EUROPEAN UNION RISK MANAGEMENT PLAN FOR KOSTAIVE

RMP version to be assessed as part of this application:

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QPPV name[a]: Mikolaj Cwik

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

[a] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation application; available on EMA website http://www.ema.europa.eu

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LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	adverse event
CD4	cluster of differentiation-4
CD8	cluster of differentiation-8
CFR	case fatality rate
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
DS	day of study
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GD	gestation day(s)
GLP	Good Laboratory Practice
IM	intramuscular(ly)
LN	lymph nodes
LNP	lipid nanoparticle
mRNA	messenger ribonucleic acid
NOAEL	no observed adverse effect level
RMP	risk management plan
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
UTR	untranslated region
VEEV	Venezuelan equine encephalitis virus
WHO	World Health Organization

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name) Brief Description	INN: zapomeran Description: Zapomeran is a single-stranded, 5'-capped messenger RNA (mRNA) replicon (self-amplifying mRNA), produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding a replicase and the spike glycoprotein of the ancestral strain of SARS-CoV-2 with the D614G mutation.
Pharmacotherapeutic group(s)(ATC Code)	Vaccines, other viral vaccines (J07BN01)
Marketing authorisation applicant	Arcturus Therapeutics Europe B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Kostaive
Marketing authorisation procedure	Centralised
Brief description of the product:	Biological class: mRNA Vaccine (lipid nanoparticle-formulated RNA product)
	Summary of mechanism of action: Kostaive is composed of a self-amplifying mRNA encoding the spike protein of SARS-CoV-2, encapsulated in lipid nanoparticles. The self-amplifying mRNA is designed to produce extra copies of mRNA within the host cells after intramuscular injection, to achieve enhanced expression of the spike protein antigen. This gives rise to neutralising antibody and cellular immune responses to the spike antigen, which contributes to protection against COVID-19. The mRNA self-amplification process is transient and does not generate infectious particles.
	Important information about its composition: Lyophilized Kostaive is composed of the drug substance mRNA-2105 and four lipid excipients: ATX-126 [di(pentadecan-8-yl)-4,4'-((((3-(dimethylamino)propyl)thio)carbonyl)azanediyl)dibutyrate], cholesterol, DSPC [1,2-distearoyl-sn-glycero-3-phosphocholine], and PEG2000-DMG [1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000] in trometamol buffer with 3 lyoprotectants (sucrose, poloxamer 188, and potassium sorbate), as well as sodium chloride. It is presented as a sterile white to off-white lyophilized cake/powder contained in a clear glass vial (Type I) with a stopper (bromobutyl rubber) and plastic flip-off cap with seal (aluminium crimp). It contains 10 mcg mRNA/mL of mRNA-2105 after reconstitution with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
Hyperlink to the Product Information	Please refer to Module 1.3.1 of this submission.
Indication in the EEA	Proposed: For active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults 18 years of age and older.

Table 1 Product Overview

Dosage in the EEA	Proposed: Kostaive is administered intramuscularly after reconstitution as a single dose of 0.5 mL. For individuals who have previously been vaccinated with a COVID-19 vaccine, Kostaive should be administered at least 5 months after the most recent dose.
Pharmaceutical form and strengths	Form: Powder for dispersion for injection (sterile). The lyophilized vaccine is a white to off-white powder. Upon reconstitution, the vaccine is an opalescent suspension (pH: 7.5 – 8.5). It is intended for intramuscular injection. Strength: One multidose vial contains 16 doses of 0.5 mL after reconstitution with 10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection. One dose (0.5 mL) contains 5 mcg of zapomeran, a COVID-19 mRNA vaccine (encapsulated in lipid nanoparticles)
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC, Anatomic Therapeutic Chemical; COVID-19, coronavirus disease 2019; EEA, European Economic Area; EU, European Union; INN, International Nonproprietary Name; mRNA, messenger ribonucleic acid; RMP, risk management plan; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication

For active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in individuals 18 years of age and older.

Incidence and prevalence

COVID-19 is a respiratory infection caused by the SARS-CoV-2, a novel coronavirus that first emerged in Wuhan City, Hubei Province, China in December 2019 (Zhu 2020). The number of COVID-19 cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern, and thus, a pandemic.

Estimates of SARS-CoV-2 incidence change rapidly. The Sponsor obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organisation that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.

As of 21 February 2023, there have been greater than 757,000,000 confirmed COVID-19 cases globally. There were 272,814,122 (36.2%) cases in Europe and 189,963,466 (25.1%) in the Americas (WHO 2020). This equates to a cumulative total number of cases of 9443.9 per 100,000 persons globally (Worldometers.info 2023). Overall, 6,850,594 COVID-19 deaths have been confirmed globally, of which 2,190,646 (32.0%) and 2,927,208 (42.7%) occurred in Europe and the Americas, respectively (WHO 2020).

Estimates of COVID-19 incidence are heavily influenced by local testing practices, testing capacity, and reporting procedures (Backhaus 2020). For example, the extent to which mild and/or asymptomatic cases are missed in official case counts is likely to vary considerably according to the testing programme of the country or region. As a result, the accuracy of COVID-19 incidence recording is subject to considerable geographic and temporal variation. Given these limitations, reported numbers should be interpreted with caution as the number of confirmed COVID-19 cases likely reflect an underestimate of the actual incidence of COVID-19 cases.

As of 19 February 2023, the 14-day COVID-19 case notification rate was 99.0 per 100,000 for the European Union (EU)/European Economic Area (EEA) (ECDC 2023). The highest incidence rates per 100,000 in the EU/EEA in the same week were reported in Austria (705), Cyprus (322), Luxembourg (287), and Greece (226), while the lowest incidence rates were reported in Bulgaria (8.7), Norway (10.6), Hungary (17.4), and Sweden (17.9) (ECDC 2023). As of 22 February 2022, the 7-day COVID-19 case notification rate was 71.6 per 100,000 in the United States (US; CDC 2023).

Overall, the number of new cases per week in the EU/EEA peaked in January 2022 to March 2022 with the emergence and rapid spread of the Omicron variants in the EU/EEA. Thereafter, COVID-19 cases gradually declined over time.

On 24 February 2023, the global prevalence of COVID-19, defined as the number of active cases per 100,000 people, was 254.9 (Worldometers 2023). The prevalence of COVID-19 in Europe on the same date was 314.4 per 100,000. The highest prevalence rates (per 100,000) were reported for Gibraltar (11,066), Estonia (6,575), and Poland (2,530), while no active cases were reported for Vatican City. For the US and Canada, the prevalence rate was 442.8 and 98.5 cases per 100,000 persons, respectively (Worldometers 2023).

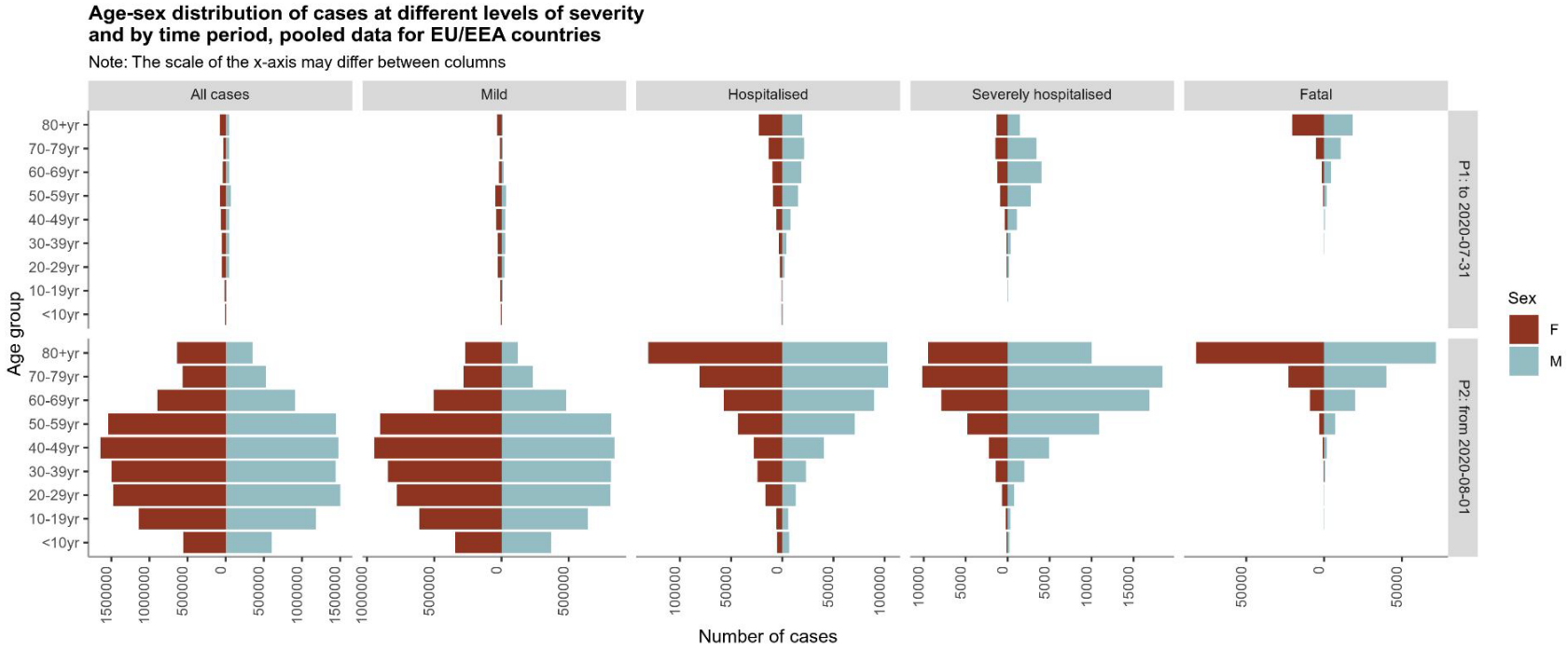
Demographics of the population in the proposed indication

Since the beginning of the pandemic, it has been clear that individuals of all ages are at risk of infection. However, knowledge of the demographics of the population is important to understand the transmission process and mortality due to COVID-19.

The ECDC has collected COVID-19 data from all EU/EEA member states, enabling the estimation of the age and sex distribution of COVID-19 cases overall and according to disease severity. Figure 1 shows surveillance data by age, sex, and disease severity updated on 04 November 2021. After this date, surveillance data were reported in a weekly report that does not include all age-based information and does not include sex-based information. According to Figure 1, the sex distribution of individuals testing positive for SARS-CoV-2 was similar across age groups in the EU/EEA. The majority of cases were among people aged between 20 and 59 years, but rates of COVID-19 hospitalisation and death were highest among males and older people.

COVID-19 case fatality rates (CFRs) have been consistently higher among men than women of all ages and across countries (Green 2021; Torres 2023). Among European countries reporting sex-disaggregated data, mortality rate ratios (M:F) were lowest in Latvia (1.1), France (1.1), and Lithuania (1.1) and highest in Denmark (3.1), Albania (2.2), and Montenegro (1.9; Global Health 2023).

