	2	9	0	6	15	0	0
	Postpartum state	0	1	0	0	1	0	0
	Pre-eclampsia	2	21	0	1	22	0	0
	Precipitate labour	0	1	0	0	1	0	0
	Pregnancy	3	9	20	106	115	0	0
	Pregnancy after post coital contraception	0	1	0	0	1	0	0
	Pregnancy on contraceptive	0	2	0	0	2	0	0
	Pregnancy on oral contraceptive	1	2	0	0	2	0	0
	Pregnancy with advanced maternal age	0	0	0	1	1	0	0
	Pregnancy with contraceptive device	1	2	0	0	2	0	0
	Premature baby	2	18	2	6	24	0	0
	Premature delivery	4	31	0	5	36	0	0
	Premature labour	5	37	2	8	45	0	0
	Premature rupture of membranes	4	18	1	4	22	0	0
	Premature separation of placenta	4	19	0	1	20	0	0
	Preterm premature rupture of membranes	1	12	1	2	14	0	0
	Prolonged labour	2	4	0	0	4	0	0
	Prolonged pregnancy	3	5	0	1	6	0	0
	Retained placenta or membranes	1	4	0	1	5	0	0
	Retroplacental haematoma	1	1	0	0	1	0	0
	Ruptured ectopic pregnancy	0	2	0	0	2	0	0
	Second trimester pregnancy	0	2	0	1	3	0	0
	Shoulder dystocia	0	2	0	0	2	0	0
	Somatic symptom disorder of pregnancy	0	1	0	1	2	0	0
	Stillbirth	9	30	0	1	31	0	0
	Subchorionic haematoma	0	4	0	1	5	0	0
	Subchorionic haemorrhage	1	2	0	4	6	0	0
	Term baby	0	1	0	0	1	0	0
	Term birth	2	5	0	0	5	0	0
	Third trimester pregnancy	0	0	1	1	1	0	0
	Threatened labour	0	2	0	0	2	0	0
	Twin pregnancy	0	3	0	0	3	0	0
	Umbilical cord abnormality	0	2	0	0	2	0	0
	Umbilical cord around neck	0	1	0	1	2	0	0
	Umbilical cord prolapse	0	2	0	0	2	0	0
	Umbilical cord short	0	0	0	1	1	0	0
	Umbilical cord thrombosis	1	1	0	0	1	0	0
	Umbilical granuloma	0	0	0	1	1	0	0
	Unintended pregnancy	2	3	0	1	4	0	0
	Unwanted pregnancy	0	0	0	1	1	0	0
	Uterine atony	0	2	0	0	2	0	0
	Uterine contractions abnormal	0	5	4	9	14	0	0
	Uterine contractions during pregnancy	0	11	2	15	26	0	0
	Uterine hypertonus	1	5	5	7	12	0	0
	Uterine irritability	1	1	0	0	1	0	0
Product issues	*** SOC TOTAL ***	7	40	3268	5421	5461	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Device breakage	0	0	0	1	1	0	0
	Device connection issue	0	1	7	407	408	0	0
	Device defective	0	0	0	1	1	0	0
	Device dislocation	2	5	0	0	5	0	0
	Device expulsion	0	2	3	4	6	0	0
	Device failure	0	1	0	0	1	0	0
	Device infusion issue	0	1	0	0	1	0	0
	Device issue	0	0	0	2	2	0	0
	Device leakage	0	2	0	2	4	0	0
	Device malfunction	0	3	0	7	10	0	0
	Device occlusion	0	3	0	3	6	0	0
	Device physical property issue	0	0	1	2	2	0	0
	Device temperature issue	0	0	0	1	1	0	0
	Drug delivery system malfunction	0	1	0	0	1	0	0
	Electromagnetic interference	0	0	0	1	1	0	0
	Inappropriate release of product for distribution	0	0	0	2	2	0	0
	Liquid product physical issue	0	0	1	16	16	0	0
	Manufacturing issue	0	0	0	1	1	0	0
	Manufacturing materials issue	0	1	0	0	1	0	0
	Manufacturing product shipping issue	0	0	0	3	3	0	0
	Manufacturing product storage issue	0	0	1	1	1	0	0
	Needle issue	0	1	1	68	69	0	0
	Oversensing	2	2	1	8	10	0	0
	Patient-device incompatibility	0	1	0	0	1	0	0
	Product after taste	0	0	1	12	12	0	0
	Product availability issue	0	0	0	55	55	0	0
	Product barcode issue	0	0	0	1	1	0	0
	Product closure issue	0	0	2	3	3	0	0
	Product colour issue	0	0	2	22	22	0	0
	Product complaint	0	0	1	4	4	0	0
	Product container issue	0	0	0	1	1	0	0
	Product container seal issue	0	0	0	1	1	0	0
	Product contamination	0	1	1	7	8	0	0
	Product contamination physical	0	1	4	46	47	0	0
	Product delivery mechanism issue	0	0	0	1	1	0	0
	Product expiration date issue	0	0	3	10	10	0	0
	Product identification number issue	0	0	0	1	1	0	0
	Product impurity	0	0	0	4	4	0	0
	Product label issue	0	1	5	14	15	0	0
	Product leakage	0	0	0	8	8	0	0
	Product lot number issue	0	1	1	3	4	0	0
	Product origin unknown	0	0	0	1	1	0	0
	Product packaging issue	0	0	0	1	1	0	0
	Product packaging quantity issue	0	0	0	7	7	0	0
	Product physical issue	0	0	0	7	7	0	0
	Product quality issue	0	1	6	81	82	0	0
	Product substitution issue	0	0	0	4	4	0	0
	Product supply issue	0	0	0	2	2	0	0
	Product tampering	0	1	0	0	1	0	0
	Product taste abnormal	0	0	2	4	4	0	0
	Product temperature excursion issue	1	1	3218	4203	4204	0	0
	Prosthetic cardiac valve malfunction	0	1	0	0	1	0	0
	Recalled product	0	1	0	0	1	0	0
	Stent malfunction	0	1	0	0	1	0	0
	Suspected counterfeit product	0	0	1	4	4	0	0
	Suspected product contamination	0	0	0	2	2	0	0
	Suspected product quality issue	0	0	1	12	12	0	0
	Suspected product tampering	0	0	1	1	1	0	0
	Syringe issue	0	1	3	367	368	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Thrombosis in device	1	3	0	0	3	0	0
	Undersensing	1	2	1	2	4	0	0
Psychiatric disorders	*** SOC TOTAL ***	1486	7462	3659	20487	27949	0	0
	Abnormal behaviour	6	66	3	78	144	0	0
	Abnormal dreams	9	31	22	220	251	0	0
	Abnormal sleep-related event	0	2	1	6	8	0	0
	Abulia	0	2	0	2	4	0	0
	Acute psychosis	2	9	0	0	9	0	0
	Acute stress disorder	3	4	0	9	13	0	0
	Adjustment disorder	2	3	2	2	5	0	0
	Adjustment disorder with depressed mood	0	5	1	1	6	0	0
	Aerophobia	3	3	0	0	3	0	0
	Affect lability	3	7	5	24	31	0	0
	Affective disorder	4	6	8	17	23	0	0
	Aggression	2	51	14	55	106	0	0
	Agitation	19	98	34	224	322	0	0
	Agoraphobia	0	4	1	2	6	0	0
	Alcohol abuse	0	1	0	0	1	0	0
	Alcohol problem	0	0	0	2	2	0	0
	Alcohol withdrawal syndrome	1	5	0	0	5	0	0
	Alcoholic hangover	0	0	1	2	2	0	0
	Alcoholism	0	5	0	0	5	0	0
	Alice in wonderland syndrome	0	1	0	1	2	0	0
	Anger	2	26	8	92	118	0	0
	Anhedonia	0	0	1	1	1	0	0
	Anorgasmia	0	2	0	1	3	0	0
	Anticipatory anxiety	1	1	1	2	3	0	0
	Antisocial behaviour	0	1	0	0	1	0	0
	Anxiety	106	502	308	2567	3069	0	0
	Anxiety disorder	4	10	14	28	38	0	0
	Apathy	20	47	107	189	236	0	0
	Aphonia psychogenic	0	1	0	0	1	0	0
	Asocial behaviour	1	1	0	0	1	0	0
	Attention deficit hyperactivity disorder	1	7	1	9	16	0	0
	Autism spectrum disorder	0	3	0	2	5	0	0
	Autoscopy	0	3	2	22	25	0	0
	Aversion	0	1	0	4	5	0	0
	Behaviour disorder	3	7	1	9	16	0	0
	Belligerence	0	3	0	0	3	0	0
	Binge drinking	0	1	0	0	1	0	0
	Binge eating	0	1	0	1	2	0	0
	Bipolar I disorder	0	3	0	0	3	0	0
	Bipolar disorder	2	12	0	1	13	0	0
	Blunted affect	0	1	0	2	3	0	0
	Body dysmorphic disorder	0	0	0	1	1	0	0
	Borderline personality disorder	0	2	1	2	4	0	0
	Boredom	0	0	2	3	3	0	0
	Bradyphrenia	3	21	15	66	87	0	0
	Breath holding	3	4	1	2	6	0	0
	Breathing-related sleep disorder	0	1	0	1	2	0	0
	Brief psychotic disorder with marked stressors	0	1	1	1	2	0	0
	Bruxism	3	12	4	37	49	0	0
	Burnout syndrome	1	2	0	2	4	0	0
	Cardiovascular somatic symptom disorder	0	0	0	1	1	0	0
	Catastrophic reaction	0	1	0	1	2	0	0
	Catatonia	1	7	0	7	14	0	0
	Change in sustained attention	0	0	0	1	1	0	0
	Chronic idiopathic pain syndrome	1	1	2	2	3	0	0
	Claustrophobia	0	0	0	6	6	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Clinomania	0	0	0	4	4	0	0
	Communication disorder	2	40	1	27	67	0	0
	Completed suicide	1	15	0	0	15	0	0
	Confabulation	0	2	0	0	2	0	0
	Confusional state	189	1121	248	1738	2859	0	0
	Constricted affect	2	2	0	2	4	0	0
	Conversion disorder	3	19	2	15	34	0	0
	Daydreaming	0	0	5	22	22	0	0
	Decreased eye contact	0	2	0	3	5	0	0
	Decreased interest	3	5	2	17	22	0	0
	Defiant behaviour	0	1	0	0	1	0	0
	Deja vu	1	2	0	2	4	0	0
	Delirium	33	294	18	43	337	0	0
	Delirium febrile	3	15	9	11	26	0	0
	Delirium tremens	0	1	0	0	1	0	0
	Delusion	8	36	11	52	88	0	0
	Delusion of grandeur	0	1	0	1	2	0	0
	Delusion of parasitosis	0	2	0	0	2	0	0
	Delusional disorder, erotomanic type	0	1	0	1	2	0	0
	Delusional disorder, persecutory type	0	1	0	0	1	0	0
	Delusional disorder, unspecified type	0	0	0	2	2	0	0
	Delusional perception	0	1	1	2	3	0	0
	Dependent personality disorder	0	0	1	1	1	0	0
	Depersonalisation/derealisation disorder	0	4	1	7	11	0	0
	Depressed mood	29	120	156	467	587	0	0
	Depression	67	220	145	519	739	0	0
	Depression suicidal	1	7	0	0	7	0	0
	Depressive symptom	0	2	2	10	12	0	0
	Derailment	1	1	0	0	1	0	0
	Derealisation	1	8	4	19	27	0	0
	Dermatillomania	0	0	0	1	1	0	0
	Dermatophagia	1	1	2	2	3	0	0
	Discouragement	0	2	4	8	10	0	0
	Disinhibition	0	1	0	1	2	0	0
	Disorganised speech	1	12	2	29	41	0	0
	Disorientation	59	304	91	764	1068	0	0
	Dissociation	5	22	7	48	70	0	0
	Dissociative amnesia	0	0	0	4	4	0	0
	Dissociative disorder	1	3	1	3	6	0	0
	Distractibility	0	1	1	9	10	0	0
	Disturbance in sexual arousal	1	2	0	1	3	0	0
	Disturbance in social behaviour	0	0	0	1	1	0	0
	Drug abuse	0	7	0	1	8	0	0
	Drug dependence	1	2	0	0	2	0	0
	Dysphemia	3	20	6	40	60	0	0
	Dysphoria	0	8	5	98	106	0	0
	Eating disorder	3	15	6	141	156	0	0
	Emetophobia	0	0	0	1	1	0	0
	Emotional disorder	6	27	16	72	99	0	0
	Emotional distress	7	45	13	118	163	0	0
	Emotional poverty	0	1	1	7	8	0	0
	Enuresis	1	16	6	26	42	0	0
	Euphoric mood	0	10	3	98	108	0	0
	Executive dysfunction	1	4	1	1	5	0	0
	Exhibitionism	0	1	0	0	1	0	0
	Exploding head syndrome	0	0	0	6	6	0	0
	Factitious disorder	0	1	0	1	2	0	0
	Fear	7	56	26	234	290	0	0
	Fear of death	4	8	7	34	42	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Fear of disease	0	0	2	12	12	0	0
	Fear of eating	0	2	0	6	8	0	0
	Fear of falling	1	1	1	8	9	0	0
	Fear of injection	0	1	0	58	59	0	0
	Fear of open spaces	0	0	0	1	1	0	0
	Fear-related avoidance of activities	0	0	0	1	1	0	0
	Feeling guilty	0	0	2	6	6	0	0
	Feeling of despair	1	11	12	43	54	0	0
	Feelings of worthlessness	0	1	1	5	6	0	0
	Female orgasmic disorder	0	0	0	2	2	0	0
	Flashback	1	1	0	3	4	0	0
	Flat affect	0	3	1	6	9	0	0
	Flight of ideas	0	1	0	0	1	0	0
	Frustration tolerance decreased	2	17	7	43	60	0	0
	Gastrointestinal somatic symptom disorder	0	0	1	1	1	0	0
	Generalised anxiety disorder	0	3	2	8	11	0	0
	Genito-pelvic pain/penetration disorder	1	2	0	2	4	0	0
	Grief reaction	0	2	0	0	2	0	0
	Habit cough	1	3	1	4	7	0	0
	Hallucination	79	579	39	88	667	0	0
	Hallucination, auditory	7	63	2	12	75	0	0
	Hallucination, olfactory	1	7	2	3	10	0	0
	Hallucination, tactile	0	2	0	0	2	0	0
	Hallucination, visual	10	72	8	18	90	0	0
	Hallucinations, mixed	4	14	0	1	15	0	0
	Head banging	2	11	1	10	21	0	0
	Helplessness	1	3	3	8	11	0	0
	Histrionic personality disorder	0	0	0	1	1	0	0
	Homicidal ideation	0	2	0	1	3	0	0
	Hostility	0	1	0	4	5	0	0
	Hydrophobia	2	2	0	0	2	0	0
	Hyperarousal	0	0	0	2	2	0	0
	Hypervigilance	1	2	3	15	17	0	0
	Hypnagogic hallucination	0	3	0	0	3	0	0
	Hypomania	0	0	1	2	2	0	0
	Illness anxiety disorder	0	0	2	2	2	0	0
	Illogical thinking	0	0	0	2	2	0	0
	Illusion	5	12	15	32	44	0	0
	Immunisation stress-related response	2	11	2	15	26	0	0
	Impaired reasoning	0	3	0	3	6	0	0
	Impatience	1	3	0	3	6	0	0
	Imperception	0	0	1	5	5	0	0
	Impulse-control disorder	1	3	0	0	3	0	0
	Impulsive behaviour	0	2	0	4	6	0	0
	Inappropriate affect	0	4	2	17	21	0	0
	Indifference	0	1	1	2	3	0	0
	Inferiority complex	0	0	1	1	1	0	0
	Initial insomnia	10	21	37	90	111	0	0
	Insomnia	260	867	883	4441	5308	0	0
	Intentional self-injury	1	5	0	0	5	0	0
	Intrusive thoughts	0	0	0	1	1	0	0
	Irritability	24	84	57	305	389	0	0
	Jamais vu	0	0	0	1	1	0	0
	Lack of spontaneous speech	1	4	0	5	9	0	0
	Laziness	0	0	1	25	25	0	0
	Learning disability	0	0	0	2	2	0	0
	Learning disorder	0	0	2	4	4	0	0
	Libido decreased	2	8	9	29	37	0	0
	Libido disorder	1	1	1	4	5	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Libido increased	0	0	8	13	13	0	0
	Limited symptom panic attack	0	1	0	0	1	0	0
	Listless	12	24	46	123	147	0	0
	Logorrhoea	1	2	1	14	16	0	0
	Loose associations	0	1	0	0	1	0	0
	Loss of dreaming	0	0	0	1	1	0	0
	Loss of libido	3	11	15	25	36	0	0
	Major depression	2	21	2	4	25	0	0
	Mania	2	11	3	28	39	0	0
	Manic symptom	0	1	0	0	1	0	0
	Menopausal depression	0	0	1	1	1	0	0
	Mental disorder	8	40	30	101	141	0	0
	Mental disorder due to a general medical condition	0	1	0	0	1	0	0
	Mental fatigue	24	61	15	51	112	0	0
	Mental status changes	6	327	3	70	397	0	0
	Middle insomnia	8	24	43	79	103	0	0
	Mixed anxiety and depressive disorder	2	5	2	3	8	0	0
	Mood altered	8	28	25	92	120	0	0
	Mood disorder due to a general medical condition	0	1	0	1	2	0	0
	Mood swings	7	23	55	130	153	0	0
	Morbid thoughts	0	2	0	3	5	0	0
	Mutism	1	3	0	0	3	0	0
	Near death experience	1	35	1	5	40	0	0
	Negative thoughts	2	4	2	6	10	0	0
	Nervousness	16	75	38	705	780	0	0
	Neuropsychiatric symptoms	0	1	0	1	2	0	0
	Neurosis	0	1	0	2	3	0	0
	Nightmare	20	68	43	255	323	0	0
	Obsessive thoughts	1	2	2	4	6	0	0
	Obsessive-compulsive disorder	0	3	2	3	6	0	0
	Obsessive-compulsive symptom	0	0	0	1	1	0	0
	Orgasm abnormal	0	0	1	4	4	0	0
	Orgasmic sensation decreased	0	0	0	1	1	0	0
	Panic attack	31	115	71	371	486	0	0
	Panic disorder	0	9	3	20	29	0	0
	Panic reaction	9	28	12	89	117	0	0
	Paramnesia	2	2	0	1	3	0	0
	Paranoia	1	22	1	39	61	0	0
	Parasomnia	0	0	0	2	2	0	0
	Parkinson's disease psychosis	0	1	0	0	1	0	0
	Paruresis	0	1	0	0	1	0	0
	Pedantic speech	0	0	0	1	1	0	0
	Perinatal depression	0	1	0	0	1	0	0
	Persecutory delusion	0	2	0	0	2	0	0
	Perseveration	0	1	0	0	1	0	0
	Persistent depressive disorder	1	1	0	2	3	0	0
	Personality change	6	10	1	11	21	0	0
	Personality disorder	0	2	0	3	5	0	0
	Phantom vibration syndrome	0	1	0	1	2	0	0
	Phobia	0	0	0	7	7	0	0
	Phobia of driving	0	0	0	3	3	0	0
	Phonophobia	2	4	2	6	10	0	0
	Pica	0	0	0	2	2	0	0
	Polydipsia psychogenic	0	1	0	0	1	0	0
	Poor quality sleep	33	117	102	404	521	0	0
	Poriomania	1	1	1	1	2	0	0
	Post-traumatic stress disorder	5	8	3	11	19	0	0
	Postictal psychosis	1	1	0	0	1	0	0
	Posturing	0	2	0	2	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Poverty of speech	0	1	0	3	4	0	0
	Pressure of speech	0	2	0	0	2	0	0
	Pseudohallucination	0	0	1	3	3	0	0
	Psychiatric symptom	4	9	3	7	16	0	0
	Psychogenic movement disorder	0	1	0	0	1	0	0
	Psychogenic pseudosyncope	0	1	0	1	2	0	0
	Psychogenic tremor	0	0	0	1	1	0	0
	Psychological trauma	0	2	0	3	S	0	0
	Psychomotor retardation	1	S	2	2	7	0	0
	Psychotic behaviour	1	1	0	0	1	0	0
	Psychotic disorder	S	49	4	28	77	0	0
	Psychotic symptom	0	1	0	0	1	0	0
	Purging	0	0	0	1	1	0	0
	Rapid eye movements sleep abnormal	0	0	1	3	3	0	0
	Reading disorder	1	7	3	20	27	0	0
	Regressive behaviour	0	1	0	0	1	0	0
	Restlessness	41	137	168	S8S	722	0	0
	Schizoaffective disorder	0	2	0	0	2	0	0
	Schizophrenia	1	9	0	1	10	0	0
	Selective eating disorder	2	2	0	1	3	0	0
	Self esteem decreased	0	1	1	1	2	0	0
	Self-induced vomiting	0	0	0	2	2	0	0
	Self-injurious ideation	0	2	0	4	6	0	0
	Sense of a foreshortened future	0	1	0	0	1	0	0
	Separation anxiety disorder	0	1	0	0	1	0	0
	Shared psychotic disorder	0	1	0	0	1	0	0
	Sleep attacks	1	3	6	9	12	0	0
	Sleep disorder	74	418	3S9	2609	3027	0	0
	Sleep disorder due to a general medical condition	0	0	0	S	S	0	0
	Sleep disorder due to general medical condition, hypersomnia type	0	0	0	2	2	0	0
	Sleep disorder due to general medical condition, insomnia type	1	1	0	3	4	0	0
	Sleep inertia	0	1	0	1	2	0	0
	Sleep talking	1	S	0	12	17	0	0
	Sleep terror	0	S	0	19	24	0	0
	Social anxiety disorder	0	1	1	S	6	0	0
	Social avoidant behaviour	1	3	3	8	11	0	0
	Social fear	0	0	0	1	1	0	0
	Soliloquy	0	1	0	7	8	0	0
	Somatic hallucination	0	1	0	0	1	0	0
	Somatic symptom disorder	3	3	0	9	12	0	0
	Somnambulism	0	8	6	13	21	0	0
	Sopor	4	11	1	8	19	0	0
	Speech sound disorder	1	2	0	6	8	0	0
	Staring	2	31	2	31	62	0	0
	Stereotypy	0	0	0	1	1	0	0
	Stress	7	37	44	207	244	0	0
	Stubbornness	0	1	0	0	1	0	0
	Substance abuse	0	1	0	0	1	0	0
	Substance-induced psychotic disorder	0	2	0	1	3	0	0
	Suicidal behaviour	0	6	0	0	6	0	0
	Suicidal ideation	29	151	4	8	159	0	0
	Suicide attempt	S	14	0	0	14	0	0
	Suspiciousness	0	0	0	3	3	0	0
	Tachyphrenia	2	S	0	16	21	0	0
	Taciturnity	0	0	0	1	1	0	0
	Tearfulness	1	9	1	27	36	0	0
	Tension	4	18	24	118	136	0	0
	Terminal insomnia	0	9	3	13	22	0	0
	Thanatophobia	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Thinking abnormal	0	30	13	146	176	0	0
	Thought blocking	0	0	1	5	5	0	0
	Tic	3	18	5	20	38	0	0
	Time perception altered	1	2	1	7	9	0	0
	Tobacco abuse	0	2	0	1	3	0	0
	Trance	0	1	0	2	3	0	0
	Violence-related symptom	0	1	0	3	4	0	0
	Vomiting psychogenic	0	0	0	2	2	0	0
	Waxy flexibility	1	1	0	0	1	0	0
Renal and urinary disorders	*** SOC TOTAL ***	567	2989	915	3217	6206	0	0
	Acute kidney injury	67	612	1	7	619	0	0
	Albuminuria	2	2	1	2	4	0	0
	Anti-glomerular basement membrane disease	0	3	0	0	3	0	0
	Anuria	2	18	4	5	23	0	0
	Atonic urinary bladder	0	1	1	2	3	0	0
	Azotaemia	1	8	0	0	8	0	0
	Bilirubinuria	0	0	1	1	1	0	0
	Bladder dilatation	0	5	1	6	11	0	0
	Bladder discomfort	2	5	13	35	40	0	0
	Bladder disorder	2	11	4	22	33	0	0
	Bladder diverticulum	0	1	0	0	1	0	0
	Bladder dysfunction	0	4	1	3	7	0	0
	Bladder hypertrophy	0	7	0	2	9	0	0
	Bladder irritation	1	3	3	5	8	0	0
	Bladder outlet obstruction	0	0	0	1	1	0	0
	Bladder pain	6	15	19	58	73	0	0
	Bladder perforation	0	1	0	0	1	0	0
	Bladder prolapse	0	0	0	1	1	0	0
	Bladder spasm	0	0	0	8	B	0	0
	Bladder sphincter atony	1	1	0	0	1	0	0
	Bladder stenosis	0	1	0	0	1	0	0
	Calculus bladder	0	1	0	0	1	0	0
	Calculus urinary	1	3	0	1	4	0	0
	Choluria	0	0	1	3	3	0	0
	Chromaturia	B	78	59	289	367	0	0
	Chronic kidney disease	7	76	1	2	78	0	0
	Costovertebral angle tenderness	1	1	3	7	B	0	0
	Crush syndrome	1	1	0	0	1	0	0
	Cystitis glandularis	1	1	0	0	1	0	0
	Cystitis haemorrhagic	3	10	0	0	10	0	0
	Cystitis interstitial	0	2	0	9	11	0	0
	Cystitis noninfective	10	14	52	83	97	0	0
	Cystitis-like symptom	0	0	0	4	4	0	0
	Diabetic nephropathy	0	2	0	0	2	0	0
	Dysuria	20	96	76	296	392	0	0
	End stage renal disease	3	26	0	0	26	0	0
	Focal segmental glomerulosclerosis	6	8	1	2	10	0	0
	Foetal renal impairment	0	2	0	0	2	0	0
	Genitourinary symptom	0	3	0	0	3	0	0
	Glomerulonephritis	6	22	3	3	25	0	0
	Glomerulonephritis acute	1	2	0	0	2	0	0
	Glomerulonephritis membranoproliferative	2	2	0	0	2	0	0
	Glomerulonephritis membranous	5	13	0	1	14	0	0
	Glomerulonephritis minimal lesion	13	25	0	0	25	0	0
	Glomerulonephritis rapidly progressive	11	19	0	0	19	0	0
	Glomerulonephropathy	2	3	0	0	3	0	0
	Goodpasture's syndrome	1	2	0	0	2	0	0
	Haematinuria	0	1	0	0	1	0	0
	Haematuria	36	122	82	255	377	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Haemoglobinuria	1	5	0	0	5	0	0
	Haemorrhage urinary tract	0	46	2	11	57	0	0
	Hydronephrosis	5	24	0	1	25	0	0
	Hydroureter	0	3	0	0	3	0	0
	Hypertonic bladder	4	6	1	9	15	0	0
	IgA nephropathy	22	55	1	3	58	0	0
	IgM nephropathy	1	1	0	0	1	0	0
	Incontinence	13	57	13	125	182	0	0
	Ketonuria	0	3	0	0	3	0	0
	Kidney enlargement	0	1	1	3	4	0	0
	Kidney fibrosis	0	2	0	0	2	0	0
	Kidney hypermobility	0	0	1	1	1	0	0
	Kidney small	0	1	0	0	1	0	0
	Leukocyturia	2	3	0	1	4	0	0
	Loin pain haematuria syndrome	0	0	1	1	1	0	0
	Loss of bladder sensation	2	4	1	4	8	0	0
	Lower urinary tract symptoms	0	1	0	3	4	0	0
	Lupus nephritis	1	5	0	0	5	0	0
	Mesangioproliferative glomerulonephritis	1	1	0	0	1	0	0
	Microalbuminuria	0	3	2	2	5	0	0
	Micturition disorder	1	5	12	25	30	0	0
	Micturition urgency	11	37	46	134	171	0	0
	Myoglobinuria	0	1	0	0	1	0	0
	Nephritic syndrome	0	2	0	0	2	0	0
	Nephritis	5	25	2	2	27	0	0
	Nephrocalcinosis	0	2	0	0	2	0	0
	Nephrolithiasis	11	112	2	12	124	0	0
	Nephropathy	0	9	0	1	10	0	0
	Nephrotic syndrome	19	45	1	2	47	0	0
	Neurogenic bladder	1	5	1	1	6	0	0
	Nocturia	2	5	3	24	29	0	0
	Oedematous kidney	0	0	0	1	1	0	0
	Oliguria	3	19	1	6	25	0	0
	Paroxysmal nocturnal haemoglobinuria	0	3	0	0	3	0	0
	Pelvi-ureteric obstruction	0	0	0	1	1	0	0
	Perinephric oedema	0	1	0	0	1	0	0
	Pollakiuria	21	105	82	391	496	0	0
	Polyuria	3	47	22	79	126	0	0
	Post infection glomerulonephritis	0	1	0	0	1	0	0
	Post micturition dribble	0	0	0	1	1	0	0
	Prerenal failure	0	1	0	0	1	0	0
	Proteinuria	9	29	14	44	73	0	0
	Pulmonary renal syndrome	0	1	0	0	1	0	0
	Pyelocaliectasis	0	2	0	0	2	0	0
	Renal arteriosclerosis	0	1	0	0	1	0	0
	Renal artery arteriosclerosis	0	1	0	0	1	0	0
	Renal artery dissection	0	1	0	0	1	0	0
	Renal artery occlusion	0	3	0	0	3	0	0
	Renal artery stenosis	0	4	0	0	4	0	0
	Renal artery thrombosis	0	5	0	0	5	0	0
	Renal atrophy	0	8	0	0	8	0	0
	Renal colic	8	18	12	19	37	0	0
	Renal cyst	1	20	5	11	31	0	0
	Renal cyst haemorrhage	0	1	0	0	1	0	0
	Renal disorder	9	46	9	48	94	0	0
	Renal embolism	0	3	0	0	3	0	0
	Renal failure	22	220	1	3	223	0	0
	Renal haemorrhage	2	6	0	0	6	0	0
	Renal impairment	20	139	6	14	153	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Renal infarct	7	35	0	0	35	0	0
	Renal injury	5	9	0	0	9	0	0
	Renal ischaemia	0	1	0	0	1	0	0
	Renal mass	0	3	0	1	4	0	0
	Renal necrosis	1	2	0	0	2	0	0
	Renal pain	53	169	242	595	764	0	0
	Renal tubular disorder	0	1	0	0	1	0	0
	Renal tubular injury	0	2	0	0	2	0	0
	Renal tubular necrosis	0	10	0	0	10	0	0
	Renal vascular thrombosis	0	4	0	0	4	0	0
	Renal vasculitis	0	1	0	0	1	0	0
	Renal vein embolism	0	1	0	0	1	0	0
	Renal vein thrombosis	2	9	0	0	9	0	0
	Single functional kidney	1	4	0	0	4	0	0
	Strangury	0	1	1	2	3	0	0
	Stress urinary incontinence	0	0	0	4	4	0	0
	Subcapsular renal haematoma	0	1	0	0	1	0	0
	Tubulointerstitial nephritis	12	22	0	0	22	0	0
	Ureteric compression	1	1	0	0	1	0	0
	Ureteric dilatation	0	2	0	1	3	0	0
	Ureteric obstruction	0	1	0	0	1	0	0
	Ureteric stenosis	0	1	0	0	1	0	0
	Ureterolithiasis	2	7	0	1	8	0	0
	Urethral caruncle	0	0	0	1	1	0	0
	Urethral haemorrhage	0	5	0	0	5	0	0
	Urethral pain	0	4	1	4	8	0	0
	Urethral stenosis	0	1	0	0	1	0	0
	Urethral ulcer	0	0	0	1	1	0	0
	Urethritis noninfective	0	0	2	4	4	0	0
	Urge incontinence	1	1	3	5	6	0	0
	Urinary bladder haemorrhage	1	9	0	0	9	0	0
	Urinary hesitation	5	8	3	11	19	0	0
	Urinary incontinence	27	127	60	336	463	0	0
	Urinary retention	18	118	9	19	137	0	0
	Urinary straining	0	2	3	3	5	0	0
	Urinary tract discomfort	0	0	2	7	7	0	0
	Urinary tract disorder	0	3	2	10	13	0	0
	Urinary tract inflammation	1	3	1	4	7	0	0
	Urinary tract obstruction	1	2	0	0	2	0	0
	Urinary tract pain	0	1	0	6	7	0	0
	Urine abnormality	1	16	8	48	64	0	0
	Urine flow decreased	2	4	2	6	10	0	0
	Urine odour abnormal	3	8	7	52	60	0	0
	Urogenital disorder	1	1	0	0	1	0	0
	Urogenital haemorrhage	0	1	0	0	1	0	0
	Vesicoureteric reflux	0	1	0	0	1	0	0
Reproductive system and breast disorders	*** SOC TOTAL ***	1766	5318	13953	30523	35841	0	0
	Abnormal uterine bleeding	3	17	2	16	33	0	0
	Abnormal withdrawal bleeding	0	0	10	34	34	0	0
	Adenomyosis	4	8	3	6	14	0	0
	Adnexa uteri mass	0	0	0	1	1	0	0
	Adnexa uteri pain	11	39	70	152	191	0	0
	Adnexal torsion	0	3	0	0	3	0	0
	Amenorrhoea	102	216	968	2115	2331	0	0
	Anisomastia	0	0	0	1	1	0	0
	Artificial menopause	0	0	1	1	1	0	0
	Atrophic vulvovaginitis	0	1	0	2	3	0	0
	Balanoposthitis	0	1	2	4	5	0	0
	Bartholin's cyst	0	0	1	4	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Benign prostatic hyperplasia	0	7	0	2	9	0	0
	Breast atrophy	0	0	0	2	2	0	0
	Breast cyst	3	12	11	27	39	0	0
	Breast discharge	3	5	6	26	31	0	0
	Breast discolouration	0	1	2	7	B	0	0
	Breast discomfort	4	12	54	123	135	0	0
	Breast disorder	1	1	6	12	13	0	0
	Breast disorder female	0	1	1	3	4	0	0
	Breast engorgement	3	8	29	41	49	0	0
	Breast enlargement	2	10	38	78	88	0	0
	Breast fibrosis	0	0	1	1	1	0	0
	Breast haematoma	1	1	2	5	6	0	0
	Breast haemorrhage	0	1	0	1	2	0	0
	Breast hyperplasia	0	1	0	0	1	0	0
	Breast induration	0	1	2	12	13	0	0
	Breast inflammation	5	8	15	46	54	0	0
	Breast mass	14	45	21	100	145	0	0
	Breast milk discolouration	0	0	0	3	3	0	0
	Breast oedema	1	7	13	24	31	0	0
	Breast pain	65	212	388	1165	1377	0	0
	Breast swelling	7	30	81	29B	328	0	0
	Breast tenderness	5	22	68	220	242	0	0
	Cervical cyst	0	0	0	1	1	0	0
	Cervical discharge	0	1	0	1	2	0	0
	Cervical dysplasia	1	1	2	5	6	0	0
	Cervical friability	0	0	2	2	2	0	0
	Cervical polyp	0	1	0	0	1	0	0
	Cervix disorder	0	1	0	2	3	0	0
	Cervix haemorrhage uterine	0	1	1	1	2	0	0
	Cervix inflammation	0	0	0	1	1	0	0
	Coital bleeding	3	3	2	4	7	0	0
	Delayed follicular ripening	0	0	1	1	1	0	0
	Dysmenorrhoea	138	493	1050	2144	2637	0	0
	Dyspareunia	0	0	1	5	5	0	0
	Ectropion of cervix	0	1	0	0	1	0	0
	Ejaculation delayed	0	2	1	2	4	0	0
	Ejaculation disorder	0	1	1	1	2	0	0
	Ejaculation failure	0	1	3	5	6	0	0
	Endometrial atrophy	0	1	0	0	1	0	0
	Endometrial disorder	1	5	3	3	8	0	0
	Endometrial hyperplasia	1	2	1	3	5	0	0
	Endometrial thickening	2	3	1	3	6	0	0
	Endometriosis	25	43	21	40	B3	0	0
	Enlarged clitoris	0	0	1	1	1	0	0
	Epididymal cyst	0	1	0	0	1	0	0
	Erectile dysfunction	28	99	28	50	149	0	0
	Erection increased	1	2	2	6	B	0	0
	Fallopian tube cyst	0	0	1	2	2	0	0
	Fallopian tube disorder	0	1	0	0	1	0	0
	Fallopian tube spasm	1	1	0	0	1	0	0
	Female reproductive tract disorder	0	0	0	1	1	0	0
	Female sexual dysfunction	0	0	0	1	1	0	0
	Feminisation acquired	0	1	0	0	1	0	0
	Fibrocystic breast disease	0	1	1	1	2	0	0
	Galactorrhoea	2	3	11	20	23	0	0
	Galactostasis	0	1	3	4	5	0	0
	Genital atrophy	0	0	1	1	1	0	0
	Genital blister	0	1	1	8	9	0	0
	Genital burning sensation	0	2	4	11	13	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Genital cyst	0	0	1	1	1	0	0
	Genital discharge	0	1	0	1	2	0	0
	Genital discolouration	0	0	0	1	1	0	0
	Genital discomfort	0	1	2	10	11	0	0
	Genital disorder	0	2	0	0	2	0	0
	Genital dysaesthesia	0	0	1	1	1	0	0
	Genital erythema	0	0	1	4	4	0	0
	Genital haemorrhage	2	16	4	8	24	0	0
	Genital hypoaesthesia	1	1	2	3	4	0	0
	Genital lesion	0	1	0	3	4	0	0
	Genital odour	0	1	0	0	1	0	0
	Genital pain	4	7	19	42	49	0	0
	Genital paraesthesia	0	0	2	3	3	0	0
	Genital rash	1	3	1	16	19	0	0
	Genital swelling	0	0	5	9	9	0	0
	Genital tract inflammation	0	1	2	3	4	0	0
	Genital ulceration	1	5	1	11	16	0	0
	Genitals enlarged	0	0	0	1	1	0	0
	Gynaecomastia	1	2	3	9	11	0	0
	Haematosalpinx	0	1	0	0	1	0	0
	Haematospermia	0	3	4	8	11	0	0
	Haemorrhagic ovarian cyst	1	4	0	1	5	0	0
	Heavy menstrual bleeding	297	967	2355	5109	6076	0	0
	Hydrometra	0	2	0	0	2	0	0
	Hypomenorrhoea	15	46	166	381	427	0	0
	Infertility	2	4	3	7	11	0	0
	Infertility female	1	2	1	4	6	0	0
	Intermenstrual bleeding	83	248	1059	2396	2644	0	0
	Labia enlarged	0	0	1	5	5	0	0
	Lactation disorder	0	1	9	36	37	0	0
	Lactation puerperal increased	0	3	4	7	10	0	0
	Male reproductive tract disorder	0	0	1	1	1	0	0
	Male sexual dysfunction	1	1	0	0	1	0	0
	Mammary duct ectasia	0	0	1	3	3	0	0
	Menometrorrhagia	15	29	91	167	196	0	0
	Menopausal disorder	0	0	0	2	2	0	0
	Menopausal symptoms	1	4	32	62	66	0	0
	Menopause delayed	1	1	2	3	4	0	0
	Menstrual discomfort	4	9	168	273	282	0	0
	Menstrual disorder	184	432	2329	4361	4793	0	0
	Menstruation delayed	114	348	799	2107	2455	0	0
	Menstruation irregular	143	410	1247	2797	3207	0	0
	Metrorrhoea	0	0	0	2	2	0	0
	Nipple disorder	0	0	0	2	2	0	0
	Nipple exudate bloody	0	1	2	3	4	0	0
	Nipple inflammation	1	1	2	10	11	0	0
	Nipple oedema	1	2	0	1	3	0	0
	Nipple pain	0	4	28	71	75	0	0
	Nipple swelling	0	0	1	9	9	0	0
	Nocturnal emission	0	0	0	1	1	0	0
	Noninfective oophoritis	1	2	0	1	3	0	0
	Oedema genital	0	0	2	4	4	0	0
	Oligomenorrhoea	15	44	362	720	764	0	0
	Oligospermia	0	0	1	1	1	0	0
	Orchitis noninfective	1	1	1	3	4	0	0
	Organic erectile dysfunction	0	5	0	6	11	0	0
	Ovarian cyst	5	19	16	37	56	0	0
	Ovarian cyst ruptured	1	6	0	0	6	0	0
	Ovarian disorder	2	4	0	4	8	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Ovarian enlargement	1	2	0	0	2	0	0
	Ovarian failure	0	2	0	0	2	0	0
	Ovarian mass	0	4	0	2	6	0	0
	Ovarian necrosis	0	1	0	0	1	0	0
	Ovarian vein thrombosis	1	6	0	0	6	0	0
	Ovulation disorder	0	1	6	15	16	0	0
	Ovulation pain	9	18	30	65	83	0	0
	Painful ejaculation	0	2	0	0	2	0	0
	Painful erection	1	1	0	3	4	0	0
	Pelvic congestion	0	0	0	3	3	0	0
	Pelvic discomfort	1	2	3	8	10	0	0
	Pelvic floor muscle weakness	0	0	1	1	1	0	0
	Pelvic haematoma	0	1	0	0	1	0	0
	Pelvic haemorrhage	1	4	0	1	5	0	0
	Pelvic organ prolapse	0	1	0	0	1	0	0
	Pelvic pain	24	70	87	234	304	0	0
	Penile burning sensation	0	1	0	0	1	0	0
	Penile curvature	1	1	0	0	1	0	0
	Penile discomfort	0	0	1	3	3	0	0
	Penile erythema	0	0	1	2	2	0	0
	Penile haematoma	0	0	1	1	1	0	0
	Penile haemorrhage	0	1	0	0	1	0	0
	Penile oedema	1	1	1	4	5	0	0
	Penile pain	1	3	0	5	8	0	0
	Penile rash	0	0	0	1	1	0	0
	Penile swelling	1	2	0	4	6	0	0
	Penile vein thrombosis	1	4	0	0	4	0	0
	Penis disorder	1	3	1	4	7	0	0
	Perineal cyst	0	0	0	1	1	0	0
	Perineal disorder	0	1	1	1	2	0	0
	Perineal haematoma	0	0	1	2	2	0	0
	Perineal pain	0	3	0	4	7	0	0
	Peyronie's disease	0	0	1	2	2	0	0
	Plasma cell mastitis	0	1	0	0	1	0	0
	Polycystic ovaries	3	7	1	11	18	0	0
	Polymenorrhagia	1	1	1	4	5	0	0
	Polymenorrhoea	56	168	1014	2001	2169	0	0
	Postmenopausal haemorrhage	163	405	293	360	765	0	0
	Premature menopause	6	10	4	8	18	0	0
	Premature ovulation	0	1	3	5	6	0	0
	Premenstrual dysphoric disorder	0	1	3	10	11	0	0
	Premenstrual headache	0	0	7	10	10	0	0
	Premenstrual pain	6	22	51	128	150	0	0
	Premenstrual syndrome	9	29	85	164	193	0	0
	Priapism	2	4	6	7	11	0	0
	Prostate tenderness	0	0	1	1	1	0	0
	Prostatic calcification	0	0	0	1	1	0	0
	Prostatic disorder	0	2	3	6	8	0	0
	Prostatic obstruction	1	1	0	0	1	0	0
	Prostatic pain	1	2	1	2	4	0	0
	Prostatitis	2	14	5	15	29	0	0
	Prostatomegaly	0	2	1	13	15	0	0
	Pruritus genital	1	3	6	20	23	0	0
	Retracted nipple	0	1	0	1	2	0	0
	Retrograde ejaculation	0	1	0	0	1	0	0
	Retrograde menstruation	0	0	0	1	1	0	0
	Scrotal irritation	0	0	1	1	1	0	0
	Scrotal oedema	0	2	1	1	3	0	0
	Scrotal pain	0	9	4	8	17	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Scrotal swelling	0	1	1	6	7	0	0
	Scrotal ulcer	0	0	0	1	1	0	0
	Semen discolouration	0	0	0	1	1	0	0
	Sexual dysfunction	2	7	2	11	18	0	0
	Shortened cervix	1	2	0	0	2	0	0
	Spermatic cord inflammation	0	0	0	1	1	0	0
	Spermatorrhoea	0	0	0	1	1	0	0
	Spontaneous ejaculation	0	0	0	1	1	0	0
	Spontaneous penile erection	1	1	0	4	S	0	0
	Superovulation	0	0	1	2	2	0	0
	Suppressed lactation	S	12	30	102	114	0	0
	Teratospermia	0	1	0	0	1	0	0
	Testicular cyst	1	2	0	0	2	0	0
	Testicular disorder	1	2	0	2	4	0	0
	Testicular mass	0	1	0	2	3	0	0
	Testicular pain	9	32	37	100	132	0	0
	Testicular swelling	3	14	S	26	40	0	0
	Testis discomfort	0	0	0	2	2	0	0
	Uterine cervix hyperplasia	0	0	0	1	1	0	0
	Uterine cervix stenosis	0	1	0	0	1	0	0
	Uterine cyst	0	0	2	3	3	0	0
	Uterine disorder	0	0	0	3	3	0	0
	Uterine enlargement	0	1	0	1	2	0	0
	Uterine haemorrhage	10	39	4	12	S1	0	0
	Uterine inflammation	0	0	2	3	3	0	0
	Uterine malposition	0	0	1	1	1	0	0
	Uterine mass	0	0	0	1	1	0	0
	Uterine pain	4	14	28	64	78	0	0
	Uterine polyp	1	4	3	8	12	0	0
	Uterine prolapse	0	1	0	0	1	0	0
	Uterine spasm	3	12	26	61	73	0	0
	Uterine tenderness	0	0	0	2	2	0	0
	Vaginal cyst	0	1	0	2	3	0	0
	Vaginal discharge	3	18	S6	111	129	0	0
	Vaginal disorder	0	0	1	2	2	0	0
	Vaginal fistula	0	1	0	0	1	0	0
	Vaginal haemorrhage	7S	281	412	1046	1327	0	0
	Vaginal lesion	0	0	0	S	S	0	0
	Vaginal mucosal blistering	0	0	0	2	2	0	0
	Vaginal odour	0	1	0	0	1	0	0
	Vaginal oedema	0	0	0	1	1	0	0
	Vaginal prolapse	0	0	0	1	1	0	0
	Vaginal ulceration	1	4	3	11	1S	0	0
	Varicocele	0	4	2	2	6	0	0
	Varicose veins pelvic	0	1	0	0	1	0	0
	Varicose veins vulval	0	0	1	1	1	0	0
	Vulva cyst	0	0	0	2	2	0	0
	Vulval disorder	0	0	0	6	6	0	0
	Vulval eczema	0	0	1	1	1	0	0
	Vulval haemorrhage	0	8	0	2	10	0	0
	Vulval oedema	1	1	0	0	1	0	0
	Vulval ulceration	S	7	0	7	14	0	0
	Vulvovaginal burning sensation	1	6	6	20	26	0	0
	Vulvovaginal discomfort	2	S	4	20	2S	0	0
	Vulvovaginal dryness	1	4	4	11	1S	0	0
	Vulvovaginal erythema	1	1	2	S	6	0	0
	Vulvovaginal inflammation	0	0	0	3	3	0	0
	Vulvovaginal pain	1	10	13	40	S0	0	0
	Vulvovaginal pruritus	1	4	S	36	40	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Vulvovaginal rash	0	0	0	6	6	0	0
	Vulvovaginal swelling	1	3	4	15	18	0	0
	Vulvovaginal ulceration	1	2	0	1	3	0	0
	Withdrawal bleed	0	0	2	5	5	0	0
Respiratory, thoracic and mediastinal disorders	*** SOC TOTAL ***	4564	25238	9744	50838	76076	1	3
	Acquired diaphragmatic eventration	2	11	3	3	14	0	0
	Acute chest syndrome	2	3	0	0	3	0	0
	Acute interstitial pneumonitis	0	2	0	0	2	0	0
	Acute lung injury	0	1	0	0	1	0	0
	Acute pulmonary oedema	10	35	0	0	35	0	0
	Acute respiratory distress syndrome	9	90	0	0	90	0	0
	Acute respiratory failure	14	526	0	0	526	0	0
	Adenoidal disorder	0	0	1	2	2	0	0
	Adenoidal hypertrophy	0	1	0	0	1	0	0
	Agonal respiration	2	13	0	0	13	0	0
	Allergic bronchitis	0	1	1	3	4	0	0
	Allergic cough	1	4	3	9	13	0	0
	Allergic respiratory disease	1	2	0	1	3	0	0
	Allergic respiratory symptom	0	0	0	5	5	0	0
	Allergic sinusitis	0	0	1	6	6	0	0
	Alveolar lung disease	1	1	0	0	1	0	0
	Alveolitis	1	2	0	0	2	0	0
	Anoxia	1	3	0	0	3	0	0
	Aphonia	10	51	49	241	292	0	0
	Apnoea	5	34	2	4	38	0	0
	Apnoeic attack	1	6	0	0	6	0	0
	Asphyxia	2	18	3	5	23	0	0
	Aspiration	4	57	0	1	58	0	0
	Asthma	133	379	169	749	1128	0	0
	Asthma exercise induced	1	2	3	7	9	0	0
	Asthma late onset	0	1	0	0	1	0	0
	Asthmatic crisis	12	37	14	20	57	0	0
	Atelectasis	1	142	1	20	162	0	0
	Autoimmune lung disease	0	1	0	0	1	0	0
	Bradypnoea	0	1	0	0	1	0	0
	Brief resolved unexplained event	0	4	0	0	4	0	0
	Bronchial disorder	0	0	3	8	8	0	0
	Bronchial haemorrhage	0	1	0	0	1	0	0
	Bronchial hyperreactivity	1	7	1	8	15	0	0
	Bronchial irritation	0	5	3	4	9	0	0
	Bronchial obstruction	1	4	3	3	7	0	0
	Bronchial oedema	0	2	0	0	2	0	0
	Bronchial secretion retention	0	2	1	3	5	0	0
	Bronchial wall thickening	0	11	0	0	11	0	0
	Bronchiectasis	1	17	0	0	17	0	0
	Bronchiolitis obliterans syndrome	0	1	0	0	1	0	0
	Bronchitis chronic	2	3	0	4	7	0	0
	Bronchopleural fistula	0	1	0	0	1	0	0
	Bronchopneumopathy	0	0	1	2	2	0	0
	Bronchospasm	12	54	12	107	161	0	0
	Bronchostenosis	1	3	0	0	3	0	0
	Catarrh	5	13	15	32	45	0	0
	Central sleep apnoea syndrome	0	0	0	2	2	0	0
	Cheyne-Stokes respiration	1	4	1	1	5	0	0
	Childhood asthma	0	2	0	3	5	0	0
	Choking	11	82	7	14	96	0	0
	Choking sensation	4	19	13	66	85	0	0
	Chronic obstructive pulmonary disease	8	147	10	61	208	0	0
	Chronic respiratory disease	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Chronic respiratory failure	0	10	0	0	10	0	0
	Confirmed e-cigarette or vaping product use associated lung injury	0	1	0	0	1	0	0
	Cough	379	2442	1996	8615	11057	0	1
	Cough decreased	0	0	0	5	5	0	0
	Cough variant asthma	0	1	2	5	6	0	0
	Cystic lung disease	0	2	0	0	2	0	0
	Dependence on respirator	1	2	0	0	2	0	0
	Diaphragm muscle weakness	0	1	0	0	1	0	0
	Diaphragmalgia	5	12	10	24	36	0	0
	Diaphragmatic disorder	0	3	0	1	4	0	0
	Diaphragmatic paralysis	2	5	0	0	5	0	0
	Diaphragmatic spasm	1	4	1	2	6	0	0
	Diffuse alveolar damage	0	2	0	0	2	0	0
	Dry throat	6	40	40	319	359	0	0
	Dysphonia	37	156	117	771	927	0	0
	Dyspnoea	1841	8210	3570	14695	22905	0	0
	Dyspnoea at rest	10	52	4	8	60	0	0
	Dyspnoea exertional	83	436	194	389	825	0	0
	Dyspnoea paroxysmal nocturnal	1	8	0	5	13	0	0
	Ear, nose and throat disorder	0	1	1	1	2	0	0
	Emphysema	4	28	1	11	39	0	0
	Eosinophilic bronchitis	0	1	0	0	1	0	0
	Eosinophilic pleural effusion	2	3	0	0	3	0	0
	Eosinophilic pneumonia	1	5	0	0	5	0	0
	Eosinophilic pneumonia acute	1	2	0	0	2	0	0
	Eosinophilic pneumonia chronic	0	1	0	0	1	0	0
	Epiglottic oedema	1	3	1	1	4	0	0
	Epiglottis ulcer	0	0	0	1	1	0	0
	Epistaxis	70	323	437	1434	1757	0	0
	Gasping syndrome	0	1	0	0	1	0	0
	Grunting	0	2	1	8	10	0	0
	Haemoptysis	29	122	13	93	215	0	0
	Haemothorax	2	4	0	0	4	0	0
	Hiccups	6	23	15	60	83	0	0
	Hyperactive pharyngeal reflex	0	0	2	2	2	0	0
	Hypercapnia	0	27	1	1	28	0	0
	Hypersensitivity pneumonitis	2	10	0	0	10	0	0
	Hyperventilation	20	93	25	250	343	0	0
	Hypocapnia	0	1	0	1	2	0	0
	Hypopnoea	17	70	11	137	207	0	0
	Hypoventilation	9	14	8	10	24	0	0
	Hypoxia	33	823	6	15	838	0	0
	Idiopathic interstitial pneumonia	0	1	0	0	1	0	0
	Idiopathic pulmonary fibrosis	2	8	0	0	8	0	0
	Immune-mediated lung disease	0	1	0	0	1	0	0
	Increased bronchial secretion	0	6	6	17	23	0	0
	Increased upper airway secretion	0	7	13	37	44	0	0
	Increased viscosity of bronchial secretion	0	0	0	1	1	0	0
	Increased viscosity of upper respiratory secretion	0	8	2	24	32	0	0
	Infantile apnoea	0	1	0	0	1	0	0
	Interstitial lung disease	26	104	0	2	106	0	0
	Intranasal hypoaesthesia	1	2	0	6	8	0	0
	Intranasal paraesthesia	0	0	1	1	1	0	0
	Irregular breathing	7	12	1	22	34	0	0
	Kussmaul respiration	0	1	0	0	1	0	0
	Laryngeal discomfort	1	1	9	32	33	0	0
	Laryngeal disorder	0	0	1	1	1	0	0
	Laryngeal haemorrhage	0	1	0	0	1	0	0
	Laryngeal inflammation	2	3	2	5	8	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Laryngeal mass	0	0	0	1	1	0	0
	Laryngeal obstruction	0	1	0	0	1	0	0
	Laryngeal oedema	14	69	7	9	78	0	0
	Laryngeal pain	1	3	3	5	8	0	0
	Laryngeal stenosis	0	1	0	0	1	0	0
	Laryngospasm	3	8	0	6	14	0	0
	Larynx irritation	0	1	4	11	12	0	0
	Low lung compliance	0	1	1	1	2	0	0
	Lower respiratory tract congestion	1	2	4	26	28	0	0
	Lung consolidation	3	59	0	4	63	0	0
	Lung cyst	0	2	0	1	3	0	0
	Lung diffusion disorder	0	0	1	1	1	0	0
	Lung disorder	11	121	15	81	202	0	0
	Lung hyperinflation	0	8	1	3	11	0	0
	Lung hypoinflation	0	2	0	0	2	0	0
	Lung infiltration	3	221	1	17	238	0	0
	Lung opacity	1	323	1	15	338	0	0
	Lupus pneumonitis	0	1	0	0	1	0	0
	Lymphangioleiomyomatosis	0	1	0	0	1	0	0
	Meconium aspiration syndrome	0	1	0	0	1	0	0
	Mediastinal disorder	0	2	0	0	2	0	0
	Mediastinal haematoma	0	1	0	0	1	0	0
	Mediastinal mass	0	4	0	1	5	0	0
	Mouth breathing	0	3	0	7	10	0	0
	Nasal cavity mass	0	1	1	1	2	0	0
	Nasal congestion	23	161	236	1968	2129	0	0
	Nasal crusting	1	1	3	9	10	0	0
	Nasal discharge discolouration	0	0	2	10	10	0	0
	Nasal discomfort	5	24	23	157	181	0	0
	Nasal disorder	1	1	1	9	10	0	0
	Nasal dryness	1	5	14	67	72	0	0
	Nasal inflammation	2	3	5	21	24	0	0
	Nasal mucosal blistering	0	0	0	3	3	0	0
	Nasal mucosal discolouration	0	0	0	1	1	0	0
	Nasal mucosal disorder	0	0	7	8	8	0	0
	Nasal obstruction	1	1	8	18	19	0	0
	Nasal odour	0	0	1	1	1	0	0
	Nasal oedema	0	5	3	31	36	0	0
	Nasal polyps	0	0	0	3	3	0	0
	Nasal pruritus	0	2	4	31	33	0	0
	Nasal septum deviation	0	0	0	5	5	0	0
	Nasal septum disorder	0	1	0	1	2	0	0
	Nasal turbinate hypertrophy	0	1	1	2	3	0	0
	Nasal ulcer	0	0	0	1	1	0	0
	Neonatal aspiration	0	3	0	0	3	0	0
	Neonatal dyspnoea	1	3	0	1	4	0	0
	Neonatal hypoxia	0	1	0	0	1	0	0
	Neonatal respiratory distress	0	1	0	0	1	0	0
	Neonatal respiratory distress syndrome	0	3	0	0	3	0	0
	Nocturnal dyspnoea	0	1	3	7	8	0	0
	Obstructive airways disorder	8	37	4	30	67	0	0
	Obstructive sleep apnoea syndrome	0	3	1	2	5	0	0
	Organising pneumonia	7	20	0	0	20	0	0
	Oropharyngeal blistering	1	20	2	4	24	0	0
	Oropharyngeal discomfort	19	72	91	786	858	0	0
	Oropharyngeal oedema	0	2	0	5	7	0	0
	Oropharyngeal pain	179	863	950	5172	6035	0	0
	Oropharyngeal plaque	1	1	3	7	8	0	0
	Oropharyngeal spasm	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Oropharyngeal swelling	1	2	3	16	18	0	0
	Orthopnoea	6	36	3	12	48	0	0
	Painful respiration	9	103	36	162	265	0	0
	Paranasal cyst	0	1	0	2	3	0	0
	Paranasal sinus discomfort	1	21	19	229	250	0	0
	Paranasal sinus haemorrhage	0	0	1	3	3	0	0
	Paranasal sinus hypersecretion	0	2	5	23	25	0	0
	Paranasal sinus hyposecretion	0	1	1	5	6	0	0
	Paranasal sinus inflammation	2	6	3	17	23	0	0
	Pharyngeal cyst	0	0	1	1	1	0	0
	Pharyngeal disorder	1	1	1	5	6	0	0
	Pharyngeal enanthema	0	1	0	1	2	0	0
	Pharyngeal erythema	3	9	9	67	76	0	0
	Pharyngeal exudate	0	0	0	1	1	0	0
	Pharyngeal haemorrhage	1	8	0	2	10	0	0
	Pharyngeal hypoaesthesia	4	17	1	133	150	0	0
	Pharyngeal inflammation	0	2	5	12	14	0	0
	Pharyngeal mass	0	0	0	1	1	0	0
	Pharyngeal oedema	6	32	11	49	81	0	0
	Pharyngeal paraesthesia	4	23	9	277	300	0	0
	Pharyngeal swelling	26	275	99	1331	1606	0	0
	Pharyngeal ulceration	0	1	1	9	10	0	0
	Pleural calcification	0	1	0	0	1	0	0
	Pleural disorder	0	1	0	2	3	0	0
	Pleural effusion	40	320	7	38	358	0	0
	Pleural fibrosis	0	1	0	1	2	0	0
	Pleural thickening	1	11	0	1	12	0	0
	Pleurisy	27	69	9	53	122	0	0
	Pleuritic pain	6	80	3	41	121	0	0
	Pneumomediastinum	2	9	0	0	9	0	0
	Pneumonitis	25	94	7	47	141	0	1
	Pneumonitis aspiration	1	3	0	0	3	0	0
	Pneumothorax	8	64	1	1	65	0	0
	Pneumothorax spontaneous	1	4	0	0	4	0	0
	Productive cough	28	225	83	493	718	0	0
	Prolonged expiration	0	1	0	0	1	0	0
	Pulmonary air leakage	0	1	0	0	1	0	0
	Pulmonary alveolar haemorrhage	5	14	0	0	14	0	0
	Pulmonary amyloidosis	0	1	0	0	1	0	0
	Pulmonary arterial hypertension	0	6	0	1	7	0	0
	Pulmonary arteriopathy	0	1	0	0	1	0	0
	Pulmonary artery dilatation	0	6	0	0	6	0	0
	Pulmonary artery occlusion	0	5	0	0	5	0	0
	Pulmonary artery stenosis	0	1	0	0	1	0	0
	Pulmonary artery thrombosis	2	11	0	0	11	0	0
	Pulmonary artery wall hypertrophy	0	2	0	1	3	0	0
	Pulmonary calcification	0	5	2	3	8	0	0
	Pulmonary cavitation	1	3	0	0	3	0	0
	Pulmonary congestion	11	167	3	20	187	0	0
	Pulmonary embolism	655	2663	13	24	2687	0	0
	Pulmonary fibrosis	5	57	0	0	57	0	0
	Pulmonary granuloma	1	16	0	0	16	0	0
	Pulmonary haematoma	0	1	0	0	1	0	0
	Pulmonary haemorrhage	5	20	0	0	20	0	0
	Pulmonary hilar enlargement	0	2	0	0	2	0	0
	Pulmonary hilum mass	0	4	0	0	4	0	0
	Pulmonary hypertension	11	66	0	0	66	0	0
	Pulmonary infarction	9	79	0	0	79	0	0