Figure 1 Age and Sex Distribution of COVID-19 Cases Reported in TESSy at Different Levels of Severity as of 04 November 2021, EEU/EFF and the UK

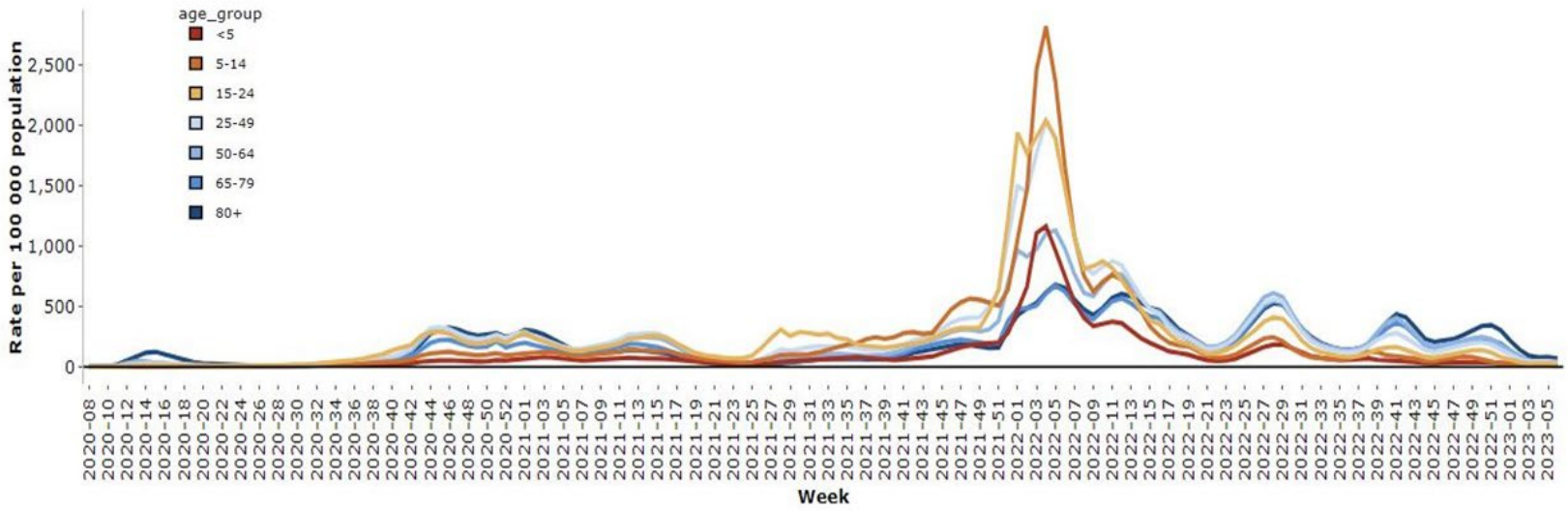


Abbreviations: COVID-19, Coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; EEU, Eurasian Economic Union; TESSy, the European surveillance system; UK, United Kingdom

Source: Data from ECDC 2021. COVID-19 Surveillance report. Week 43, 2021. 04 November 2021. "2.2 Age-sex pyramids." Accessed 26 March 2022

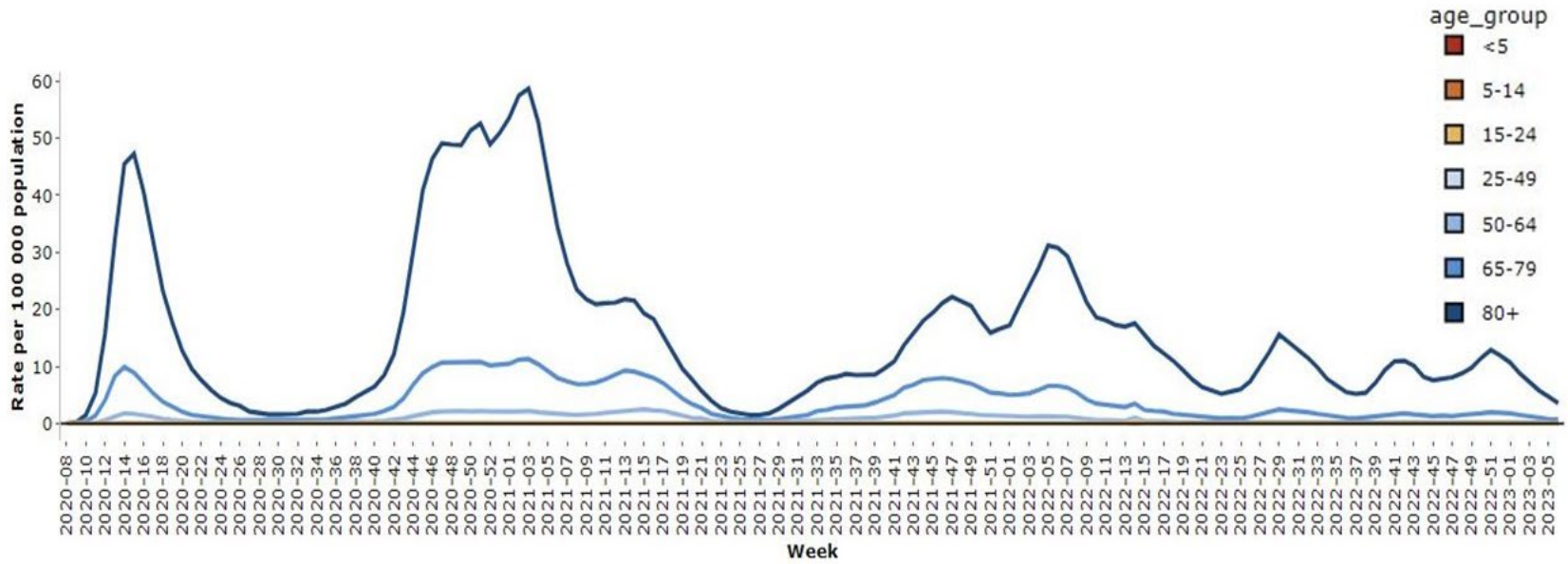
Figure 2 presents the trends in cases according to age up to February 2023. Rates per 100,000 persons were largely similar across age groups up until between December 2021 and March 2022 when the number of new cases was highest among people aged below 50 years. Thereafter, incidence rates were highest among older age groups. Mortality rates have consistently been highest among patients aged 80 years and above up until February 2023 (Figure 3). Between May 2022 and July 2022, mortality rates were similar according to age, a likely reflection of the rollout of vaccinations to older age groups initially.

Figure 2 Trends in New Confirmed COVID-19 Cases by Week Between February 2020 and February 2023



Abbreviations: COVID-19, Coronavirus disease 2019
Source: ECDC 2023

Figure 3 Trends in COVID-19 Deaths by Week Between February 2020 and February 2023



Abbreviations: COVID-19, Coronavirus disease 2019
Source: ECDC 2023

Main existing treatment options

As of 12 April 2023, 7 COVID-19 vaccines have been authorised for COVID-19 prevention in the EU, including Comirnaty (BioNTech and Pfizer), COVID-19 Vaccine Valneva, Nuvaxovid (Novavax), Spikevax (Moderna), Vaxzevria (AstraZeneca), Jcovden (Janssen), VidPrevtyn Beta (Sanofi Pasteur), and Bimervax (HIPRA Human Health; EMA 2023). Adapted versions of Comirnaty and Spikevax have also been approved in September 2022 and October 2022, respectively, as booster vaccinations to provide broader protection against different virus variants (Omicron BA.1 and Omicron BA.4-5).

An overview of the characteristics of the COVID-19 vaccines authorised in the EU is provided in Table 2 summarising the type of technology used to develop the vaccine ("Platform"), variant of virus the vaccine primarily targets, use for primary or booster vaccination, and the populations in which the vaccine is used (EMA 2023).

Table 2 Overview of the Characteristics of COVID-19 Vaccines Authorised in the European Union

Vaccine	Platform	Strain	Use	Population
Comirnaty (BioNTech/Pfizer)	mRNA	Original strain	Primary vaccination	≥6 months
			Booster	≥5 years
		Original strain + Omicron BA.1 variant (adapted)	Booster	≥12 years
		Original strain + Omicron BA.4-5 variant (adapted)	Booster	≥5 years
Spikevax (Moderna)	mRNA	Original strain	Primary vaccination	≥6 months
			Booster	≥6 years
		Original strain + Omicron BA.1 variant (adapted)	Booster	≥6 years
		Original strain + Omicron BA.4-5 variant (adapted)	Booster	≥6 years
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain	Primary vaccination	≥18 years
			Booster	≥18 years
Jcovden (Janssen)	Adenoviral vector	Original strain	Primary vaccination	≥18 years
			Booster	≥18 years
Nuvaxovid (Novavax)	Protein-based adjuvanted	Original strain	Primary vaccination	≥12 years
			Booster	≥18 years
COVID-19 Vaccine Valneva (Valneva)	Inactivated adjuvanted	Original strain	Primary vaccination	18-50 years
			Booster	18-50 years
VidPrevtyn Beta (Sanofi Pasteur)	Protein-based adjuvanted	Beta variant	Booster	≥18 years

Table 2 Overview of the Characteristics of COVID-19 Vaccines Authorised in the European Union

Vaccine	Platform	Strain	Use	Population
Bimervax (HIPRA Human Health)	Protein-based adjuvanted	Alpha and beta variants	Booster	≥16 years

Abbreviations: COVID-19, Coronavirus disease 2019; RNA, Ribonucleic acid
Source: Adapted From EMA 2023

The treatment of COVID-19 depends upon the stage and severity of disease, as well as upon the individual risks of developing severe COVID-19, such as age and comorbidities. Patients with mild illness usually recover on an outpatient basis with supportive care and isolation to prevent disease transmission. Antipyretics and analgesics (i.e., paracetamol and non-steroidal anti-inflammatory drugs) and antitussives are recommended for symptomatic therapy of fever, headache, myalgias, and cough (WHO 2022). Moderate illness requires monitoring for progression of symptoms and may require hospitalisation. Patients with severe COVID-19 symptoms may require supportive care and oxygen supplementation via non-invasive or mechanical ventilation (WHO 2022).

Table 3 summarises the non-vaccine medicines authorised for COVID-19 treatment in the EU as of November 2022 (EMA 2022a and EMA 2022b).

Monoclonal antibodies targeting the spike protein of the SARS-CoV-2 – Evusheld (tixagevimab / cilgavimab), Regkirona (regdanvimab), Ronapreve (casirivimab / imdevimab), RoActemra (tocilizumab), and Xevudy (sotrovimab) – are authorised to prevent the progression of the disease (e.g., hospitalisations and death) in patients at increased risk of developing severe COVID-19. In December 2022, however, European Medicines Agency's (EMA's) Emergency Task Force has cautioned that monoclonal antibodies targeting the Spike protein and currently authorised for COVID-19 may not be effective against emerging strains of SARS-CoV-2 (EMA 2022c). Recent laboratory studies showed that authorised monoclonal antibodies do not significantly neutralise BQ.1 and BQ.1.1, which are expected to become the dominant strains in the EU in early 2023 (EMA 2022c). Antiviral treatments such as Paxlovid (nirmatrelvir) and Veklury (remdesivir) with different mechanisms of action and not targeting Spike are expected to retain their activity against the emerging strains (EMA 2022c).

Another approved therapy includes Kineret (anakinra), an interleukin-1 receptor antagonist that reduces inflammation and is indicated in patients at risk of developing severe respiratory failure.

Additionally, Lagevrio (molnupiravir) is currently under CHMP's evaluation for COVID-19 treatment and can already be used in the EU to treat COVID-19 following review under Article 5(3) (EMA 2022d).

The use of systemic corticosteroids is recommended for treatment of patients with COVID-19 requiring oxygen, while use of corticosteroids is not recommended for patients with mild COVID-19 infections (WHO 2022).

Table 3 Non-vaccine Treatments Authorised in the European Union to Treat COVID-19 Following Evaluation by the EMA

Name	Producer	Type of Drug	Marketing Authorisation Granted	Target Population
Regkirona (regdanvimab)	Celltrion	monoclonal antibody	12/11/2021	Patients at increased risk of developing severe COVID-19
Kineret (anakinra)	Swedish Orphan Biovitrum AB	immunosuppressant	17/12/2021	Patients with pneumonia requiring supplemental oxygen; patients at risk of developing severe respiratory failure
Paxlovid (PF-07321332, ritonavir)	Pfizer	antiviral	28/01/2022	Patients at increased risk of developing severe COVID-19
Evusheld (tixagevimab / cilgavimab)	AstraZeneca	monoclonal antibody	25/03/2022	Patients at increased risk of developing severe COVID-19
Veklury (remdesivir)	Gilead	viral RNA polymerase inhibitor	08/08/2022	Patients with pneumonia requiring supplemental oxygen; patients at increased risk of developing severe COVID-19
Ronapreve (casirivimab / imdevimab)	Roche	monoclonal antibody	12/11/2022	Patients at increased risk of developing severe COVID-19
RoActemra (tocilizumab)	Roche	monoclonal antibody	07/12/2022	Patients with severe COVID-19 treated with corticosteroids and requiring supplemental oxygen
Xevudy (sotrovimab)	GSK	monoclonal antibody	17/12/2022	Patients at increased risk of developing severe COVID-19

Table 3 Non-vaccine Treatments Authorised in the European Union to Treat COVID-19 Following Evaluation by the EMA

Name	Producer	Type of Drug	Marketing Authorisation Granted	Target Population
Lagevrio (molnupiravir)[a]	Merck; Ridgeback Therapeutics	antiviral	12/14/2021[b]	Patients at increased risk of developing severe COVID-19

Abbreviations: COVID-19, Coronavirus disease 2019; EMA, European Medicine Agency; RNA, ribonucleic acid

a Marketing authorisation application submitted.

b This medicine can be used in the EU to treat COVID-19 after CHMP review under Article 5(3).

Source: Adapted from EMA 2022a

Natural history of COVID-19

SARS-CoV-2 is transmitted from human to human via respiratory droplets, direct contact, or through airborne transmission in enclosed places. Factors such as physical proximity to others and poor ventilation in closed spaces, working within close proximity to other people, and being a resident of long-term care facilities and nursing homes can increase a person's risk of initial infection (Bouffanais 2020). The COVID-19 incubation period may last up to 14 days from exposure, though the estimated median time from exposure to symptom onset ranges from 4 to 6 days (McAloon 2020; Dhouib 2021; Alene 2021).

Symptoms, Severity and Progression

The severity and frequency of symptoms of COVID-19 infection vary by SARS-CoV-2 variant and patient characteristics, including vaccination status (Whitaker 2022; Menni 2022). The clinical manifestation of COVID-19 can vary from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome, critical illness, and death. Up to 50% of cases do not develop clinical symptoms, though this proportion decreases considerably with patient age and in patients with comorbidities (Sah 2021; Syangtan 2021). In children and young people, an estimated 14.6% to 42% of cases are asymptomatic (Viner 2021).

The majority of COVID-19 cases are mild, typically defined as the absence of pneumonia. In mild symptomatic cases, the most common symptoms include dry cough, fever, and fatigue (Grant 2020). Other symptoms include chills, sore throat, headaches, appetite loss, anosmia, and ageusia (Whitaker 2022; Menni 2022). In children and young people under age 20 years, a systematic review found that fever occurred in 46% to 64.2% of cases and cough occurred in 32% to 55.9% of cases, while all other symptoms were present in less than 20% of cases (Viner 2021).

In the majority of mild cases, patients are typically advised to self-isolate at home and manage the symptoms with over-the-counter medicines. However, patients with initially mild symptoms may progress to critical illness and require hospitalisation within one week (Kartsonaki 2021). Among 439,922 hospitalised COVID-19 patients recruited from 49 countries by The International Severe Acute Respiratory and Emerging Infections

Consortium (ISARIC), the median time from symptom onset to admission was 2 (interquartile range: 7) days (Kartsonaki 2021). In England, 2.42% of 1,067,859 confirmed Omicron COVID-19 cases and 3.28% of 448,843 confirmed Delta COVID-19 cases required any hospital attendance, including admissions and accident and emergency visits (Nyberg 2022).

Although the majority of COVID-19 patients (around 80%) will experience non-severe disease, 15% will have severe disease (oxygen saturation <90%, pneumonia, severe respiratory distress) and 5% will have critical disease (acute respiratory distress syndrome, sepsis, septic shock, or other conditions requiring life-sustaining therapies such as mechanical ventilation or vasopressor therapy; Long 2022).

The most common complications of severe COVID-19 include cardiac, neurologic, gastrointestinal, and dermatologic complications (Long 2022). Of cardiac complications, dysrhythmias, acute coronary syndrome, heart failure, and myocarditis are present in over 20% of patients admitted to the intensive care unit. Around 80% of COVID-19 patients experience some form of neurologic complications, ranging from headache and dizziness (40% of patients), change in taste or smell (80%) to seizure, encephalopathy, and cerebral ischemia (Lechien 2020). Gastrointestinal symptoms are also common (more than 30%), including nausea and vomiting (more than 60%), loss of appetite (40%), diarrhoea (50%), and abdominal pain (10%). Complications such as acute liver injury, cholecystitis, pancreatitis, ileus, pseudo-obstruction, and mesenteric ischemia may occur in patients with critical disease (Silva 2020). Haematologic complications (i.e., venous thromboembolic events, including pulmonary embolism) are common, especially in patients with critical disease (Klok 2020). Finally, dermatologic complications are less common (0.4% to 20% of cases), including erythema livedo reticularis, vesicular eruptions, maculopapular lesions, and areas of thickened erythema resembling chilblains (Recalcati 2020). In a systematic review of 44 peer-reviewed studies with 14,866 hospitalised COVID-19 patients, an estimated 18.5% required invasive-mechanical ventilation, 15% developed acute cardiac injury, and 14% developed acute respiratory distress syndrome (Potere 2020). However, most of these studies were conducted early in the pandemic before specific treatments were available.

The severity of COVID-19 varies according to the SARS-CoV-2 variant. In a large US prospective study, the Delta variant was associated with the most severe disease, followed by the Alpha variant and then the Omicron variant among unvaccinated adults admitted to hospital with COVID-19 (Lauring 2022).

Mortality

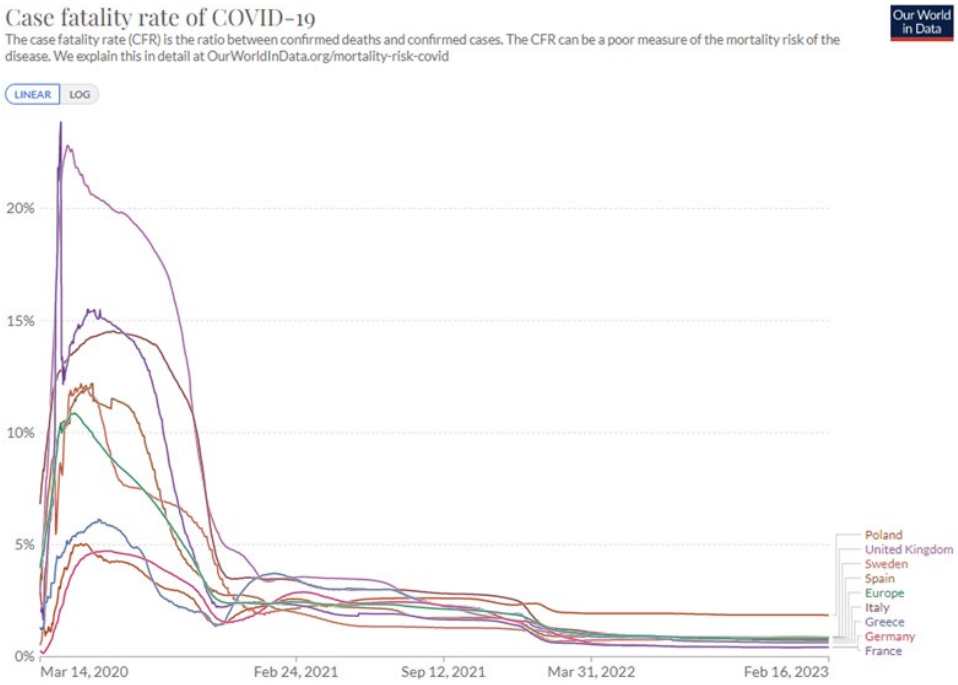
As of 21 February 2023, there were 272,539,330 confirmed cases and 2,188,301 confirmed deaths in the European Region (WHO 2020), with 537 newly reported deaths in the last week of that reporting period.

Reported measures of mortality vary geographically due to differing population demographics, mitigation responses, healthcare facilities, and vaccination rates (Mattiuzzi 2021). The United Kingdom (UK) is the country with the highest number of COVID-19 deaths in Europe (excluding the Russian Federation), with over 205,540 deaths as of 16 February 2023. Italy (187,551 deaths), Germany (167,124 deaths), and France (160,982 deaths) were also among the countries with the most deaths in Europe (WHO 2020).

On average, the COVID-19 mortality since the beginning of the pandemic has been of 2,141 deaths per million people in Europe (WHO 2020). The mortality rates were higher in Eastern Europe; Bulgaria, Bosnia and Herzegovina, and Hungary were the countries with a greater number of deaths per million people (more than 5,400, 4,900, and 4,900 per million, respectively). Germany, Italy, France, Spain, and the UK each had a mortality rate between 2,000 and 3,000 per million people, while the mortality rates in Northern European Countries (excluding the UK) have been below 2,000 per million people (WHO 2020).

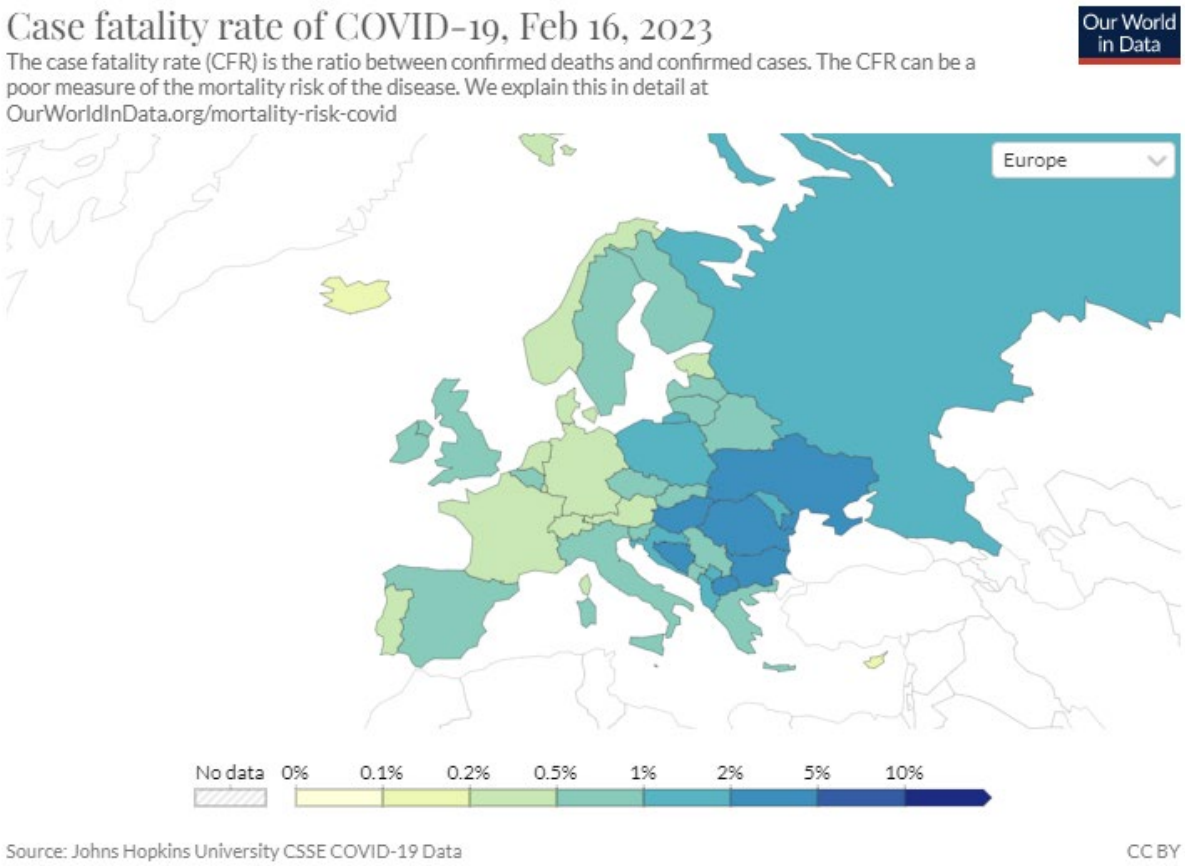
The CFR, defined as the ratio between the confirmed deaths and confirmed cases, varied temporally from the initial stages of the pandemic in 2020 to the beginning of 2023 (Figure 4) mainly because of different testing capacity during the early period of the COVID-19 pandemic, although evolution of treatment protocols as experience of disease management grew and availability of specific treatments likely also contributed. Another major factor that has influenced the CFR is the introduction of COVID-19 vaccines in late 2020. For example, Switzerland had fully vaccinated 68.8% of its population by November 2022. The peak of death rates was registered during December 2021. For unvaccinated, fully vaccinated without booster populations, and fully vaccinated with booster, the death rates were around 11, 2, and 0.3, respectively (Our World in Data 2023). The CFR dropped from over 10% on average in Europe in April 2020, with peaks > 20% in France and UK, to < 2% in early 2023.