	Pulmonary interstitial emphysema syndrome	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Pulmonary mass	8	89	4	31	120	0	0
	Pulmonary microemboli	1	5	0	0	5	0	0
	Pulmonary oedema	32	260	0	8	268	0	0
	Pulmonary oedema neonatal	0	1	0	0	1	0	0
	Pulmonary pain	21	86	76	296	382	0	0
	Pulmonary sarcoidosis	2	7	0	0	7	0	0
	Pulmonary sensitisation	0	0	0	1	1	0	0
	Pulmonary thrombosis	23	268	0	1	269	0	0
	Pulmonary toxicity	0	1	0	0	1	0	0
	Pulmonary vascular disorder	0	8	1	2	10	0	0
	Pulmonary vasculitis	0	2	0	0	2	0	0
	Pulmonary venous hypertension	0	1	0	0	1	0	0
	Pulmonary venous thrombosis	1	2	0	0	2	0	0
	Rales	1	40	2	16	56	0	0
	Reactive airways dysfunction syndrome	0	0	0	1	1	0	0
	Reflux laryngitis	0	2	0	2	4	0	0
	Respiration abnormal	13	76	35	146	222	0	0
	Respiratory acidosis	2	8	0	1	9	0	0
	Respiratory alkalosis	0	3	0	1	4	0	0
	Respiratory arrest	20	172	0	2	174	0	0
	Respiratory depression	0	20	0	0	20	0	0
	Respiratory depth decreased	2	4	3	5	9	0	0
	Respiratory disorder	13	82	35	104	186	0	0
	Respiratory disorder neonatal	0	1	0	0	1	0	0
	Respiratory distress	49	286	41	59	345	0	0
	Respiratory failure	57	363	0	0	363	0	0
	Respiratory fatigue	3	8	11	21	29	0	0
	Respiratory gas exchange disorder	0	0	0	1	1	0	0
	Respiratory muscle weakness	0	3	0	2	5	0	0
	Respiratory symptom	7	51	5	50	101	0	0
	Respiratory tract congestion	0	152	2	579	731	0	0
	Respiratory tract haemorrhage	3	7	1	2	9	0	0
	Respiratory tract inflammation	0	0	0	1	1	0	0
	Respiratory tract irritation	0	5	5	28	33	0	0
	Respiratory tract oedema	5	16	1	2	18	0	0
	Respiratory tract ulceration	0	1	0	0	1	0	0
	Restrictive pulmonary disease	0	5	0	0	5	0	0
	Rhinalgia	1	9	10	51	60	0	0
	Rhinitis allergic	0	5	9	35	40	0	0
	Rhinorrhoea	59	282	397	2783	3065	0	0
	Rhonchi	0	10	2	9	19	0	0
	Sinonasal obstruction	1	3	4	10	13	0	0
	Sinus congestion	5	35	23	304	339	0	0
	Sinus disorder	1	16	6	146	162	0	0
	Sinus pain	19	81	44	195	276	0	0
	Sinus polyp	0	1	0	0	1	0	0
	Sleep apnoea syndrome	7	30	7	34	64	0	0
	Small airways disease	0	2	0	0	2	0	0
	Sneezing	15	66	126	814	880	0	0
	Snoring	0	11	1	23	34	0	0
	Sputum discoloured	2	44	5	33	77	0	0
	Sputum increased	3	9	5	10	19	0	0
	Sputum retention	0	1	2	4	5	0	0
	Status asthmaticus	0	1	0	0	1	0	0
	Stertor	1	1	0	0	1	0	0
	Stridor	4	21	2	23	44	0	0
	Suffocation feeling	4	15	13	41	56	0	0
	Tachypnoea	12	151	7	107	258	0	0
	Throat clearing	1	13	2	113	126	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Throat irritation	32	162	139	1811	1973	0	0
	Throat lesion	0	0	0	1	1	0	0
	Throat tightness	26	297	70	1680	1977	0	0
	Tonsillar cyst	0	1	0	0	1	0	0
	Tonsillar disorder	0	0	0	6	6	0	0
	Tonsillar erythema	0	3	2	9	12	0	0
	Tonsillar haemorrhage	0	1	0	0	1	0	0
	Tonsillar hypertrophy	2	19	8	87	106	0	0
	Tonsillar inflammation	0	2	11	26	28	0	0
	Tonsillar ulcer	0	0	0	2	2	0	0
	Tonsillolith	0	0	0	3	3	0	0
	Tracheal compression	0	1	0	0	1	0	0
	Tracheal disorder	0	1	0	0	1	0	0
	Tracheal diverticulum	0	1	0	0	1	0	0
	Tracheal inflammation	0	1	1	4	5	0	0
	Tracheal oedema	0	1	0	0	1	0	0
	Tracheal pain	2	4	5	10	14	0	0
	Tracheal stenosis	0	1	0	0	1	0	0
	Tracheomalacia	0	1	0	0	1	1	1
	Transient tachypnoea of the newborn	0	0	0	1	1	0	0
	Upper airway obstruction	0	2	0	1	3	0	0
	Upper respiratory tract congestion	0	4	1	23	27	0	0
	Upper respiratory tract inflammation	0	0	4	6	6	0	0
	Upper respiratory tract irritation	0	1	0	1	2	0	0
	Upper-airway cough syndrome	1	11	5	132	143	0	0
	Use of accessory respiratory muscles	0	3	1	7	10	0	0
	Vocal cord cyst	1	1	0	0	1	0	0
	Vocal cord disorder	0	3	1	6	9	0	0
	Vocal cord dysfunction	0	5	1	6	11	0	0
	Vocal cord inflammation	0	1	1	3	4	0	0
	Vocal cord scarring	0	0	0	1	1	0	0
	Vocal cord thickening	0	0	0	2	2	0	0
	Wheezing	42	327	52	831	1158	0	0
	Yawning	3	8	7	41	49	0	0
Skin and subcutaneous tissue disorders	*** SOC TOTAL ***	4325	15773	20462	124232	140005	0	0
	Acne	12	43	90	305	348	0	0
	Acne cystic	0	0	2	7	7	0	0
	Actinic keratosis	0	0	1	5	5	0	0
	Acute cutaneous lupus erythematosus	1	2	0	0	2	0	0
	Acute febrile neutrophilic dermatosis	3	9	1	3	12	0	0
	Acute generalised exanthematous pustulosis	2	12	1	3	15	0	0
	Alopecia	67	167	341	841	1008	0	0
	Alopecia areata	15	29	55	93	122	0	0
	Alopecia totalis	0	2	0	1	3	0	0
	Alopecia universalis	1	2	2	5	7	0	0
	Androgenetic alopecia	0	1	1	5	6	0	0
	Angioedema	192	827	114	167	994	0	0
	Anhidrosis	0	1	0	0	1	0	0
	Anogenital lichen planus	0	0	1	1	1	0	0
	Autoimmune blistering disease	1	1	0	0	1	0	0
	Autoimmune dermatitis	0	1	0	0	1	0	0
	Blister	48	186	131	999	1185	0	0
	Blister rupture	0	4	1	14	18	0	0
	Blood blister	1	12	3	49	61	0	0
	Brachioradial pruritus	0	0	1	2	2	0	0
	Bromhidrosis	0	1	0	0	1	0	0
	Brow ptosis	0	1	0	0	1	0	0
	Bullous haemorrhagic dermatosis	1	3	1	1	4	0	0
	Butterfly rash	0	1	2	16	17	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Capillaritis	2	3	1	2	5	0	0
	Cellulite	0	0	0	5	5	0	0
	Chloasma	0	0	1	1	1	0	0
	Chronic cutaneous lupus erythematosus	1	2	0	0	2	0	0
	Chronic pigmented purpura	0	0	2	4	4	0	0
	Chronic spontaneous urticaria	8	17	20	24	41	0	0
	Circumoral oedema	0	0	1	7	7	0	0
	Circumoral swelling	2	3	7	27	30	0	0
	Cold sweat	74	405	214	1661	2066	0	0
	Cold urticaria	1	3	6	19	22	0	0
	Cutaneous lupus erythematosus	2	5	0	0	5	0	0
	Cutaneous sarcoidosis	1	2	1	1	3	0	0
	Cutaneous symptom	1	2	2	21	23	0	0
	Cutaneous vasculitis	22	64	6	7	71	0	0
	Cutis verticis gyrata	0	0	0	1	1	0	0
	Dandruff	1	1	3	8	9	0	0
	Decubitus ulcer	1	8	2	10	18	0	0
	Dermal cyst	2	8	6	14	22	0	0
	Dermatitis	19	61	77	280	341	0	0
	Dermatitis acneiform	1	5	10	65	70	0	0
	Dermatitis allergic	25	84	97	382	466	0	0
	Dermatitis atopic	9	20	32	63	83	0	0
	Dermatitis bullous	7	83	26	45	128	0	0
	Dermatitis contact	5	11	13	87	98	0	0
	Dermatitis diaper	0	0	0	2	2	0	0
	Dermatitis exfoliative	1	1	1	1	2	0	0
	Dermatitis exfoliative generalised	4	15	3	4	19	0	0
	Dermatitis herpetiformis	0	0	1	2	2	0	0
	Dermatitis psoriasiform	2	2	3	11	13	0	0
	Dermatomyositis	6	20	0	1	21	0	0
	Dermatosis	1	1	5	13	14	0	0
	Diabetic foot	1	1	0	0	1	0	0
	Diffuse alopecia	2	2	13	24	26	0	0
	Drug eruption	2	15	13	57	72	0	0
	Drug reaction with eosinophilia and systemic symptoms	4	27	0	0	27	0	0
	Dry skin	21	73	60	405	478	0	0
	Dyshidrotic eczema	1	9	6	26	35	0	0
	Ecchymosis	13	46	37	142	188	0	0
	Eczema	52	116	221	640	756	0	0
	Eczema asteatotic	0	0	2	4	4	0	0
	Eczema nummular	1	2	6	19	21	0	0
	Eczema vesicular	0	0	0	1	1	0	0
	Eczema weeping	1	1	2	3	4	0	0
	Eosinophilic cellulitis	0	1	1	1	2	0	0
	Ephelides	1	1	2	8	9	0	0
	Epidermolysis	0	3	0	0	3	0	0
	Erythema	208	1122	1890	17458	18580	0	0
	Erythema annulare	1	1	6	21	22	0	0
	Erythema dyschromicum perstans	0	0	0	1	1	0	0
	Erythema elevatum diutinum	1	1	0	1	2	0	0
	Erythema marginatum	0	0	2	2	2	0	0
	Erythema multiforme	32	252	26	43	295	0	0
	Erythema nodosum	18	40	43	100	140	0	0
	Erythrodermic psoriasis	2	2	0	0	2	0	0
	Erythrosis	0	0	2	3	3	0	0
	Excessive granulation tissue	0	0	0	1	1	0	0
	Exfoliative rash	1	7	5	58	65	0	0
	Facial wasting	0	0	0	1	1	0	0
	Fixed eruption	2	3	2	10	13	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Flagellate dermatitis	1	2	0	0	2	0	0
	Fordyce spots	0	0	0	2	2	0	0
	Generalised bullous fixed drug eruption	0	1	0	1	2	0	0
	Granuloma annulare	0	3	6	19	22	0	0
	Granuloma skin	0	0	0	1	1	0	0
	Granulomatous dermatitis	0	1	0	1	2	0	0
	Guttate psoriasis	1	3	6	16	19	0	0
	Haemorrhage subcutaneous	4	24	3	3	27	0	0
	Haemorrhage subepidermal	0	1	0	1	2	0	0
	Haemosiderin stain	0	1	0	1	2	0	0
	Hair colour changes	0	0	7	15	15	0	0
	Hair disorder	1	1	1	8	9	0	0
	Hair growth abnormal	2	2	6	15	17	0	0
	Hair growth rate abnormal	0	0	0	1	1	0	0
	Hair texture abnormal	0	1	5	17	18	0	0
	Hand dermatitis	0	3	12	22	25	0	0
	Hangnail	0	1	0	0	1	0	0
	Heliotrope rash	0	1	0	1	2	0	0
	Henoch-Schonlein purpura	9	27	9	17	44	0	0
	Herpes gestationis	0	0	0	1	1	0	0
	Hidradenitis	3	7	11	17	24	0	0
	Hirsutism	0	0	1	2	2	0	0
	Hyperhidrosis	321	1647	1032	8182	9829	0	0
	Hyperkeratosis	0	1	2	11	12	0	0
	Hyperkeratosis follicularis et parafollicularis	2	2	0	0	2	0	0
	Hypersensitivity vasculitis	2	12	0	0	12	0	0
	Hypertrophic scar	0	0	0	1	1	0	0
	Hypohidrosis	0	0	2	7	7	0	0
	Hypotrichosis	0	1	0	2	3	0	0
	Ichthyosis acquired	0	0	0	1	1	0	0
	Idiopathic angioedema	0	3	0	0	3	0	0
	Idiopathic urticaria	3	6	4	11	17	0	0
	Ingrown hair	0	2	0	2	4	0	0
	Interstitial granulomatous dermatitis	0	0	1	2	2	0	0
	Intertrigo	0	2	0	2	4	0	0
	Ischaemic skin ulcer	0	2	0	0	2	0	0
	Itching scar	0	3	1	12	15	0	0
	Keloid scar	0	1	3	8	9	0	0
	Keratosis pilaris	0	0	0	13	13	0	0
	Leukoplakia	0	0	0	1	1	0	0
	Lichen planopilaris	1	1	1	4	5	0	0
	Lichen planus	7	16	25	49	65	0	0
	Lichen sclerosus	1	2	6	17	19	0	0
	Lichenification	0	0	1	3	3	0	0
	Lichenoid keratosis	0	1	4	10	11	0	0
	Linear IgA disease	1	3	0	0	3	0	0
	Lipoatrophy	0	1	0	1	2	0	0
	Lipodystrophy acquired	0	2	0	1	3	0	0
	Lipohypertrophy	0	0	0	2	2	0	0
	Livedo reticularis	5	23	7	91	114	0	0
	Lividity	2	6	0	0	6	0	0
	Lymphomatoid papulosis	0	1	0	0	1	0	0
	Macule	1	5	13	57	62	0	0
	Madarosis	0	1	4	11	12	0	0
	Mechanical urticaria	60	66	284	336	402	0	0
	Melanoderma	0	0	0	1	1	0	0
	Milia	0	0	0	4	4	0	0
	Miliaria	5	29	9	103	132	0	0
	Mucocutaneous disorder	0	1	0	1	2	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Mucous membrane pemphigoid	1	1	0	0	1	0	0
	Nail bed bleeding	0	0	2	2	2	0	0
	Nail bed inflammation	0	0	3	5	5	0	0
	Nail bed tenderness	0	0	1	2	2	0	0
	Nail cuticle fissure	0	0	1	1	1	0	0
	Nail discolouration	1	2	4	22	24	0	0
	Nail disorder	1	8	4	10	18	0	0
	Nail dystrophy	0	0	1	1	1	0	0
	Nail growth abnormal	1	1	0	3	4	0	0
	Nail hypertrophy	0	0	0	1	1	0	0
	Nail psoriasis	0	1	1	4	5	0	0
	Nail ridging	1	1	1	2	3	0	0
	Needle track marks	0	0	2	8	8	0	0
	Neurodermatitis	2	7	50	71	78	0	0
	Neuropathic pruritus	0	0	0	1	1	0	0
	Neuropathic ulcer	0	0	0	1	1	0	0
	Neutrophilic dermatosis	0	2	0	3	5	0	0
	Night sweats	97	383	271	1382	1765	0	0
	Nodular rash	0	2	0	5	7	0	0
	Non-scarring alopecia	0	0	2	2	2	0	0
	Oculomucocutaneous syndrome	1	10	0	0	10	0	0
	Oedema blister	0	0	0	3	3	0	0
	Onychalgia	1	2	2	8	10	0	0
	Onychoclasis	1	3	6	14	17	0	0
	Onycholysis	0	0	1	2	2	0	0
	Onychomadesis	0	2	2	5	7	0	0
	Pain of skin	39	181	171	917	1098	0	0
	Palmar erythema	0	3	4	19	22	0	0
	Palmar-plantar erythrodysaesthesia syndrome	0	5	3	15	20	0	0
	Palmoplantar keratoderma	1	1	0	0	1	0	0
	Palmoplantar pustulosis	2	4	1	2	6	0	0
	Palpable purpura	0	1	0	2	3	0	0
	Panniculitis	1	6	1	4	10	0	0
	Papule	4	14	55	201	215	0	0
	Papulopustular rosacea	0	0	0	1	1	0	0
	Parakeratosis	0	0	0	2	2	0	0
	Parapsoriasis	0	1	4	6	7	0	0
	Peau d'orange	0	0	0	2	2	0	0
	Pemphigoid	16	65	0	4	69	0	0
	Pemphigus	7	22	1	3	25	0	0
	Perioral dermatitis	1	2	8	18	20	0	0
	Pernio-like erythema	1	1	1	2	3	0	0
	Petechiae	31	186	97	426	612	0	0
	Photodermatosis	0	0	0	1	1	0	0
	Photosensitivity reaction	7	36	25	144	180	0	0
	Pigmentation disorder	3	9	8	49	58	0	0
	Piloerection	2	15	14	65	80	0	0
	Pityriasis	2	4	1	6	10	0	0
	Pityriasis lichenoides et varioliformis acuta	1	1	1	2	3	0	0
	Pityriasis rosea	8	17	52	136	153	0	0
	Pityriasis rubra pilaris	3	5	2	5	10	0	0
	Plantar erythema	0	1	0	2	3	0	0
	Polymorphic light eruption	0	0	1	2	2	0	0
	Post inflammatory pigmentation change	0	1	0	0	1	0	0
	Progressive facial hemiatrophy	2	2	0	0	2	0	0
	Prurigo	3	4	8	27	31	0	0
	Pruritus	610	1956	3344	22843	24799	0	0
	Pruritus allergic	1	3	4	12	15	0	0
	Psoriasis	47	90	183	337	427	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Purpura	15	67	28	151	218	0	0
	Purpura fulminans	0	1	0	0	1	0	0
	Pustular psoriasis	2	2	1	2	4	0	0
	Pyoderma gangrenosum	1	4	0	1	5	0	0
	Rash	635	2506	4750	23773	26279	0	0
	Rash erythematous	101	511	403	5980	6491	0	0
	Rash follicular	0	0	0	3	3	0	0
	Rash macular	43	173	244	2371	2544	0	0
	Rash maculo-papular	6	40	49	242	282	0	0
	Rash morbilliform	6	10	16	82	92	0	0
	Rash papular	19	109	98	1592	1701	0	0
	Rash pruritic	95	367	627	5070	5437	0	0
	Rash rubelliform	0	0	1	2	2	0	0
	Rash scarlatiniform	0	1	1	6	7	0	0
	Rash vesicular	6	34	73	289	323	0	0
	Rebound psoriasis	0	1	0	0	1	0	0
	Rosacea	3	7	25	70	77	0	0
	SJS-TEN overlap	0	1	0	0	1	0	0
	Sarcoid-like reaction	1	1	0	0	1	0	0
	Scab	3	17	13	106	123	0	0
	Scar discomfort	1	1	1	1	2	0	0
	Scar pain	1	5	4	25	30	0	0
	Sebaceous gland disorder	0	0	1	1	1	0	0
	Seborrhoea	0	0	2	8	8	0	0
	Seborrhoeic dermatitis	1	1	11	16	17	0	0
	Segmented hyalinising vasculitis	1	3	0	0	3	0	0
	Sensitive skin	27	131	80	565	696	0	0
	Skin atrophy	0	3	1	12	15	0	0
	Skin burning sensation	48	136	167	814	950	0	0
	Skin depigmentation	0	3	5	13	16	0	0
	Skin discharge	1	2	1	5	7	0	0
	Skin discolouration	25	157	121	1025	1182	0	0
	Skin discomfort	1	6	19	71	77	0	0
	Skin disorder	119	229	286	450	679	0	0
	Skin dystrophy	0	0	0	1	1	0	0
	Skin erosion	4	7	4	26	33	0	0
	Skin exfoliation	14	64	72	424	488	0	0
	Skin fissures	4	5	12	25	30	0	0
	Skin fragility	0	0	0	1	1	0	0
	Skin haemorrhage	6	16	29	89	105	0	0
	Skin hyperpigmentation	0	1	2	26	27	0	0
	Skin hyperplasia	0	0	1	1	1	0	0
	Skin hypertrophy	0	2	5	20	22	0	0
	Skin hypopigmentation	1	2	1	4	6	0	0
	Skin indentation	1	3	0	11	14	0	0
	Skin induration	2	4	5	133	137	0	0
	Skin irritation	16	44	54	289	333	0	0
	Skin laxity	0	0	2	5	5	0	0
	Skin lesion	4	38	27	289	327	0	0
	Skin lesion inflammation	0	0	0	4	4	0	0
	Skin maceration	0	1	0	2	3	0	0
	Skin mass	4	19	25	258	277	0	0
	Skin necrosis	1	13	0	1	14	0	0
	Skin odour abnormal	1	5	13	44	49	0	0
	Skin oedema	0	2	5	16	18	0	0
	Skin plaque	5	11	8	44	55	0	0
	Skin reaction	48	146	251	1777	1923	0	0
	Skin sensitisation	1	12	10	70	82	0	0
	Skin striae	0	1	3	11	12	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Skin swelling	12	29	46	387	416	0	0
	Skin texture abnormal	2	4	3	31	35	0	0
	Skin tightness	4	18	22	267	285	0	0
	Skin ulcer	4	32	12	49	81	0	0
	Skin ulcer haemorrhage	0	1	0	2	3	0	0
	Skin warm	15	194	71	4425	4619	0	0
	Skin weeping	2	12	7	32	44	0	0
	Skin wrinkling	0	3	2	27	30	0	0
	Solar dermatitis	0	0	3	6	6	0	0
	Solar lentigo	0	0	0	1	1	0	0
	Solar urticaria	1	2	0	3	5	0	0
	Spider naevus	0	0	2	3	3	0	0
	Splinter haemorrhages	0	0	0	3	3	0	0
	Stasis dermatitis	0	2	1	2	4	0	0
	Stevens-Johnson syndrome	8	45	1	1	46	0	0
	Sticky skin	0	0	1	11	11	0	0
	Subacute cutaneous lupus erythematosus	1	6	0	0	6	0	0
	Subcutaneous drug absorption impaired	0	0	0	1	1	0	0
	Subcutaneous emphysema	1	4	0	2	6	0	0
	Superficial inflammatory dermatosis	0	3	0	1	4	0	0
	Sweat discolouration	0	0	0	3	3	0	0
	Sweat gland disorder	1	1	0	0	1	0	0
	Symmetrical drug-related intertriginous and flexural exanthema	0	3	0	0	3	0	0
	Systemic lupus erythematosus rash	1	2	0	3	5	0	0
	Target skin lesion	1	6	1	2	8	0	0
	Telangiectasia	2	2	0	6	8	0	0
	Toxic epidermal necrolysis	4	8	0	0	8	0	0
	Toxic skin eruption	3	13	1	1	14	0	0
	Transient acantholytic dermatosis	1	2	3	4	6	0	0
	Trichodynia	0	0	6	9	9	0	0
	Trichorrhexis	0	0	3	8	8	0	0
	Umbilical erythema	0	0	2	2	2	0	0
	Urticaria	699	1514	3134	12137	13651	0	0
	Urticaria aquagenic	0	2	1	1	3	0	0
	Urticaria cholinergic	0	1	4	5	6	0	0
	Urticaria chronic	37	47	106	121	168	0	0
	Urticaria contact	1	1	3	4	5	0	0
	Urticaria papular	2	4	1	15	19	0	0
	Urticaria physical	1	1	6	6	7	0	0
	Urticaria pigmentosa	1	1	0	0	1	0	0
	Urticaria pressure	0	0	3	4	4	0	0
	Urticaria thermal	0	0	0	4	4	0	0
	Urticaria vesiculosa	0	0	1	3	3	0	0
	Urticarial dermatitis	0	0	2	5	5	0	0
	Urticarial vasculitis	4	15	2	2	17	0	0
	Vancomycin infusion reaction	0	0	0	1	1	0	0
	Vascular purpura	0	4	1	1	5	0	0
	Vasculitic rash	1	5	2	8	13	0	0
	Venous ulcer pain	0	1	0	0	1	0	0
	Vitiligo	2	11	11	34	45	0	0
	Yellow skin	4	13	5	38	51	0	0
Social circumstances	*** SOC TOTAL ***	247	1543	795	4740	6283	0	0
	Abstains from alcohol	0	2	0	0	2	0	0
	Abstains from recreational drugs	0	1	0	0	1	0	0
	Alcohol use	0	3	0	3	6	0	0
	Anal sex	0	1	0	0	1	0	0
	Bedridden	25	85	166	659	744	0	0
	Blood donor	0	0	0	1	1	0	0
	Blood product transfusion dependent	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Bottle feeding	0	0	0	1	1	0	0
	Breast feeding	4	7	5	31	38	0	0
	Cardiac assistance device user	1	13	0	2	15	0	0
	Caregiver	1	1	0	1	2	0	0
	Contraindication to medical treatment	0	1	0	0	1	0	0
	Contraindication to vaccination	0	3	0	4	7	0	0
	Convalescent	0	1	0	0	1	0	0
	Corrective lens user	0	1	2	4	5	0	0
	Death of pet	0	0	0	1	1	0	0
	Dental prosthesis user	0	0	1	1	1	0	0
	Dependence on oxygen therapy	1	9	0	0	9	0	0
	Device dependence	1	3	0	0	3	0	0
	Disability	6	49	1	4	53	0	0
	Economic problem	0	2	0	0	2	0	0
	Educational problem	0	0	2	2	2	0	0
	Ex-tobacco user	0	1	0	0	1	0	0
	Excessive exercise	0	0	1	1	1	0	0
	Exercise lack of	0	1	0	5	6	0	0
	Familial risk factor	0	0	0	2	2	0	0
	Family stress	0	0	0	2	2	0	0
	Fasting	0	1	0	8	9	0	0
	Feeding tube user	0	8	0	2	10	0	0
	Foot prosthesis user	0	0	0	1	1	0	0
	Foreign travel	0	2	0	0	2	0	0
	Hearing aid user	0	3	0	1	4	0	0
	Hearing disability	0	3	0	8	11	0	0
	Housebound	0	4	0	4	8	0	0
	Illiteracy	0	1	0	0	1	0	0
	Immobile	6	53	1	10	63	0	0
	Immobilisation prolonged	0	2	0	0	2	0	0
	Impaired ability to use machinery	0	2	2	4	6	0	0
	Impaired driving ability	9	124	20	239	363	0	0
	Impaired quality of life	5	25	31	65	90	0	0
	Impaired work ability	95	486	252	1946	2432	0	0
	Imprisonment	0	1	0	0	1	0	0
	Inability to afford medication	0	0	0	1	1	0	0
	Inadequate diet	0	1	0	0	1	0	0
	Insurance issue	0	0	0	1	1	0	0
	Job dissatisfaction	0	0	1	8	8	0	0
	Living alone	0	0	0	1	1	0	0
	Loss of employment	0	2	0	5	7	0	0
	Loss of personal independence in daily activities	54	391	234	1412	1803	0	0
	Menarche	0	2	0	1	3	0	0
	Menopause	7	13	11	29	42	0	0
	Mental disability	0	0	0	3	3	0	0
	Multigravida	0	1	0	2	3	0	0
	Multiparous	0	0	1	1	1	0	0
	Non-tobacco user	0	1	0	0	1	0	0
	Organ donor	0	2	0	0	2	0	0
	Orthosis user	0	6	0	1	7	0	0
	Overwork	0	0	0	4	4	0	0
	Paralytic disability	0	0	0	1	1	0	0
	Partner stress	0	0	1	1	1	0	0
	Patient uncooperative	0	2	0	0	2	0	0
	Physical assault	0	1	0	2	3	0	0
	Physical disability	1	6	0	6	12	0	0
	Planning to become pregnant	0	0	0	1	1	0	0
	Postmenopause	1	2	1	3	5	0	0
	Refusal of examination	0	0	0	1	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Refusal of treatment by patient	0	7	0	10	17	0	0
	Refusal of treatment by relative	0	1	0	0	1	0	0
	Refusal of vaccination	0	1	0	6	7	0	0
	Retirement	0	1	0	2	3	0	0
	Sick leave	21	25	42	44	69	0	0
	Sick relative	0	3	0	2	5	0	0
	Sight disability	2	6	1	6	12	0	0
	Sitting disability	1	13	10	37	50	0	0
	Social problem	0	1	0	2	3	0	0
	Spousal abuse	0	1	0	0	1	0	0
	Stress at work	0	1	0	4	5	0	0
	Substance use	0	1	0	5	6	0	0
	Tanning	0	0	0	1	1	0	0
	Tattoo	0	0	1	3	3	0	0
	Threat of redundancy	0	1	0	0	1	0	0
	Tobacco user	0	4	0	1	5	0	0
	Unemployment	0	0	0	2	2	0	0
	Unhealthy diet	0	0	0	1	1	0	0
	Vegan	0	0	0	1	1	0	0
	Victim of abuse	0	1	0	0	1	0	0
	Walking aid user	2	93	6	84	177	0	0
	Walking disability	1	12	1	11	23	0	0
	Water pollution	1	5	0	5	10	0	0
	Wheelchair user	2	36	1	17	53	0	0
Surgical and medical procedures	*** SOC TOTAL ***	1262	3409	2668	4993	8402	0	0
	Abdominal cavity drainage	0	2	0	0	2	0	0
	Abortion induced	3	11	1	5	16	0	0
	Abscess drainage	1	4	0	7	11	0	0
	Acrochordon excision	0	0	0	1	1	0	0
	Acupuncture	0	2	0	1	3	0	0
	Adhesiolysis	0	1	0	0	1	0	0
	Adrenocortical steroid therapy	0	0	2	2	2	0	0
	Airway patency device insertion	0	1	0	0	1	0	0
	Amputation	1	3	0	0	3	0	0
	Anaesthesia procedure	0	0	0	1	1	0	0
	Analgesic therapy	0	0	10	12	12	0	0
	Anaphylaxis prophylaxis	0	0	0	8	8	0	0
	Anaphylaxis treatment	0	0	0	1	1	0	0
	Aneurysm repair	0	2	0	0	2	0	0
	Aneurysmectomy	0	0	0	1	1	0	0
	Angioplasty	0	6	0	1	7	0	0
	Ankle operation	0	2	0	0	2	0	0
	Antiallergic therapy	0	0	3	5	5	0	0
	Antibiotic therapy	0	0	1	3	3	0	0
	Anticoagulant therapy	0	216	0	12	228	0	0
	Antidepressant therapy	0	0	0	1	1	0	0
	Antiplatelet therapy	0	2	0	0	2	0	0
	Aortic aneurysm repair	0	1	0	0	1	0	0
	Aortic valve repair	0	1	0	0	1	0	0
	Aortic valve replacement	0	5	0	0	5	0	0
	Apheresis	0	1	0	0	1	0	0
	Appendicectomy	1	31	0	6	37	0	0
	Arterial angioplasty	0	1	0	0	1	0	0
	Arterial catheterisation	0	1	0	0	1	0	0
	Arterial repair	0	1	0	0	1	0	0
	Arterial stent insertion	0	1	0	1	2	0	0
	Arteriovenous fistula operation	0	2	0	1	3	0	0
	Arthrodesis	0	0	2	2	2	0	0
	Arthroscopic surgery	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Artificial insemination	0	0	0	1	1	0	0
	Artificial skin graft	0	0	0	1	1	0	0
	Assisted fertilisation	0	0	1	1	1	0	0
	Asthma prophylaxis	1	2	0	3	5	0	0
	Atrial appendage closure	0	1	0	0	1	0	0
	Atrial appendage resection	0	1	0	0	1	0	0
	Axillary lymphadenectomy	0	0	3	9	9	0	0
	Bed rest	3	14	15	92	106	0	0
	Behavioural therapy	0	0	0	1	1	0	0
	Bile duct stent insertion	0	1	0	0	1	0	0
	Bladder catheter permanent	0	1	0	0	1	0	0
	Bladder catheter removal	0	1	0	0	1	0	0
	Bladder catheterisation	0	16	0	2	18	0	0
	Bladder neoplasm surgery	1	1	0	0	1	0	0
	Bladder operation	0	0	0	1	1	0	0
	Blood donation	0	0	0	1	1	0	0
	Bone marrow transplant	1	1	0	0	1	0	0
	Botulinum toxin injection	0	0	0	1	1	0	0
	Brain operation	0	2	0	0	2	0	0
	Breast conserving surgery	0	1	0	0	1	0	0
	Breast operation	0	1	0	1	2	0	0
	COVID-19 immunisation	1092	1214	1976	2299	3513	0	0
	Caesarean section	6	19	1	4	23	0	0
	Canalith repositioning procedure	0	1	0	0	1	0	0
	Cancer surgery	0	0	0	2	2	0	0
	Cardiac ablation	0	17	1	3	20	0	0
	Cardiac operation	0	8	0	4	12	0	0
	Cardiac pacemaker insertion	4	36	0	3	39	0	0
	Cardiac pacemaker replacement	0	0	0	1	1	0	0
	Cardiac resynchronisation therapy	1	4	0	0	4	0	0
	Cardioplegia	1	1	0	0	1	0	0
	Cardiopulmonary bypass	0	2	0	0	2	0	0
	Cardioversion	0	42	5	21	63	0	0
	Carotid artery bypass	0	1	0	0	1	0	0
	Carotid artery stent insertion	0	2	0	0	2	0	0
	Carotid endarterectomy	0	1	0	0	1	0	0
	Carpal tunnel decompression	0	1	0	0	1	0	0
	Cast application	0	3	0	0	3	0	0
	Cataract operation	0	2	1	2	4	0	0
	Catheter management	0	0	0	2	2	0	0
	Catheter placement	0	7	0	0	7	0	0
	Catheter removal	0	1	0	0	1	0	0
	Cautery to nose	0	0	0	2	2	0	0
	Central nervous system stimulation	0	0	0	1	1	0	0
	Central venous catheterisation	0	9	0	0	9	0	0
	Cerebral artery stent insertion	0	1	0	0	1	0	0
	Cerebral endovascular aneurysm repair	0	2	0	0	2	0	0
	Cerebrospinal fluid drainage	0	1	0	0	1	0	0
	Cerumen removal	0	0	0	1	1	0	0
	Cervix cerclage procedure	1	1	0	0	1	0	0
	Chemical peel of skin	0	0	1	1	1	0	0
	Chemotherapy	0	8	0	2	10	0	0
	Chest tube insertion	0	9	0	0	9	0	0
	Chest tube removal	0	2	0	0	2	0	0
	Chiropractic	0	1	0	1	2	0	0
	Cholecystectomy	0	16	0	3	19	0	0
	Cholelithotomy	0	1	0	1	2	0	0
	Cochlea implant	0	2	0	0	2	0	0
	Colectomy	0	3	0	1	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Colectomy total	0	1	0	0	1	0	0
	Colon operation	0	1	0	0	1	0	0
	Colonic lavage	0	1	0	0	1	0	0
	Colostomy	0	1	0	0	1	0	0
	Compression garment application	0	3	0	0	3	0	0
	Contraception	0	0	0	1	1	0	0
	Cooling therapy	0	0	0	4	4	0	0
	Coronary angioplasty	0	3	0	0	3	0	0
	Coronary arterial stent insertion	2	29	0	1	30	0	0
	Coronary artery bypass	2	11	0	1	12	0	0
	Cows milk free diet	0	2	0	0	2	0	0
	Cranioplasty	0	1	0	0	1	0	0
	Craniotomy	0	4	0	0	4	0	0
	Cryotherapy	0	1	1	1	2	0	0
	Cyst drainage	0	2	0	2	4	0	0
	Debridement	0	4	0	1	5	0	0
	Decompressive craniectomy	0	2	0	0	2	0	0
	Dental care	0	0	1	4	4	0	0
	Dental impression procedure	0	0	0	1	1	0	0
	Dental local anaesthesia	0	0	1	1	1	0	0
	Dental operation	0	0	0	2	2	0	0
	Depilation	0	0	0	1	1	0	0
	Dermal filler injection	0	3	0	6	9	0	0
	Detoxification	0	1	0	0	1	0	0
	Diabetes mellitus management	0	1	0	0	1	0	0
	Diabetic diet	0	1	0	0	1	0	0
	Dialysis	0	20	0	0	20	0	0
	Dialysis device insertion	0	1	0	0	1	0	0
	Diathermy	0	0	1	1	1	0	0
	Diuretic therapy	0	4	0	0	4	0	0
	Drain placement	0	5	0	0	5	0	0
	Drainage	0	3	0	19	22	0	0
	Drug withdrawal maintenance therapy	0	1	0	0	1	0	0
	Ear irrigation	0	0	0	1	1	0	0
	Ear tube insertion	0	1	0	1	2	0	0
	Ectopic pregnancy termination	0	2	0	0	2	0	0
	Elective procedure	0	1	0	0	1	0	0
	Electrocauterisation	0	1	0	0	1	0	0
	Electroconvulsive therapy	0	1	1	1	2	0	0
	Electrolyte substitution therapy	0	1	0	0	1	0	0
	Emergency care	3	3	0	7	10	0	0
	Endarterectomy	0	1	0	0	1	0	0
	Endobronchial valve implantation	0	1	0	0	1	0	0
	Endodontic procedure	0	0	0	5	5	0	0
	Endometrial ablation	0	2	0	0	2	0	0
	Endotracheal intubation	3	132	0	3	135	0	0
	Enteral nutrition	0	3	0	0	3	0	0
	Epidural injection	0	0	0	1	1	0	0
	Euthanasia	0	1	0	0	1	0	0
	Explorative laparotomy	0	1	0	0	1	0	0
	Exploratory operation	0	2	0	0	2	0	0
	Extubation	0	8	0	0	8	0	0
	Eye drop instillation	0	0	0	1	1	0	0
	Eye exercises	0	1	0	0	1	0	0
	Eye irrigation	1	1	0	1	2	0	0
	Eye laser surgery	0	0	0	1	1	0	0
	Eye muscle recession	0	0	0	1	1	0	0
	Eye operation	0	2	4	6	8	0	0
	Eyeglasses therapy	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Eyelid cyst removal	0	0	0	1	1	0	0
	Faecal disimpaction	0	2	0	0	2	0	0
	Fallopian tube operation	0	1	0	1	2	0	0
	Fascial operation	0	1	0	0	1	0	0
	Fasciotomy	0	1	0	1	2	0	0
	Finger amputation	1	2	0	0	2	0	0
	Fluid intake restriction	0	7	0	0	7	0	0
	Fluid replacement	0	0	0	3	3	0	0
	Foot amputation	0	1	0	0	1	0	0
	Foot operation	0	1	0	2	3	0	0
	Fraction of inspired oxygen	0	4	0	0	4	0	0
	Gallbladder operation	0	2	0	1	3	0	0
	Gastrointestinal decompression	0	1	0	1	2	0	0
	Gastrointestinal disorder prophylaxis	0	1	0	0	1	0	0
	Gastrointestinal tube insertion	0	8	0	1	9	0	0
	Gastrointestinal tube removal	0	1	0	0	1	0	0
	Gastrostomy	0	6	0	0	6	0	0
	Gluten free diet	0	1	0	0	1	0	0
	Haematoma evacuation	0	1	0	1	2	0	0
	Haemodialysis	0	19	0	0	19	0	0
	Haemofiltration	0	3	0	0	3	0	0
	Haemorrhoid operation	0	0	0	1	1	0	0
	Haemostasis	0	2	1	1	3	0	0
	Hearing aid therapy	0	1	1	1	2	0	0
	Heart valve operation	0	2	0	0	2	0	0
	Heart valve replacement	1	1	0	0	1	0	0
	Heat therapy	0	0	0	1	1	0	0
	Hepatectomy	0	1	0	0	1	0	0
	Hepatic embolisation	0	1	0	0	1	0	0
	Hepatitis B immunisation	0	0	0	1	1	0	0
	Hernia hiatus repair	0	1	0	0	1	0	0
	Hernia repair	0	1	0	2	3	0	0
	High intensity focused ultrasound	0	1	0	0	1	0	0
	Hip arthroplasty	0	4	0	6	10	0	0
	Hip surgery	0	4	0	0	4	0	0
	Hormonal contraception	0	0	1	3	3	0	0
	Hormone replacement therapy	1	1	0	0	1	0	0
	Hormone therapy	0	1	0	1	2	0	0
	Hospice care	0	3	0	2	5	0	0
	Hospitalisation	27	279	4	8	287	0	0
	Hyperbaric oxygen therapy	0	0	0	1	1	0	0
	Hysterectomy	2	3	0	1	4	0	0
	Ileostomy	0	1	0	0	1	0	0
	Immune enhancement therapy	0	0	0	1	1	0	0
	Immune tolerance induction	0	0	1	1	1	0	0
	Immunisation	8	20	31	88	108	0	0
	Immunochemotherapy	0	1	0	0	1	0	0
	Immunoglobulin therapy	0	26	0	0	26	0	0
	Immunosuppressant drug therapy	0	1	0	0	1	0	0
	Implantable cardiac monitor insertion	0	6	1	1	7	0	0
	Implantable defibrillator insertion	1	4	1	1	5	0	0
	In vitro fertilisation	0	0	0	1	1	0	0
	Incentive spirometry	0	1	0	0	1	0	0
	Incisional drainage	0	4	0	1	5	0	0
	Infection prophylaxis	0	0	0	1	1	0	0
	Influenza immunisation	1	1	0	2	3	0	0
	Infusion	0	11	0	8	19	0	0
	Inguinal hernia repair	0	1	0	0	1	0	0
	Injection	0	8	0	7	15	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Inner ear operation	0	1	0	0	1	0	0
	Insulin therapy	0	3	0	0	3	0	0
	Intensive care	2	178	0	3	181	0	0
	Interchange of vaccine products	42	84	500	1820	1904	0	0
	Internal fixation of fracture	0	0	0	1	1	0	0
	Intestinal resection	0	3	0	0	3	0	0
	Intra-cerebral aneurysm operation	1	1	0	0	1	0	0
	Intra-uterine contraceptive device insertion	0	0	2	2	2	0	0
	Intramedullary rod insertion	0	1	0	0	1	0	0
	Intraosseous access placement	0	1	0	0	1	0	0
	Intrauterine contraception	0	0	1	2	2	0	0
	Joint arthroplasty	0	1	1	1	2	0	0
	Joint fluid drainage	0	2	2	2	4	0	0
	Joint injection	0	4	0	4	8	0	0
	Joint stabilisation	0	1	0	1	2	0	0
	Knee arthroplasty	0	10	2	9	19	0	0
	Knee operation	0	2	0	6	8	0	0
	Labour induction	0	3	0	1	4	0	0
	Labour stimulation	0	0	0	1	1	0	0
	Laparoscopic surgery	0	4	0	1	5	0	0
	Laparotomy	0	2	0	0	2	0	0
	Large intestinal polypectomy	0	1	0	0	1	0	0
	Laxative supportive care	0	0	1	1	1	0	0
	Leg amputation	0	7	0	0	7	0	0
	Lesion excision	0	0	0	1	1	0	0
	Life support	0	9	0	1	10	0	0
	Light anaesthesia	1	1	0	0	1	0	0
	Limb immobilisation	3	6	1	25	31	0	0
	Limb operation	0	0	0	1	1	0	0
	Lip cosmetic procedure	0	1	0	0	1	0	0
	Lipolysis procedure	0	0	0	1	1	0	0
	Lipoma excision	0	1	0	0	1	0	0
	Liver transplant	0	1	0	0	1	0	0
	Lung assist device therapy	0	2	0	0	2	0	0
	Lung lobectomy	0	1	0	0	1	0	0
	Lung transplant	0	1	0	0	1	0	0
	Lymphadenectomy	1	6	0	1	7	0	0
	Magnetic therapy	0	0	0	1	1	0	0
	Manual lymphatic drainage	0	1	0	2	3	0	0
	Mass excision	1	1	0	12	13	0	0
	Mastectomy	0	2	0	2	4	0	0
	Mechanical ventilation	3	60	0	5	65	0	0
	Medical device removal	0	3	0	0	3	0	0
	Medical diet	0	3	0	1	4	0	0
	Medical induction of coma	2	6	0	0	6	0	0
	Medical procedure	0	0	0	1	1	0	0
	Menstrual cycle management	0	1	53	90	91	0	0
	Micrographic skin surgery	0	1	0	0	1	0	0
	Mineral supplementation	1	2	0	0	2	0	0
	Mitral valve repair	0	1	0	0	1	0	0
	Mitral valve replacement	0	1	0	0	1	0	0
	Monoclonal antibody immunoconjugate therapy	0	1	0	2	3	0	0
	Nasal cavity packing	0	0	0	1	1	0	0
	Nasal operation	0	0	0	1	1	0	0
	Neck surgery	0	0	0	1	1	0	0
	Nephrostomy	0	3	0	0	3	0	0
	Nerve block	0	3	1	8	11	0	0
	Neurosurgery	0	1	0	0	1	0	0
	Nitrate compound therapy	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Nothing by mouth order	0	2	0	0	2	0	0
	Office visit	0	0	0	1	1	0	0
	Omentectomy	0	1	0	0	1	0	0
	Oophorectomy	0	2	0	0	2	0	0
	Open reduction of fracture	0	3	0	1	4	0	0
	Oral contraception	0	0	4	10	10	0	0
	Oral surgery	0	0	1	2	2	0	0
	Orchidectomy	0	1	0	0	1	0	0
	Ostomy bag placement	0	1	0	0	1	0	0
	Ovarian operation	0	1	0	0	1	0	0
	Ovulation induction	0	0	0	1	1	0	0
	Oxygen therapy	1	2	1	4	6	0	0
	Pacemaker generated rhythm	0	1	0	0	1	0	0
	Pain management	0	1	0	1	2	0	0
	Palliative care	1	1	0	0	1	0	0
	Pancreatectomy	0	1	0	0	1	0	0
	Parenteral nutrition	0	1	0	0	1	0	0
	Patient isolation	0	3	0	4	7	0	0
	Patient restraint	0	0	0	1	1	0	0
	Pelvic floor muscle training	0	0	0	1	1	0	0
	Pelvic operation	0	1	0	0	1	0	0
	Percutaneous coronary intervention	0	6	0	0	6	0	0
	Pericardial drainage	0	10	0	0	10	0	0
	Pericardial excision	0	4	0	0	4	0	0
	Peripheral nerve decompression	1	2	0	2	4	0	0
	Peripheral nerve neurostimulation	0	0	0	1	1	0	0
	Peripheral nerve operation	0	0	0	1	1	0	0
	Phlebotomy	0	0	1	1	1	0	0
	Physiotherapy	0	0	0	1	1	0	0
	Physiotherapy chest	0	1	0	0	1	0	0
	Plasmapheresis	0	8	0	1	9	0	0
	Platelet transfusion	0	6	0	1	7	0	0
	Pleural decortication	0	1	0	0	1	0	0
	Pneumococcal immunisation	0	0	0	2	2	0	0
	Polypectomy	0	1	0	2	3	0	0
	Positive airway pressure therapy	0	65	0	3	68	0	0
	Post coital contraception	0	0	1	1	1	0	0
	Post procedural drainage	0	1	0	0	1	0	0
	Posterior fossa decompression	0	1	0	0	1	0	0
	Preoperative care	0	0	0	1	1	0	0
	Product substitution	0	0	0	3	3	0	0
	Prone position	0	6	0	1	7	0	0
	Prophylaxis of nausea and vomiting	0	2	0	0	2	0	0
	Prostatectomy	0	1	0	0	1	0	0
	Prostatic operation	0	3	0	0	3	0	0
	Pulmonary endarterectomy	0	1	0	0	1	0	0
	Pulmonary resection	0	0	0	1	1	0	0
	Pulmonary valve replacement	0	1	0	0	1	0	0
	Quarantine	0	0	0	2	2	0	0
	Radical hysterectomy	0	1	0	0	1	0	0
	Radiotherapy	0	2	0	1	3	0	0
	Radiotherapy to lymph nodes	0	0	0	1	1	0	0
	Red blood cell transfusion	0	6	0	0	6	0	0
	Rehabilitation therapy	0	0	1	2	2	0	0
	Removal of foreign body from oesophagus	0	1	0	0	1	0	0
	Removal of inert matter from skin or subcutaneous tissue	0	0	0	1	1	0	0
	Renal artery embolisation	1	1	0	0	1	0	0
	Renal stone removal	0	0	0	2	2	0	0
	Renal transplant	0	1	0	0	1	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Resuscitation	12	72	0	4	76	0	0
	Salpingectomy	0	0	1	2	2	0	0
	Salpingostomy	0	0	1	1	1	0	0
	Sclerotherapy	1	1	0	0	1	0	0
	Sedative therapy	0	1	0	0	1	0	0
	Seizure prophylaxis	0	0	0	1	1	0	0
	Self-medication	0	0	0	1	1	0	0
	Seroma drainage	0	2	0	0	2	0	0
	Shoulder arthroplasty	0	2	0	0	2	0	0
	Shoulder operation	0	2	0	3	5	0	0
	Sinus operation	0	4	0	25	29	0	0
	Skin implant	0	0	0	1	1	0	0
	Small intestinal obstruction reduction	1	1	0	0	1	0	0
	Small intestinal resection	0	1	0	0	1	0	0
	Smoking cessation therapy	0	0	0	1	1	0	0
	Specialist consultation	1	3	4	13	16	0	0
	Spinal anaesthesia	0	0	1	1	1	0	0
	Spinal cord operation	0	1	0	0	1	0	0
	Spinal decompression	0	1	0	0	1	0	0
	Spinal fusion surgery	0	3	0	1	4	0	0
	Spinal laminectomy	0	1	0	0	1	0	0
	Spinal manipulation	0	1	0	0	1	0	0
	Spinal nerve stimulator implantation	0	1	0	0	1	0	0
	Spinal operation	2	3	0	1	4	0	0
	Splenectomy	0	7	0	0	7	0	0
	Splenic artery embolisation	0	1	0	0	1	0	0
	Splint application	0	2	0	1	3	0	0
	Stem cell transplant	0	0	1	3	3	0	0
	Stent placement	0	25	0	6	31	0	0
	Stent removal	0	0	0	1	1	0	0
	Sternotomy	0	2	0	0	2	0	0
	Steroid therapy	0	1	0	2	3	0	0
	Subdural haematoma evacuation	0	2	0	0	2	0	0
	Surgery	2	44	1	23	67	0	0
	Suture insertion	0	2	0	0	2	0	0
	Tendon sheath incision	0	1	0	0	1	0	0
	Tenotomy	0	0	0	1	1	0	0
	Tetanus immunisation	0	0	0	3	3	0	0
	Therapeutic embolisation	0	4	0	0	4	0	0
	Therapeutic gargle	0	0	0	1	1	0	0
	Therapeutic hypothermia	0	1	0	0	1	0	0
	Therapeutic procedure	0	2	0	0	2	0	0
	Therapy cessation	0	2	1	4	6	0	0
	Therapy change	1	1	3	6	7	0	0
	Therapy interrupted	1	2	1	6	8	0	0
	Thoracic cavity drainage	0	2	0	0	2	0	0
	Thoracic operation	0	1	0	0	1	0	0
	Thoracotomy	0	2	0	0	2	0	0
	Thrombectomy	0	33	0	2	35	0	0
	Thromboembolectomy	0	5	0	0	5	0	0
	Thrombolysis	1	10	0	0	10	0	0
	Thymectomy	0	0	0	1	1	0	0
	Thyroid hormone replacement therapy	0	0	1	1	1	0	0
	Thyroidectomy	1	2	0	1	3	0	0
	Toe amputation	0	2	0	0	2	0	0
	Tonsillectomy	0	0	0	1	1	0	0
	Tooth extraction	1	5	2	14	19	0	0
	Tooth restoration	0	0	0	1	1	0	0
	Tracheostomy	0	4	0	0	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Tracheostomy tube removal	0	1	0	0	1	0	0
	Transfusion	2	28	0	9	37	0	0
	Transplant	0	1	0	1	2	0	0
	Trendelenburg position	0	1	0	0	1	0	0
	Tumour excision	1	2	0	0	2	0	0
	Ureteral stent insertion	0	4	0	0	4	0	0
	Urethral bulking agent injection	0	0	0	1	1	0	0
	Uterine dilation and curettage	1	11	2	5	16	0	0
	Uterine dilation and evacuation	0	1	0	0	1	0	0
	Vaccine coadministration	0	0	1	1	1	0	0
	Vagal nerve stimulator implantation	0	0	0	1	1	0	0
	Varicose vein operation	0	0	0	1	1	0	0
	Vascular graft	2	5	0	0	5	0	0
	Vascular operation	0	1	0	0	1	0	0
	Vasodilation procedure	0	1	1	1	2	0	0
	Vena cava filter insertion	0	3	0	0	3	0	0
	Vena cava filter removal	0	1	0	0	1	0	0
	Ventricular assist device insertion	0	2	0	0	2	0	0
	Ventricular cisternostomy	1	2	0	0	2	0	0
	Ventricular drainage	0	1	0	0	1	0	0
	Vessel harvesting	0	1	0	0	1	0	0
	Vitrectomy	0	1	0	0	1	0	0
	Vocal cord polypectomy	0	1	0	0	1	0	0
	Volvulus repair	0	1	0	0	1	0	0
	Wean from ventilator	0	1	0	0	1	0	0
	Weight loss diet	0	0	1	1	1	0	0
	Withdrawal of life support	0	1	0	0	1	0	0
	Wound closure	0	0	0	1	1	0	0
	Wound drainage	0	1	0	1	2	0	0
	Wound treatment	0	4	0	0	4	0	0
	X-ray therapy to lung	0	0	0	1	1	0	0
Vascular disorders	*** SOC TOTAL ***	2281	9985	2888	14808	24793	0	0
	Accelerated hypertension	0	8	2	4	12	0	0
	Achenbach syndrome	0	0	1	3	3	0	0
	Air embolism	0	1	0	0	1	0	0
	Aneurysm	3	24	1	5	29	0	0
	Aneurysm ruptured	4	10	1	1	11	0	0
	Angiodysplasia	0	1	0	0	1	0	0
	Angiopathy	0	9	5	18	27	0	0
	Aortic aneurysm	5	25	0	5	30	0	0
	Aortic aneurysm rupture	0	8	0	0	8	0	0
	Aortic arteriosclerosis	1	28	0	2	30	0	0
	Aortic dilatation	0	9	0	0	9	0	0
	Aortic disorder	0	4	0	2	6	0	0
	Aortic dissection	17	48	0	0	48	0	0
	Aortic dissection rupture	2	4	0	0	4	0	0
	Aortic embolus	0	1	0	0	1	0	0
	Aortic occlusion	0	5	0	0	5	0	0
	Aortic perforation	0	1	0	0	1	0	0
	Aortic rupture	1	2	0	0	2	0	0
	Aortic stenosis	3	15	0	1	16	0	0
	Aortic thrombosis	3	17	0	0	17	0	0
	Aortitis	0	4	0	0	4	0	0
	Arterial disorder	0	0	1	5	5	0	0
	Arterial haemorrhage	0	2	0	0	2	0	0
	Arterial insufficiency	2	2	0	0	2	0	0
	Arterial occlusive disease	2	18	0	3	21	0	0
	Arterial rupture	1	2	0	0	2	0	0
	Arterial spasm	0	3	1	1	4	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Arterial stenosis	0	4	0	0	4	0	0
	Arterial thrombosis	8	23	0	1	24	0	0
	Arteriosclerosis	3	52	1	7	59	0	0
	Arteriovenous fistula	0	3	0	0	3	0	0
	Arteritis	0	2	1	2	4	0	0
	Artery dissection	5	16	0	0	16	0	0
	Axillary vein thrombosis	1	10	0	2	12	0	0
	Behcet's syndrome	1	8	1	3	11	0	0
	Blood pressure fluctuation	30	85	79	241	326	0	0
	Blood pressure inadequately controlled	0	4	0	7	11	0	0
	Bloody discharge	1	6	4	20	26	0	0
	Blue toe syndrome	2	6	5	16	22	0	0
	Brachiocephalic artery occlusion	0	1	0	0	1	0	0
	Brachiocephalic vein thrombosis	0	6	0	1	7	0	0
	Capillary disorder	0	1	4	10	11	0	0
	Capillary fragility	2	6	3	21	27	0	0
	Capillary leak syndrome	9	16	0	0	16	0	0
	Carotidynia	0	1	0	0	1	0	0
	Circulatory collapse	119	266	22	39	305	0	0
	Claudication of jaw muscles	0	1	1	3	4	0	0
	Collateral circulation	0	0	0	1	1	0	0
	Cryoglobulinaemia	0	1	0	0	1	0	0
	Cyanosis	31	129	31	187	316	0	0
	Deep vein thrombosis	354	1656	40	80	1736	0	0
	Dependent rubor	0	0	1	1	1	0	0
	Dialysis hypotension	0	0	0	1	1	0	0
	Diastolic hypertension	0	2	2	3	5	0	0
	Diastolic hypotension	0	0	1	1	1	0	0
	Distributive shock	0	3	0	0	3	0	0
	Dry gangrene	0	1	0	0	1	0	0
	Embolism	14	48	2	2	50	0	0
	Embolism arterial	5	16	0	0	16	0	0
	Embolism venous	3	25	0	0	25	0	0
	Endothelial dysfunction	0	0	0	1	1	0	0
	Erythromelalgia	0	3	1	4	7	0	0
	Essential hypertension	4	20	2	10	30	0	0
	Extravasation blood	0	3	1	5	8	0	0
	Extremity necrosis	1	4	0	0	4	0	0
	Femoral artery embolism	0	1	0	0	1	0	0
	Fibromuscular dysplasia	0	3	0	0	3	0	0
	Flushing	32	204	183	2999	3203	0	0
	Giant cell arteritis	14	49	3	19	68	0	0
	Granulomatosis with polyangiitis	5	11	0	0	11	0	0
	Haematoma	46	142	205	604	746	0	0
	Haemodynamic instability	1	8	0	0	8	0	0
	Haemorrhage	86	526	40	117	643	0	0
	Haemorrhagic infarction	0	4	0	0	4	0	0
	Haemorrhagic vasculitis	0	2	0	0	2	0	0
	Hot flush	71	354	520	2263	2617	0	0
	Hyperaemia	3	8	8	18	26	0	0
	Hypertension	327	1237	647	2776	4013	0	0
	Hypertension neonatal	0	1	0	0	1	0	0
	Hypertensive crisis	65	237	29	41	278	0	0
	Hypertensive emergency	6	33	1	1	34	0	0
	Hypertensive urgency	2	20	0	0	20	0	0
	Hypoperfusion	0	3	0	0	3	0	0
	Hypotension	99	764	251	1328	2092	0	0
	Hypotensive crisis	1	2	0	1	3	0	0
	Hypovolaemic shock	1	12	0	0	12	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Iliac artery arteriosclerosis	0	1	0	0	1	0	0
	Iliac artery disease	0	0	1	1	1	0	0
	Iliac artery embolism	0	1	0	0	1	0	0
	Iliac artery occlusion	1	8	0	0	8	0	0
	Iliac artery stenosis	0	2	0	0	2	0	0
	Iliac vein stenosis	0	1	0	0	1	0	0
	Infarction	16	41	1	1	42	0	0
	Inferior vena cava dilatation	0	7	0	0	7	0	0
	Inferior vena cava syndrome	1	1	0	0	1	0	0
	Intermittent claudication	3	11	1	2	13	0	0
	Internal haemorrhage	8	56	0	1	57	0	0
	Ischaemia	13	53	1	3	56	0	0
	Ischaemic limb pain	0	1	0	1	2	0	0
	Jugular vein distension	2	4	0	0	4	0	0
	Jugular vein embolism	0	1	0	0	1	0	0
	Jugular vein occlusion	0	5	0	1	6	0	0
	Jugular vein thrombosis	7	35	1	2	37	0	0
	Kawasaki's disease	0	0	0	1	1	0	0
	Labile blood pressure	3	6	8	27	33	0	0
	Labile hypertension	0	2	1	5	7	0	0
	Leriche syndrome	0	1	0	0	1	0	0
	Lower limb artery perforation	0	1	0	0	1	0	0
	Lymphangiopathy	0	0	1	1	1	0	0
	Lymphoedema	18	63	41	142	205	0	0
	Lymphorrhoea	0	0	0	1	1	0	0
	Lymphostasis	0	0	0	1	1	0	0
	MAGIC syndrome	1	1	0	0	1	0	0
	Malignant hypertension	0	3	0	0	3	0	0
	May-Thurner syndrome	0	4	0	1	5	0	0
	Microangiopathy	6	8	0	2	10	0	0
	Microembolism	3	9	0	0	9	0	0
	Microscopic polyangiitis	0	2	2	2	4	0	0
	Necrosis ischaemic	1	3	0	0	3	0	0
	Neurogenic shock	0	6	0	4	10	0	0
	Obstructive shock	0	1	0	0	1	0	0
	Orthostatic hypertension	0	1	0	3	4	0	0
	Orthostatic hypotension	5	36	9	66	102	0	0
	Paget-Schroetter syndrome	1	2	0	0	2	0	0
	Pallor	27	179	74	1346	1525	0	0
	Paradoxical embolism	0	1	0	0	1	0	0
	Pelvic venous thrombosis	12	28	0	0	28	0	0
	Penetrating aortic ulcer	0	2	0	0	2	0	0
	Peripheral arterial occlusive disease	6	14	0	5	19	0	0
	Peripheral artery aneurysm	1	2	0	1	3	0	0
	Peripheral artery occlusion	4	18	0	0	18	0	0
	Peripheral artery stenosis	1	4	0	0	4	0	0
	Peripheral artery thrombosis	6	48	2	4	52	0	0
	Peripheral circulatory failure	2	10	6	22	32	0	0
	Peripheral coldness	59	226	197	885	1111	0	0
	Peripheral embolism	4	16	1	3	19	0	0
	Peripheral ischaemia	3	25	10	15	40	0	0
	Peripheral vascular disorder	11	23	67	161	184	0	0
	Peripheral vein occlusion	0	5	0	1	6	0	0
	Peripheral vein stenosis	0	1	0	0	1	0	0
	Peripheral vein thrombus extension	0	5	0	0	5	0	0
	Peripheral venous disease	3	15	9	22	37	0	0
	Periphlebitis	0	1	0	0	1	0	0
	Phlebitis	28	51	40	91	142	0	0
	Phlebitis deep	0	1	0	2	3	0	0