Figure 4 Case Fatality Rate of COVID-19 in Europe



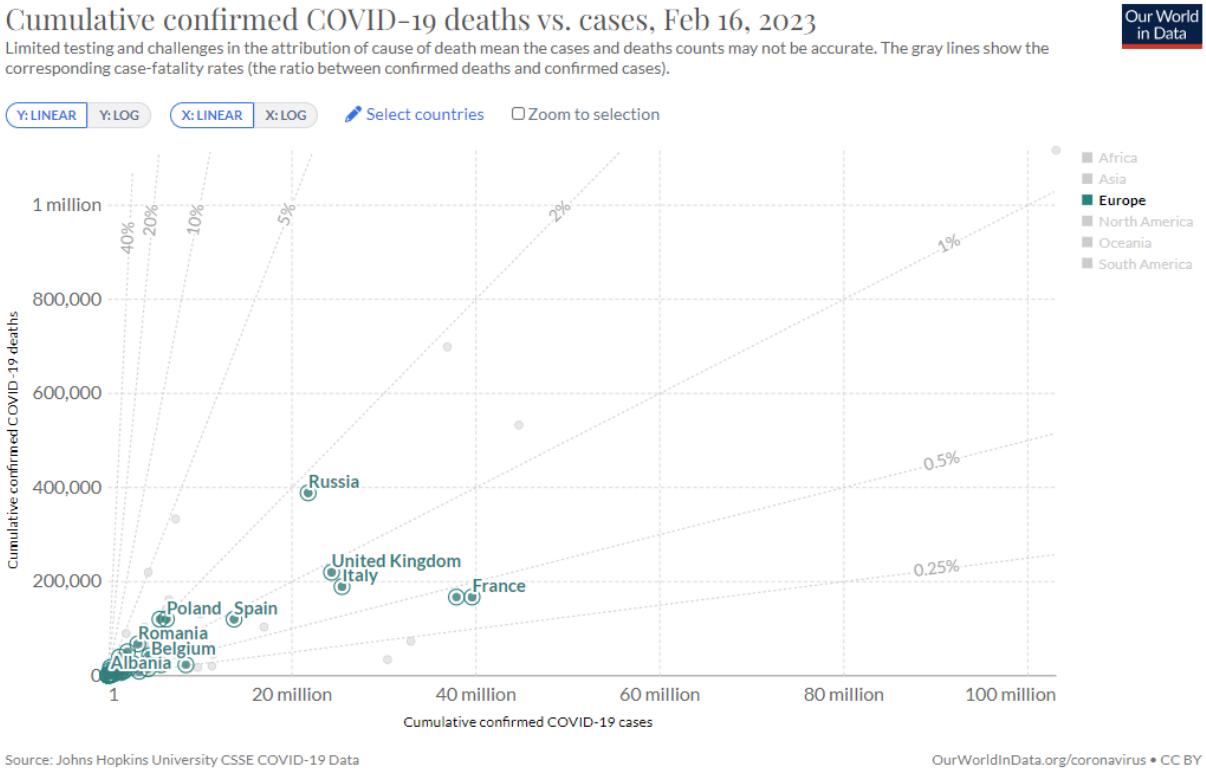
Abbreviations: COVID-19, Coronavirus disease 2019
Source: Our World in Data 2023a, Accessed 16 February 2023.
As of 16 February 2023, the CFR is ~0.8 % on average across Europe, with geographical variability ranging from 0.1% in Iceland to 4% in Bosnia and Herzegovina (Our World in Data 2023a, Figure 4, Figure 5, and Figure 6). Overall, the COVID-19 CFR was inversely associated with the number of available general hospitals, physicians, and nurses, across European countries (Mattiuzzi 2021).

Figure 5 Case Fatality Rate of COVID-19 in Europe as of 16 February 2023



Abbreviation: COVID-19, Coronavirus disease 2019
Source: Our World in Data 2023a, Accessed 16 February 2023.

Figure 6 Cumulative Confirmed COVID-19 Deaths vs. Cases as of 16 February 2023



Abbreviations: COVID-19, Coronavirus disease 2019
Source: Our World in Data 2023a, Accessed 16 February 2023.

A recent German study reported that mortality among 561,379 hospitalised patients was 17% overall and 33% in intensive care units (Kloka 2022). Overall mortality rates peaked in April 2020 and January 2021 (21.2% and 23.0%, respectively; Kloka 2022). Crude mortality rates between 15.8% and 23.7% were observed among hospitalised COVID-19 patients during the first 3 waves of the epidemic in Italy (Giacomelli 2022). However, mortality rates for COVID-19 patients are declining over time, most likely due to a greater understanding of COVID-19 and its treatment, widespread vaccination and variants associated with milder illness (Gray 2021; Iuliano 2022).

Long-term complications of COVID-19

Various terms and definitions (‘post-acute COVID-19’ [from 3 to 12 weeks] and ‘chronic COVID-19’ for symptoms extending beyond 12 weeks) have been used to describe signs and symptoms that continue or develop after acute COVID-19 (Greenhalgh 2020). However, the term ‘long COVID’ is commonly used and includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Recent evidence indicates that the risk of post-COVID-19 syndrome has decreased according to strain (46% for original strains, 35% for Delta, and 14% for Omicron strains), though this may partly be explained by widespread vaccine deployment (Willan 2023).

Both adults and children experience symptoms beyond the duration of acute COVID-19 illness (> 4 weeks). Evidence shows that adults experience fatigue (51%), dyspnoea (38%), cough (28%), sleep disturbances or difficulties (36%), anxiety or depression (22%), hair loss (22%), cognitive impairment (24%), and difficulty concentrating (25%). A systematic review of 31 articles showed that after recovery, COVID-19 patients aged 18 to 49 years' experience persistent fatigue (39% to 73% of assessed persons), breathlessness (39% to 74%), decreased quality of life (44% to 69%), impaired pulmonary function, abnormal clinical findings including pulmonary fibrosis (39% to 83%), evidence of pericarditis/myocarditis (3% to 26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5% to 3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33% to 36%; Willi 2021).

Children (aged ≤ 18 years) experience symptoms such as lack of concentration, short-term memory loss, and/or difficulty doing everyday tasks (NICE 2022). A cohort study composed of 171 children found that 8% of children had long COVID-19 symptoms, including post-viral cough (4%) for a period of 3 to 8 weeks, fatigue (2%) for 6 to 8 weeks, or both post-viral cough and fatigue (1%; Say 2021).

Important comorbidities

The presence of comorbidities is an important factor associated with the severity of COVID-19. In a meta-analysis of 88 cohort studies with data on 6,653,207 patients in the hospital setting, comorbidities were inclusive of diabetes, obesity, hypertension, history of heart failure, ischaemic heart disease, cancer, chronic obstructive pulmonary disease, chronic respiratory disease, chronic kidney disease, and neurological conditions (ECDC 2023; Vardavas 2022).

Table 4 summarises the prevalence of comorbidities among COVID-19 patients in the EU/EEA. Irrespective of the disease severity, the most common comorbidities are inclusive of cardiac disorder, diabetes, cancer, and chronic lung disease excluding asthma.

Table 4 Preconditions Among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 4 November 2021

	EU/EEA, reported on 12 August 2021			
	Mild (%)	**Hospitalised (%)**	**Severe (%)**	**Fatal (%)**
Total, N	2,196,678	368,145	54,504	118,934
None	76.1	37.3	31.6	24.5
Cardiac disorder, excluding hypertension	9	24.3	23.5	31
Diabetes	5.1	16.3	20.1	18.6
Cancer, malignancy	3.1	8.3	9.6	10.7
Chronic lung disease, excluding asthma	1.8	3.6	4.3	3.6
Current smoking	0.9	0.1	0.2	0.1
Asthma	0.9	1.3	1.4	1.1

Table 4 Preconditions Among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 4 November 2021

	EU/EEA, reported on 12 August 2021			
	Mild (%)	**Hospitalised (%)**	**Severe (%)**	**Fatal (%)**
Hypertension	0.8	2.9	3.2	3.7
Neuromuscular disorder, chronic neurological	0.8	1.8	1.4	2.4
Other endocrine disorder (excluding diabetes)	0.4	0.2	0.1	0.1
Kidney-related condition, renal disease	0.3	1.7	1.9	2.6
Liver-related condition, liver disease	0.3	0.6	0.7	0.6
Obesity	0.3	0.4	1.1	0.3
HIV / other immune deficiency	0.2	0.7	0.7	0.5
Rheumatic diseases including arthritis	0.1	0.1	0.1	0
Haematological disorders	0	0.2	0.1	0.1
Tuberculosis	0	0	0	0
Asplenia	0	0	0	0

Abbreviations: COVID-19, Coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; TESSy, The European surveillance system

Source: ECDC 2021. COVID-19 Surveillance report. Week 43, 2021. 4 November 2021 (b). "3 Risk - groups most affected. 3.1 Preconditions: frequency distribution by severity". https://COVID19-surveillance-report.ecdc.europa.eu.

A Swedish study found that unvaccinated cases and those who received only 1 vaccine dose were similar with respect to comorbidities during the Delta and Omicron period, while vaccinated cases (with more than one dose) during the Omicron period had fewer comorbidities than during the Delta period. Some of the comorbidities were inclusive of cardiovascular diseases, diabetes or obesity, kidney or liver diseases, respiratory diseases, neurological diseases, and cancer or immunosuppressed states (Kahn 2022).

In conclusion, people with comorbidities, such as cardiac disorder, diabetes, cancer, chronic lung diseases (excluding asthma), neuromuscular disorder, seizure disorder, kidney-related condition, obesity, and an immunocompromised status are classified as a high-risk population who are more likely to be hospitalised when infected with SARS-CoV-2 and a priority population for COVID-19 vaccination.

Of cases in community settings, a history of heart failure, stroke, diabetes, and end-stage renal disease are risk factors for mortality (ECDC 2023).

PART II: MODULE SII – NONCLINICAL PART OF THE SAFETY SPECIFICATION

Arcturus has developed several self-amplifying mRNA (sa-mRNA) lipid nanoparticle (LNP)-based COVID-19 (LUNAR®-COV19) vaccines. ARCT-021 was a COVID-19 first-generation vaccine candidate, which encoded the SARS-CoV-2 spike protein in its native conformation (Wuhan strain, hereafter called ancestral strain). This vaccine has been tested in Phases 1/2 and 2 clinical trials in Singapore and US. Subsequent to this vaccine starting clinical trials in humans, emerging research showed that the prefusion-stabilised spike protein was more immunogenic than the native conformation (Pallesen 2017; Kirchdoerfer 2016). Arcturus therefore advanced ARCT-154, encoding a prefusion-stabilised spike protein, into clinical trials using the nonclinical and clinical data from ARCT-021. The drug substances of ARCT-021 and ARCT-154 (mRNA-2002 and mRNA-2105, respectively) consist of a self-replicating mRNA replicon. The mRNA of both vaccines is composed of a single-stranded 11.860 kb mRNA consisting of a 5' cap, a 5' untranslated region (UTR), the reading frame of replicase, the transgene UTR, the reading frame of the transgene encoding for the primary structure of the full-length SARS-CoV-2 spike glycoprotein, the 3′ UTR, and the poly-A tail. The open-reading frames code for 4 replicase proteins, derived from Venezuelan equine encephalitis virus (VEEV), expressed within the replicase region (nonstructural protein [nsp1, nsp2, nsp3, and nsp4]), and the transgene region, which encodes for the SARS-CoV-2 spike glycoprotein. The spike glycoprotein is divided into 2 domains, S1 and S2. The angiotensin-converting enzyme 2 (ACE2) receptor-binding domain (RBD) is encoded within the S1 domain. The S2 domain encodes for the intracellular fusion domain, a transmembrane domain, and a cytoplasmic domain. After LNP-mediated RNA entry into the cytoplasm, the replicase is translated and produces minus- and plus-strand copies of the original mRNA drug substance as well as drives transcription of the encoded SARS-CoV-2 spike glycoprotein, which is subsequently translated by cellular machinery.

Nonclinical evaluation of Kostaive was supported by preclinical pharmacology studies, including viral challenge studies, tissue distribution studies, and nonclinical safety studies conducted with ARCT-021 and ARCT-154, both similar LNP sa-mRNA COVID-19 vaccines that encodes for a different SARS-CoV-2 spike glycoprotein. The major changes to the mRNA sequence of Kostaive were made to improve translation efficiency and immunogenicity of the encoded spike glycoprotein. As the changes made to the mRNA of Kostaive versus ARCT-021 or ARCT-154 are not substantial and only constitute a change of antigen within the same platform, the nonclinical safety study of ARCT-154 and the nonclinical safety studies supporting clinical development of ARCT-021 also fully support the development of Kostaive. This strategy is consistent with the platform approach described as follows:

- By the US Food and Drug Administration in Guidance for the Development and Licensure of Vaccines to Prevent COVID-19 (FDA 2020), and
- By the WHO in Evaluation of the Quality, Safety and Efficacy of Messenger RNA Vaccines for the Prevention of Infectious Diseases: Regulatory Considerations (WHO 2021).

Standalone safety pharmacology studies were not conducted. Pharmacology (immunogenicity) and tissue distribution studies in mice evaluating the distribution and clearance of the vaccine components, 2 good laboratory practice (GLP) repeat-dose local tolerability/reactogenicity toxicity studies in rabbits, and a GLP fertility, embryofoetal, and postnatal development study conducted in rabbits have been completed with ARCT-021. A GLP repeat-dose local tolerability/reactogenicity toxicity study has also been conducted with Kostaive. Nonclinical pharmacology studies in mice and nonhuman primates have been conducted with Kostaive and another LNP-replicon COVID-19 vaccine, ARCT-165. The New Zealand White rabbit was chosen as the toxicology species as they are commonly used for vaccines.

Primary preclinical pharmacology studies for ARCT-154 are listed in Table 5. Secondary pharmacology studies for ARCT-021 are summarised in Table 6.

Table 5 Tabular Listing of Primary Pharmacology Studies for ARCT-154

Type of Study	Species/ Strain	Method of Administration	Doses/ Concentrations	Sex/ No. per Group	Noteworthy Findings	Study Number
Immunogenicity	Mouse/ (BALB/c)	IM	2 mcg	Female/5	ARCT-154 showed higher receptor-binding inhibition to the ancestral strain and Alpha (B.1.1.7) variant spike glycoprotein compared to Beta (B.1.351) and Gamma (P.1) variants by Day 14 post-vaccination.	ARC21-032
Immunogenicity	Cynomolgus Macaque	IM	7.5 mcg	Males/4	ARCT-154 produced higher receptor-binding inhibition to ancestral strain and Alpha variant compared to Beta and Gamma variants by Day 14 and Day 28. Equivalent receptor-binding inhibition to the ancestral strain and all variants was observed 14 days after second vaccination.	ARC 21-036

Abbreviations: BALB/c, bagg albino; IM, intramuscular; No., number.

Table 6 Tabular Listing of Secondary Pharmacology Studies for ARCT-021

Type of Study	Species/ Strain	Method of Administration	Doses/ Concentrations	Sex/ No. per Group	Noteworthy Findings	Study Number
Transcriptomics	Mouse / C57BL/6	IM	0.2 mcg, 2.0 mcg, 10 mcg	Female/4	At Day 1, genes in the Type-I IFN pathways were the most highly expressed in animals injected with ARCT-021 when compared with conventional RNA or PBS. Genes associated with the inflammatory response were mostly downregulated following ARCT-021 vaccination when compared with conventional RNA or PBS. At Day 7, immune gene expression showed clear differences after ARCT-021 vaccination when compared with PBS control. No difference was observed between animals vaccinated with conventional RNA and PBS.	GSY02
Immunogenicity	Mouse / C57BL/6	IM	0.2 mcg, 2.0 mcg, 10 mcg	Female/5	Dose-dependent increase in $CD8^+$ T cells and balanced Th1 $CD4^+$-helper cell immune response. ELISpot results support high percentage of spike-glycoprotein-specific T cells. Transcriptomic analysis of blood Day 1 post-vaccination shows a lack of systemic inflammatory response.	ARC-02
Immunogenicity	Mouse / C57BL/6	IM	0.2 mcg, 2.0 mcg, 10.0 mcg	Female/5	ARCT-021 elicited an RNA-dose-dependent IgG response following the first dose that lasted up to Day 60 (one month after the second dose) whereas the comparator conventional (i.e., non-self-replicating) mRNA elicited a lower IgG response that plateaued at Day 10.	ARC-03
Immunogenicity	Mouse/ BALB/c	IM	0.2 mcg, 2.0 mcg, 10.0 mcg	Female/5	ARCT-021 vaccine anti-spike glycoprotein IgG response peaked 40 to 60 days post-vaccination whereas anti-S IgG titre from traditional mRNA vaccine was lower and peaked at Day 10 after single vaccination. Neutralising	ARC20-086

Table 6 Tabular Listing of Secondary Pharmacology Studies for ARCT-021

Type of Study	Species/ Strain	Method of Administration	Doses/ Concentrations	Sex/ No. per Group	Noteworthy Findings	Study Number
					antibody titres continued to increase up to Day 60. IgG antibody binding to S1, S2 and RBD of spike glycoprotein was higher for ARCT-021 than traditional mRNA vaccine. Increased anti-S IgG avidity to S compared to mRNA vaccine. Day 30 endpoint titres for ratio of anti-S IgG2a/anti-Sgp IgG1 was >1 indicative of Th1 immune response.	
Viral Challenge	Mouse / K18-hACE2	IM	2 mcg, 10 mcg	Female/5	Vaccination with ARCT-021 provided clearance of SARS-CoV-2 from lung and brain when compared with unvaccinated animals. Vaccination at both doses resulted in complete protection against a lethal SARS-CoV-2 infection.	GSY03
Immunogenicity	Rhesus Macaque	IM	5 mcg, 20 mcg	Female/5	Required 2 vaccinations 28 days apart to observe dose-dependent neutralising antibody titres. Additional increase in neutralising antibody titres obtained with boost vaccination 120 days after second prime vaccination. T cells observed after single vaccination. Further increase observed 30 days after second prime vaccination and peaked at Day 90 post-vaccination.	ARC20-123
Viral Challenge	Rhesus Macaque	IM	Single prime vaccination 20 mcg 40 mcg	Female/12	Neutralising antibody titres were only observed after the second vaccination of the 5-mcg and 20-mcg RNA doses, and 7 days after virus challenge for the 20-mcg and 40-mcg RNA doses. A 3-log reduction in virus genomes in lungs for the 5-mcg and 20-mcg 1 day after virus challenge. No detectable virus was observed 3 days post-challenge for 20 mcg and 5 days post-challenge for 5 mcg. A 1.5-log reduction in virus genomes was observed for	B05864
			2 × prime vaccinations 28 days apart	Male/12		

Table 6 Tabular Listing of Secondary Pharmacology Studies for ARCT-021

Type of Study	Species/ Strain	Method of Administration	Doses/ Concentrations	Sex/ No. per Group	Noteworthy Findings	Study Number
			5 mcg 20 mcg		the 20-mcg and 40-mcg RNA single vaccinations 1 day post-challenge and increased to 3 logs by Day 7 post-challenge for the 20-mcg RNA single vaccination.	
Immunogenicity	Mouse	IM	0.2 mcg, 2 mcg	Female/5	Anti-SARS-CoV-2 spike protein IgGs were detected in serum in a time- and dose-dependent manner for both liquid and lyophilized ARCT-021; PBS did not elicit an immunogenic response. For the 2-mcg comparison, no statistically significant differences were observed, demonstrating that liquid and lyophilized drug products were comparable.	ARC20-212

Abbreviations: ACE2, angiotensin-converting enzyme 2; BALB/c, bagg albino; ELISpot, enzyme-linked immune absorbent spot; IgG, immunoglobulin G; IM, intramuscular; mRNA, messenger RNA; No., number; RBD, receptor-binding domain; Sgp, spike glycoprotein.

Key safety findings from nonclinical studies and relevance to human usage

Tissue Distribution

The tissue distribution of the replicon mRNA, the novel ATX-126 lipid, and the SARS-CoV-2 S glycoprotein were analysed following a single intramuscular (IM) vaccination in mice and from a limited set of tissues from the GLP 4-week toxicity study of ARCT-021 in rabbits. Additionally, the concentration of replicon mRNA and ATX-126 were also determined in the placenta and foetal tissue from the GLP fertility, embryofoetal, and postnatal development study in rabbits.

Following a single IM administration of 25 mcg or 50 mcg of ARCT-021 (replicon mRNA dose) in mice, plasma and tissues, including liver, kidney, spleen, brain, heart, lung, inguinal and popliteal lymph nodes (LN), ovaries, testes, and site of injection (rectus femoris muscle) were evaluated at various time points up to 31 days post dose to characterise the distribution and clearance of replicon mRNA, ATX-126, and the SARS-CoV-2 S glycoprotein. Replicon mRNA was detected in plasma and all tissues at 2 hours post dose (earliest time point evaluated) and cleared from all tissues by Day 31 except for the muscle where, at Day 31 post dose, it was detected at very low concentrations for the 25-mcg dose group, and muscle and popliteal and inguinal LN for the 50-mcg dose. The presence of replicon mRNA in the LN and spleen could be the result of systemic exposure as it was detected in the plasma but could be also due to trafficking of immune cells from the site of administration of the vaccine. The overall tissue concentrations of the replicon mRNA based on average male/female maximum concentration (C_{max}) values for 25 mcg and 50 mcg doses were muscle > inguinal LN > popliteal LN > spleen > liver > heart > ovary ≈ lung > kidney > testes > brain.

ATX-126 lipid was detected in all plasma and tissues at the earliest time point (2 hours post dose) but was detected only at very low concentrations in 1 sample of the brain at 50 mcg and was not detected at all at 25 mcg. The highest concentrations were observed in the inguinal LN and muscle, followed by the popliteal LN, with the other tissues having substantially lower concentrations ranging from 10-fold lower (liver) to 300-fold lower (testes). The overall tissue concentrations based on average male/female C_{max} values were inguinal LN >/≈ muscle >/≈ popliteal LN > liver > spleen ≈ ovary > testes ≈ lung ≈ kidney ≈ heart.

ATX-126 was detected at very low concentrations in all tissues (except the brain) by Day 31 post dose. For both the 25 and 50 mcg doses, most of the tissues contained <1% of the administered dose by Day 31 post dose, except the muscle and liver, which had an average of 3% and 4% respectively for the 25 and 50 mcg doses.

The highest concentrations of the SARS-CoV-2 S glycoprotein were observed in the muscle, the target tissue, with very low concentrations detected in the lung and ovaries, which cleared by Day 15 except in the LN, where it could have been introduced by immune cell trafficking rather than by transduction of the mRNA in the tissue. The transient expression of the SARS-CoV-2 S glycoprotein is sufficient to stimulate a potent neutralising antibody response. While replicon mRNA, ATX-126, and the SARS-CoV-2 S glycoprotein were detected in other tissues besides the muscle, no ARCT-021 histopathology effects were observed in these tissues in 2-week and 4-week GLP repeat-dose ARCT-021 toxicology studies in rabbits.

The tissue concentrations of replicon mRNA and ATX-126 were also evaluated in rabbits following repeat dosing (3 biweekly vaccinations, Days 1, 15, and 29) of ARCT-021 at doses of 20 mcg and 40 mcg (dose of replicon mRNA) in plasma and a panel of the following tissues: brain, heart, liver, kidney, lung, spleen, injection site (muscle, 2 of the 4 injection sites), mesenteric LNs, ovaries, and testes for ATX-126; and liver, lung, spleen, injection site (muscle), mesenteric LNs, and ovaries for replicon mRNA obtained from the 4-week repeat-dose toxicity study in rabbits. Samples were taken at each of the respective necropsies on Study Days 31 (Main Cohort) and 57 (Recovery Cohort). There were 4 sites of injection for the muscle, but only 2 of the 4 injection sites were analysed for replicon mRNA and ATX-126.

Replicon mRNA was not detected in the muscle, mesenteric LN, ovary, liver, or lung at Day 31 and Day 57 (except in 1 sample out of 10 muscle samples which had very low replicon mRNA concentrations at Day 31). Replicon mRNA was detected at low concentrations in the spleen at Day 31 from both dose groups. ATX-126 was detected in a dose-dependent manner in the plasma (Day 31 only), liver, ovaries, spleen, injection site (muscle), and mesenteric LNs (one animal in the 40-mcg dose group on Day 31) but was not detected in the kidney, heart, lung, brain, or testes. The SARS-CoV-2 S glycoprotein was not detected in any tissue.

Note that the tissue concentrations of ATX-126 observed in both the mice and the rabbits overestimate the amount of ATX-126 that an individual will receive with an annual vaccine. For both studies, animals were dosed on an absolute basis relative to the human dose and, as such, the tissue distribution and clearance of the mRNA-2002 and ATX-126 is not likely to be representative of human organ exposure because translation of systemic exposure to LNP-mRNA therapeutics from animals to humans is typically performed on a mg/kg basis rather than based on the absolute dose administered. For the 25-mcg mouse dose, each mouse received 525 mcg (equivalent to ~21 mg/kg) of ATX-126 lipid. For a vaccine dose of 5 mcg, each person will receive approximately 105 mcg of ATX-126 lipid, which is equivalent to 1.5 mcg/kg of ATX-126 (assuming a 70-kg human body weight). Thus, with each annual vaccine, a person will receive 14,000-fold less ATX-126 lipid compared with what the mouse received (assuming a 0.02 kg mouse body weight), corrected on a mg/kg basis.

Likewise, to translate the tissue distribution data from the 4-week GLP repeat-dose toxicology study in rabbits to humans, note that the rabbits received 3 biweekly vaccinations, whereas the vaccine will be administered as an annual boost. For the 20-mcg rabbit dose, each rabbit received 420 mcg of ATX-126 (equivalent to 127 mcg/kg, assuming an average rabbit weight of 3.3 kg). Using the 0.32 conversion factor for rabbit dose to human equivalent dose outlined in the US Food and Drug Administration guidance on maximum safe starting doses (FDA 2005), the human equivalent dose would be 41 mcg/kg. For the 5-mcg annual vaccine dose, each person will receive 105 mcg of ATX-126 in each dose, which is equivalent to 1.5 mcg/kg (assuming a 70 kg human body weight). Thus, the study provides a safety margin of 27 (41 mcg/kg/1.5 mcg/kg).