		Spontaneous, including competent authorities (worldwide) and literature				Total Spontaneous	Non-interventional post-marketing	
		Serious		Non-Serious			Serious	
SOC_TERM	PT	Interval	Cumulative	Interval	Cumulative	Cumulative All	Interval	Cumulative
	Phlebitis superficial	6	13	8	14	27	0	0
	Polyarteritis nodosa	1	4	0	0	4	0	0
	Poor peripheral circulation	5	18	15	43	61	0	0
	Popliteal artery entrapment syndrome	0	1	0	0	1	0	0
	Post thrombotic syndrome	0	0	1	1	1	0	0
	Prehypertension	0	1	0	1	2	0	0
	Raynaud's phenomenon	19	32	43	106	138	0	0
	Secondary hypertension	0	1	0	0	1	0	0
	Shock	15	99	0	1	100	0	0
	Shock haemorrhagic	3	14	0	0	14	0	0
	Shock symptom	0	7	1	3	10	0	0
	Spider vein	1	2	5	18	20	0	0
	Subclavian artery embolism	0	1	0	0	1	0	0
	Subclavian artery occlusion	0	1	0	0	1	0	0
	Subclavian artery thrombosis	1	2	0	0	2	0	0
	Subclavian vein occlusion	0	2	0	0	2	0	0
	Subclavian vein thrombosis	4	26	0	0	26	0	0
	Superficial vein prominence	0	1	1	16	17	0	0
	Superficial vein thrombosis	35	111	34	133	244	0	0
	Susac's syndrome	1	2	0	0	2	0	0
	Systolic hypertension	1	4	2	4	8	0	0
	Thrombophlebitis	50	90	25	87	177	0	0
	Thrombophlebitis migrans	0	1	0	0	1	0	0
	Thrombosed varicose vein	0	0	1	2	2	0	0
	Thrombosis	318	1719	36	150	1869	0	0
	Varicophlebitis	1	5	4	9	14	0	0
	Varicose ulceration	1	1	0	0	1	0	0
	Varicose vein	8	22	18	86	108	0	0
	Varicose vein ruptured	0	0	0	2	2	0	0
	Vascular calcification	0	6	0	1	7	0	0
	Vascular compression	0	0	1	3	3	0	0
	Vascular insufficiency	0	0	1	2	2	0	0
	Vascular occlusion	1	8	0	1	9	0	0
	Vascular pain	6	24	36	85	109	0	0
	Vascular rupture	1	7	3	8	15	0	0
	Vascular wall discolouration	0	0	0	1	1	0	0
	Vasculitis	36	101	30	91	192	0	0
	Vasculitis necrotising	2	4	0	1	5	0	0
	Vasoconstriction	0	1	0	7	8	0	0
	Vasodilatation	1	11	14	85	96	0	0
	Vasospasm	0	2	1	5	7	0	0
	Vein collapse	0	2	0	2	4	0	0
	Vein discolouration	0	4	2	17	21	0	0
	Vein disorder	5	9	6	43	52	0	0
	Vein rupture	0	11	1	5	16	0	0
	Vena cava thrombosis	4	19	0	0	19	0	0
	Venous aneurysm	0	0	0	1	1	0	0
	Venous haemorrhage	0	2	0	1	3	0	0
	Venous occlusion	4	15	3	4	19	0	0
	Venous thrombosis	32	90	11	24	114	0	0
	Venous thrombosis limb	65	133	11	28	161	0	0
	Vessel perforation	1	1	0	1	2	0	0
	Visceral congestion	1	3	0	0	3	0	0
	White coat hypertension	0	0	0	2	2	0	0
	Withdrawal hypertension	0	0	0	2	2	0	0
[Total]		90390	378799	443518	1804330	2183129	2	18