The placental and foetal concentrations of replicon mRNA and ATX-126 were also evaluated in samples taken at Caesarean section gestation days (GDs) 0, 14, and 28 from rabbits in the GLP rabbit fertility, embryofoetal, and postnatal development study following the IM administration of 10 or 20 mcg of ARCT-021 (dose of mRNA) 28 days before mating (Day 1

of Study [DS 1]), 14 days prior to mating (DS 15) and GDs 0, 14, and 28. Replicon mRNA was not detected in the foetal tissues or placenta in samples (taken at Caesarean section on GD 28) in the GLP rabbit fertility, embryofoetal, and postnatal development study following the IM administration of 10 or 20 mcg of ARCT-021 (dose of mRNA) 28 days before mating (DS 1), 14 days prior to mating (DS 15) and GDs 0, 14, and 28, but was detected at low concentrations in 2 of 42 maternal plasma samples from the 10-mcg dose group, and in 3 of 43 maternal plasma samples in the 20-mcg dose group. Low concentrations of replicon mRNA were detected in 1 of 20 foetal plasma samples in the 10-mcg dose group. ATX-126 was not detected in the foetal plasma or foetal tissues from any dose group but was detected in the placenta and maternal plasma in the 10 mcg and 20 mcg ARCT-021 dose groups.

Repeat-dose Toxicity Studies

ARCT-021 was well tolerated with no adverse effects in a 2-week (IM vaccination on Days 1 and 15) GLP repeat-dose toxicology study and a 4-week (IM vaccination on Days 1, 15, and 29) GLP repeat-dose toxicology study conducted in rabbits at doses of 20 mcg and 40 mcg of ARCT-021 (dose of replicon mRNA). In both studies, the administration of ARCT-021 was associated with non-adverse, mild, and transient injection site reactions that resolved 2 to 4 days post injection, transient increases in body temperature that resolved 24 to 48 hours post dose, transient increases in c-reactive protein and cytokines, and inflammation at the site of injection. The inflammation was not adverse and was composed of minimal to moderate (rarely marked) acute inflammation and mononuclear inflammatory infiltrates in the muscle, myofiber degeneration/necrosis, myofiber regeneration, subcutaneous mixed inflammation and/or fibrosis, and intermittent haemorrhage in both dose groups. The inflammation at the injections sites was generally similar between the 20-mcg and 40-mcg dose groups, although the 40-mcg dose group had a slightly higher incidence or severity of certain findings. Findings tended to be more prominent and/or acute in nature (increased myofiber degeneration/necrosis, heterophilic inflammation, mononuclear infiltrates of muscle, subcutaneous fibrosis and inflammation/infiltration) at the more recent injection sites (injection sites were rotated) compared to the older injection sites, where severity and incidence were notably decreased. The severity and incidence of inflammatory infiltration, fibrosis, and myofiber degeneration/necrosis decreased at the recovery euthanasia, demonstrating partial recovery. Neutralising and SARS-CoV-2 spike-specific IgG antibodies were observed in vaccinated rabbits. There was no exacerbation of any finding with repeat dosing. None of the findings were considered adverse and were all consistent with a pharmacological response to the vaccine, and as such the no observed adverse effect level (NOAEL) was 40 mcg for both studies.

ARCT-154 was well tolerated with no adverse effects in a 4-week GLP repeat-dose toxicology study in rabbits at doses of 16.75, 25.1, and 33.55 mcg on DS 1, 15, and 29). No ARCT-154-related effects were noted on body weights, clinical observations, Draize scores at the injection sites, ophthalmology, urinalysis, C-reactive protein, and macroscopic observations. The administration of ARCT-154 was associated with non-adverse transient increases in body temperature that resolved by 48 hours post dose and transient increases in serum C--reactive protein. ARCT-154-related microscopic findings were confined to the spleen and LN (mandibular and mesenteric). Increased lymphocyte cellularity occurred in the germinal centres of the splenic white pulp of main termination males and females at doses >16.75 mcg and did not occur in vehicle/control animals. An increased incidence and

severity of increased lymphocyte cellularity was also present in the cortex of mandibular LN of terminal females at >25.1 mcg and in the mesenteric LN of females at 33.55 mcg. Lymphoid findings were considered non-adverse and likely a normal physiologic response to antigenic stimulation. Other microscopic findings were observed in the injection sites at the terminal necropsy; however, these findings were considered a response to the injection procedure rather than a direct effect of ARCT-154. Injection site changes were considered non-adverse, as the incidence and severity were low. At the end of the recovery period, increased lymphocyte cellularity remained in germinal centres of the spleen in males at doses >16.75 mcg and in females at 16.75 mcg and 25.1 mcg. Increased lymphocyte cellularity also remained in the mandibular LN of females at doses >16.75 mcg. The incidence of injection site findings was greatly reduced at the end of the recovery period and considered a response to the injection procedure rather than a direct effect of ARCT-154. Injection site changes were considered non-adverse, as the incidence and severity were low. Anti-SARS-CoV-2 spike protein total IgG levels were elevated in all animals. None of the findings were considered adverse and were consistent with a pharmacological response to the vaccine, and as such the NOAEL was 33.55 mcg.

Genotoxicity

Genotoxicity studies were not conducted with ARCT-021 or ARCT-154 as they are not considered necessary for the licensure of vaccines (WHO 2005; Siebach 2021). Genotoxicity studies conducted with ARCT-810 (another Arcturus LNP-formulated mRNA product under clinical development that includes a similar lipid to that of Kostaive) for the treatment of ornithine transcarbamylase deficiency and the empty LNP (no mRNA) were both negative in GLP genotoxicity studies; bacterial mutagenicity assay (Ames test), in vitro mammalian cell assay (human peripheral blood lymphocytes), and an in vivo rodent micronucleus assay in studies conducted according to ICH S2 guidelines. An in-silico analysis of potential bacterial mutagenesis for ATX-126 was negative. Based on this weight of evidence, Kostaive is not expected to be genotoxic.

Reproductive/Developmental Toxicity

The potential effects of ARCT-021 on fertility and embryofoetal and postnatal development were evaluated in a GLP study conducted in rabbits. Maternal administration of ARCT-021 at doses of 10 and 20 mcg (dose of replicon mRNA) 28 days before mating (DS 1), 14 days prior to mating (DS 15), and on GDs 0, 14, and 28 (rabbits assigned to the Natural Delivery phase) resulted in maternal effects that were considered adverse in the 20-mcg dose group composed of a statistically significant body weight loss on GDs 28 to 29, a reduction in group mean body weight gains in the overall gestation interval on GDs 0 to 29, and a statistically significant reduction in food consumption on GDs 28 to 29 (Natural Delivery phase) compared with controls. These maternal effects did not have any effects on fertility, development of the embryo and foetus, or postnatal development. Neutralising antibodies and SARS-CoV-2 spike-specific IgG antibodies were detected in ARCT-021-vaccinated pregnant mothers, foetuses, and offspring. Detection of SARS-CoV-2 spike-specific antibodies in foetuses and offspring indicates successful transplacental transfer of spike-specific IgG from vaccinated mothers to their foetuses. The maternal NOAEL was 10 mcg, and the developmental NOAEL was 20 mcg.

Summary of Nonclinical Safety Findings

The findings in the toxicology studies in rabbits with ARCT-021 and ARCT-154 primarily represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended population. Importantly, no ARCT-021-related effects were observed on fertility or embryofoetal or postnatal development. The key safety findings regarding Kostaive from nonclinical studies and their relevance to human usage are presented in Table 7. Furthermore, the nonclinical experience with ARCT-021 suggests low risk of vaccine-associated enhanced respiratory disease based on Th1-biased response and complete protection of mice and nonhuman primates from lung disease and death following lethal challenge with SARS-CoV-2. In addition, there was no evidence of vaccine-associated disease enhancement.

Table 7 Key Safety Findings and Relevance to Human Usage

Key Safety Findings from Nonclinical Studies [a,b]	Relevance to Human Usage
Safety Pharmacology	
NHP Challenge Model No evidence of vaccine-elicited disease enhancement. **Mouse Challenge Model** Complete protection from lung disease and death	Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs.
Toxicity[b]	
Injection Site Reactions Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical repeat-dose toxicology studies.	In common with other vaccines, Kostaive administration has the potential to generate injection site reactions such as oedema and erythema at the injection sites.
Inflammation and Immune Activation Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondarily, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed.	In common with all vaccines, Kostaive administration has the potential to generate inflammation, which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins.
Developmental and Reproductive Toxicity No vaccine-related effects on fertility, development of the embryo and foetus, or postnatal development were observed in a DART study. Adverse effects on maternal body weight parameters and food consumption were observed in rabbits at 5 doses (20 mcg each) at 14-day intervals, which is 4-fold greater than the 5 mcg given as 2 doses at 28-day intervals recommended dose of Kostaive.	No effects are anticipated at the highest dose of Kostaive on body weight, pregnant women, or their offspring and on WOCBP. Transient decreases in food consumption correlated with weight loss and reduction in overall body weight gain were observed in pregnant rabbits at the highest dose of ARCT-021 tested.

Abbreviations: COVID-19, coronavirus disease 2019; CT, clinical trial, DART, developmental and reproductive toxicology; NHP, nonhuman primate; RBC, red blood cells, WBC, white blood cells; WHO, World Health Organisation, WOCBP, women of childbearing potential

a Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted in accordance with the 2005 WHO vaccine guideline, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases (WHO 2005). In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.

b Based on audited study data.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

In the pivotal Vinbiocare Biotechnology Joint Stock Company-sponsored trial (ARCT-154-01), as of the data extraction date (12 January 2023), a total of 17,101 participants were randomised to either ARCT-154 or placebo. Of these, a total of 16,393 participants received at least 1 dose of Kostaive as a primary vaccination regimen during the study.

The detailed description of vaccine exposures by completed studies in healthy participants (ARCT-021-01, ARCT-021-02, and ARCT-021-04) is shown in Table 8, and the detailed description of vaccine exposures by ARCT-154 studies (Arcturus-sponsored and non-Arcturus-sponsored) is shown in Table 9.

Table 8 Cumulative Exposure of ARCT-021 from Trials

Trial	ARCT-021	Placebo	Total
ARCT-021-01	78	28	**106**
ARCT-021-02	12	0	**12**
ARCT-021-04	498	145	**581**
ARCT-165-01	12	0	**12**
Total	**600**	**173**	**723**

Table 9 Cumulative Exposure of ARCT-154 from Trials

Study	ARCT-154 exposed (primary series)	ARCT-154 exposed (3rd Dose)	ARCT-154: total exposure
ARCT-154-01	16,393	483	**16,393**
ARCT-154-J01	0	420	**420**
ARCT-165-01[a]	0	12	**12**
ARCT-021-04	42	0	42
Total	**16,435**	**915**	**16,867**

To date, 3 clinical trials (ARCT-021-01, ARCT-021-02, and ARCT-021-04) have been completed for ARCT-021. The demographic data of ARCT-021-01 are presented in Table 10. The demographic data of two additional studies, ARCT-154-01 and ARCT-165-01, are presented in Table 11.

Table 10 Cumulative Exposure to ARCT-021 from Clinical Trial ARCT-021-01 by Age and Sex

Age Range	Number of Participants		
	Male	Female	Total
21 to 71 years	57	21	78

Note: Data from completed clinical trials as of 19 July 2021.

Table 11 Cumulative Exposure to ARCT-154 from Clinical Trials by Age Group and by Sex

	Number of Participants		
Study	**by Age Group**	**by Sex**	**Total**
ARCT-154-01	18-64 (n=15375) ≥ 65 (n=1020) 18-59 (n= 13611) ≥ 60 (n= 2784)	Male (n=8097) Female (n=8298)	**16395**[a]
ARCT-154-J01	18-64 (n=408) ≥ 65 (n=12)	Male (n=172) Female (n=248)	**420**
ARCT-165-01	Cohort B 21-64 (n=12) ≥ 65 (n=0) 21-59 (n=11) ≥ 60 (n=1) Cohort A (NA)	Cohort B Male (n=5) Female (n=7) Cohort A (NA)	**12** **22**

a Two study participants in Phase 3b [Placebo (Dose 1 and 2) / ARCT-154 (Dose 3 and 4)] only received Dose 4 but not Dose 3 of ARCT-154. These 2 are included as they received 1 dose.

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical study ARCT-154-01 within the development programme for Kostaive

A single pivotal trial (ARCT-154-01) was conducted with Kostaive. Participants were excluded from Study ARCT-154-01 enrolment based on the criteria summarised in Table 12. Detailed descriptions of all inclusion and exclusion criteria for the clinical trials are provided in the individual study protocols.