Appendix 4.1 Tabular Summary of Safety Signals

mRNA-1273 Reporting interval: 01 Jan 2022 to 18 Jun 2022

Table 20.1 Tabular summary of safety signals new, ongoing or closed during the reporting interval

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Autoimmune hepatitis	02 Dec 2021	Closed (evaluation done)	19 Jan 2022	Health Authority Request	The signal of Autoimmune hepatitis (AIH) was triggered from PRAC signal assessment report (EPITT 19750) (dated 02 Dec 2021), based on the available evidence from case reports published in the literature and submitted to Eudravigilance (EV). Following assessment based on the review of all available sources, no cases of AIH were reported in the CT setting. Analysis from the Company global safety database retrieved 165 cases, 11 cases (7%) were suggestive of AIH, and of these, 8 cases were considered as related (including cases where only temporal association with elasomeran was reported). No disproportionate reporting of AIH was found in EVDAS or VAERS. The O/E analysis for PT AID did not provide observed counts higher-than-expected. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described AIH and mRNA vaccine but none showed a direct temporal association with mRNA vaccines against Covid-19 disease. No plausible pathognomonic findings were found to support a possible causal association between the administration of elasomeran and the occurrence of AIH. In conclusion MAH considered AIH in association with elasomeran as a refuted	RTQ	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. AIH will continue to be monitored through routine PV surveillance.		
Giant Cell Arteritis	28 Jan 2022	Closed (evaluation done)	22 Feb 2022	VigiBase Literature Article Other (TGA Request)	The signal was triggered by TGA's Medicines and Vaccines Investigation and Surveillance (MAVIS) Section review of giant cell arteritis (GCA) with elasomeran, based on the publication of case reports of GCA in association with COVID vaccines (including mRNA platform vaccines), and disproportionate reporting to the WHO's Vigibase. Following MAH assessment based on the review of all available sources, no cases of giant cell arteritis (GCA) were reported in the CT setting. A total of 48 GCA cases were retrieved from the Company global safety database out of which 14 fulfilled the diagnostic criteria for GCA (based on the American college of rheumatology 1990 criteria for the classification of giant cell arteritis). WHO causality assessment for the 14 confirmed GCA cases was: possible (4 cases, mainly based on the sole criteria of temporal association), conditional (3 cases), unassessable (2 cases) and unlikely (5 cases). The O/E analysis did not provide observed counts higher-than-expected when assuming 25% of	Signal Evaluation Report	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					cases were reported. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described GCA and mRNA vaccine but overall did not provide evidence of causal association between mRNA vaccines or elasomeran and GCA. In conclusion MAH considered GCA in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. GCA will continue to be monitored through routine PV surveillance.		
Amenorrhea	14 Feb 2022	Closed (evaluation done)	30 Mar 2022	Health Authority Request	The signal of amenorrhea was triggered by PRAC (EPITT No. 19781), having considered the available evidence from national reviews (post marketing cases and published studies). Following MAH assessment based on the review of all available sources, no cases of amenorrhea were reported in the mRNA-1273 arm the CT setting. A total of 1,589 cases of amenorrhea (11.3% (180) serious, 12.0% (191) medically confirmed) were retrieved from the Company global safety database. Primary amenorrhea is defined as the absence of menarche by age 15 years. Secondary amenorrhea is defined as absence of spontaneous menstrual	RTQ	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					bleeding for six months in a patient who previously had menstrual bleeding. Considering the challenge of missing information when analyzing spontaneous reports to characterize the full clinical course of events related to amenorrhea, only 1 case contained complete menstrual history and time-to-onset. This patient received the first dose of elasomeran at cycle day 16, luteal phase, and experienced amenorrhea, missed one cycle, after vaccination. An FSH performed 33 days after vaccination was elevated "suggesting early menopause." The O/E analysis did not provide observed counts higher-than-expected when assuming 25% of cases were reported. Literature search results did not provide evidence of a causal association between mRNA vaccines or mRNA-1273 and amenorrhea and published studies were lacking comparisons with unvaccinated subjects. In conclusion MAH considered amenorrhea in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. Amenorrhea will continue to be monitored through routine PV surveillance.		
Heavy	14 Feb	Closed	30 Mar	Health	The signal of heavy menstrual bleeding	RTQ	Routine

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
menstrual bleeding	2022	(evaluation done)	2022	Authority Request	(HMB) was triggered by PRAC (EPITT No. 19780) having considered the available evidence from national reviews (post marketing cases and published studies). Following assessment based on the review of all available sources, 6 cases of menorrhagia (1 with placebo, 5 with mRNA-1273) were reported in the CT setting. All were non-serious, and all had medical history that provided an alternate etiology. A total of 4000 cases of HMB (24.7% (988) serious, 12.6% (546) medically confirmed) were retrieved from the Company global safety database. Menstrual cycle features such as volume, pain and premenstrual syndrome symptoms are subjective and often collected, in health care as well as research, by self-report. HMB is defined as a menstrual volume that interferes with the patient's physical, social, emotional, and/or material quality of life. It is a common gynecologic problem affecting 1 out of every 4-5 women. Considering the subjectivity of HMB definition and challenge of missing information when analyzing spontaneous reports, only 14 cases contained sufficient data to characterize the clinical course of events (vaccination date, last menstrual period, menstruation characteristics (length, frequency)) related to HMB. From these 14 cases, no unusual pattern in time of menstrual		Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					cycle in relation to vaccination was found and majority of cases (71%) had alternate etiologies (e.g. age 45+, obesity, postpartum status, medical history of breast cancer, hypothyroidism, inflammatory bowel syndrome). The O/E analysis did not provide observed counts higher-than-expected when assuming 25% of cases were reported. Literature search results did not provide evidence of a causal association between mRNA vaccines or mRNA-1273 and HMB and published studies were lacking comparisons with unvaccinated subjects. In conclusion MAH considered HMB in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. HMB will continue to be monitored through routine PV surveillance.		
Urticaria	18 Mar 2022	Closed (evaluation done)	22 Apr 2022	Health Authority Request VigiBase Literature Article	This signal was triggered by Swissmedic following review of the WHO databases Vigilyze and the literature. Following evaluation based on the review of all available sources performed by MAH, there was an emerging pattern of urticaria following vaccination with mRNA-1273, mainly driven by the review of the post-marketing data. In mRNA-1273 Study P301 Part A PT	RTQ	Update RSI (CCDS, SmPC)

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					Urticaria was reported in 0.33% of participants. Cumulative review of the Company safety database showed a bimodal distribution of urticaria onset with events most frequently reported on days 0-3 and 6-11 with a relative increased proportion of events reported in these windows with dose 3 as compared with doses 1 and 2. Most frequently reported medical history in patients with urticaria involved allergies and hypersensitivity (drug hypersensitivity (22%), food allergy (8%), asthma (6%), seasonal allergy (4%) and hypersensitivity (4%)). Overall urticaria was predominantly non-serious and generally self-limiting. No correlation could be found with regards to local vs systemic urticaria and dosing. Literature search results did not provide evidence of a causal association between mRNA vaccines or mRNA-1273 and urticaria other than a temporal association. In conclusion MAH considered urticaria in association with elasomeran as an identified risk (not important). Urticaria will be included in the elasomeran core company datasheet.		
Corneal graft rejection	11 Apr 2022	Closed (evaluation done)	01 Jun 2022	Health Authority Request EudraVigilance /EVDAS Literature	The signal of Corneal Graft Rejection (CGR) was triggered from PRAC on 11 Apr 2022 (EPITT 19792) based on case reports (mainly from the literature) reported to EudraVigilance (EV). The most common cause of corneal graft	RTQ	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
				Article	failure is allogenic rejection. 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. Following MAH assessment based on the review of all available sources, no cases of CGR were reported in the CT setting. Analysis from the Company global safety database retrieved 9 cases (including 1 duplicate and 5 cases from the literature). CGR reports were mostly serious, occurred predominantly in the age group 75+ years, mostly within 7 days after the 1st dose of the vaccine. As per WHO-UMC causality assessment, 2 cases were assessed as possibly related, 2 as conditional, 3 as unlikely and 2 as unassessable. The observed reporting rate of CGR with elasomeran (0.003 cases per 100,000 persons), was below the lower bound of estimated reference range (0.25 per 100,000 persons). Stratification of O/E analyses by age and gender showed similar results. Review of the literature retrieved 13 published case reports of CGR (including 5 with elasomeran). The infrequency of the reports and the associated confounders, as well as the lack of clinical, pathological and detailed ophthalmological information did not		

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					provide evidence for a causal relationship between elasomeran and CGR. The mechanism of CGR occurring in close proximity to vaccination, remains unconfirmed for all vaccines including tetanus toxoid, Yellow Fever, Hepatitis B, Influenza and Covid-19 vaccines. In conclusion MAH considered CGR in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. CGR will continue to be monitored through routine PV surveillance.		
IgA Nephropathy	08 Jul 2022	Closed (Signal Refuted)	22 Jul 2022	Health Authority Request EudraVigilance /EVDAS Spontaneous Reports	MAH considered IgA nephropathy as a validated signal following review of PRAC PSUR assessment report of covering period from 30 Jun 2021 to 31 Dec 2021, highlighting the fact that IgA nephropathy was delineated from other renal PTs, both in disproportionality analyses as well as in case reviews, although cumulative evidence is not sufficient to warrant amendment of the product information. Most common symptom of IgA nephropathy is blood in the urine, however the definitive diagnosis is by renal biopsy, therefore, due to the silent nature of the disease, the estimation of its incidence rate is difficult.	Signal Evaluation Report	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					Following MAH assessment based on the review of all available sources, no cases of IgA nephropathy were reported in the CT setting. Analysis from the Company global safety database retrieved 54 cases (including 34 de novo IgA cases and 20 IgA flare cases), of which 27 cases were literature reports. All but one flare cases resolved or were resolving at time of reporting. The three cases requiring dialysis had other confounding co-morbidities. The observed reporting rate of IgA nephropathy with elasomeran 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). Review of the literature indicated that post-vaccination IgA nephropathy's clinical signs, symptoms and treatment were similar to those of "typical" IgA nephropathy, and no pathognomonic signs or symptoms that link IgA nephropathy to vaccination were found. The European Renal Association and the		

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
					European Vasculitis Society raised in Mar 2022 the reassuring recommendation that patients with immune-mediated kidney diseases should follow national guidance on vaccination. In conclusion MAH considered IgA nephropathy in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed, the very low reporting rate (< 1 case per 10 million doses administered) and lack of pathophysiological mechanism. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. IgA nephropathy will continue to be monitored through routine PV surveillance		
Heavy menstrual bleeding (re-evaluation)	13 Jun 2022	Ongoing	NA	Health Authority Request	A signal of heavy menstrual bleeding (HMB) was evaluated as a refuted signal in Mar2022 (EPITT No 19780). A new signal for HMB was opened based on PRAC Signal AR (dated 13/Jun/2022) where PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present and agreed that the MAH of COVD-19 mRNA vaccine (nucleoside-modified) elasomeran, should provide an updated cumulative review of heavy menstrual bleeding post-vaccination by 24 Aug 2022.	RTQ	Evaluation ongoing

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Amenorrhea (re-evaluation)	13 Jun 2022	Ongoing	NA	Health Authority Request	A signal of amenorrhea was evaluated as a refuted signal in Mar 2022 (EPITT No 19781). A new signal for amenorrhea was opened based on PRAC Signal AR (dated 13 Jun 2022) where PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present and agreed that the MAH of COVD-19 mRNA vaccine (nucleoside-modified) elasomeran, should provide an updated cumulative review of amenorrhea events post-vaccination in the PSUR with the DLP of 18 Dec 2022.	PBRER/PSUR/MSSR RTQ	Evaluation ongoing

Appendix 4.2 Signal Evaluation Reports

Appendix 4.2a: Signal Evaluation report: Autoimmune hepatitis

Signal Evaluation Report

for

mRNA-1273

on

Autoimmune Hepatitis

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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 Autoimmune hepatitis in association with the administration of mRNA-1273 in adult patients ≥18yo, based on all information available to the MAH at the time of document preparation.

1.1 Source of the Signal

The PRAC requested the MAH of Spikevax (Moderna Biotech Spain, S.L.) having considered the available evidence from case reports published in the literature and submitted to EudraVigilance (EV), the PRAC has agreed that MAH of Spikevax (Moderna Biotech Spain, S.L.) should submit by 02 February 2022 a cumulative review (i.e. clinical trial and post-marketing data incl. any published studies or case reports) of all evidence concerning the association between the vaccination with Spikevax and autoimmune hepatitis.

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.

Autoimmune Hepatitis (AIH) is a non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favorable response to immunosuppression (e.g. with corticosteroids). The disease, if untreated, often leads to cirrhosis, liver failure and death. It is well established that AIH is a clinically distinct syndrome characterized by a large heterogeneity of clinical, laboratory and histological manifestations. Therefore, AIH should be considered in any patient with acute or chronic liver disease, particularly if hypergammaglobulinemia is present, and if the patient has features of other autoimmune diseases.

The disease also affects males (25-30% of all AIH patients) and may present at any age and in all ethnic groups. In most studies, a bimodal age pattern at presentation has been reported with one peak during childhood/teenage years and another in middle age between the 4th and 6th decade of life. Recent studies have shown that an increasing number of patients are diagnosed also at older ages (above 65 years). Recently it has been shown that appropriate attention should also be paid to the health-related quality of life (HRQoL) parameters, since a high rate of previously unrecognized mental impairment with depression and anxiety symptoms are present in patients with AIH. manifestations were reported in 31% cases at diagnosis (Bhattacharjee & Banerjee, 2020).

Probable Mechanism(s) for Vaccine-associated Autoimmune Hepatitis

Several hypotheses are been presented in several articles reporting cases of patients with AIH following COVID-19 mRNA vaccination. Among those it is postulated that COVID-19 mRNA vaccination, through activation of the innate immune system and subsequent non-specific activation of autoreactive lymphocytes, may lead to the development of autoimmune diseases including AIH or trigger a drug-induced liver injury with features of AIH (McShane et al, 2021). The trigger, if any, may become more apparent over time, especially following withdrawal of immunosuppression.

Other authors have suggested that given that the COVID-19 mRNA vaccines lacks immune adjuvants, genetic susceptibility, exposure to foreign peptides homologous to human peptides (molecular mimicry), and immune system stimulation by vaccine adjuvant may not be part of the problem, but the homology between the SARS-CoV-2 spike protein and soluble liver antigen may be a clue: i) similar native or glycosylated amino acid epitopes shared between the protein expressed in the host after vaccination and soluble liver antigen, and ii) structural similarities between the proteins. It is also possible that other liver autoantigens (different from SLA) share sequence homology with the protein expressed by the host after SARS-CoV-2 vaccination with mRNA vaccines. In other words, the mechanism for the development of autoimmune hepatitis is still not well understood. AIH has also been reported following immunization with other vaccines (not directed against SARS-CoV2, e.g. seasonal influenza, HPV). Causative mechanisms are similarly unclear for these cases.

3 Review of Data from All Sources

The assessment of Autoimmune hepatitis 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 Autoimmune hepatitis was cumulatively reviewed in the MAH clinical database with a data-lock point (DLP) of 04 May 2021, searched using the following MedDRA v 24.0 preferred term "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury" was performed in P301 study and there were zero cases observed.

3.2 External Databases

VAERS and EVDAS were reviewed for the PTs: Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury

- VAERS: No disproportionality in EB05.
    - Acute hepatic failure (EB05: 0.621), Autoimmune hepatitis (EB05: 0.909), Drug-induced liver injury (EB05: 0.58), Hepatic failure (EB05: 0.649), Hepatitis acute (EB05: 0.731), Hepatitis fulminant (EB05: 0.493), Hepatitis toxic (EB05: 0.621), Hepatocellular injury (EB05: 0.621), Hepatotoxicity (EB05: 0.516), Immune-mediated hepatic disorder (EB05: 0.425), Immune-mediated hepatitis (EB05: 0.47), and Liver injury (EB05: 0.54).

- EVDAS: The PT relevant of Autoimmune hepatitis showed ROR < 2

Overall, no Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines in Adults) in VAERs as of 31 Dec 2021.

3.3 Non-clinical Data
Not applicable

3.4 Epidemiological studies

To conduct the observed to expected analysis MAH has referred to the disease incidence rates identified in published source a US population-based study using administrative healthcare claims to identify reference rates for autoimmune hepatitis. Cumulatively, autoimmune hepatitis

was reported in 165 cases with broad definition* (reporting rate of 0.51 per 100,000 person-years) and 45 cases with narrow definition of PT of autoimmune hepatitis only (reporting rate 0.14 per 100,000 person-years). The cumulative reporting rate (0.51 per 100,000 person-years) was below the US-bases estimates (Esposito et al., 2018), which suggests an expected incidence of 3.10 per 100,000 person-years (998 cases expected, rate-ratio 0.17, 95% CI 0.14, 0.19). Stratum specific estimates show that the observed number of cases were lower compared to expected cases in all age and gender strata. Sensitivity analysis assuming that 50% and 25% of exposed cases are captured in the reporting rate with no false positive error also suggest that the observed to expected rate ratios are not greater than 1, other than in males (rate ratio of 1.36, 95% CI 1.13, 1.63). Interpretation of potential increases in sensitivity analyses for this outcome is complicated by low observed and expected case counts (Table 1).

Table-1: Observed/Expected Analyses Stratified by Age and Gender, Autoimmune hepatitis, Expected Rates from the United States

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			
Hepatobiliary								
Autoimmune hepatitis (expanded definition)								
Reference (Esposito et al., 2018) *								
All	32,189,820	165	0.51	998	3.10	0.17 (0.14, 0.19)	0.33 (0.29, 0.37)	0.66 (0.6, 0.73)
By age								
<12 years	48,285	1	2.07	0	0.49	NA	*NA*	*NA*
12-17 years	917,410	1	0.11	4	0.49	0.22 (0.02, 1.99)	*0.44 (0.08, 2.43)*	*0.89 (0.22, 3.56)*
18-24 years	2,897,084	3	0.10	38	1.32	0.08 (0.02, 0.25)	*0.16 (0.07, 0.37)*	*0.31 (0.16, 0.6)*
25-39 years	7,081,760	31	0.44	169	2.39	0.18 (0.12, 0.27)	*0.37 (0.27, 0.49)*	*0.73 (0.58, 0.92)*
40-49 years	4,828,473	26	0.54	115	2.39	0.23 (0.15, 0.34)	*0.45 (0.32, 0.63)*	*0.9 (0.69, 1.17)*
50-64 years	8,369,353	38	0.45	424	5.07	0.09 (0.06, 0.12)	*0.18 (0.14, 0.23)*	*0.36 (0.3, 0.43)*
65-74 years	4,828,473	40	0.83	305	6.31	0.13 (0.09, 0.18)	*0.26 (0.21, 0.34)*	*0.53 (0.43, 0.64)*
75+ years	3,218,982	22	0.68	203	6.31	0.11 (0.07, 0.17)	*0.22 (0.16, 0.3)*	*0.43 (0.34, 0.56)*
By gender								
Male	15,290,164	68	0.44	200	1.31	0.34 (0.26, 0.45)	*0.68 (0.55, 0.84)*	*1.36 (1.13, 1.63)*
Female	16,899,655	96	0.57	811	4.80	0.12 (0.1, 0.15)	*0.24 (0.2, 0.28)*	*0.47 (0.42, 0.53)*
By age and gender								
Male								
<12 years	22,935	0	0.00	0	0.21	NA	*NA*	*NA*
12-17 years	435,770	0	0.00	1	0.21	NA	*NA*	*NA*
18-24 years	1,376,115	2	0.15	8	0.56	0.26 (0.06, 1.23)	*0.52 (0.16, 1.73)*	*1.04 (0.39, 2.78)*
25-39 years	3,363,836	9	0.27	34	1.01	0.26 (0.13, 0.55)	*0.53 (0.3, 0.94)*	*1.06 (0.66, 1.69)*
40-49 years	2,293,525	9	0.39	23	1.01	0.39 (0.18, 0.84)	*0.78 (0.42, 1.44)*	*1.55 (0.92, 2.62)*

50-64 years	3,975,443	19	0.48	85	2.14	0.22 (0.14, 0.37)	*0.45 (0.3, 0.65)*	*0.89 (0.65, 1.22)*
65-74 years	2,293,525	21	0.92	61	2.67	0.34 (0.21, 0.56)	*0.69 (0.46, 1.02)*	*1.37 (0.99, 1.91)*
75+ years	1,529,016	6	0.39	41	2.67	0.15 (0.06, 0.35)	*0.29 (0.15, 0.56)*	*0.59 (0.36, 0.97)*
Female								
<12 years	25,350	0	0.00	0	0.76	NA	*NA*	*NA*
12-17 years	481,641	1	0.21	4	0.76	0.27 (0.03, 2.45)	*0.55 (0.1, 2.99)*	*1.09 (0.27, 4.38)*
18-24 years	1,520,969	1	0.07	31	2.04	0.03 (0, 0.24)	*0.06 (0.02, 0.27)*	*0.13 (0.05, 0.36)*
25-39 years	3,717,924	21	0.56	138	3.70	0.15 (0.1, 0.24)	*0.31 (0.22, 0.43)*	*0.61 (0.47, 0.8)*
40-49 years	2,534,948	17	0.67	94	3.70	0.18 (0.11, 0.3)	*0.36 (0.24, 0.54)*	*0.72 (0.53, 0.99)*
50-64 years	4,393,910	19	0.43	345	7.85	0.06 (0.03, 0.09)	*0.11 (0.08, 0.15)*	*0.22 (0.17, 0.28)*
65-74 years	2,534,948	19	0.75	248	9.77	0.08 (0.05, 0.12)	*0.15 (0.11, 0.22)*	*0.31 (0.24, 0.4)*
75+ years	1,689,966	16	0.95	165	9.77	0.1 (0.06, 0.16)	*0.19 (0.13, 0.28)*	*0.39 (0.29, 0.52)*

**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.*

3.5 Review of the Pharmacovigilance Database

Post marketing data for potential signal of autoimmune hepatitis events were retrieved from the Company safety database using the following MedDRA preferred terms: "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury" with a data-lock point (DLP) of 31 December 2021, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Cases from all sources and relevant literature were reviewed.

Of note, throughout the document for simplicity autoimmune hepatitis is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e. "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

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

The MAH performed a review of all cases of autoimmune hepatitis derived from all sources. The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 31 December 2021, for Spikevax. Search criteria used the PTs of "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury". Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches were described for cumulative cases.

Cases were classified into two categories, following the Simplified diagnostic criteria of the International Autoimmune Hepatitis Group (EASL Clinical Practice Guidelines, 2015):

- Definite autoimmune hepatitis: 7 Points
- Probable autoimmune hepatitis 6 Points
- Those cases for which there were insufficient information to provide a diagnostic classification were classified as 'Unassessable'.

See Figure-1 for simplified diagnostic criteria

Figure-1. Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

ANA= antinuclear antibodies SMA= smooth muscle antibodies LKM= liver kidney microsomal antibodiesSLA= soluble liver antigens LP= liver pancreas
Addition of points achieved for all autoantibodies (maximum, two points).
Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interfacehepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation.
Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all thefeatures considered typical.
Atypical = showing signs of another diagnosis, like steatohepatitis.

For those cases classified as definite and probable AIH, the company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

3.7 Results

Cumulatively, through 31 Dec 2021, a total of 165 cases (171 events) of autoimmune hepatitis (AIH)-related terms have been reported, with 138 (74.3%) cases medically confirmed. There were 163 serious cases with 22 cases with a fatal outcome. The majority of the reports were in females 96 (58.2%) and in patients >50 years of age (Table 2).

Table 2: Number and Percentage of Cases Reporting Autoimmune Hepatitis Related Cases by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
<2	0	0	0	0	1	0.6	1	0.6
12-15	1	0.6	0	0	0	0	1	0.6
18-29	3	1.8	5	3.0	0	0	8	4.8
30-39	19	11.5	6	3.6	0	0	25	15.2
40-49	17	10.3	9	5.5	0	0	26	15.8
50-64	19	11.5	19	11.5	0	0	38	23.0
65-74	19	11.5	21	12.7	0	0	40	24.2
75+	16	9.7	6	3.6	0	0	22	13.3
Missing	2	1.2	2	1.2	0	0	4	2.4
Grand total	**96**	**58.2**	**68**	**41.2**	**1**	**0.6**	**165**	**100.0**

The majority of the events were reported under the PT of autoimmune hepatitis (46; 26.9%), followed by the PT of hepatic failure (33; 19.3%), and liver injury (24; 14.0%) (Table 3)

Table 3: Count of Events Reporting Autoimmune Hepatitis Related Events Cumulative to 31 Dec 2021

PT	Total # Events	% Total Events
Autoimmune hepatitis	46	26.9
Hepatic failure	33	19.3
Liver injury	24	14.0
Hepatitis acute	21	12.3
Acute hepatic failure	17	9.9
Hepatocellular injury	11	6.4
Drug-induced liver injury	10	5.8
Hepatotoxicity	3	1.8
Hepatitis fulminant	2	1.2
Immune-mediated hepatitis	2	1.2
Hepatitis toxic	1	0.6
Immune-mediated hepatic disorder	1	0.6
Grand total	**171**	**100.0**

There were no important differences between AIH-related events reported after dose 1 (28.7%) and those reported after dose 2 (30.4%). There were only 3 reports received after a dose 3 administration (Table 4).

Table 4. Number and Percent of Events of Autoimmune Hepatitis by Dose Numberand Time to Onset (TTO) - Cumulative to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***49***	***28.7%***
	0 days	4	2.3%
	01-02	9	5.3%
	03-04	7	4.1%
	05-06	2	1.2%
	07-13	9	5.3%
	14-29	14	8.2%
	30+	4	2.3%
Dose 2	***Subtotal***	***52***	***30.4%***
	0 days	7	4.1%
	01-02	9	5.3%
	03-04	6	3.5%
	05-06	3	1.8%
	07-13	7	4.1%
	14-29	7	4.1%
	30+	13	7.6%
Dose 3	***Subtotal***	***3***	***1.8%***
	01-02	1	0.6%
	03-04	1	0.6%
	07-13	1	0.6%
Unknown	***Subtotal***	***67***	***39.2%***
	Missing	67	39.2%
Grand total		**171**	**100.0%**

Cases Classification by the Simplified diagnostic criteria of the International AutoimmuneHepatitis Group

Out of the 165 case reports that were identified using the search criteria described above, there were two cases that were duplicate and one case report that was miscoded ([redacted] was a cases of myocarditis injury that was mistakenly coded to liver injury).

After evaluation of the rest of the cases, there were 155 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course,

laboratory data, dose and/or time-to-onset. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications.

There were 7 case reports that were considered confirmed AIH according to the EASL Simplified diagnostic criteria. All those reports were considered possible according to the WHO causality assessment (Appendix-1).

Review of Autoimmune Hepatitis Exacerbations

There were only 7 cases identified as confirmed cases of AIH utilizing the Simplified diagnostic criteria of the International Autoimmune Hepatitis Group. None of the cases had previous reported history of AIH, and all except one had confounding factors including associated medical histories that included polycythemia vera, type 2 diabetes, recent (3 months prior) COVID-19 infection, Hashimoto's disease and other confounding medical histories. Additionally, concomitant medications use that have been associated with hepatitis, increased liver enzymes, etc., including prolonged use of statins, hormone replacement therapy, peginterferon alfa were additional confounders in these cases.

There are two reports ([redacted] and [redacted] both literature reports and included in the 7 cases above mentioned, that are suggestive of positive rechallenge after receiving dose 2 of the vaccine. A complete resolution of the initial symptoms was not reported, and any additional information regarding complete clinical course information was not provided. According to the authors the patients were well before their diagnosis of AIH, but it recognized that AIH may be present in an otherwise asymptomatic person.

Those two cases were classified as possible according to the WHO-UMC standardized causality assessment based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded. There were more women (5) than men (2) which is what have been described in the general population where AIH preferentially affects women more than men by a ratio of 3.6/1.0

4 Literature Review

Clinical literature search review:

A cumulative literature search in PubMed in PubMed as of 31 December 2021 was performed using the following search criteria, (Acute hepatic failure) OR (Autoimmune hepatitis)) OR (Drug-induced liver injury)) OR (Hepatic failure)) OR (Hepatitis acute)) OR (Hepatitis fulminant)) OR (Hepatitis toxic)) OR (Hepatocellular injury)) OR (Hepatotoxicity)) OR (Immune-mediated hepatic disorder)) OR (Immune-mediated hepatitis)) OR (Liver injury))) AND ((mRNA-1273)) or (Moderna Covid-19 Vaccine)) or (mRNA 1273)) or (mRNA1273)) or (mRNA COVID vaccination)))) AND (("2020/11/01"[Date - Publication] : "2021/12/31"[Date - Publication])).

Review of these retrieved literature articles suggest a small number of articles describing Autoimmune hepatitis and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against Covid-19 disease. There are not pathognomonic findings to link vaccine to these adverse events.

Overall, there was a small number of articles describing Autoimmune Hepatitis and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against Covid-19 disease. There are not pathognomonic findings to link vaccine to these adverse events.

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

A cumulative search of global safety database as of 31 December 2021, was performed and the search retrieved 165 cases (171 events). In summary, out of the 165 identified cases, after evaluation of the rest of the cases, there were 155 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course, laboratory data, dose and/or time-to-onset. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications. there were 7 cases were confirmed AIH according to the EASL Simplified diagnostic criteria,

There were more women (5) than men (2) which is what have been described in the general population where AIH preferentially affects women more than men by a ratio of 3.6/1.05 (Lucey, 2014). As of 31 December 2021, there have been 827,274,740 doses of Spikevax distributed worldwide, with 559,872,937 doses that are estimated to have been administered. With 7 reported cases classified as confirmed cases of AIH, the reporting rate of AIH after administration of Spikevax is 0.01 per million doses administered.

No unique or novel risk factors were identified from this small aggregate sample. Insufficient information was present in the literature to suggest an occurrence between SpikeVax administration and the event of AIH. Furthermore, the Observed to expected ratio confirms that the event is very rare and significant disproportionality was not identified in EVDAS. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers cases of autoimmune hepatitis a validated signal which was refuted and the MAH will continue to evaluate reports received using routine surveillance.

6 Conclusion

Overall, Based on the analysis of all the safety data available as of 31 December 2021, the MAH considers that cases included under AIH, these reports are heavily confounded, and do not provide sufficient information to establish a causal relationship to the administration of SPIKEVAX. No new safety issue of concern was identified. The available data does not warrant an update change to the label/SmPC and/or the RMPs. The MAH will continue to monitor events for AIH using routine pharmacovigilance surveillance.

7 References

Bhattacharjee S, Banerjee M. Immune Thrombocytopenia Secondary to COVID-19: a Systematic Review. SN Compr Clin Med. 2020;2(11):2048-2058. doi: 10.1007/s42399-020-00521-8. Epub 2020 Sep 19. PMID: 32984764; PMCID: PMC7501509.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015 Oct;63(4):971-1004. doi: 10.1016/j.jhep.2015.06.030. Epub 2015 Sep 1. Erratum in: J Hepatol. 2015 Dec;63(6):1543-4. PMID: 26341719.

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.

Lucey MR, Vierling JM. Clinical presentation and natural history of autoimmune hepatitis. Clin Liver Dis (Hoboken). 2014 Feb 10;3(1):9-11. doi: 10.1002/cld.304. PMID: 30992880; PMCID: PMC6448693.

McShane C, Kiat C, Rigby J, Crosbie Ó. The mRNA COVID-19 vaccine - A rare trigger of autoimmune hepatitis? J Hepatol. 2021 Nov;75(5):1252-1254. doi: 10.1016/j.jhep.2021.06.044. Epub 2021 Jul 8. PMID: 34245804; PMCID: PMC8264276.

Appendix-1: Assessment of Cases that are Identified as AIH through EASL Simplified diagnostic criteria

Case ID	Country	Report Type	PT	Event Seriousness	ALL PTs	Age	Gender	Event Outcome	Medical History	Concomitant Medications	Dose #	TTO	EASL	WHO	Confounders	MAH Comment	WW Identifier
[redacted]	[redacted]	Regulatory Authority	Autoimmune hepatitis	Serious	Autoimmune hepatitis, Product dose omission issue	62	Male	Recovering/Resolving	Diabetes mellitus(C); Ischaemic cardiomyopathy(C)	CRESTOR; METFIN; ASASANDOZ; ROSUVASTATIN	Dose I	7	AIH	Possible	possible liver impact of the underlying diabetes and cardiomyopathy, although liver ultrasound did not show fatty liver.	62 years old male with medical history of type 2 diabetes and ischemic heart disease and long history of statin use who 7 days after the 1st dose of SPikevax experienced jaundiced, and had tender hepatomegaly without ascites. Laboratiry results showed elevated liver enzimes, Blood alkaline phosphatase, bilirubin, IgG, Positive: ANA	[redacted]

																at a titer of 1:640 with fine speckled indirect immunofluorescence pattern on HEp2 cells, positive anti-gastric parietal cells antibody at a titer of 1:320. Polymerase chain reaction was negative for hepatitis A, B, C, E. An abdominal ultrasound was normal. Liver histology showed inflammatory portal infiltrate with interface hepatitis, lobular and centrilobular inflammation with centrilobular necrosis, in absenc	

																e of fibrosis and steatosis. The patient was treated with prednisone at a dose of 40 mg once a day. The patient did not develop signs of encephalopathy, and after a transient worsening of INR to 1.4, he showed spontaneous improvement of serum bilirubin, INR and transaminase levels, and autoimmune hepatitis was considered resolving. Important risk factor in this report is the prolonge use of statin. Increases in	

																serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. According to the EASL this case is considered a confirmed case of AIH. According to the WHO causality assessment this report is possibl	

																e based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded.	

[redacted]		Literature-Non-Study	Autoimmune hepatitis	Serious	Autoimmune hepatitis, Herpes virus infection	76	Female	Not Recovered/Not Resolved	COVID-19(H); Hypothyroidism(C); Transitional cell carcinoma(H); Hypotension (H)	MIDODRINE; ZOLPIDEM; LEVOTHYROXINE	Dose 1	12	AIH	Possible	yes, prior COVID19 and other autoimmune disease (Hashimoto)	Literature arricle for a 76 years old female with medical history Hashimoto thyroiditis and prior COVID-19 infection 3 months prior to receive her 1st dose of Spikevax, and who 2 to 3 days after the 1st dose experienced dark urine, weight loss and fatigue. Patient was seeing 5 weeks later and found to have elevated liver enzymes, anti-smooth muscle antibody (titer 1:1280, against F-Actin,	[redacted]

																no specific immunofluorescence pattern observed), liver kidney microsome type 1 antibody and anti-soluble liver antigen antibody were negative. An abdominal ultrasound showed a slightly enlarged and hyperechogenic liver without biliary duct dilatation. Important risk factors exist in this patient including the short TTO of 2 days as well as her medical history of Hashimoto thyroiditis and very	

																recent COVID-19 infection, as well as the use of levothyroxine which is labelled for elevations in liver function test. 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]		Literature - Non-Study	Autoimmune hepatitis	Serious	Autoimmune hepatitis, Jaundice	71	Female	Recovering/Resolving	Cholecystectomy; Hip arthroplasty; Osteoarthritis (H)	PARACETAMOL	Dose 1	4	AIH	Possible	yes, paracetamol	71 years old male with medical history of cholecystectomy, osteoarthritis, and hip replacement who 4 days after the 1st dose of Spikevax developed jaundice and was found to have elevated liver enzymes, negative results for HBV, HCV, HEV, EBV, CMV, HIV, HAV. Other test and diagnostic results were compatible with the diagnosis of AIH. But according to the authors drugs, toxins	[redacted]

																or infections could not be ruled out as aetiological agents. Important confounding factor in this report is the short TTO of 4 days after vaccination. 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]		Literature - Non-Study	Autoimmune hepatitis	Serious	Autoimmune hepatitis, Influenza like illness, Intentional dose omission, Malaise	56	Female	Recovering/Resolving		ROSUVASTATIN	Dose 1	35	A1H	Possible	yes, statins	56 years old female with unknown medical history who around 35 days after the 1st dose of SPikevax experienced jaundice, feeling unwell and anorexia and was found to have elevated liver enzimes, as other abnormal laboratory results and was diagnosed with AIH. Important risk factor in this report is the prolonge use of statin. Increases in serum transaminases [AST (SGOT) or ALT (SGPT	[redacted]

																)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. According to the EASL this case is considered a confirmed case of AIH. According to the WHO causality assessment this report is possible based on temporal association betwee	

																n the use of the product and the start of the events; a causal relationship cannot be excluded.	

[redacted]		Literature - Non-Study	Autoimmune hepatitis	Serious	Abdominal pain, Autoimmune hepatitis, Choluria, Jaundice	65	Female	Unknown	Polycythaemia vera(H)	ACETYLSALICYLIC ACID; SERTRALINE; ESOMEPRAZOLE	Dose 1	14	A1H	Possible	yes, polycythemia is involved in thrombosis Budd Chiari leading to liver failure which was not the clinical presentation here	65-year-old female patient with medical history of Polycythemia vera (JAK2 V617F positive polycythemia vera under pegylated interferon), who approximately 2 weeks after the first dose of Spikevax developed jaundice, choluria, abdominal pain, and was found to have elevated liver enzymes, Antinuclear antibody was positive, immunoglobulin G elevated. Liver biopsy showed	[redacted]

																marked expansion of the portal tracts, severe interface hepatitis and multiple confluent foci of lobular necrosis, and was diagnosed with AIH. Important risk factor associated with this report is the concomitant use of of peginterferon alfa for the treatment of Polycythemia vera which has a boxed warning for the development or exacerbation of autoimmune disorders including hepatitis.	

																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]		Literature - Non-Study	Autoimmune hepatitis	Serious	Autoimmune hepatitis, Drug-induced liver injury, Inappropriate schedule of product administration, Jaundice	47	Male	Unknown			Dose 2	3	AIH	Possible	No medical history reported - According to authors patient completely well	A 47-year-old Caucasian man, who according to the authors was previously completely well, and 3 days after his 1st dose of Spikevax experienced malaise and jaundice. 4 days later was found to have elevated bilirubin, liver enzymes, and albumin, Blood count, renal function and international normalized ratio were normal. He denied paracetamol use and reported minimal alcohol intake.	[redacted]

																Ultrasound scan, CT thorax, abdomen and pelvis and MRI pancreas performed to exclude malignancy, showed no significant findings. Serum IgG was raised at 25.1 g/L (normal 6-16), IgM 2.2 g/L (0.5-2) and serum was positive for anti-nuclear antibody. Serological tests for HAV, HBV, HCV, HEV, EBV and CMV were negative. His jaundice faded and LFTs improved: bilirubin falling a	

																month later. Ten days later the patient received his 2nd Moderna vaccine dose and the jaundice returned a few days after. Blood tests 18 days later found elevated billirubin, ALT, and a raised prothrombin time (PT). On examination, he was alert, deeply jaundiced, with hepatomegaly but no ascites. Repeat abdominal ultrasound showed a mildly fatty liver, patent portal and hepatic vein flow, with	

																no ascites. Review of the liver biopsy showed acute active hepatitis: widespread areas of bridging necrosis, marked interface hepatitis, lymphoplasmatic inflammation including eosinophils, ballooned hepatocytes, multi-nucleated giant cells, and emperipolesis. There was minimal fibrosis, Ishak stage 1. According to the authors the pattern of injury on histology was consist	

																ent with acute hepatitis, with features of autoimmune hepatitis or possible drug-induced liver injury (DILI), triggering an autoimmune-like hepatitis. Even though important information is missing in this report including any laboratory results that may also explain the sudden changes in liver enzymes in this patient, the positive rechallenge observe in the patient after receiving the second dose of Spikevax makes	

																this report according to the WHO causality assessment possible based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded.	

[redacted]		Literature-Non-Study	Autoimmune hepatitis	Serious	Autoimmune hepatitis	41	Female	Unknown	Premature menopause(H); Hormone therapy		Unknown	Unknown	AlH	Possible	none reported-HRT for unknown time but unlikely affecting liver	41-year-old female with past medical history of premature ovarian failure undergoing substitutive hormonal therapy with no side effects. After receiving the first dose of SARS-CoV-2 Moderna vaccine (mRNA-1273) the patient presented epigastric pain, nausea and vomiting. These symptoms lasted for 3 weeks and then decreased in intensity. Seven days after the second dose,	[redacted]

																symptoms reappeared with higher intensity and were associated with choluria and jaundice. Liver tests showed aspartate aminotransferase 993 IU/L, alanine aminotransferase 1,312 IU/L, total bilirubin 2.3 mg/dl (peak of 8.5 mg/dl), gamma-glutamyltransferase 209 IU/L, alkaline phosphatase 190 IU/L. Laboratory results were negative for hepatitis A, B, C, E, cytomegalovirus, Epstein-Bar	

																virus, herpes simplex virus type 1 and 2, and herpes 6 virus. Antinuclear antibody (1:80), anti-smooth muscle antibody (1:40), anti-soluble liver antigen (anti-SLA), anti-liver cytosol were positive. IgG levels were elevated (20.8 g/L). Liver ultrasound was normal. The liver biopsy (2.5 cm, 19 portal tracts) showed a marked expansion of the portal tracts with a dense inflammatory infiltrate composed of lymph	

																ocytes and plasma cells, severe interface hepatitis and lobular inflammation with dispers e necroinflammatory foci, apoptotic bodies and hepatocyte ballooning. Masson's trichrome staining showed no signs of parenchymal or perisinusoidal fibrosis. The score of simplified diagnostic criteria of the International Autoimmune Hepatitis Group was 8 (definite diagnosis of AIH). Important	

																risk factor associated with this report is the use of hormone replacement therapy. Even though important information is missing in this report including any laboratory results that may also explain the sudden elevation in liver enzymes in this patient, the positive rechallenge observe in the patient after receiving the second dose of Spikevax makes this report according to the WHO causality assess	

																ment possible based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded.	

Appendix 4.2b: Signal Evaluation report: Giant Cell Arteritis

Signal Evaluation Report

for

mRNA-1273

on

Giant Cell Arteritis

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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 Giant Cell Arteritis in association with the administration of mRNA-1273 in adult patients ≥18yo, based on all information available to the MAH at the time of document preparation.

1.1 Source of the Signal

On 28-Jan-2022, the Australia TGA contacted Moderna:
The TGA's Medicines and Vaccines Investigation and Surveillance (MAVIS) Section is reviewing the signal of giant cell arteritis (GCA) with SPIKEVAX. We are now writing to request that Moderna add GCA to the SPIKEVAX adverse events of special interest (AESI) list.
The basis for this request is the publication of case reports of GCA in association with COVID vaccines (including mRNA platform vaccines), and disproportionate reporting to the WHO's Vigibase. This will facilitate enhance pharmacovigilance and consistency with the monitoring that is taking place for other COVID vaccines.

Moderna responded to the TGA that the MAH does not agree to add giant cell arteritis (GCA) to the SPIKEVAX AESI list. The AESI list is largely derived from SPEAC, and we have not been routinely adding AESIs on the basis of health authority requests. Instead, we consider that the TGA request meets the criteria for a "validated safety signal," and will therefore plan to conduct formal signal evaluation to address the agency's concern.

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.

General Description on Disease (Giant Cell Arteritis):

Giant cell arteritis (GCA), or temporal arteritis, is a systemic inflammatory vasculitis of unknown etiology that occurs in older persons and can result in a wide variety of systemic, neurologic, and ophthalmologic complications. GCA is the most common form of systemic vasculitis in adults. Other names for GCA include arteritis cranialis, Horton disease, granulomatous arteritis, and arteritis of the aged. GCA is classified as a large-vessel vasculitis but typically also involves medium and small arteries, particularly the superficial temporal arteries—hence the term temporal arteritis. In addition, GCA most commonly affects the ophthalmic, occipital, vertebral, posterior ciliary, and proximal vertebral arteries.

GCA should always be considered in the differential diagnosis of a new-onset headache in patients 50 years of age or older with an elevated erythrocyte sedimentation rate. Temporal artery biopsy remains the criterion standard for diagnosis of this granulomatous vasculitis. However, increasing evidence supports the use of imaging studies for diagnosis in patients at high clinical risk. Visual loss is one of the most significant causes of morbidity in GCA. Permanent visual impairment may occur in as many as 20% of patients, and, in some cases, GCA can cause bilateral blindness. Newly recognized GCA should be considered a true neuro-ophthalmic emergency. Prompt initiation of treatment may prevent blindness and other potentially irreversible ischemic sequelae of GCA. Corticosteroids are the mainstay of therapy. In steroid-resistant cases, drugs such as tocilizumab, cyclosporine, azathioprine, or methotrexate may be used as steroid-sparing agents. The typical patient with GCA remains on steroid therapy for roughly 2 years.

Histopathology:

GCA is marked by transmural inflammation of the intima, media, and adventitia of affected arteries, as well as patchy infiltration by lymphocytes, macrophages, and multinucleated giant cell. Mural hyperplasia can narrow the arterial lumen, resulting in distal ischemia. Age and female sex are established risk factors for GCA, a genetic component seems likely, and infection may have a role. One school of thought considers GCA and polymyalgia rheumatica to be different manifestations of the same disease process, while others see them as closely related but different diseases. Common signs and symptoms of GCA reflect the involvement of the temporal artery and other medium-sized arteries of the head and the neck and include visual disturbances,

headache, jaw claudication, neck pain, and scalp tenderness. Constitutional manifestations, such as fatigue, malaise, and fever, may also be present.

Pathophysiology:

The exact etiology of giant cell arteritis remains unknown. GCA is primarily a disease of cell-mediated immunity, which is thought to arise as a maladaptive response to endothelial injury. The adventitia is the likely site of initial immunologic injury and is considered the immunological center of the disorder, while the intima and media are the histological center. The primary inflammatory response involves the activation of dendritic cells in the adventitia of arteries by an unknown antigen, with production of chemokines that recruit CD4+T helper cells. Activated CD4+ T helper cells polarize into Th1 cells (producing interferon gamma) and Th17 cells (producing interleukin 17). It is known that mRNA-1273 induces the Th1 phenotype of CD4+ T–cell).

GCA Following Other Vaccines has Limited Applicability to mRNA-1273:

Varicella zoster virus (VZV) vaccine has been associated with GCA, however the VZV vaccine is a live attenuated form which is mechanistically different from mRNA-1273, Furthermore, VZV is neurotrophic and itself may result in certain manifestations that may be similar to those associated with GCA.