Table 12 Study ARCT 154-01 Enrolment Exclusions and Rationale

Population	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Individuals who are less than 18 years of age	To avoid administration in a vulnerable population until the benefit/risk of Kostaive is established in adults.	No	Proposed indication does not include individuals <18 years of age
Individuals who are pregnant or lactating	To avoid administration in a vulnerable population until the benefit/risk of Kostaive is established in adults.	Yes	Not applicable
Individuals with an immunosuppressive or immunodeficient state, asplenia, recurrent severe infections, or individuals known to be HIV positive	Immunosuppressed or immunocompromised individuals are at higher risk of diminished immune and efficacy responses following vaccination.	Yes	Not applicable
Individuals who have received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids within 6 months of any dose of vaccine (except systemic corticosteroid courses less than 14 days in length and completed at least 28 days prior to any dose of vaccine and inhaled/nebulized, intra-articular, intrabursal, or topical corticosteroids.	Administration of immunosuppressive and cytotoxic agents may confound the evaluation of vaccine safety, immunogenicity, and efficacy.	Yes	Not applicable

Table 12 Study ARCT 154-01 Enrolment Exclusions and Rationale

Population	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Individuals with significant infection or other acute illness (with or without fever)	Permitting individuals with a significant acute illness would confound the interpretation of safety data following vaccination.	No	The avoidance of administration of vaccines to individuals who are significantly unwell due to another illness is a common medical practice. Vaccination is often deferred to a time of clinical recovery/stabilisation.
Individuals with a known history of COVID-19 or positive SARS-CoV-2 test	Individuals with a known history of COVID-19 or a positive SARS-CoV-2 test were not enrolled to avoid confounding the interpretation of efficacy and immunogenicity data after primary vaccination.	No	Safety data following vaccination with Kostaive is available for individuals who had exposure to/illness relating to SARS-CoV-2 during the clinical trials.
Individuals with a known history of anaphylaxis, urticaria, or other significant adverse reaction to the Kostaive vaccine or its excipients	Individuals with a known history of hypersensitivity to the vaccine components are at increased risk of severe hypersensitivity reactions when receiving another vaccine with these components.	No	The avoidance of administration of vaccines to individuals who have a history of severe hypersensitivity to the known ingredients of a vaccine is a common medical practice, although administration of the vaccine under close medical supervision may be an option.
Individuals with a known history of anaphylaxis to other vaccines	Individuals with a known history of anaphylaxis following vaccination with other vaccines are at increased risk of anaphylaxis to new vaccines when received.	No	The avoidance of administration of vaccines to individuals who have a history of severe hypersensitivity to other vaccines is a common medical practice, although administration of the vaccine under close medical supervision may be an option.

Table 12 Study ARCT 154-01 Enrolment Exclusions and Rationale

Population	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing)
Individuals with a bleeding disorder considered a contraindication to intramuscular injection or phlebotomy	Individuals with a history of bleeding disorders are at increased risk of haemorrhage/haematoma following intramuscular vaccination.	No	The avoidance of intramuscular injection of vaccines in individuals with coagulopathies is a common medical practice. However, risks may be reduced by pre- and post-vaccination application of ice packs and use of a smaller gauge needle for injection.
Individuals who have previously received MERS-CoV, SARS-CoV, or SARS-CoV-2 vaccines	Immunisation with other coronavirus vaccines may confound the analysis of vaccine safety, immunogenicity, and efficacy.	No	Minimal potential clinical impact on the target population.
Individuals who have received a live replicating vaccine within 28 days or a licensed inactivated or non-replicating vaccine within 14 days of any dose of vaccine	Administration of other vaccines will confound the evaluation of safety.	No	The safety profile of Kostaive is not expected to differ in these individuals when properly administered.
Individuals who have received systemic immunoglobulins or blood products within 3 months prior to any vaccine dose	Administration of systemic immunoglobulins or blood products is expected to confound the evaluation of vaccine immunogenicity responses to vaccination.	No	The safety profile of Kostaive is not expected to differ in these individuals when properly administered.
Individuals with underlying clinically significant acute or unstable chronic medical conditions	Administration of vaccine doses to individuals with clinically significant and active medical conditions may interfere with the assessment of vaccine safety.	Yes	Not applicable
Individuals with an inability to comply with the study procedures	Individuals with challenges complying with study protocol procedures may lead to missing or misleading data.	No	The safety profile of Kostaive is not expected to differ in these individuals when properly administered.

Abbreviations: COVID-19, Coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical trials are limited in size and, therefore, unlikely to detect very rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

As summarised in Table 13, exposure to Kostaive in some special populations has been limited, and no epidemiologic studies have been conducted in pregnant or breastfeeding women, paediatric participants (<18 years of age), and specific subpopulations that were excluded from the Kostaive programme.

Table 13 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes for Kostaive

Type of Special Population	Exposure
Pregnant women	There is limited experience with use of Kostaive vaccine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or postnatal development. Therefore, administration of Kostaive in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Through 12 January 2023, there were 34 pregnancies reported following exposure to Kostaive or placebo (Data remain blinded and no other pregnancies have been reported in the other clinical trials).
Breastfeeding women	Breastfeeding women were not initially included in the Kostaive clinical development programme. It is unknown whether Kostaive vaccine is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kostaive and any potential adverse effects on the breastfed newborn/infant/toddler from Kostaive or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. There were no reported cases of exposure during breastfeeding in the Kostaive clinical trial programme. Women who were breastfeeding were excluded from study participation.
Participants with relevant comorbidities Participants with hepatic impairment Participants with renal impairment Participants with cardiovascular impairment Immunocompromised participants Participants with a disease severity different from inclusion criteria in clinical trials	Healthy participants with pre-existing stable chronic disease, defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 6 weeks before enrolment, were included. This allowed enrolment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI >30 kg/m^2, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity. In both the ARCT-154 (N=748) and placebo (N=253) groups in Study ARCT-154-01 for Phases 1, 2, and 3a, 58.6% of participants reported at least 1 AE. The most frequent AE by SOC was Gastrointestinal disorders, being reported by 17.4% of participants in

Table 13 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes for Kostaive

Type of Special Population	Exposure
	the ARCT-154 and placebo groups. For Phase 3b, 45.9% of participants reported at least 1 AE. The most frequent AE by SOC was Surgical and medical procedures, being reported by 11.3% of participants in the ARCT-154 and placebo groups. Participants with potential immunodeficient status and participants with unstable chronic disease were excluded from the study population.
Population with relevant different ethnic origin/race	The majority of participants' exposure information and their comorbidities included Asian population in the Kostaive clinical trials; however, a smaller portion of exposure information also included US in the ARCT-021-04 study and South African populations in the ARCT-165-01 study.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric participants	The safety and effectiveness in individuals younger than 18 years of age have not yet been established. The use in adolescents aged between 12 and 18 years is not in scope for the proposed indication. No children 12 to <18 years of age received Kostaive.
Elderly (≥60 years old)*	Clinical studies of Kostaive included participants 60 years of age and over (maximum age of 89), please see the demographic distribution as per the studies: • For Study ARCT-021-01 (≥56 years old): Total 29 participants • For Study ARCT-021-02 (≥56 to 80 years old): Total 16 participants • For Study ARCT-021-04 (≥56 years old): Total 256 participants • For Study ARCT-154-01 (≥60 years old): Total 2,910 participants • For Study ARCT-154-J01 (≥65 years old): Total 12 participants

Abbreviations: AE, adverse event; BMI, body mass index; COVID-19, Coronavirus disease 2019; SOC, system organ class.
* Phase 1 studies included age range from 56 years.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Kostaive was approved in Japan on 28 November 2023. Kostaive has not been launched in Japan as of the finalization of this risk management plan (RMP).

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Potential for misuse for illegal purposes

Kostaive does not have characteristics that would make it attractive for use for illegal purposes; therefore, there is only a low potential for Kostaive misuse for illegal purposes.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

In accordance with EMA RMP guidance for COVID-19 vaccines, the factors below were taken into consideration for the generation of the safety specification and are not determined to be identified or potential risks.

- The vaccine construct and the formulation. Kostaive consists of non-infectious, self-amplifying RNA (mRNA-2105) in a lipid-based formulation, which delivers the RNA to cells in the immunised person. Kostaive is a vaccine comprising mRNA encoding for SARS-CoV-2 S glycoprotein and that is contained within an LNP and is intended for the prevention of COVID-19, the disease caused by SARS-CoV-2 infection. Kostaive is taken up by antigen-presenting cells and myocytes following IM injection. Subsequent translation of the SARS-CoV-2 full length- S glycoprotein antigen is anticipated to result in induction of antigen specific- CD4+, CD8+, and antibody responses with T-cell and B-cell memory, resulting in immunity to SARS-CoV-2 and/or the corresponding variants via immune responses specific for the S glycoprotein. There is no toxicity associated with the LNP or its metabolism. Vacuolation of hepatocytes was observed in rat toxicity studies, which is believed to be associated with the uptake of the LNP and was without evidence of any effect on liver function.
- The degradation of the active substance/antigen may have potential impact on safety related to Kostaive; (e.g., for mRNA-based vaccines). Like endogenous mRNA in the cytosol, vaccine RNA in cytosol is degraded. The COVID-19 mRNA vaccine contains no known toxic products from the degradation of the RNA or the lipids in the formulation.
- Kostaive does not contain adjuvant.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP include:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance (namely through signal detection and adverse reaction reporting), and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice)

- Hypersensitivity reactions, including anaphylaxis

Hypersensitivity reactions (including anaphylaxis) are a well-known risk with vaccines and are typically diagnosed and managed by healthcare providers according to routine institution standard clinical practice.

In Study ARCT-154-01, hypersensitivity reactions were observed in 0.15% of adults in the ARCT-154 vaccine group and in 0.11% of adults in the placebo group. The hypersensitivity

reactions were mostly mild or moderate in intensity and resolved completely without sequelae. Therefore, the risk of hypersensitivity is not considered to significantly impact the benefit-risk profile of the ARCT-154 vaccine.

Risks with minimal clinical impact on patients (in relation to the severity of the disease prevented)

- Local injection site reaction: Injection site tenderness, Injection site pain, Injection site swelling, Injection site erythema
- Systemic reactogenic events: Fever, Chills, Fatigue, Headache, Myalgia, Arthralgia, Nausea, Dizziness, Vomiting, and Diarrhoea

In acknowledgment of the EMA coreRMP19 guidance, the reactogenicity profile of Kostaive is discussed below with respect to observed differences in solicited reactogenicity systemic events between Dose 1 and Dose 2. The observed differences do not impact the safety profile of the vaccine.

Reactogenicity

ARCT-154-01 Study

At the time of the safety extraction date (12 January 2023), reactogenicity data (local or systemic) were available for 4791 participants (≥18 to <60 years of age) and 813 participants ≥60 years of age participating who received the first or second dose of Kostaive in the Phase 3b portion of the ARCT-154-01 study. For Phases 1,2, and 3a, reactogenicity data (local or systemic) were available for 705 participants who received the first or second dose of Kostaive. The reactogenicity data were collected by participants via electronic or paper diary that solicited reporting of local and systemic adverse events (AEs) for 7 days after each vaccine administration.

Solicited Local Reactions

Solicited local AEs within 7 days post-vaccination

In the combined analysis of Phases 1, 2, and 3a Kostaive groups, within the 7-day period after the first dose, solicited local AEs were reported by 586/748 (78.3%) of ARCT-154 participants and 51/253 (20.2%) of placebo participants. Tenderness and Injection site pain were the most frequent local symptoms reported after the first dose by 550/748 (73.5%) and 485/748 (64.8%) of ARCT-154 participants and 51/253 (20.2%) and 34/253 (13.4%) of placebo participants, respectively. Grade 3 AEs of Tenderness and Injection site pain after the first dose were experienced by 26 (3.5%) and 6 (0.8%) of ARCT-154 and 0 and 1 (0.4%) of placebo participants, respectively, after the first vaccination.

In Phase 3b of the study, within the 7-day period after the first dose, solicited local AEs were reported by 3474/7927 (43.8%) of ARCT-154 participants and 858/7886 (10.9%) of placebo participants. The majority of solicited local AEs reported were mild (Grade 1) and moderate (Grade 2) in intensity. The frequency of severe (Grade 3) local solicited AEs was 47/7927 (0.6%) in the ARCT-154 group and 1/7886 (0.0%) in the placebo group.

Tenderness and Injection site pain were the most frequent local symptoms, being reported after the first dose by 3003/7927 (37.8%) and 3029/7927 (38.2%) of ARCT-154 participants and 659/7886 (8.4%) and 676/7886 (8.6%) of placebo participants, respectively. Severe

(Grade 3) AEs of Injection site tenderness and pain after the first dose were experienced by 32/7927 (0.4%) and 29/7927 (0.4%) of ARCT-154 participants and 0/7886 (0%) of placebo participants, respectively.

The incidence of solicited local AEs after the second doses tended to be lower than that of the first dose.