There has been speculation of an association between influenza vaccines and GCA. Viral components included in influenza vaccines vary from year to year, on the basis of the expected type of influenza virus, however considering that a restricted number of vaccine adjuvants have been used for decades enhancing the immune response to co-administered antigens, it is the adjuvant component that may be implicated in the development of GCA.

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3 Review of Data from All Sources

The assessment of Giant cell arteritis (GCA) 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 GCA was cumulatively reviewed in the MAH clinical database with a data-lock point (DLP) of 04 May 2021, searched using the following MedDRA v 24.0 preferred term "Giant cell arteritis" was performed in P301 study and there were zero cases observed.

3.2 External Databases

VAERS and EVDAS were reviewed for the PTs: Giant cell arteritis

- VAERS: No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines in Adults) in VAERS as of 31 Jan 2022; Giant cell arteritis (EB05: 0.591)

- EVDAS: The PT of Giant cell arteritis showed Disproportionality and ROR was 3.14. Overall, Data from EVDAS showed disproportionality as ROR was 3.14. These cases from EVDAS are included in the review of PM data, and most do not meet the ACR criteria for GCA; this appears as a non-significant disproportionality.

3.3 Non-clinical Data

Not applicable

3.4 Epidemiological studies

Giant cell arteritis was reported in 50 cases cumulatively (reporting rate 0.15 per 100,000 person-years). The cumulative reporting rate was below the expected rate as per Muratore et al 2021(expected rate 8.30 per 100,000 person-years). The population-based study in Northern Italy was a retrospective cohort study and included all incident GCA diagnosed over 12-year period (January 2005 – December 2016). . Stratification of observed to expected analyses produced similar findings - estimates of incidence from the US were more consistent with each other and may be a more appropriate comparator given that a large majority of cases originated in the United States. No subgroups showed a reporting rate that exceeded the expected incidence; the likelihood of severe underreporting is reduced, given enhanced public awareness of GCA as a potential risk associated with some COVID-19 vaccines. As such, these analyses do not presently suggest an increased incidence beyond expectation (Table 1).

Table-1: Observed/Expected Analyses Stratified by Age and Gender, Giant cell arteritis, Expected Rates from the United States

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			
All	33,332,403	50	0.15	2,767	8.30	0.02 (0.01, 0.02)	0.04 (0.03, 0.04)	0.07 (0.06, 0.08)
By age								
<12 years	49,999	0	0.00	4	8.30	NA	*NA*	*NA*
12-17 years	949,973	0	0.00	79	8.30	NA	*NA*	*NA*
18-24 years	2,999,916	0	0.00	249	8.30	NA	*NA*	*NA*
25-39 years	7,333,129	0	0.00	609	8.30	NA	*NA*	*NA*
40-49 years	4,999,860	0	0.00	415	8.30	NA	*NA*	*NA*
50-64 years	8,666,425	6	0.07	719	8.30	0.01 (0, 0.02)	*0.02 (0.01, 0.03)*	*0.03 (0.02, 0.05)*
65-74 years	4,999,860	19	0.38	415	8.30	0.05 (0.03, 0.07)	*0.09 (0.07, 0.13)*	*0.18 (0.14, 0.23)*
75+ years	3,333,240	24	0.72	277	8.30	0.09 (0.06, 0.13)	*0.17 (0.13, 0.24)*	*0.35 (0.28, 0.44)*
By gender								
Male	15,866,224	18	0.11	841	5.30	0.02 (0.01, 0.03)	*0.04 (0.03, 0.06)*	*0.09 (0.07, 0.11)*
Female	17,466,179	32	0.18	1,886	10.80	0.02 (0.01, 0.02)	*0.03 (0.03, 0.04)*	*0.07 (0.06, 0.08)*
By age and gender								
Male								
<12 years	23,799	0	0.00	1	5.30	NA	*NA*	*NA*
12-17 years	452,188	0	0.00	24	5.30	NA	*NA*	*NA*
18-24 years	1,427,960	0	0.00	76	5.30	NA	*NA*	*NA*

25-39 years	3,490,569	0	0.00	185	5.30	NA	*NA*	*NA*
40-49 years	2,379,934	0	0.00	126	5.30	NA	*NA*	*NA*
50-64 years	4,125,218	2	0.05	219	5.30	0.01 (0, 0.04)	*0.02 (0.01, 0.05)*	*0.04 (0.02, 0.07)*
65-74 years	2,379,934	10	0.42	126	5.30	0.08 (0.04, 0.15)	*0.16 (0.1, 0.25)*	*0.32 (0.22, 0.45)*
75+ years	1,586,622	5	0.32	84	5.30	0.06 (0.02, 0.15)	*0.12 (0.06, 0.23)*	*0.24 (0.15, 0.39)*
Female								
<12 years	26,199	0	0.00	3	10.80	NA	*NA*	*NA*
12-17 years	497,786	0	0.00	54	10.80	NA	*NA*	*NA*
18-24 years	1,571,956	0	0.00	170	10.80	NA	*NA*	*NA*
25-39 years	3,842,559	0	0.00	415	10.80	NA	*NA*	*NA*
40-49 years	2,619,927	0	0.00	283	10.80	NA	*NA*	*NA*
50-64 years	4,541,207	2	0.04	490	10.80	0 (0, 0.02)	*0.01 (0, 0.02)*	*0.02 (0.01, 0.03)*
65-74 years	2,619,927	10	0.38	283	10.80	0.04 (0.02, 0.07)	*0.07 (0.04, 0.11)*	*0.14 (0.1, 0.2)*
75+ years	1,746,618	5	0.29	189	10.80	0.03 (0.01, 0.06)	*0.05 (0.03, 0.1)*	*0.11 (0.07, 0.17)*

*Rates presented per 100,000 person-years. Compared to Otite 2020.

3.5 Review of the Pharmacovigilance Database

Post marketing data for potential signal of Giant cell arteritis events were retrieved from the Company safety database using the following MedDRA preferred term: "Giant cell arteritis" with a data-lock point (DLP) of 31 January 2022, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Cases from all sources and relevant literature were reviewed.

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

The MAH performed a review of all cases of GCA derived from all sources. The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 31 January 2022, for Spikevax. Search criteria used the PT of "Giant cell arteritis". Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches were described for cumulative cases including fatal cases.

The events were classified using American College of Rheumatology (ACR) 1990 Criteria for the Classification of Giant Cell Arteritis. For the purposes of establishing a case definition, an

ICSR shall represent a case of GCA if it provides information to satisfy at least 3 of the 5 ACR criteria (Figure -1).

Figure 1: 1990 Criteria for the Classification of Giant Cell (temporal) Arteritis

Criterion	Definition
1. Age at disease onset ≥50 years	Development of symptoms or findings beginning at age 50 or older
2. New headache	New onset of or new type of localized pain in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. Elevated erythrocyte sedimentation rate	Erythrocyte sedimentation rate ≥50 mm/ hour by the Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

3.7 Results

A cumulative search through 31 January 2022 retrieved 50 cases (51 events) that were reviewed and assessed according to ACR criteria and categorized utilizing the WHO-UMC system for standardized case causality assessment (WHO 2013). Most reports were received from regulatory authorities (41, 82.0%). The majority of cases (26; 52.0%) were reported from the United States (26, 52.0%) followed by the European Economic Area (17; 34.0%). When dose number was known, the majority of GCA events were reported after the 1st dose (14; 25.5%). No fatal cases were reported. An overall summary of these cases is presented in **Table-1.**

Table 1: Overall Summary of Post-marketing Data for GCA as of 31 January 2022

Category	Number
Number of cases	50 Cases (40 serious)
Number of events	51 (39 Medically confirmed)
Median age	74.0 y/o (Min 55.0/Max:89.0)
Female/ Male/Missing	32/18/0
Report type	Regulatory Authority: 41 cases (82.0%) Spontaneous: 8 cases (16.0%) Literature-Non-Study: 1 case (2.0%)
Case distribution by region	United States 26 (52.0); European Economic Area 17 (34.0%); Switzerland 3 (6.0%); United Kingdom 3 (6.0%) and Asia 1 (2.0%)

Fatal outcome	0 Cases
Dose number Dose 1 Dose 2 Dose 3 Unknown	 16 events (31.4%) 14 events (25.5%) 1 event (2.9%) 20 events (39.2%)

Of the 50 cases, 18 (36.0%) involved male patients and 32 (64.0%) involved female patients with a median patient age of 74.0 (min: 55.0/ max: 89.0). Most of the cases were reported in the elderly ≥75 years age group (24; 48.0%).

Table 2: Number and Percentage of Spontaneous Cases of Giant Cell Arteritis (GCA) Reported by Age and Gender for the SPIKEVAX. Cumulative to 31 January 2022

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
50-64	4	8.0	2	4.0	6	12.0
65-74	9	18.0	10	20.0	19	38.0
75+	19	38.0	5	10.0	24	48.0
Missing	0	0	1	2.0	1	2.0
Grand total	32	64.0	18	36.0	50	100.0

Average time to onset was 18.0 days (SD 28.4) with a median of 6 days (0-112). Events were reported more frequently after the 1st dose (31.4%%) and then after the 2nd dose (27.5%) then 3rd dose (2.0%). No specific pattern with respect to TTO was observed (**Table 3**).

Table 3: Time to Onset by Dose Number as of 31 January 2022

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	*Subtotal*	*16*	*31.4*
	0 days	1	2.0
	01-02	4	7.8
	05-06	4	7.8
	07-13	4	7.8
	14-29	1	2.0
	30+	2	3.9
Dose 2	*Subtotal*	*14*	*27.5*
	0 days	2	3.9
	01-02	2	3.9
	03-04	1	2.0
	05-06	1	2.0

Dose Number	TTO All Doses (Days)	# Events	% Events
	07-13	2	3.9
	14-29	3	5.9
	30+	3	5.9
Dose 3	*Subtotal*	*1*	*2.0*
	01-02	1	2.0
Unknown	*Subtotal*	*20*	*39.2*
	Missing	20	39.2
Grand total		**51**	**100.0**

Cases were categorized by WHO-UMC criteria (Appendix-1) and classified as a case of GCA case and not a GCA case following the American College of Rheumatology (ACR) 1990 Criteria for the Classification of Giant Cell Arteritis (Hunder et al, 1990). There were 14 cases that met 3 of the 5 criteria to be classified as cases of GCA as per ACR criteria. The 36 reports that did not meet ACR criteria for GCA and/or were deemed to be unlikely/unassessable/conditional in relation to mRNA-1273 using WHO causality assessment criteria. Of the 14 cases that met ACR criteria, 4 categorized as possible in causal association as per WHO criteria are presented below. For detailed information on ACR and WHO see (Appendix-1).

[redacted] Medically confirmed report of a 75 y/o female who experienced symptoms of GCA one day post dose 1 of mRNA-1273 and diagnosed with GCA on day 5 by temporal artery biopsy. While relevant clinical information such as medical history and concomitant medications is not provided, based on the temporal association, WHO causality is assessed as possibly related.

[redacted] Consumer report of a 73 y/o male with history of heart disease, kidney disorder, hypertension, diabetes, and concomitant medications including insulin, use of anticoagulants, use of statins, among others, who 5 days after the 1st dose of Spikevax developed arthalgia, back pain, neck pain. After the 2nd dose of the vaccine, reported pain in right arm/shoulder area intensified and spread making normal activities of life difficult, necessitating help from his partner. 13 days later the patient received a cortisone shot in right shoulder and an MRI showed inflammation of the shoulder with laboratory results showing elevated ESR. 69 days after his 2nd dose was diagnosed with PMR, with suspicion of GCA for which a biopsy was performed but results not provided. Confounding evaluation is the patient's advanced age which places him at a greater risk for both PMR and GCA as well as the lack of medical history, further information on his polypharmacy and lack of diagnostic results. WHO causality is therefore assessed as possible based on temporal association between the use of the product and the start of the event.

[redacted]HCP report of a 76 y/o female who received dose 1 of

mRNA-1273 on an unknown date and experienced symptoms including headache and temporomandibular joint syndrome two days post dose 2 of mRNA-1273 and was diagnosed with GCA on day 58 by temporal artery biopsy. Minimal information is provided, and confounding conditions include occipital neuralgia, however based on the temporal association with vaccinations, WHO causality is assessed as possibly related.

[redacted]Consumer report of a 62 y/o male, who on the same day as dose 2 and 28 days after dose 1 of mRNA-1273, experienced symptoms including headache and pyrexia with CRP 135, and diagnosed with GCA on an unknown date by temporal artery biopsy. Minimal information is provided, and assessment is confounded by history of Lyme disease, however based on the temporal association, WHO causality is assessed as possibly related.

Table 4: Tabulated summary of Cases Qualified for Giant cell arteritis (GCA) Criteria

Case ID	Age (Years)/Sex/ Country	ALL PTs	Event Seriousness (GCA)	Dose # prior to onset	WHO	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy	MAH Comment
[redacted]	75/ F[redacted]	Dyspnoea, Face oedema, Fatigue, **Giant cell arteritis**, Headache, Infection, Inflammation, Lip swelling, Mental status changes	Serious	Dose 1	Possible	Y	Y	Unk	ESR 108	Positive	TTO 1 day without alt etiology, however minimal information is provided. Temporally associated.
	76/ F[redacted]	Back pain, Ear pain, **Giant cell arteritis**, Headache, Lymph node pain, Lymphadenopathy, Neck pain, Pain of skin, Temporomandibular joint syndrome	Non-Serious	Dose 2	Possible	Y	Y	Y	ESR 67	Positive	TTO 6 days post Dose-1. Limited information. Temporally associated.
	73/ M/[redacted]	Arthralgia, Back pain, **Giant cell arteritis**, Inflammation, Loss of personal independence in daily activities, Mobility decreased, Neck pain, Pain in extremity, Polymyalgia rheumatica, Sleep disorder	Serious	Dose 1	Possible	Y	neck pain	Unk	ESR 98	Unk	Confounding evaluation is the patient's advanced age which places him at a greater risk for both PMR and GCA as well as the lack of medical history, further information on his polypharmacy and lack of diagnostic results. temporally associated.
	62/ M[redacted]	Chills, Fatigue, **Giant cell arteritis**, Headache, Night sweats, Pyrexia	Non-Serious	Dose 2	Possible	Y	Y	Unk	CRP 135	Positive	TTO 2 Days post Dose-2. confounded by history of Lyme disease and temporally associated.
	75/ M/[redacted]	Blindness, **Giant cell arteritis**	Serious	Dose 1	Conditional	Y	Unk	Unk	ESR increased	Positive	TTO 8 days, minimal information, need clarity on PMH and drug allergy
	76/ F[redacted]	**Giant cell arteritis**, Headache, Migraine, Vision blurred, Visual impairment	Serious	Dose 1	Unlikely	Y	Y	Unk	UNk	Positive	TTO 78d, h/o Hashimoto's
	75/ F[redacted]	Dysmorphism, Eye swelling, **Giant cell arteritis**, Headache, Lip swelling	Serious	Dose 1	Unlikely	Y	Y	Unk	Unk	Positive	TTO 1 day and reported h/o HA and jaw pain make causal association unlikely
	70/ F[redacted]	Eye pain, Facial pain, **Giant cell arteritis**, Headache, Mastication disorder, Night sweats, Sleep disorder, Visual impairment	Non-Serious	Dose 1	Conditional	Y	Y	Unk	ESR high nl	Inconclusive	TTO same day with workup 2 months later confounded by conmeds; bopsy reported as inconclusive yet also

											Temporal artery arteritis; CT inconclusive.
[redacted]	75/ F/[redacted]	Cranial nerve disorder, Diplopia, Eye pain, Fatigue, **Giant cell arteritis**, Pain, Pain of skin, Tenderness	Non-Serious	Dose 2	Unlikely	Y	Y	Y	ESR 51.2, CRP 52	Unk	TTO 112-140 days
	75/ M/[redacted]	Blindness, Giant cell arteritis	Serious	Unknown	Conditional	Y	Unk	Unk	High ESR	Positive	Consumer report needing medical confirmation
	67/ F/[redacted]	Asthenia, C-reactive protein increased, Confusional state, **Giant cell arteritis**, Headache, Nausea, Palpitations, Red blood cell sedimentation rate increased, Respiratory distress	Serious	Dose 1	Unassessable	Y	Y	Unk	ESR 34, CRP 24 CP	Positive	Minimal information
	81/ F/[redacted]	Ear pain, Eye pain, **Giant cell arteritis**, Headache, Musculoskeletal stiffness, Pain in jaw	Serious	Dose 2	Unlikely	Y	Y	Unk	Unk	Positive	TTO 54 days confounded by comorbidities and commends
	76/ F/[redacted]	Blindness, Blindness unilateral, **Giant cell arteritis**, Headache, Immunosuppression, Optic ischaemic neuropathy	Serious	Dose 2	Unlikely	Y	Y	Unk	ESR high and CRP high	Positive	Unlikely with same day TTO
	78/ Italy/[redacted]	**Giant cell arteritis**	Serious	Unknown	Unassessable	Y	Y	Unk	Unk	Positive	TTO 3 days with minimal information provided

4 Literature Review

Clinical literature search review:

A literature search was performed 31 Jan 2022 using PubMed, with the following criteria (Giant Cell Arteritis) AND (Spikevax)) OR (mRNA-1273)) OR (mRNA 1273)) OR (mRNA1273)) OR (Moderna Covid19 Vaccine)).

Focused Search for Mechanism of Action:
Search 1: (Giant Cell Arteritis) AND (Moderna Covid19 Vaccine)) AND (("2020/11/01"[Date - Publication]: "2022/01/31"[Date - Publication])): Retrieved 1 articles

Search 1: ((Giant Cell Arteritis) AND (mRNA-1273)) AND (("2020/11/01"[Date - Publication] : "2022/01/31"[Date - Publication])) : Retrieved 2 articles

Results:

- **Summary:** A cumulative search as of 31 Jan 2022 retrieved 686 articles.
- There was a small number of articles describing Giant Cell Arteritis and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against Covid-19 disease. There are not pathognomonic findings to link vaccine to these adverse events.

Conclusion: Literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and Giant Cell Arteritis

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

A cumulative search of global safety database as of 31 January 2022, was performed and the search retrieved 50 cases (51 events). In summary, out of the 50 identified cases, there were 14 cases meeting the ACR criteria for GCA. Causality assessment did not identify any certain or probable cases causally associated with Spikevax administration. Four (8.0%) cases were considered possible based on the temporal association. In these instances, alternate etiologies existed with co-existing diseases, medical history or other concomitant drugs confounded the analysis.

No unique or novel risk factors were identified from this small aggregate sample. Insufficient information was present in the literature to suggest a hypothesis for a causal association rather than a chance occurrence between Spikevax administration and the event of GCA. Furthermore, the Observed to expected ratio confirms that the event is very rare and significant disproportionality was not identified in EVDAS or VAERS.

6 Conclusion

Based on the analysis of all available safety data as of 31 January 2022, the MAH considers that there is no sufficient information to establish a causal relationship between the administration of Spikevax and the development of giant cell arteritis. The signal is refuted and no change to the reference safety information, labeling or risk management plan is required. No new or emerging safety issue of concern was identified The MAH will continue to monitor events for GCA using routine pharmacovigilance surveillance.

7 References

Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990 Aug;33(8):1122-8. doi: 10.1002/art.1780330810. PMID: 2202311.

Muratore F, Boiardi L, Mancuso P, Restuccia G, Galli E, Marvisi C, Macchioni P, Rossi PG, Salvarani C. Incidence and prevalence of large vessel vasculitis (giant cell arteritis and Takayasu arteritis) in northern Italy: A population-based study. Semin Arthritis Rheum. 2021 Aug;51(4):786-792. doi: 10.1016/j.semarthrit.2021.06.001. Epub 2021 Jun 7. PMID: 34148007

Appendix-1: Assessment of Causality of Cases with ACR Definition

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]			Regulatory Authority	Giant cell arteritis	Male	Dose 1	8	Conditional	TTO 8 days, minimal information, need clarity on PMH and drug allergy	Yes	75	Unk	unk	ESR increased	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	78	Unlikely	TTO 78d, h/o Hashimoto's	Yes	76	Yes	unk	unk	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	1	Unlikely	TTO 1 day and reported h/o HA and jaw pain make causal association unlikely	Yes	75	Yes	unk	unk	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	1	Possible	Medically confirmed report of a 75 y/o female who experienced symptoms of GCA one day post dose 1 of mRNA-1273 and diagnosed with GCA on day 5 by temporal artery biopsy. While relevant clinical information such as medical history and concomitant medications is not provided, based on the temporal association, WHO causality is assessed as possibly related.	Yes	75	Yes	unk	ESR 108	positive
			Spontaneous	Giant cell arteritis	Male	Unknown		Unassessable		No	82	Unk	unk	unk	results not provided

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]			Regulatory Authority	Giant cell arteritis	Female	Dose 1	7	Unassessable	Minimal information	No	87	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	16	Conditional	TTO 16 days with minimal information and workup results not provided	No	79	Yes	negative	CRP 28	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unlikely	Consumer report needing medical confirmation but presentation not consistent with GCA	No	70	Yes	unk	CRP high, ESR high	unk
			Regulatory Authority	Giant cell arteritis	Male	Dose 1	6	Possible	Consumer report of a 73 y/o male with history of heart disease, kidney disorder, hypertension, diabetes, and concomitant medications including insulin, use of anticoagulants, use of statins, among others, who 5 days after the 1st dose of Spikevax developed arthalgia, back pain, neck pain. After the 2nd dose of the vaccine, reported pain in right arm/shoulder area with intensified and spread immediately making normal activities of life difficult, necessitating help from his partner. 13 days later the patient	Yes	73	neck pain	unk	ESR 98	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
									received a cortisone shot in right shoulder and an MRI showed inflamation of shoulder with laboratory results showing elevated ESR. 69 days after his 2nd dose was diagnosed with PMR, with suspicion of GCA for which a biopsy was performed but results not provided. Confounding evaluation is the patient's advanced age which places him at a greater risk for both PMR and GCA as well as the lack of medical history, further information on his polypharmacy and lack of diagnostic results. WHO causality is therefore assessed as possible based on temporal association between the use of the product and the start of the event.					
[redacted]			Regulatory Authority	Giant cell arteritis	Female	Dose 1	1	Unassessable		No	76	Unk	unk	unk	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]			Spontaneous	Giant cell arteritis	Male	Unknown		Conditional	Consumer report needing medical confirmation	Yes	75	Unk	unk	high ESR	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	21	Unasscssable		No	83	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	5	Unassessable	Minimal information	Yes	67	Yes	unk	ESR 34, CRP 24 CP	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	54	Unlikely	TTO 54 days confounded by comborbidiites and conmeds	Yes	81	Yes	unk	unk	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	1	Unassessable		No	82	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Male	Dose 1	5	Unassessable	Minimal information confounded by CN IV paralysis/palsy	No	67	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	40	Conditional	Confounded by CLL	No	70	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unlikely	Retinal artery occlusion secondary to extensive CV, renal, hepatic disease, and has h/o meningioma. TA no diagnostically supported.	No	69	No	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	5	Unassessable	Insufficient information	No	68	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Male	Unknown		Unassessable		No	69	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Male	Unknown		Unlikely	Presentation suggestive of vascular disorder in a patient with significant	No	60	Unk	unk	CRP high	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
									cardiovascular history						
[redacted]			Regulatory Authority	Giant cell arteritis	Male	Unknown		Unassessable	TTO 4 days	No	80	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	0	Unlikely	Unlikely with same day TTO	Yes	76	Yes	unk	ESR high and CRP high	positive
			Regulatory Authority	Giant cell arteritis	Male	Dose 2	4	Possible		No	71	Unk	unk	CRP 42.4, ESR 40	normal
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	28	Conditional	Incomplete details	No	67	Yes	unk	Elevated ESR, CRP	unk
			Regulatory Authority	Giant cell arteritis	Male	Unknown		Unlikely	TTO 4 months, small intestine neuroendocrine tumour	No	74	Unk	unk	CRP 97	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Duplicate	Duplicate	Duplicate	76	Duplicate	Duplicate	Duplicate	Duplicate
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unassessable		No	76	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unassessable	TTO 3 days with minimal information provided	Yes	78	Yes	unk	unk	positive - "diagnosed with giant cell arteritis with biopsy and positron emission tomography."
			Regulatory Authority	Giant cell arteritis	Male	Dose 1	10	Unassessable		No	65	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unassessable	Minimal information is provided	No	55	Unk	unk	unk	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]															
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	92	Unassessable	TTO 92 days with minimal information	No	71	Unk	unk	unk	results not reported
			Regulatory Authority	Giant cell arteritis	Female	Dose 3	2	Unassessable	Consumer report with minimal information	No	63	Unk	vein at the left temporal was swollen and bumpy and painful to touch	unk	unk
			Spontaneous	Giant cell arteritis	Female	Unknown		Unassessable	Consumer report with minimal information and conmeds for which indications are not known	No	85	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unlikely	Retinal vein occlusion in setting of prior coagulopathy. "Was checked for temporal arteritis but inflammatory markers normal," "some time ago had a raised dimer" "The patient report relate to possible blood clots or low platelet counts was reported as Yes."	No	58	Unk	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unassessable	Minimal information	No	86	Yes	unk	unk	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]			Spontaneous	Giant cell arteritis	Male	Dose 1	13	Possible	Clinical onset same day with progression	No		Yes	negative	CRP 38	negative
			Regulatory Authority	Giant cell arteritis	Female	Unknown		Unlikely	TTO same day with presentation consistent with vascular disorder (on anti-HTN meds) rather than vasculitis	No	77	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	0	Conditional	TTO same day with workup 2 months later confounded by conmeds; bopsy reported as inconclusive yet also Temporal artery arteritis; CT inconclusive.	Yes	70	Yes	unk	ESR high nl	inconclusive
			Regulatory Authority	Giant cell arteritis	Male	Dose 2	2	Unlikely	H/o GCA considered to be the pre-existing condition aggravated; confounded by lymphoma	No	73	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	2	Possible	HCP report of a 76 y/o female who received dose 1 of mRNA-1273 on an unknown date and experienced symptoms including HA, TMJ syndrome two days post dose 2 of mRNA-1273 and diagnosed with GCA on day 58 by temporal artery biopsy.	Yes	76	Yes	y	ESR 67	positive

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]									Minimal information is provided and confounding conditions include occipital neuralgia, however based on the temporal association, WHO causality is assessed as possibly related.						
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	22	Conditional		No	69	Unk	unk	unk	unk
			Spontaneous	Giant cell arteritis	Male	Dose 2	0	Possible	Consumer report of a 62 y/o male who on the same day as dose 2 and 28 days after dose 1, experienced symptoms including HA and pyrexia with CRP 135, and diagnosed with GCA on an unknown date by temporal artery biopsy. Minimal information is provided and assessment is confounded by history of Lyme disease, however based on the temporal association, WHO causality is assessed as possibly related.	Yes	62	Yes	unk	CRP 135	positive
			Regulatory Authority	Giant cell arteritis	Female	Dose 1	6	Conditional	Possibly PMR only; confounded by peripheral neuropathy; x-ray and other lab tests performed	No	87	Yes	unk	unk	unk

Case ID	WW Identifier	Country	Report Type	PT	Patient Gender	Dose no prior to onset	TTO All Doses	WHO	MAH Comment	1990 ACR Classification for GCA	Age at disease onset >=50 years	New Pain in the Head	Temporal artery abnormality	Elevated erythrocyte sedimentation rate	Abnormal artery biopsy
[redacted]									but results not available						
			Regulatory Authority	Giant cell arteritis	Female	Dose 2	9	Possible	Likley PMR	No	56	Yes	unk	CRP 289.3	unk
			Spontaneous	Giant cell arteritis	Male	Unknown		Unassessable	TTO 16 days withi minimal information	No	67	Yes	unk	unk	unk
			Spontaneous	Giant cell arteritis	Female	Dose 2	112	Unlikely	TTO 112-140 days	Yes	75	Yes	y	ESR 51.2, CRP 52	unk
			Spontaneous	Giant cell arteritis	Male	Unknown		Conditional	Retinal artery occlusion possibly due to ASCVD? Cardiac workup performed but results not provided.	No	72	Unk	unk	high ESR and CRP	negative
			Regulatory Authority	Giant cell arteritis	Male	Unknown		Unassessable	Inflammatory rheumatism v GCA	No	89	Unk	unk	unk	unk
			Literature-Non-Study	Giant cell arteritis	Female	Unknown		Unassessable	Minimal information provided and thickening of B/L carotid arteries is inconsistent with GCA	No	82	Yes	unk	unk	unk
			Regulatory Authority	Giant cell arteritis	Male	Dose 2	7	Conditional	Basis for diagnosis of PMR v GCA in unkown and results of diagnostic investigation not provided	No	73	Yes	unk	unk	unk

Appendix-4: Literature Review Full Text

Appendix 4.2c: Signal Evaluation report: Amenorrhea

Signal Evaluation Report

for

mRNA-1273

on

Amenorrhoea

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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 Amenorrhoea in association with the administration of mRNA-1273 in adult patients ≥18yo, 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 national reviews (post marketing cases and published studies), the PRAC has agreed that the MAH for COVID-19 mRNA Vaccine Spikevax (Moderna Biotech Spain, S.L.) should perform a cumulative review of all cases of Amenorrhoea from all sources, including, but not limited to, available data from clinical trials, literature and post marketing exposure. The MAH should provide answers to the below List of Questions concerning clinical trials, literature, case overview and review, possible mechanism of action and exposure in females of childbearing. Please see (Appendix-1) for complete list of questions

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.

Amenorrhea in a female of reproductive age is related to the disturbance of normal hormonal, physiological mechanism, or female anatomic abnormalities. The normal physiological mechanism works by balancing hormones and providing feedback between the hypothalamus, pituitary, ovaries, and uterus.

Physciologicaly, menstruation is controlled by the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, and it works on the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and these two hormones from the pituitary act on ovaries and ovaries finally make estrogen and progesterone to work on the uterus to carry out the follicular and secretory phase of the menstrual cycle. Prolactin also influences the menstrual cycle as it suppresses the release of LH and FSH form the pituitary. Similarly, thyroid hormone also affects the menstrual cycle; low levels of thyroid hormone stimulate the release of TRH from the hypothalamus, which in turn increases both TSH and prolactin release. This increase in prolactin suppresses the release of LH and FSH through a negative feedback mechanism. Amenorrhea can be caused by any mechanism that disrupts this hypothalamic-pituitary-ovarian axis, whether that it be by hormonal imbalance or by disruption of feedback mechanisms. It can also be caused by deviation from the normal anatomy of the reproductive organs of a female can also cause amenorrhea.

To date, there is no definitive evidence to demonstrate association between menstrual disorder and vaccination. The relationship between amenorrhea and Spikevax is unclear. A proposed hypothetical biological mechanism is that vaccination may hypothetically affect ovarian hormone production and/or the endometrial response at menses through the ACE2 receptors have been found on ovarian and endometrial tissue. However, there has been no empirical evidence to support this hypothesis.

3 Review of Data from All Sources

The assessment of Amenorrhea 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 Amenorrhea was cumulatively reviewed in the MAH clinical database with a data-lock point (DLP) of 04 May 2021, searched using the following MedDRA v 24.0 preferred term Amenorrhoea, Delayed menarche, and Premature menopause, was performed in P301 study and there is one case observed in placebo group.

- This case was in 41-year-old female with depression, migraine and psoriasis, experienced time-limited period of amenorrhea on study day 48 and 5 days after first and second placebo doses. It was a non-serious, medically attended event. She was treated with oral progesterone therapy and amenorrhea resolved on study day 74.

3.2 External Databases

VAERS and EVDAS were reviewed for the PTs: Amenorrhoea, Delayed menarche, and Premature menopause

- VAERS: following are the EB05 observed for PTs related to topic of Amenorrhoea
  - Amenorrhoea (EB05: 0.708); Delayed menarche (EB05: 0.000); and Premature menopause (EB05: 0.586)

- EVDAS: The PT relevant of Amenorrhoea showed ROR < 2 other than Amenorrhoea.
  - Amenorrhoea (ROR: 2.77); Delayed menarche (ROR: 0.67); and Premature menopause (ROR: 0.55)

3.3 Non-clinical Data

Investigator Brochure IB (v8.0 dated 20 Dec 2021) showed that Developmental and reproductive toxicity (DART) studies in pregnant and lactating female Sprague Dawley rats were performed to assess the potential effects of mRNA-1273 on fertility and pre and postnatal. No mRNA-1273-related effects or changes in mating and fertility and ovarian/uterine examinations were observed.

3.4 Epidemiological studies

As such, these analyses do not presently suggest an increased incidence beyond expectation. The observed number of cases of amenorrhea, cumulatively were 1573 with the reporting rate of 0.05 per 100 person-years (Table *below*). These were less compared to the expected number of cases (N = 10,9363 with reporting rate of 3.3 per 100 person-years). The overall and age-specific rate ratio was below 0.10. The sensitivity analysis (assuming 25% and 50% capture of the observed

cases) does not change the interpretation. In conclusion the observed rates of amenorrhea was lower than expected background rates (Table 1).

Table-1: Observed/Expected Analyses Stratified by Age and Gender, Amenorrhoea

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	Rates	Cases	Rates			
All	3,314,041	1573	0.05	109363	3.3	0.01 (0.01, 0.02)	0.03 (0.03, 0.03)	0.06 (0.06, 0.06)
Female								
<12 years	4971	0	0.00	164	3.3	NA	NA	NA
12-17 years	94450	14	0.01	3117	3.3	0 (0, 0.01)	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)
18-24 years	298264	220	0.07	9843	3.3	0.02 (0.02, 0.03)	0.04 (0.04, 0.05)	0.09 (0.08, 0.1)
25-39 years	729089	298	0.04	24060	3.3	0.01 (0.01, 0.01)	0.02 (0.02, 0.03)	0.05 (0.05, 0.05)
40-49 years	497106	381	0.08	16405	3.3	0.02 (0.02, 0.03)	0.05 (0.04, 0.05)	0.09 (0.09, 0.1)
50-64 years	861651	79	0.01	28434	3.3	0 (0, 0)	0.01 (0, 0.01)	0.01 (0.01, 0.01)
65-74 years	497106	0	0.00	16405	3.3	NA	NA	NA
75+ years	331404	1	0.00	10936	3.3	NA	NA	NA

3.5 Review of the Pharmacovigilance Database

Post marketing data for validated signal of Amenorrhoea events were retrieved from the Company safety database using the following three MedDRA preferred term: Amenorrhoea, Delayed menarche and Premature menopause with a data-lock point (DLP) of 15 February 2022, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Cases from all sources and relevant literature were reviewed.

Of note, throughout the document for simplicity Amenorrhoea is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e., Amenorrhoea, Delayed menarche and Premature menopause.

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

The MAH performed a review of all cases of Amenorrhoea derived from all sources. The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 15 February 2022, for Spikevax. Search criteria used the PTs of Amenorrhoea, Delayed menarche and Premature menopause. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches to identify the cases that met case definition of Amenorrhea.

The events were classified using the following definition: The International Federation of Gynecology and Obstetrics (FIGO)-Abnormal Uterine Bleeding case definition for Amenorrhoea was used.

- Secondary amenorrhea defined as absence of spontaneous menstrual bleeding for six months in a patient who previously had menstrual bleeding
- Included cases reporting absent menstruation <6 months that was unresolved or with unknown outcome

3.7 Results

Cumulatively search as of 15 February 2022, retrieved 1589 cases that were reviewed, of which (191) are medically confirmed cases and 135 were serious not medically conformed cases. These were reviewed with FIGO definition, and a causality assessment was provided utilizing the WHO-UMC standardized case causality assessment (WHO 2013).

Of the reported 1589 cases (1612 events), A vast majority (90.5%) of the events were non-serious.

Table 4: Events by Preferred Term and Seriousness

PT	Non-Serious		Serious		Total Count of Events	Total % Events
	Count of Events	% Of Events	Count of Events	% Of Events		
Amenorrhoea	1,453	90.1	146	9.1	1,599	99.2
Premature menopause	5	0.3	6	0.4	11	0.7
Delayed menarche	1	0.1	1	0.1	2	0.1
Grand total	1,459	90.5	153	9.5%	1,612	100.0

Of the reported events, 46.5% had a missing dose, when dose is known, 25% of events occurred after first dose and 27% after second dose and 1.2% after the third dose. There was no unusual pattern or clustering by dose. Respondents reporting onset of amenorrhea a few days (e.g., 0-5 days) after Spikevax were most likely already moving towards having a later or absent menstruation given that vaccination was just a few days or on the day menstruation was due. It is very difficult to interpret the TTO without putting it into context of the menstrual cycle.

Table 3: Distribution of Events by Dose Number and TTO All Doses

Dose Number	TTO All Doses (Days)	Total # of Events	Total % of Events
Dose 1	*Subtotal*	*403*	*25.0*
	0 days	116	7.2
	01-02	43	2.7
	03-04	26	1.6
	05-06	17	1.1
	07-13	71	4.4
	14-29	91	5.6
	30+	39	2.4
Dose 2	*Subtotal*	*440*	*27.3*
	0 days	133	8.3
	01-02	59	3.7
	03-04	22	1.4
	05-06	16	1.0
	07-13	46	2.9
	14-29	90	5.6
	30+	74	4.6
Dose 3	*Subtotal*	*20*	*1.2*
	0 days	3	0.2
	01-02	9	0.6
	03-04	1	0.1
	05-06	2	0.1
	07-13	2	0.1
	14-29	1	0.1
	30+	2	0.1
Unknown	*Subtotal*	*749*	*46.5*
	Missing	749	46.5
Grand total		**1,612**	**100.0**

Review of the 1589 cases, 12% of cases were reported by health care professional.

Table 6: Distribution of Cases by Medical Confirmation

Health Care Professional (HCP)	Total # of Cases	Total % of Cases
Medically Confirmed	191	12.0
Not Medically Confirmed	1,398	88.0
Grand total	1,589	100.0

of these 1589 cases, 191 medically confirmed cases and serious not medically conformed cases (135) were reviewed with FIGO definition, and a causality assessment was provided utilizing the WHO-UMC standardized case causality assessment (WHO 2013). Of the 326 cases, one case was identified One case with date of vaccination and onset, known previous menstruation pattern; this review highlighted the challenges with using spontaneous data to explore this topic which includes high level of missing data (e.g., menstrual history, medical history, concomitant medications, clinical course including testing and duration) with spontaneous reports.

- [redacted]: 35-year-old female LMP 5/18/21 with no reported relevant medical history or concomitant medications, received the first dose of Spikevax at cycle day 16, luteal phase, and experienced amenorrhea, missed one cycle, after vaccination. An FSH performed 33 days after vaccination was elevated "suggesting early menopause." The event was unresolved at time of report. Given temporal association, causality is possible.

4 Literature Review

A focused literature search and review was performed using PubMed and Google Scholar databases. Multiple search strategies were used to identify articles related to amenorrhea and the COVID-19 pandemic, SARS-CoV-2 infection, and COVID-19 mRNA vaccine, Spikevax. Appendix A summarizes the search strategies.

- Of the 230 unique articles captured, two reported on amenorrhea after vaccination with Spikevax. The two studies were signal detection studies using spontaneous reports reporting on percentages of reports or events were amenorrhea out of all reports of menstrual disorders (Table)

Study	Sample Size	Amenorrhea (% of menstrual reports with preferred term of amenorrhea)*
Netherland Pharmacovigilance Centre Lareb	N= 17,735 (2,025 reports (11.4%) for Moderna Vaccine)	Total Number of reports for Amenorrhea = 3,198 Total Number of reports= 17,735 Total Number of reports for Amenorrhea (Moderna Vaccine) = 363 Total Number of reports (Moderna Vaccine) = 2,025
Zhang B et al	N= 13,118 cases for COVID-19 vaccines (2,748 (20.95%) cases for Moderna vaccine 13,13 cases for non-COVID-19 vaccines)	Covid-19 Vaccines =1,655 cases (12.62%) Non-Covid Vaccines = 301 cases (22.92%) Moderna Vaccine = 453 cases (16.48%)

*Denominator: reports of menstrual disorders after a COVID-19 vaccine

There is a dearth of information regarding amenorrhea after Spikevax; the two published literature are limited because of use of spontaneous reports with high level of missing data, reporting bias, an un-vaccinated comparator group.

Conclusion: Overall, the published data currently does not support an association between amenorrhea and Spikevax.

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

This validated signal was detected in the context of PRAC request for review on amenorrhea. The global safety database was queried including validated, clinical, and spontaneous worldwide cases received from all sources (HCP, regulators, literature, and consumers) reported from the mRNA-1273 vaccine (Moderna COVID -19 vaccine).

Approximately 800 million doses of mRNA-1273 administered to ~400 million individuals as of 31 Dec 2021. Although product specific and international data on demographic characteristics of vaccine recipients are limited, US distribution across all products shows more use in women (52.5%) and individuals older than 50 years of age (47.5%). Observed reporting rate for post-marketing data is below background incidence rates.

The Literature search results provided no relevant source of reports of events of amenorrhea after vaccination. Data were insufficient to be considered supportive evidence of potential causal association between mRNA vaccines and amenorrhea. Clinical trial data available as of 04 May 2021 showed 1 case with limited information. Cumulatively, a total of 1589 cases have been reported that are being associated with the PTs related to the topic of amenorrhea and accounted for approximately 99.2% of the Amenorrhea.

Of the 1589 cases, 326 qualified for review as medically confirmed cases and serious not-medically confirmed cases. The review of these 326 cases identified, one (1) case that meet the definition of Amenorrhea. Based on the WHO-UMC system, this case was possibly related due to temporal association.

6 Conclusion

Although there have been reports of menstrual changes including amenorrhea after vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification. There are few published articles on amenorrhea after COVID-19 vaccination including Spikevax. The two available articles identified are not able to determine the frequency with which people experience amenorrhea following Spikevax or determine whether there is a link between Spikevax and amenorrhea; the articles were limited due high level of missing data in spontaneous reports, lack of an unvaccinated control group, selection and recall bias.

Despite these limitations, findings from studies on menstrual changes in general (e.g., Edelman et al. and Trogstad et al.) were reassuring, the reported changes were small compared to natural variation and quickly reverse. Last there is no clear biological plausibility linking Spikevax and amenorrhea; the one case identified through case review of post-marketing data was only temporally associated with Spikevax.

Overall, based on the analysis of all available safety data as of 15 February 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and the development of amenorrhea. No new or emerging safety issue of concern was identified. The available data does not warrant an update or change to the label/SmPC and/or the RMPs. The MAH will continue to monitor events for amenorrhea using routine pharmacovigilance surveillance.

7 References

Ding T, Wang T, Zhang J, Cui P, Chen Z, Zhou S, Yuan S, Ma W, Zhang M, Rong Y, Chang J, Miao X, Ma X, Wang S. Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study. Front Med (Lausanne). 2021 Mar 19;8:635255. doi: 10.3389/fmed.2021.635255. PMID: 33816526; PMCID: PMC8017139.

Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5;139(4):481–9. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109; PMCID: PMC8936155.

Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, Kraker von Schwarzenfeld A, Acuna J. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS One. 2021 Oct 20;16(10):e0258314. doi: 10.1371/journal.pone.0258314. PMID: 34669726; PMCID: PMC8528316.

Pettersson F, Fries H, Nillius SJ. Epidemiology of secondary amenorrhea I. Incidence and prevalence rates. Am J Obstet Gynecol. 1973;117(1):80-86. doi:10.1016/0002-9378(73)90732-1

Trogstad, L. (2022). Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3998180

The Netherlands Pharmacovigilance Centre Lareb received an unprecedented amount of reports of menstrual disorders with administration of COVID-19 vaccines.https://www.lareb.nl /media/uoneih5z/signals_2021_menstrual_disorders-and-postmenopausal_bleeding-and-covid-19-vaccines.pdf

Zhang B, Yu X, Liu J, Liu P. COVID-19 vaccine and Menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System. https://assets.researchsquare.com/files/rs-1388159/v1/28dc1c53-1698-4d49-9a46-3d95d1f36833.pdf?c=1646942221

Appendix-1: List of Questions from PRAC

ITEM 1: Clinical trials

The MAH should provide an overview and clinical evaluation of cases of amenorrhoea, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for amenorrhoea, concomitant medication, patient medical history including previous menstruation pattern, duration of the event and outcome. This information should be considered in the context of the total number of females, including of childbearing potential participating in the study. The MAH should clarify how adverse events related to amenorrhoea were reported, i.e. if these were solicited adverse events or spontaneously reported by the participants.

ITEM 2: Published literature

The MAH should perform a literature review on the possible association between amenorrhoea and COVID-19 mRNA vaccine Spievax. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al.3, Nguyen et al.4 and Edelman et al.5.

ITEM 3: Case overview

The MAH should list the number of reported cases of the preferred term amenorrhoea stratified by:

- worldwide and region
- country in the EU/EEA
- dose number in series
- seriousness
- reporter (medically/non-medically confirmed)
- positive rechallenge.

ITEM 4: Case review

The case review should prioritise serious and/or medically confirmed cases, where information on risk factors and medical history is included. Special focus should be given to cases in which the previous menstruation pattern is known.

The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case. The MAH should provide for all cases a clear breakdown of the number of cases that were either supportive of causality/ unsupportive due to presence of other causes, risk factors, underlying conditions, confounding medication/ unassessable.

The following information should be stratified:

- Details of medically relevant co-reported adverse events (if any)
- Cases in which women used hormonal contraception (including hormonal intrauterine devices)
- Cases with other types of intrauterine devices
- Information on pregnancy status
- Cases that received heterologous primary or booster schemes.

If available, the MAH should provide information on when vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information on the menstrual cycle is known and discuss whether a pattern might exist.
When excluding cases from the review, a justification for doing so should be provided by the MAH (e.g. amenorrhoea cases excluded because of pregnancy).
Based on a review of case reports with inconclusive causality due to confounding factors and/or lacking information, the MAH should provide a nuanced discussion of whether Spikevax may have aggravated the condition in cases where causality cannot be firmly established.

ITEM 5: Mechanism of action
The MAH should discuss the pathophysiology of amenorrhoea and whether any biological plausibility/mechanism of action exists.

ITEM 6: Exposure in females of childbearing potential
The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Spikevax.

Appendix-2: LITERATURE SEARCH CRITERIA USED FOR AMENORRHOEA ARTICLES EXTRACT

A literature search was conducted using PubMed of the National Library of Medicine (PubMed NLM) and Google Scholar using the search strategies listed below.

Spikevax and Amenorrhea

PubMed NLM

((((((((((("Menorrhagia") OR ("Heavy Menstrual Bleeding")) OR ("Menstrual Bleeding, Heavy")) OR ("Hypermenorrhea")) OR ("Heavy Period*")) OR ("Post Menopausal bleeding")) OR ("Amenorrhea")) OR ("Dysmenorrhea")) OR ("Menorrhagia")) OR ("Oligomenorrhea")) OR ("Premenstrual Syndrome")) OR ("%Menstru%")) 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 vaccines"[tw] OR "mRNA Vaccines"[tw]))

Google Scholar

Amenorrhea OR “Delayed menarche” OR “Premature menopause”OR “Menstruation Disturbances” AND COVID-19 Vaccines

SARS-CoV-2 Infection and Amenorrhea

PubMed NLM

((("Amenorrhea" [Mesh]) OR (Delayed menarche (TW))) OR (Premature menopause (TW))) AND (COVID-19)

Google Scholar

Amenorrhea OR “Delayed menarche” OR “Premature menopause”OR “Menstruation disturbances” AND COVID-19

COVID-19 Pandemic and Heavy Menstrual Bleeding

PubMed NLM: menstrua* AND (COVID* OR "sars-cov*" OR "coronavirus" OR "lockdown")

Appendix 4.2d: Signal Evaluation report: Heavy menstrual bleeding

Signal Evaluation Report

for

mRNA-1273

on

Heavy Menstrual Bleeding

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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 Heavy Menstrual Bleeding (HMB) in association with the administration of mRNA-1273 in adult patients ≥18yo, 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 national reviews (post marketing cases and published studies), the PRAC has agreed that the MAH for COVID-19 mRNA Vaccine Spikevax (Moderna Biotech Spain, S.L.) should perform a cumulative review of all cases of heavy menstrual bleeding from all sources, including, but not limited to, available data from clinical trials, literature and post marketing exposure. The MAH should provide answers to the below List of Questions concerning clinical trials, literature, case overview and review, possible mechanism of action and exposure in females of childbearing. Please see (Appendix-1) for complete list of questions

2 Background

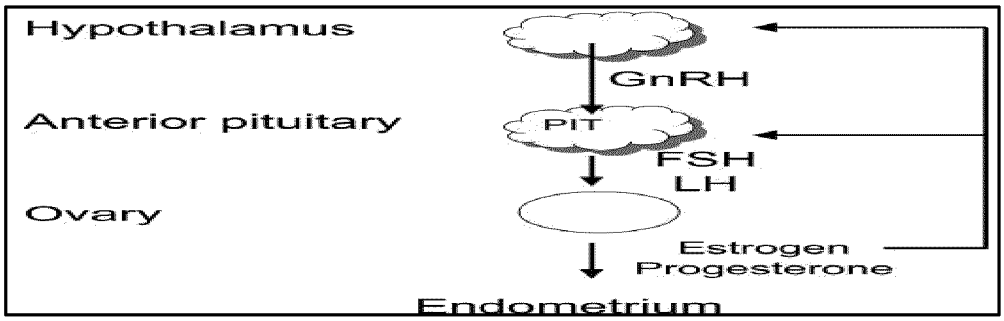
Product: The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, 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.

Accumulating discussions on social media indicating that women have experienced menstrual changes. As of 9 March 2022, more than 50,000 reports of menstrual changes or unexpected vaginal bleeding following covid-19 vaccination have been reported through the yellow card surveillance. Similar reports received by the US vaccine adverse event reporting system (VAERS).

Overall, to date there is no definitive evidence to demonstrate an association between menstrual disorder and vaccination. The basic biology of the menstrual cycle is a complex, coordinated sequence of events. Normal variations exist's within women over the lifespan. Menstrual cycle features such as volume, pain and PMS symptoms are subjective1,2 and data are necessarily collected, in health care as well as research, by self-report. Menstrual disorders are very common, as perturbed by environmental factors such as stress, extreme exercise, eating disorders, obesity, and infection.

Hypothetical Biological Mechanisms: The relationship between heavy menstrual bleeding and Spikevax is unclear. Some hypothetical biological mechanisms in the literature include the presence of ACE-2 receptions on the ovaries and endometrium that could affect hormone production or endometrial response, inflammatory response mediated by immune cells as well as alterations in coagulation system.

Figure 1: General Overview of the Important Factors in the Menstrual Cycle



Reference:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC2913133/#:~:text=The%20basic%20biology%20of%20the,%2C%20eating%20disorders%2C%20and%20obesity.

3 Review of Data from All Sources

The assessment of Heavy menstrual bleeding 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 HMB was cumulatively reviewed in the MAH clinical database with a data-lock point (DLP) of 04 May 2021, searched using the following MedDRA v 24.0 preferred term " 'Heavy menstrual bleeding', 'Menometrorrhagia', and 'Polymenorrhagia', was performed" was performed in P301 study and there were six cases observed of which 5 were in mRNA vaccinated subjects and 1 was in placebo group. Details of these cases are presented in (Table 1).

Table-1: Clinical Trial Data as of 04 May 2022 (All ages, overall stage) Unsolicited TEAEs, P301

ID	Age	Tx Code	Relevant Medical History	Relevant Concomitant Medications	TTO first dose, days	TTO second dose, days	PI Causality	Duration (days)	Outcome
[redacted]	20	mRNA-1273	Attention Deficit Disorder Menorrhagia	Not Available	114	85	Not related	N/A	Ongoing
	49	mRNA-1273	Not Available	Combined oral contraceptive	31	5	Not related	8	Recovered /Resolved
	44	mRNA-1273	Hypothyroidism	Levothyroxine	32	5	Related	6	Recovered /Resolved
	56	mRNA-1273	Uterine fibroids Breast cancer	Letrozole	57	29	Not related	121	Recovered /Resolved
	23	mRNA-1273	Irregular menstruation	Nexplanon	2	N/A	Related	N/A	Ongoing
	38	Placebo	Obesity Tubal ligation	Not Available	79	49	Not related	75	Recovered /Resolved

***Postmenopausal*

3.2 External Databases

VAERS and EVDAS were reviewed for the PTs: Heavy menstrual bleeding, Menometrorrhagia, and Polymenorrhagia

- VAERS: following are the EB05 observed for these PTs. No Disproportionality was observed
    - Heavy menstrual bleeding (EB05: 0.777); Menometrorrhagia (EB05: 0.687); and Polymenorrhagia (EB05: 0.383)

- EVDAS: The PT relevant of HMB showed ROR < 2 other than Heavy menstrual bleeding.
    - Heavy menstrual bleeding (ROR: 3.68); Menometrorrhagia (ROR: 1.94); and Polymenorrhagia (ROR: 1.22)

3.3 Non-clinical Data

Investigator Brochure IB (v8.0 dated 20 Dec 2021) showed that Developmental and reproductive toxicity (DART) studies in pregnant and lactating female Sprague Dawley rats were performed to assess the potential effects of mRNA-1273 on fertility and pre and postnatal. No mRNA-1273-related effects or changes in mating and fertility and ovarian/uterine examinations were observed.

3.4 Epidemiological studies

As such, these analyses do not presently suggest an increased incidence beyond expectation. The observed to expected analysis for menstrual disorders included observed cases of heavy menstrual bleeding (heavy menstrual bleeding, menometrorrhagia, and polymenorrhagia) and amenorrhea (amenorrhea, delayed menarche, and premature menopause). For this analysis we have included only cases with known female gender. Stahlman et al. has characterized the incidence in menorrhagia in active service women, US Armed Forces from 2012-2016. The incidence rate was similar to the incidence of heavy menstrual bleeding in general practice in Netherlands (2004 -2013)[1].

The cumulative number of cases with heavy menstrual bleeding were 3940 (reporting rate of 0.12 per 100 person-years). These were less compared to the expected number of cases (N = 36,1230 with reporting rate of 10.09 per 100 person-years). The overall and the age-specific rate ratio was lower than 0.05 (Table below). The sensitivity analysis (assuming 25% and 50% capture of the observed cases) does not change the interpretation. In conclusion the observed rates of amenorrhea were lower than expected background rates.

Table-2: Observed/Expected Analyses Stratified by Age for Heavy menstrual bleeding

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	Rates	Cases	Rates			
All	3,314,041	3940	0.12	361230	10.9	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)
Female								
<12 years	4971	0	0.00	220	4.42	NA	NA	NA
12-17 years	94450	18	0.02	4175	4.42	0 (0, 0.01)	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)
18-24 years	298264	370	0.12	12945	4.34	0.03 (0.03, 0.03)	0.06 (0.05, 0.06)	0.11 (0.11, 0.12)
25-39 years	729089	1900	0.26	73857	10.13	0.03 (0.02, 0.03)	0.05 (0.05, 0.05)	0.1 (0.1, 0.11)
40-49 years	497106	1084	0.22	179952	36.2	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)
50-64 years	861651	260	0.03	311918	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)
65-74 years	497106	2	0.00	179952	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)
75+ years	331404	1	0.00	119968	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)

3.5 Review of the Pharmacovigilance Database

Post marketing data for validated signal of heavy menstrual bleeding events were retrieved from the Company safety database using the following three MedDRA preferred term: Heavy menstrual bleeding', 'Menometrorrhagia', and 'Polymenorrhagia' with a data-lock point (DLP) of 15 February 2022, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Cases from all sources and relevant literature were reviewed.

Of note, throughout the document for simplicity HMB is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e., Heavy menstrual bleeding', 'Menometrorrhagia', and 'Polymenorrhagia'.

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

The MAH performed a review of all cases of HMB derived from all sources. The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 15 February 2022, for Spikevax. Search criteria used the PTs of Heavy menstrual bleeding', 'Menometrorrhagia', and 'Polymenorrhagia'. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches to identify the cases that met case definition of HMB.

As most of these cases were spontaneous in nature with limited information, the review was focused on medically confirmed cases and the serious not-medically confirmed cases. All these events were classified using the following definition: The International Federation of Gynecology and Obstetrics (FIGO)-Abnormal Uterine Bleeding case definition for heavy menstrual bleeding was used.

- Heavy menstrual bleeding is defined as a volume that interferes with the patient's physical, social, emotional, and/or material quality of life

3.7 Results

Cumulatively, as of 15 February 2022, this search yielded a total of 4000 cases with 4,309 events, of which 998 cases were serious. Of these cases 546 were medically confirmed, no fatal cases were reported. The most frequently reported event assessed as serious or non-serious was PT Heavy menstrual bleeding. Table-4, summarizes the reported events per seriousness.

Table 4: Event Counts by PT and Event Seriousness for HMB (Cumulative)

PT	Non-Serious		Serious		Total # of Events	Total % of Events
	# Events	% of Total Events	# Events	% of Total Events		
Heavy menstrual bleeding	3,371	78.2	829	19.2	4,200	97.5
Menometrorrhagia	89	2.1	16	0.4	105	2.4
Polymenorrhagia	3	0.1	1	0.0	4	0.1
Grand total	3,463	80.4	846	19.6	4,309	100.0

Events by Dose and Time to Onset: 39% of events with missing dose, 31% of events occurred after first dose and 24% after second dose and 7% after the third dose. There was no unusual pattern and clustering seen regarding dose (keeping in mind that more dose 1 vaccines has been administered compared to dose 2 and dose 3) and time-to-onset. However, it is very difficult to interpret the TTO without putting it into context of the menstrual cycle

Table 5: Event Time to Onset by Dose

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	*Subtotal*	*1,318*	*30.6*
	0 days	198	4.6
	01-02	268	6.2
	03-04	119	2.8
	05-06	88	2.0
	07-13	266	6.2
	14-29	255	5.9
	30+	124	2.9
Dose 2	*Subtotal*	*1,021*	*23.7*
	0 days	141	3.3
	01-02	210	4.9
	03-04	107	2.5
	05-06	57	1.3
	07-13	125	2.9
	14-29	205	4.8
	30+	176	4.1
Dose 3	*Subtotal*	*282*	*6.5*
	0 days	31	0.7
	01-02	92	2.1
	03-04	33	0.8
	05-06	20	0.5
	07-13	55	1.3
	14-29	41	1.0
	30+	10	0.2
Unknown	*Subtotal*	*1,688*	*39.2*
	Missing	1,688	39.2
Grand total		**4,309**	**100.0**

Cases by Reporter Type: 13.7% of cases were reported by health care professional and majority of the cases (86.4) were reported as Not Medically Confirmed

Table 6: Distribution of Cases by Medical Confirmation

Health Care Professional (HCP)	Total # of Cases	Total % of Cases
Medically Confirmed	546	13.7
Not Medically Confirmed	3,454	86.4
Grand total	**4,000**	**100.0**

of these 4000 cases, 546 medically confirmed cases and serious not medically conformed cases (701) were reviewed with FIGO definition, and a causality assessment was provided utilizing the WHO-UMC standardized case causality assessment (WHO 2013). Of the 1247 cases, 14 cases with date of vaccination and onset, known previous menstruation pattern; this review highlighted the challenges with using spontaneous data to explore this topic which includes the high level of missing data (e.g., menstrual history, medical history, concomitant medications, clinical course including testing and duration) with spontaneous reports.

The median age of the 14 cases was 38.5 years (range: 21-50), 21% (3/14) received heterologous boosters (Pfizer BioNTech vaccine for their primary series), 43% (6/14) reported use of hormonal contraception including Mirena IUD and Nexplanon. There was no unusual pattern or clustering by dose and time to onset as well as time of vaccination during menstrual cycle

Based on the WHO-UMC system all 14 cases were possibly related due to temporal association, however 71% of them had medical conditions or concomitant medications (including age $\geq$ 45 years, obesity, postpartum status, h/o breast cancer, hypothyroidism, and inflammatory bowel syndrome) that provided an alternate etiology.

4 Literature Review

Clinical literature search review:

A focused literature search and review was performed using PubMed and Google Scholar databases. Multiple search strategies (**Appendix 2**) were used to identify articles related to heavy menstrual bleeding and the COVID-19 pandemic, SARS-CoV-2 infection, and COVID-19 mRNA vaccine, Spikevax.

Of the 230 unique articles captured, five discussed heavy menstrual bleeding after vaccination with Spikevax. Three articles were cross-sectional studies and two presented spontaneous, post-authorization data (Netherlands and United States of America). Although the cross-sectional studies reported that 20-41% women vaccinated with Spikevax reported heavy menstrual bleeding after vaccination, compared to prior menstrual pattern, the studies were limited because they lacked an unvaccinated comparator group which is crucial given heavy menstrual bleeding is common; additionally, some published studies have indicated that the pandemic itself was associated with changes in menstruation. Additionally, the studies were limited due to recall bias, use of unvalidated questionnaires and selection bias. The published data currently does not support an association between heavy menstrual bleeding and Spikevax.

Edelman et al.: The authors analyzed prospectively tracked menstrual cycle data using an existing menstrual cycle tracking app (Natural Cycles) and included 3,959 individuals (vaccinated 2.403 [35% received Spikevax] and unvaccinated 1,556) aged 18-45 years with normal cycle lengths who logged at least six consecutive cycles. In the adjusted models, the first dose of vaccine had no effect on timing of the subsequent period, while the second dose was associated with a delay of 0.45 days (98.75% confidence interval 0.06 to 0.84). Most affected were the 358 individuals who received both doses of the vaccine in the same cycle, reporting a 2.32 day (98.75% CI 1.59 to 3.04) delay to their next period. In all groups, cycle lengths returned to normal by two cycles after vaccination. The study limitations include study population that might not be generalizable to the U.S. population (Natural Cycle users are more likely to be White, college educated, not using hormonal contraception and have lower BMIs) or individuals whose menstruation is not consistent with normal cycle lengths (e.g., obese persons), self-reported data and lack of data on SARS-CoV-2 status of the study population. However, the findings are reassuring and did not find any population-level clinically meaningly change in menstrual cycle length associated with COVID-19 vaccination.

Trogstad et al.: The authors analyzed data collected from mobile-phone questionnaire obtained from a pre-existing population-based Norwegian Young Adult Cohort of 5688 women aged 18-30 year. They were asked whether they had experienced specific menstrual changes (such as unexpected breakthrough bleeding or worse than normal period pain) in the cycles before and after each vaccine dose. The prevalence of any menstrual disturbance was 37.8% prior to vaccination, highlighting the high level of variation in normal cycles. The study identified heavier than normal bleeding as the change most associated with vaccination (first dose: relative risk 1.9, 95% confidence interval 1.69 to 2.13; second dose:1.84, 1.66 to 2.03). The study limitations include lack of an unvaccinated comparator group, recall bias, and use of unvalidated questionnaire. Although, this study found an increase in heavier bleeding after vaccination, it also showed that menstrual disturbances are generally common regardless of vaccination.

Nguyen et al.: The authors analyzed menstrual cycle data using an existing menstrual cycle tracking app (Natural Cycles) and included 18,076 individuals accounting for 214,426 cycles. Data from March-September 2019 (pre-pandemic) to March-September 2020 (during pandemic) were compared to determine difference in proportion of users experiencing menstrual changes. 45.4% of the app users reported more pandemic-related stress. Changes in average cycle and menstruation lengths were not clinically significant, remaining at 29 and 4 days, respectively. The authors concluded that the COVD-19 pandemic did not induce population-level changes to ovulation and menstruation among women using a mobile app to track menstrual cycles and predict ovulation. The study limitations include self-reported data, recall bias, and potential limited generalizability of results given their study population (well-educated women over age of 30, from high income countries).

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

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

This validated signal was detected in the context of PRAC request for review on HMB. The global safety database was queried including validated, clinical, and spontaneous worldwide cases received from all sources (HCP, regulators, literature, and consumers) reported from the mRNA-1273 vaccine (Moderna COVID -19 vaccine).

Approximately 800 million doses of mRNA-1273 administered to ~400 million individuals as of 31 Dec 2021. Although product specific and international data on demographic characteristics of vaccine recipients are limited, US distribution across all products shows more use in women (52.5%) and individuals older than 50 years of age (47.5%). Observed reporting rate for post-marketing data is below background incidence rates.

The Literature search results provided no relevant source of reports of events of HMB after vaccination. Data were insufficient to be considered supportive evidence of potential causal association between mRNA vaccines and HMB. Clinical trial data available as of 04 May 2021 showed 6 cases with limited information. Cumulatively, a total of 4000 cases have been reported that are being associated with the PTs related to the topic of HMB of which most (97.5%) of the cases are from PT heavy menstrual bleeding.

Of these 1247 qualified for review as medically confirmed cases and serious not-medically confirmed cases. The review of these 1247 cases identified, 14 cases that meet the definition of HMB. Based on the WHO-UMC system all 14 cases were possibly related due to temporal association, however 71% of them had medical conditions or concomitant medications (including age $\geq$ 45 years, obesity, postpartum status, h/o breast cancer, hypothyroidism, and inflammatory bowel syndrome) that provided an alternate etiology.

6 Conclusion

Although there have been reports of heavy menstrual bleeding after vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification. The studies identified are not able to determine the frequency with which people experience heavy menstrual bleeding following Spikevax or determine whether there is a link between Spikevax and heavy menstrual bleeding; studies were limited due to lack of unvaccinated control group, recruitment of participants retrospectively, use of unvalidated questionnaires, selection and recall bias.

Despite the limitations, findings from these studies were reassuring, the reported changes were small compared to natural variation and quickly reverse. Last there is no clear biological plausibility linking Spikevax and heavy menstrual bleeding; all cases reviewed (clinical trial and post-marketing data) were only temporally associated with Spikevax and a vast majority of them had medical conditions or were on concomitant medications that provided alternate etiologies.

Overall, based on the analysis of all available safety data as of 15 February 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and the development of heavy menstrual bleeding. No new or emerging safety issue of concern was identified. The MAH will continue to monitor events for HMB using routine pharmacovigilance surveillance.

7 References

Ding T, Wang T, Zhang J, Cui P, Chen Z, Zhou S, Yuan S, Ma W, Zhang M, Rong Y, Chang J, Miao X, Ma X, Wang S. Analysis of Ovarian Injury Associated With COVID-19 Disease in Reproductive-Aged Women in Wuhan, China: An Observational Study. Front Med (Lausanne). 2021 Mar 19;8:635255. doi: 10.3389/fmed.2021.635255. PMID: 33816526; PMCID: PMC8017139.

Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5;139(4):481–9. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109; PMCID: PMC8936155.

Khan SM, Shilen A, Heslin KM, Ishimwe P, Allen AM, Jacobs ET, Farland LV. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. Am J Obstet Gynecol. 2022 Feb;226(2):270-273. doi: 10.1016/j.ajog.2021.09.016. Epub 2021 Sep 20. PMID: 34555320; PMCID: PMC8452349.

Katharine MN Lee, Eleanor J Junkins, Urooba A Fatima, Maria L Cox, Kathryn BH Clancy. Characterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccination. medRxiv 2021.10.11.21264863; doi: https://doi.org/10.1101/2021.10.11.21264863

Li K, Chen G, Hou H, Liao Q, Chen J, Bai H, Lee S, Wang C, Li H, Cheng L, Ai J. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. Reprod Biomed Online. 2021 Jan;42(1):260-267. doi: 10.1016/j.rbmo.2020.09.020. Epub 2020 Sep 29. PMID: 33288478; PMCID: PMC7522626.

Madendag, I. C., Madendag, Y., & Ozdemir, A. T. (2022). COVID-19 disease does not cause ovarian injury in women of reproductive period: An observational before-and-after COVID-19 study. *Reproductive Biomedicine Online*. https://doi.org/10.1016/j.rbmo.2022.03.002

Male, V. (2021). Effect of COVID-19 vaccination on menstrual periods in a retrospectively recruited cohort. *medRxiv*, 2021.11.15.21266317. https://doi.org/10.1101/2021.11.15.21266317

Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, Kraker von Schwarzenfeld A, Acuna J. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS One. 2021 Oct 20;16(10):e0258314. doi: 10.1371/journal.pone.0258314. PMID: 34669726; PMCID: PMC8528316.

Stahlman S, PhD, Williams MVF, MA, Taubman MSB, PhD. Incidence and burden of gynecologic disorders, active component service women, U.S. Armed Forces, 2012–2016. Medical Surveillance Monthly report.

Trogstad, L. (2022). Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3998180

The Netherlands Pharmacovigilance Centre Lareb received an unprecedented amount of reports of menstrual disorders with administration of COVID-19 vaccines.https://www.lareb.nl /media/uoneih5z/signals_2021_menstrual_disorders-and-postmenopausal_bleeding-and-covid-19-vaccines.pdf

Zhang B, Yu X, Liu J, Liu P. COVID-19 vaccine and Menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System. https://assets.researchsquare.com/files/rs-1388159/v1/28dc1c53-1698-4d49-9a46-3d95d1f36833.pdf?c=1646942221

Appendix-1: List of Questions from PRAC

ITEM 1: Clinical trials

The MAH should provide an overview and clinical evaluation of cases of heavy menstrual bleeding, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for heavy menstrual bleeding, concomitant medication, patient medical history including previous menstruation pattern, duration of the event and outcome. This information should be considered in the context of the total number of females, including of childbearing potential participating in the study.
The MAH should clarify how adverse events related to heavy menstrual bleeding were reported, i.e. if these were solicited adverse events or spontaneously reported by the participants.

ITEM 2: Published literature

The MAH should perform a literature review on the possible association between heavy menstrual bleeding and COVID-19 mRNA vaccine Spikevax. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al.3 , Nguyen et al.4 and Edelman et al.5 .

ITEM 3: Case overview

The MAH should list the number of reported cases of the preferred term heavy menstrual bleeding stratified by:

- worldwide and region
- country in the EU/EEA
- dose number in series
- seriousness
- reporter (medically/non-medically confirmed)
- positive rechallenge.

ITEM 4: Case review

The case review should prioritise serious and/or medically confirmed cases, where information on risk factors and medical history is included. Special focus should be given to cases in which the previous menstruation pattern is known, and to cases of heavy menstrual bleeding with positive rechallenge.
The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case. The MAH should provide for all cases a clear breakdown of the number of cases that were either supportive of causality/ unsupportive due to presence of other causes, risk factors, underlying conditions, confounding medication/ unassessable.
The following information should be stratified:

- Details of medically relevant co-reported adverse events (if any)
- Cases in which women used hormonal contraception (including hormonal intrauterine devices)
- Cases with other types of intrauterine devices
- Cases that received heterologous primary or booster schemes.

If available, the MAH should provide information on when vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information on the menstrual cycle is known and discuss whether a pattern might exist.
When excluding cases from the review, a justification for doing so should be provided by the MAH. Based on a review of case reports with inconclusive causality due to confounding factors and/or lacking information, the MAH should provide a nuanced discussion of whether Spikevax may have aggravated the condition in cases where causality cannot be firmly established.

ITEM 5: Mechanism of action
The MAH should discuss the pathophysiology of heavy menstrual bleeding and whether any biological plausibility/mechanism of action exists.

ITEM 6: Exposure in females of childbearing potential.
The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Spikevax.

Appendix-1: LITERATURE SEARCH USED for HEAVY MENSTRUAL BLEEDING

A literature search was conducted using PubMed of the National Library of Medicine (PubMed NLM) and Google Scholar using the search strategies listed below.

PubMed NLM

(((((((Menorrhagia) OR (Heavy Menstrual Bleeding)) OR (Menstrual Bleeding, Heavy)) OR (Hypermenorrhea)) OR (Heavy Period*)) OR (Post Menopausal bleeding)) OR (%Menstru%)) 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])Google Scholar

Menorrhagia OR “Heavy Menstrual Bleeding” OR Hypermenorrhea OR “Heavy Period*” OR “Post menopausal bleeding” OR %Menstru% AND COVID-19 Vaccines

SARS-CoV-2 Infection and Heavy Menstrual Bleeding

PubMed NLM

Menorrhagia OR "Heavy Menstrual Bleeding" OR "Menstrual Bleeding OR Heavy" OR Hypermenorrhea OR "Heavy Period*" OR "Post menopausal bleeding" AND Covid-19

Google Scholar

Menorrhagia OR “Heavy Menstrual Bleeding” OR Hypermenorrhea OR Heavy Period* OR “Post menopausal bleeding” OR %Menstru% AND COVID-19

COVID-19 Pandemic and Heavy Menstrual Bleeding

PubMed NLM: menstrua* AND (COVID* OR "sars-cov*" OR "coronavirus" OR "lockdown")

Appendix 4.2e: Signal Evaluation report: Urticaria

Signal Evaluation Report

for

mRNA-1273

on

Urticaria

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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 Urticaria in association with the administration of mRNA-1273 in adult patients ≥18yo, based on all information available to the MAH at the time of document preparation.

1.1 Source of the Signal

On 18 Mar 2022, SwissMedic requested the MAH based on the following review of all available information out of case reports to Swissmedic, the WHO database Vigilyze and literature, we request a provision of a cumulative safety report with regards to the relation of Spikevax and urticaria at the latest by **29 April 2022.** The cumulative safety report shall contain data from all sources. The safety report shall provide responses to at least the following questions:

1. Assessment of causality of cases from clinical studies, spontaneous sources and literature. In all cases, a rationale for causality shall be provided.
2. The safety report shall investigate possible risk factors including discussion if any patterns or trends can be identified with regards to risk factors.
3. O/E-analyses- as possible- stratified for age, gender and dose. The analyses shall clearly state all used background rates and rationales. Several risk windows shall be considered.
4. An overview of published literature, including a discussion of the literature concerning plausible mechanism.
5. The need for updating the label/SmPC and/or the RMPs shall be discussed. Please take a position that urticaria may occur, even delayed and persisting for longer period of times as well as recurrent.

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.

General Description on Disease (Urticaria):

Urticaria, or hives (sometimes referred to as welts or wheals), is a common disorder, with a prevalence of approximately 20 percent in the general population. A typical urticarial lesion is an intensely pruritic, erythematous plaque. Urticaria is sometimes accompanied by angioedema, which is swelling deeper in the skin. A presumptive trigger, such as a drug, food ingestion, insect sting, or infection, may be identifiable in patients with new-onset urticaria, although no specific cause is found in many cases, particularly when the condition persists for weeks or months.

Urticaria (with or without angioedema) is commonly categorized by its chronicity:

- Acute urticaria — Urticaria is considered acute when it has been present for less than six weeks.
- Chronic urticaria — Urticaria is considered chronic when it is recurrent, with signs and symptoms recurring most days of the week, for six weeks or longer.

The period of six weeks is somewhat arbitrary and simply represents a timeframe in which new cases of urticaria usually resolve. More than two-thirds of cases of new-onset urticaria are classified as acute. The lesions of acute and chronic urticaria are identical in appearance. At the time of onset, it is not possible to differentiate the two disorders.

Pathophysiology and Etiology

Urticaria is mediated by cutaneous mast cells in the superficial dermis. Basophils have also been identified in lesional biopsies. Mast cells and basophils release multiple mediators upon activation including histamine (which causes itching) and vasodilatory mediators (which cause localized swelling in the uppermost layers of the skin). The same process gives rise to angioedema when mast cells deeper in the dermis and subcutaneous tissues are activated. The potential causes of new-onset urticaria are numerous, although no specific etiology can be identified in many patients. Acute urticaria is more likely to have an identifiable etiology compared with chronic urticaria. The different etiologies activate mast cells through various mechanisms.

3 Review of Data from All Sources

The assessment of Urticaria 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.

The MAH performed a review of all cases of urticaria derived from all sources. The global safety database was queried cumulatively through 15 February 2022 for all valid, spontaneous case reports received from HCPs, HAs, consumers, and the literature using the MedDRA Preferred term (PT) Urticaria. Case data were reviewed, with a focus on events reported after Dose-3.

3.1 Clinical Trial Data

The topic of Urticaria was cumulatively reviewed in the MAH clinical database with a data-lock point (DLP) of 04 May 2021, searched using the following MedDRA v 24.0 preferred term "Urticaria" was performed in P301 study.

The search retrieved 100 (0.33 %) patients who experienced urticaria out of a study population of 30,346 patients (15,162 participants on placebo; 15,184 participants on mRNA-1273).

Overall, there was no significant difference in the rate of urticaria events observed with vaccine-treated subjects compared to placebo-treated subjects, with the exception of the cases in the 6–13 day post-vaccination time frame in which 2-3 times more patients experienced urticaria who received mRNA-1273 than those who received placebo. Of the 13 subjects in the TTO group 6-13 days, 9 subjects had medical history of allergic condition (7 in mRNA-1273 arm and 2 in placebo arm). Table 1 shows number of subjects who experienced urticaria with time to onset (TTO) at 0-3- and 6-13-days post vaccination.

Table 1 shows number of subjects who experienced urticaria with time to onset (TTO) at 0-3- and 6-13-days post vaccination.

Table 1: TTO of Urticaria by Vaccination and Placebo Treated Subjects

PT and TTO (Days)	mRNA-1273 n=15184	Placebo n= 15162	Grand Total N=30346
Urticaria	54 (0.36)	46 (0.30)	100 (0.33)
0-3 Days	4 (0.03)	3 (0.02)	7 (0.02)
6-13 Days	10 (0.07)	3 (0.02)	13 (0.04)
Other*	40 (0.26)	40 (0.26)	80 (0.26)

**Other represents the TTO not within the 0-3 days nor 6-13 days*

3.2 External Databases

VAERS and EVDAS were reviewed for the PT of Urticaria and neither of these databases showed disproportionality of EB05 or ROR

- VAERS: No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS as of 15 Feb 2022; Urticaria (EB05: 1.131; N=12823)

- EVDAS: The PT of Urticaria did not show Disproportionality as the ROR was <1. The observed ROR for Urticaria was (0.99; N=4148).

3.3 Non-clinical Data
Not applicable

3.4 Epidemiological studies
As of 15th February 2022, approximately 566 million doses of Spikevax were administered in 84 countries. US accounted for 36.5% of doses administered and Switzerland accounted for 1.7% of doses administered.

Incidence of Urticaria is not very well described, Lapi et al, 2016 characterized annual incidence of chronic spontaneous urticaria, in this article authors used Longitudinal Patient Databases established in Italy since 1988. This database includes medical records from approximately 1000 general practitioners throughout Italy. Total of 14,859 patients observed between 2002-2013 (68.12% females). Reference rate includes individuals with chronic spontaneous urticaria, therefore, underestimated compared to all types of spontaneous urticaria.

The default risk window for Observed to Expected (O/E) analyses is assumed to be 21 days, and calculations were run using the *overall* number of observed cases. In addition, O/E calculations were run for 3-day risk and 7-day risk window, based on the bimodal peaks of time to onset Also, dose specific O/E analysis were run for all three risk windows – 21-day, 7-day, and 3-day risk window.

Considering the 21-day risk window, there were 10,636 observed cases of urticaria cumulatively (reporting rate of 32.53 per 100,000 person-years). The observed reporting rate was much lower than the expected incidence rate of 130 per 100,000 person-years (rate ratio of 0.25, 95% CI 0.24, 0.26). The results of age and gender stratification did not show elevated rate ratio for any strata. The sensitivity analysis assuming 50% and 25% capture of observed cases, show an elevated rate ratio in number of strata. However, these findings should be interpreted with caution as the estimated incidence rate includes only individuals with chronic spontaneous urticaria.

Table 6 presents results of the dose specific O/E analysis for three selected risk windows (3-day risk window, 7-day risk window, and 21-day risk window). The observed reporting rates for overall and dose specific were lower than the expected reporting rates, except for Dose 1 with 3-day risk window.

Table-1: O/E Analysis stratified for Age, and Gender considering 21-day risk window as of 15th February 2022

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			
Reference: Lapi et al 2016								
All	32,695,513	10636	32.53	42504	130.00	0.25 (0.24, 0.26)	0.5 (0.49, 0.51)	1 (0.99, 1.01)
By age								
<12 years	49,043	1	2.04	64	130.00	0.02 (0, 0.11)	0.03 (0.01, 0.13)	0.06 (0.02, 0.17)
12-17 years	931,822	45	4.83	1211	130.00	0.04 (0.03, 0.05)	0.07 (0.06, 0.09)	0.15 (0.13, 0.17)
18-24 years	2,942,596	597	20.29	3825	130.00	0.16 (0.14, 0.17)	0.31 (0.29, 0.33)	0.62 (0.59, 0.66)
25-39 years	7,193,013	2877	40.00	9351	130.00	0.31 (0.3, 0.32)	0.62 (0.6, 0.64)	1.23 (1.2, 1.26)
40-49 years	4,904,327	2111	43.04	6376	130.00	0.33 (0.32, 0.35)	0.66 (0.64, 0.69)	1.32 (1.28, 1.37)
50-64 years	8,500,833	2357	27.73	11051	130.00	0.21 (0.2, 0.22)	0.43 (0.41, 0.44)	0.85 (0.83, 0.88)
65-74 years	4,904,327	1451	29.59	6376	130.00	0.23 (0.21, 0.24)	0.46 (0.44, 0.48)	0.91 (0.88, 0.94)
75+ years	3,269,551	658	20.13	4250	130.00	0.15 (0.14, 0.17)	0.31 (0.29, 0.33)	0.62 (0.59, 0.65)
By gender								
Male	15,563,064	1920	12.34	12450	80.00	0.15 (0.15, 0.16)	0.31 (0.3, 0.32)	0.62 (0.6, 0.63)
Female	17,132,449	8505	49.64	27412	160.00	0.31 (0.3, 0.32)	0.62 (0.61, 0.63)	1.24 (1.22, 1.26)
By age and gender								
Male								
<12 years	23,345	0	0.00	19	80.00	NA	NA	NA
12-17 years	443,547	24	5.41	355	80.00	0.07 (0.04, 0.1)	0.14 (0.1, 0.18)	0.27 (0.22, 0.34)
18-24 years	1,400,676	141	10.07	1121	80.00	0.13 (0.11, 0.15)	0.25 (0.22, 0.29)	0.5 (0.45, 0.56)
25-39 years	3,423,874	514	15.01	2739	80.00	0.19 (0.17, 0.21)	0.38 (0.35, 0.4)	0.75 (0.71, 0.79)
40-49 years	2,334,460	360	15.42	1868	80.00	0.19 (0.17, 0.22)	0.39 (0.35, 0.42)	0.77 (0.72, 0.83)
50-64 years	4,046,397	401	9.91	3237	80.00	0.12 (0.11, 0.14)	0.25 (0.23, 0.27)	0.5 (0.47, 0.53)
65-74 years	2,334,460	265	11.35	1868	80.00	0.14 (0.12, 0.16)	0.28 (0.26, 0.31)	0.57 (0.53, 0.61)
75+ years	1,556,306	143	9.19	1245	80.00	0.11 (0.1, 0.14)	0.23 (0.2, 0.26)	0.46 (0.42, 0.51)
Female								
<12 years	25,699	1	3.89	41	160.00	0.02 (0, 0.18)	0.05 (0.01, 0.2)	0.1 (0.03, 0.27)
12-17 years	488,274	21	4.30	781	160.00	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)	0.11 (0.09, 0.13)
18-24 years	1,541,920	455	29.51	2467	160.00	0.18 (0.17, 0.2)	0.37 (0.34, 0.4)	0.74 (0.69, 0.78)
25-39 years	3,769,139	2347	62.27	6031	160.00	0.39 (0.37, 0.41)	0.78 (0.75, 0.81)	1.56 (1.51, 1.61)
40-49 years	2,569,867	1738	67.63	4112	160.00	0.42 (0.4, 0.45)	0.85 (0.81, 0.88)	1.69 (1.63, 1.76)
50-64 years	4,454,437	1945	43.66	7127	160.00	0.27 (0.26, 0.29)	0.55 (0.52, 0.57)	1.09 (1.06, 1.13)
65-74 years	2,569,867	1179	45.88	4112	160.00	0.29 (0.27, 0.31)	0.57 (0.55, 0.6)	1.15 (1.1, 1.2)

75+ years	1,713,245	514	30.00	2741	160.00	0.19 (0.17, 0.21)	0.38 (0.35, 0.4)	0.75 (0.71, 0.79)

Please see Appendix-1 for O/E Analysis with Different Risk Windows

3.5 Review of the Pharmacovigilance Database

Post marketing data for potential signal of Urticaria events were retrieved from the Company safety database using the following MedDRA preferred term: "Urticaria" with a data-lock point (DLP) of 15 February 2022, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Cases from all sources and relevant literature were reviewed.

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

The MAH performed a review of all cases of Urticaria derived from all sources. The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 15 February 2022, for Spikevax. Search criteria used the PT of "Urticaria". Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches were described for cumulative cases including any fatal cases.

3.7 Results

Cumulatively, through 15 Feb 2022, a total of 10,636 case reports (10,807 events, 171 events reported twice with more than 70% with unknown dose and outcome) including the PT Urticaria were received. Of these, 7,119 reports were medically confirmed. These correspond to 1,523 serious cases, none of which had a fatal outcome. The majority of these cases were from the United States (63.8%). Of the 10,636 cases 578 were on Dose 3 with 181 serious cases. No significant trends were observed in age, gender or outcome of the events in all Doses vs Dose-3. There was temporal change in reporting by region, with a shift towards a greater proportion of cases reported from the UK compared to the rest of the world for dose 3 (associated with changes in booster vaccination recommendations in the UK). Additional details are provided in **Table 2**.

Table 2: Overall Summary of Post-marketing Data for Urticaria as of 15 February 2022

	Number (All Doses)	**Number (Dose#3)**
Number of cases	10636 Cases (1523 serious)	578 Cases (181 serious)
Number of events	10807 (7119 Medically confirmed)	583 (160 Medically confirmed)
Median age, years	45.0 (range: 0-101)	44.0 (range: 15-89)
Female/ Male/Missing	8505 (80.0%)/1920 (18.1%)/211 (2.0%)	394 (68.2%)/168 (29.1%)/16 (2.8%)

Case distribution by region	United States 6785 (63.8%); European Economic Area 2153 (63.8%); United Kingdom 650 (6.1%); Switzerland 257 (2.5%); Canada 79 (0.7); Asia 699 (6.6%), Latin America 2 (0.0%) and Middle East 1 (0.0)	United Kingdom 243 (42.0%); United States 211 (36.5%); European Economic Area 48 (8.3%); Switzerland 57 (9.9%); Canada 7 (1.2); and Asia 12 (1.8%)
Fatal outcome	0 Cases	0 Cases

Of the cumulative 10636 cases, 1920 (18.1%) involved male patients and 8505 (80.0%) involved female patients with a median patient age of 47.0. no specific trend in particular age group was observed though most of the cases were reported in the patients ≥50 years age group (4468; 42.0%). For additional details see Table-3

Table 3: Number and Percentage of Spontaneous Cases of Urticaria (URTICARIA) Reported by Age and Gender for the SPIKEVAX. Cumulative to 15 February 2022

Age Group	Female		Male		Unknown		Total # of Cases	Total % of Cases
	# Cases	% of Cases	# Cases	% of Cases	# Cases	% of Cases		
<2	1	0.0	0	0	0	0	1	0.0
12-15	16	0.2	19	0.2	0	0	35	0.3
16-17	5	0.0	5	0.0	0	0	10	0.1
18-29	1066	10.0	271	2.5	1	0.0	1338	12.6
30-39	1736	16.3	384	3.6	16	0.2	2136	20.1
40-49	1738	16.3	360	3.4	13	0.1	2111	19.8
50-64	1945	18.3	401	3.8	11	0.1	2357	22.2
65-74	1179	11.1	265	2.5	7	0.1	1451	13.6
75+	515	4.8	143	1.3	2	0.0	660	6.2
Missing	304	2.9	72	0.7	161	1.5	537	5.0
Grand total	8505	80.0	1920	18.1	211	2.0	10636	100.0

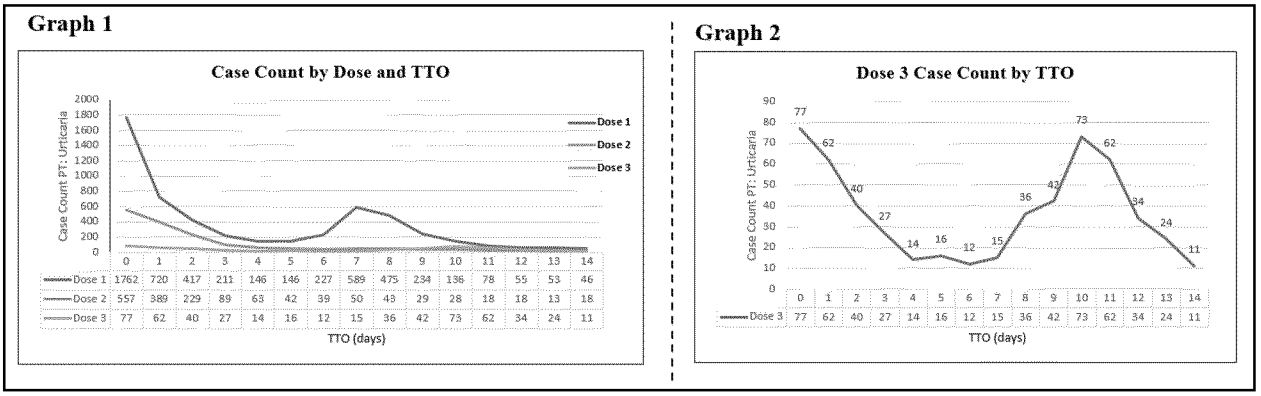
Events were reported more frequently after the 1st dose (50.7%) and then after the 2nd dose (16.3%) then 3rd dose (5.4%). No specific pattern with respect to TTO was observed (**Table 4**).

Table 4: Time to Onset by Dose Number as of 15 February 2022

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	*Subtotal*	*5,484*	*50.7*
	0 days	1,762	16.3
	01-02	1,137	10.5
	03-04	357	3.3
	05-06	373	3.5
	07-13	1,620	15.0
	14-29	184	1.7
	30+	51	0.5
Dose 2	*Subtotal*	*1,759*	*16.3*
	0 days	557	5.2
	01-02	618	5.7
	03-04	152	1.4
	05-06	81	0.7
	07-13	199	1.8
	14-29	91	0.8
	30+	61	0.6
Dose 3	*Subtotal*	*583*	*5.4*
	0 days	77	0.7
	01-02	102	0.9
	03-04	41	0.4
	05-06	28	0.3
	07-13	286	2.6
	14-29	37	0.3
	30+	12	0.1
Dose 4	*Subtotal*	*1*	*0.0*
	0 days	1	0.0
Unknown	*Subtotal*	*2,980*	*27.6*
	Missing	2,980	27.6
Grand total		10,807	100.0

Upon review of the cases, time to onset for urticaria was observed to be clustered in the first 3 days post vaccination (days 0-3) followed by another cluster of events occurring days 6-13. The numbers of and events reported decreased with subsequent doses which is consistent with fewer patients receiving doses 2 and 3. However, the bimodal pattern of urticaria occurrence following each dose persisted and was particularly prominent with dose 3 as shown in Figure 1 of graph 1 and 2

Figure-1: Time to Onset for All Doses (Graph-1) and Dose 3 alone (Graph-2)



This pattern suggests a possible causal association between Spikevax and the occurrence of urticaria on post-vaccination days 0-3 and days 6-13 for all doses.

Upon medical review of cases, both localized injection site urticaria and non-localized systemic urticaria were noted, however no correlation could be made with regards to local vs systemic urticaria and dosing. In addition, many reports did not describe distribution of urticaria.

There were no trends identified with regards to concomitant medications. Review of medical history revealed that the most frequently reported medical history involved allergic and/or hypersensitivity conditions which suggests a predisposition for patients who have these conditions to develop urticaria.

Table 5: Most Frequently Observed Medical History in the Subjects with AE of Urticaria

Medical History	Count of Unique Cases	%
Drug hypersensitivity	2287	22%
Food allergy	802	8%
Hypertension	678	6%
Asthma	605	6%
Seasonal allergy	472	4%
Hypersensitivity	456	4%

In general, the events of urticaria were predominantly non-serious and a more than half of events had an unknown outcome. At the time of reporting 33.8% had not resolved and 26.9% had unknown outcome. In addition, 9690 events did not have data regarding duration; of the 1117 events with duration information the average duration was 7.8 days (standard deviation: 19.9 days), and median was 3 days (range: -1, 369 days). Given the limitations of the post authorization reports which often lack follow-up and complete case details (i.e., outcome and duration data), the MAH is unable to assess the persistence of urticaria.

Table 6: Event Outcome

Event Outcome	# of Total Events	% of Total Events
Not Recovered/Not Resolved	3,658	33.8%
Recovered/Resolved	3,201	29.6%
Recovered/Resolved with Sequelae	44	0.4%
Recovering/Resolving	1,002	9.3%
Unknown	2,902	26.9%
Grand total	**10,807**	**100%**

4 Literature Review

Clinical literature search review:

A literature search was performed 15 February 2022 using PubMed, details of the search criteria is provided in Appendix 2. A cumulative search as of 31 Mar 2022 was performed in PubMed. None of the identified articles provided evidence of a direct causal association between the COVID-19 mRNA vaccines and urticaria. It should be noted that a few articles suggested a speculative hypothesis of an association between the polyethylene glycol stabilizer in Spikevax and urticaria, however no uniform consensus was noted. Please see **Appendix-2** for search criteria used and summaries of selected articles including the two (2) requested literature articles (Larson et al and Pitlick et al) by Swissmedic.

4.1 Non-clinical literature search review:

Not applicable

5 Discussion

A cumulative search of global safety database as of 15 February 2022, was performed and the search retrieved 10636 cases (10807 events). Upon medical review of cases, both localized injection site urticaria and non-localized systemic urticaria were noted, however no correlation could be made with regards to local vs systemic urticaria and dosing. In addition, many reports did not describe distribution of urticaria. There were no trends identified with regards to concomitant medications. Review of medical history revealed that the most frequently reported medical history involved allergic and/or hypersensitivity conditions which suggests a predisposition for patients who have these conditions to develop urticaria. No unique or novel risk factors were identified other than medical history of allergic reactions reported an event of Urticaria more frequently than general population. Given the limitations of the post authorization reports which often lack follow-up and complete case details (i.e., outcome and duration data), the MAH is unable to assess the persistence of urticaria.

6 Conclusion

Based on the review of the cumulative safety information available as of 15 February 2022, with particular attention to data collected in the post-authorization experience, there is evidence to suggest a possible causal association between Spikevax and urticaria in a non-localized distribution, occurring in a bimodal timeframe during days 0-3 and 6-13 following vaccination reported after all doses of vaccination including Dose-3. Given the limitations of the post authorization reports which often lack follow-up and complete case details (i.e., outcome and duration data), the MAH is unable to assess the persistence of urticaria.

The signal is confirmed and the current safety information for Moderna mRNA-1273 vaccine describes urticaria in association with injection site reactions. As this assessment identifies urticaria occurring in a pattern different from that described in the current safety information, Moderna will update the safety information to reflect urticaria as an adverse reaction observed in the post-authorization experience.

7 References

Larson V, Seidenberg R, Caplan A, Brinster NK, Meehan SA, Kim RH. Clinical and histopathological spectrum of delayed adverse cutaneous reactions following COVID-19 vaccination. J Cutan Pathol. 2022 Jan;49(1):34-41. doi: 10.1111/cup.14104. Epub 2021 Aug 8. PMID: 34292611; PMCID: PMC8444807.

Pitlick MM, et al. Delayed systemic urticarial reactions following mRNA COVID-19 vaccination. Allergy Asthma Proc. 2022 Jan 1;43(1):40-43. doi: 10.2500/aap.2022.43.210101. PMID: 34983709; PMCID: PMC8749242.

Johnston MS, et al. Delayed Localized Hypersensitivity Reactions to the Moderna COVID-19 Vaccine: A Case Series. JAMA Dermatol. 2021 Jun 1;157(6):716-720. doi: 10.1001/jamadermatol.2021.1214. PMID: 33978670; PMCID: PMC8117061.

McMahon DE, et al. Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: A registry-based study. J Am Acad Dermatol. 2022 Jan;86(1):113-121. doi: 10.1016/j.jaad.2021.09.002. Epub 2021 Sep 10. PMID: 34517079; PMCID: PMC8431833.

Grieco T, Ambrosio L, Trovato F, Vitiello M, Demofonte I, Fanto M, Paolino G, Pellacani G. Effects of Vaccination against COVID-19 in Chronic Spontaneous and Inducible Urticaria (CSU/CIU) Patients: A Monocentric Study. J Clin Med. 2022 Mar 25;11(7):1822. doi: 10.3390/jcm11071822. PMID: 35407429; PMCID: PMC8999670.

Appendix-1: Evaluation – O/E Analysis with Different Risk Windows

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			
21-day risk window (21 days post-vaccination)								
All	32,695,513	10636	32.53	42504	130.00	0.25 (0.24, 0.26)	0.5 (0.49, 0.51)	1 (0.99, 1.01)
Dose								
Dose 1	14,507,169	5421	37.37	18859	130.00	0.29 (0.28, 0.3)	0.57 (0.56, 0.59)	1.15 (1.13, 1.17)
Dose 2	11,863,838	1720	14.50	15423	130.00	0.11 (0.11, 0.12)	0.22 (0.21, 0.23)	0.45 (0.43, 0.46)
Dose 3	6,324,506	562	8.89	8222	130.00	0.07 (0.06, 0.07)	0.14 (0.13, 0.15)	0.27 (0.26, 0.29)
7 -day risk window (6-13 days post vaccination)								
Dose 1	4,835,723	1822	37.68	6286	130.00	0.29 (0.28, 0.31)	0.58 (0.56, 0.6)	1.16 (1.12, 1.2)
Dose 2	3,954,613	238	6.02	5141	130.00	0.05 (0.04, 0.05)	0.09 (0.08, 0.1)	0.19 (0.17, 0.2)
Dose 3	2,108,169	295	13.99	2741	130.00	0.11 (0.1, 0.12)	0.22 (0.2, 0.24)	0.43 (0.4, 0.46)
3 -day risk window (0-3 days post vaccination)								
Dose 1	2,072,453	3094	149.29	2694	130.00	1.15 (1.09, 1.21)	2.3 (2.2, 2.4)	4.59 (4.41, 4.79)
Dose 2	1,694,834	1225	72.28	2203	130.00	0.56 (0.52, 0.6)	1.11 (1.05, 1.18)	2.22 (2.11, 2.34)
Dose 3	903,501	204	22.58	1175	130.00	0.17 (0.15, 0.2)	0.35 (0.31, 0.39)	0.69 (0.64, 0.76)

Appendix-2: Literature Analysis and Search Criteria Used

The following search criteria was used to search the PubMed

(((((((Urticaria)) or (Hives)) 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])

Summary of relevant articles:

1. Larson V, Seidenberg R, Caplan A, Brinster NK, Meehan SA, Kim RH. Clinical and histopathological spectrum of delayed adverse cutaneous reactions following COVID-19 vaccination. J Cutan Pathol. 2022 Jan;49(1):34-41. doi: 10.1111/cup.14104. Epub 2021 Aug 8. PMID: 34292611; PMCID: PMC8444807.

    - Retrospective case series of patients who underwent skin biopsy procedure for cutaneous eruptions after receiving either Pfizer-BioNTech or Moderna vaccine between January 1, 2021 and May 31, 2021. Twenty-one patients were selected. Twelve patients (7 patients received SPIKEVAX) were identified as having a delayed hypersensitivity reaction to the vaccine.
    - Reactions followed both Dose 1 and 2. Latency ranged from several hours following Dose 1 to two weeks after Dose 2. The authors then go on to cite a study by Johnston MS, et al which refers to "COVID Arm": a transient and localized erythematous eruption around injection site that may occur between 7 to 10 days after the first dose of the vaccine.
2. Pitlick MM, et al. Delayed systemic urticarial reactions following mRNA COVID-19 vaccination. Allergy Asthma Proc. 2022 Jan 1;43(1):40-43. doi: 10.2500/aap.2022.43.210101. PMID: 34983709; PMCID: PMC8749242.

    - Retrospective case series of 12 patients referred to the Mayo Clinics in Rochester, Minnesota and Jacksonville, Florida from January 19, 2021, to April 30, 2021, for evaluation of delayed systemic urticarial reactions following mRNA COVID-19 vaccination. Eleven of the 12 patients had reactions to Dose 1. Three patients had delayed reactions from 3 to 5 days post vaccination. Median time to symptom

resolution was 4 days. The mechanism of allergic reactions, both immediate and delayed, is currently unknown, although a T-cell response to active and inactive vaccine components (ex: Polyethylene Glycol) have been proposed as possible culprits. Delayed systemic urticarial reactions after mRNA COVID-19 vaccination were not life-threatening and were not contraindicated to subsequent vaccination.

3. Johnston MS, et al. Delayed Localized Hypersensitivity Reactions to the Moderna COVID-19 Vaccine: A Case Series. JAMA Dermatol. 2021 Jun 1;157(6):716-720. doi: 10.1001/jamadermatol.2021.1214. PMID: 33978670; PMCID: PMC8117061.

    - Retrospective case series study at Yale New Haven Hospital in New Haven, Connecticut which describes localized cutaneous injection-site reactions to SPIKEVAX in 16 patients referred to clinic from January 20, 2021 through February 12, 2021. Study concludes "COVID Arm" is not contraindicated for subsequent vaccination. Fifteen of the 16 patients developed localized cutaneous reactions after Dose 1. The median onset of the reactions was 7 days (2 to 12 days) after vaccine administration with a median duration of 5 days. Eleven of those 16 patients developed a reaction to Dose 2 , but more quickly with a median onset of 2 days following administration. These reactions (dubbed "COVID Arm") are consistent with clinical and histopathological examination findings for delayed-type hypersensitivity reactions. The mechanism is unknown, but the timing and histopathologic examination findings suggest cell-mediated immunity associated with delayed-type hypersensitivity reactions. Author suggests that the delayed reaction may be associated with T-cell response to vaccine excipients (specifically Polyethylene Glycol), lipid nanoparticle, or mRNA component.

4. McMahon DE, et al. Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: A registry-based study. J Am Acad Dermatol. 2022 Jan;86(1):113-121. doi: 10.1016/j.jaad.2021.09.002. Epub 2021 Sep 10. PMID: 34517079; PMCID: PMC8431833.

    - Registry-based study aimed at improving the characterization of dermatologic reactions to COVID-19 vaccination through an analysis of biopsy reports and corresponding clinical photographs from cases entered into the American Academy of Dermatology or International League of Dermatological Societies Registry. The 803 cases were reported. SPIKEVAX accounted for 69% of the reports. Sixty-two percent of the adverse reactions were reported by women.

    - The most common reported morphologies were local injection site reaction, delayed large local reactions, urticaria, morbilliform, zoster and papulosquamous eruptions. Study defined delayed reaction as occurring more than 4 days after vaccination. Of the 803 cases, 301 total reports were described as "delayed large local reactions occurring 4 days or more from vaccination". Most urticarial eruptions did not lead to anaphylaxis or severe adverse events with the second dose. The mechanism is unknown, but histopathology of delayed large local reactions showed perivascular lymphocytic infiltrates with eosinophils and mast cells, consistent with a delayed T-cell mediated hypersensitivity reaction.

5. Grieco T, Ambrosio L, Trovato F, Vitiello M, Demofonte I, Fanto M, Paolino G, Pellacani G. Effects of Vaccination against COVID-19 in Chronic Spontaneous and Inducible Urticaria (CSU/CIU) Patients: A Monocentric Study. J Clin Med. 2022 Mar 25;11(7):1822. doi: 10.3390/jcm11071822. PMID: 35407429; PMCID: PMC8999670.

This article re-iterates the concept of type I allergic reactions following COVID-19 vaccinations is mainly due to polyethylene glycole (PEG) and structurally related polysorbate-80 were considered as potential triggers of both IgE and non-IgE-mediated reactions and also reference to Gambichler et al., which is described in Johnston MS, et al. *In conclusion, according to our sample, COVID-19 vaccination in the CSU/CIU can be considered safe and is advisable. Cases of exacerbation or worsening of the disease appear to be transient and can be managed by antihistamine therapies. Patients with well-controlled urticaria (assessed by UAS7 < 16) who undergo Omalizumab seem to be more protected against potential urticaria flares and AEFI. In general, for patients with CSU, anti-SARS-CoV-2 vaccines also currently maintain a good general safety profile.*