Solicited Systemic AEs

Solicited systemic AEs within 7 days post vaccination

In the Kostaive group of the pooled analysis of Phases 1, 2, and 3a, the most frequently reported systemic AE was fatigue after the first or second dose: Grade 1 (346 [46.3%] participants), Grade 2 (160 [21.4%] participants), and Grade 3 (25 [3.3%] participants). Myalgia and headache were also commonly reported AEs: Grade 1 (263 [35.2%] participants), Grade 2 (118 [15.8%] participants), and Grade 3 (14 [1.9%] participants); and Grade 1 (248 [33.2%] participants), Grade 2 (118 [15.8%] participants), and Grade 3 (18 [2.4%] participants), respectively.

In Phase 3b of the study, within the 7-day period after the first dose, these solicited AEs were reported by 2816/7927 (35.5%) of ARCT-154 participants and 2499/7886 (31.7%) of placebo participants. The majority of solicited systemic AEs were mild (Grade 1) or moderate (Grade 2) in intensity. Solicited systemic AEs of severe intensity (Grade 3) were reported by 115/7927 (1.5%) of ARCT-154 participants and 35/7886 (0.4%) of placebo participants.

Fatigue, Headache, and Myalgia were the most frequent systemic symptoms, with Fatigue being reported by 2344/7927 (29.6%) of ARCT-154 participants and 1307/7886 (16.6%) of placebo participants, Headache being reported by 1925/7927 (24.3%) of ARCT-154 participants and 1235/7886 (15.7%) of placebo participants, and Myalgia being reported by 1615/7927 (20.4%) of ARCT-154 participants and 692/7886 (8.8%) of placebo participants.

The incidence of solicited systemic AEs after the second dose tended to be lower than that of the first dose.

The solicited local and systemic AEs of pain and tenderness and systemic AEs of Fatigue, Headache, Myalgia, and Arthralgia encountered within 7 days after injection are the same as those commonly observed in other approved mRNA vaccines. Most of the solicited AEs were mild and moderate in severity, did not require medical intervention, and resolved within 2 to 3 days after vaccination.

ARCT-154-J01 Study

Solicited Local Reactions

Solicited local AEs within 7 days post-vaccination

As of 27 March 2023, solicited local AEs were reported in 398 (94.8%) participants in the ARCT-154 group and 395 (96.8%) participants in the Comirnaty group. The most frequently reported solicited local AEs both in the ARCT-154 group and the Comirnaty group were Injection site tenderness (388 [92.4%] participants and 391 [95.8%] participants, respectively), followed by Injection site pain (352 [83.8%] participants and 358 [87.7%] participants, respectively). Solicited local AEs of Grade 3 or higher were reported in 3 (0.7%) participants in the ARCT-154 group and 4 (1.0%) participants in the Comirnaty group. The

majority of solicited local AEs in the ARCT-154 group were reported within 1 to 2 days after study vaccine administration and resolved within 4 to 5 days after onset.

Solicited Systemic AEs

Solicited systemic AEs within 7 days post vaccination

Solicited systemic AEs were reported in 276 (65.7%) participants in the ARCT-154 group and 255 (62.5%) participants in the Comirnaty group. Of these, solicited systemic AEs related to study vaccine (as assessed by investigators) were reported in 274 (65.2%) participants in the ARCT-154 group and 253 (62.0%) participants in the Comirnaty group. The most frequently reported solicited systemic AE was Malaise in both groups (188 [44.8%] participants in the ARCT-154 group and 176 [43.1%] participants in the Comirnaty group). Solicited systemic AEs of Grade 3 or higher were reported in 6 (1.4%) participants in the ARCT-154 group and 7 (1.7%) participants in the Comirnaty group. The most frequently reported solicited systemic AEs of Grade 3 or higher in the ARCT-154 group were Malaise and Headache (3 [0.7%] participants each), while those in the Comirnaty group were Malaise and Chills (4 [1.0%] participants each). The majority of solicited systemic AEs in the ARCT-154 group were reported within 1 to 3 days after study vaccination and resolved within 2 to 3 days after onset.

Other reasons for considering that the risks are not important:

- Potential of prolonged self-amplification
- Potential for host genome integration

While the LUNAR-COV19 sa-mRNA vaccines are similar in composition to other conventional (non-self-amplifying) mRNA vaccines, sa-mRNA vaccines differ in that the encoded replicase (VEEV nonstructural proteins [nsP]1-4) produces both minus- and plus-strand copies of the administered RNA drug substance. Therefore, additional theoretical risks that potentially pertain to or are amplified by the replicase have been evaluated. One such risk is the potential of prolonged amplification of the administered mRNA. The mechanism of alphavirus genomic replication and the amplification of the LUNAR-COV19 sa-mRNA drug substance are considered to be similar, as they depend on the translation and processing of the encoded replicase. In alphaviruses, minus-strand synthesis dominates early after infection and translation due to a complex formed by uncleaved nsP1-3 of the replicase that favours minus-strand synthesis. As the concentration of nsP1-3 increases, the cysteine protease activity of nsP2 cleaves nsP1-3 into its component proteins, which then forms an alternative complex that favours plus-strand synthesis and transcription of downstream genes (Shirako 1994; Lemm 1994; Rupp 2015; Carrasco 2018). Minus strand synthesis is required to make the plus strand and for continued replication/amplification. Because the elements of the replicase are conserved in the LUNAR-COV19 sa-mRNA vaccine, a similar process likely occurs. This is supported by the following observation: while sa-mRNA leads to higher and more durable RNA concentration than conventional mRNA at the same dose, after an early peak of RNA concentration at 2 hours post-injection, the concentration of sa-mRNA decreases over a 2-week period with only a minimum of sa-mRNA detected at the final 30-day time point. Given the self-limiting nature of alphavirus replication in humans and the consistent decrease of sa-mRNA in the muscle and liver over a 2-week period after IM administration, there is no evidence that prolonged self-amplification is a likely risk.

As with any nucleic acid-based drug, the chance of genomic integration must be considered. Alphavirus replication and transcription have been shown to take place on the cytoplasmic side of endosomal membranes (Froshauer 1988; Carrasco 2018). This is in contrast to adenoviruses, which extensively reorganise the host cell nucleus during its replication cycle (Hidalgo 2019) and leads to a low frequency of integration (Wang 2022). Nevertheless, a portion of nsP2, a component of the VEEV replicase, has been shown to translocate to the nucleus. However, nuclear nsP2 has been shown to block host cellular transcription through the degradation of Rpb1, which helps alphaviruses evade cellular host immunity (Akhrymuk 2012). There is no indication that nuclear nsP2 plays any role in viral genomic replication in the nucleus or results in viral integration into the host genome. A literature review focusing on several search terms (alphavirus + integration, alphavirus + insertion, VEEV + integration, VEEV + insertion performed 20 April 2023) did not reveal any studies that indicated that alphaviruses, or VEEV specifically, integrated or destabilised host-genomic DNA. The general consensus in the literature is that alphaviruses are among a class of viruses, unlike adenoviruses or retroviruses, that are transient and do not carry the risk of host genome integration.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: None

Important Potential Risk: Myocarditis and pericarditis

Risk-benefit impact: Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening. While the data available from other mRNA vaccine manufacturers suggests the rare risk of primarily mild myocarditis or pericarditis without sequelae following vaccination, no cases have been observed to date with Kostaive/ARCT-021/ARCT-165.

Important Potential Risk: Thromboembolic events

Risk-benefit impact: Thromboembolic events are common underlying mechanism of myocardial infarction, ischemic stroke, venous thromboembolism, and the leading global cause of mortality. Considering the anticipated benefits of the vaccine, a lower risk of thromboembolic events after vaccination compared to SARS-CoV-2 infection, and the risk minimisation measures in place, the impact of this risk on the benefit-risk balance of Kostaive is acceptable.

Missing Information: Use in pregnancy and while breastfeeding

Risk-benefit impact: The safety profile of the vaccine is not fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study. Accordingly, maternal COVID-19 impact to either embryo or foetus and the impact of breastfeeding on the infant are not known.

Obtaining long-term follow-up on women who were pregnant or breastfeeding at or around the time of vaccination is important, so that any potential negative consequences to the pregnancy or infant can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy or infant.

Missing Information: Use in immunocompromised patients

Risk-benefit impact: The safety profile of the vaccine is not known in immunocompromised individuals due to their exclusion from the pivotal clinical study. The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.

Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk-benefit impact: There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

Missing Information: Interaction with other vaccines

Risk-benefit impact: Kostaive will be used in individuals who may also receive other vaccines. There is insufficient information at present to determine if co-administration of Kostaive with other vaccines may affect the efficacy or safety of either vaccine. The randomized controlled study to evaluate the immunogenicity, reactogenicity, and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in adults is planned.

Missing Information: Long-term safety data

Risk-benefit impact: The long-term safety profile of Kostaive is not fully known at present. Safety data has been collected for up to 12 months in studies ARCT-154-01 and ARCT-154-J01 and 2 studies are planned with follow-up periods of 6 months. The long-term safety profile is to be characterised through active surveillance for safety and routine pharmacovigilance.

Missing Information: Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Risk-benefit impact: There is limited information in individuals with significant, unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) who are potentially at risk of severe COVID-19.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

No important risks have yet been identified for Kostaive. Important potential risks are presented in Table 14. The data analysed to evaluate these risks are derived from Studies ARCT-154-01 and ARCT-154-J01.

Table 14 Important Potential Risk: Myocarditis and Pericarditis

Potential mechanisms	The MOA of myocarditis and pericarditis has not been fully characterised. Hypotheses for the MOA include an immune-stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination, or a hypersensitivity response.
Evidence source(s) and strength of evidence	Myocarditis and pericarditis have been reported in postmarketing surveillance of mRNA COVID-19 vaccines.
Characterisation of the risk	No cases of myocarditis and pericarditis have been reported from the Kostaive/ARCT-021 clinical trial experience through the data extraction date of 12 January 2023 for ARCT-154-01 study and data cut date of 27 March 2023 for ARCT-154-J01 study.
	Conclusion: Surveillance will continue.
Risk factors and risk groups	Postauthorisation reports from other mRNA vaccine manufacturers have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the ECDC and US CDC and FDA have found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine, however, cases have also been observed in adult males and females of a broader age range following dose 1 and dose 2 of the vaccination.
Preventability	Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients.

Table 14 Important Potential Risk: Myocarditis and Pericarditis

Impact on the risk-benefit balance of the biologic product	While the data available from other mRNA COVID-19 vaccine manufacturers suggests the rare risk of primarily mild myocarditis or pericarditis without sequelae following vaccination, no cases have been observed to date with Kostaive/ARCT-021. The benefits of prevention of severe COVID-19 outweigh the risks.
Public health impact	Considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

Abbreviations: COVID-19, coronavirus disease 2019; CT, clinical trial; ECDC, European Centers for Disease Control and Prevention; EU, European Union; FDA, Food and Drug Administration; MOA, mechanism of action; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; US CDC, United States Centers for Disease Control and Prevention

a Search criteria: Standardised MedDRA Query - Noninfectious myocarditis/pericarditis [narrow] was used to search the database for myocarditis and pericarditis events.

Please note that the CT dataset from the safety database includes only cases reported as SAEs.

Table 15 Important Potential Risk: Thromboembolic Events

Potential mechanisms	The mechanism by which Kostaive may cause thromboembolic events has not yet been elucidated
Evidence source(s) and strength of evidence	Several observational studies indicate an increased rate of coagulation disorders following COVID-19 vaccines (Vaxzevria: RR, 2.01 [95% CI, 1.75-2.31]; Comirnaty: RR, 1.12 [95% CI, 1.07-1.19]; and Spikevax: RR, 1.26 [95% CI, 1.07-1.47]) (Dag Berild 2022).
Characterisation of the risk	The frequency of thromboembolic events in vaccine recipients administered Kostaive has not yet been established. In total, 43 SAEs with thromboembolic events were identified in studies with Kostaive. Among 12 thromboembolic events reported within 28 days after any study vaccination, 6 events were reported after the study vaccine and 6 events were reported after controls (5 events after placebo dose and 1 event after ChAdOx-1S). Two SAEs after the study vaccine and 1 SAE after controls were assessed as related to vaccination.
Risk factors and risk groups	Elderly age, prolonged hospitalisation/immobilisation, cancer, thyroid disease, oral contraceptive use, surgery, and pre-existing cardiovascular disease including prior deep vein thrombosis/ischaemia, phlebitis or cerebrovascular ischaemic attack, and hypertension. The risk of thromboembolism is also increased with inflammatory bowel disease. Lifestyle factors, including smoking, physical inactivity and increased weight.
Preventability	Healthcare professionals should be alert to the signs and symptoms of thromboembolic events in vaccine recipients, especially those with cardiovascular risk factors, including myocardial infarction, unstable angina, cerebrovascular ischaemic attack, transient ischemic attack, and heart failure requiring hospitalization.
Impact on the risk-benefit balance of the biologic product	Thromboembolic events range from a simple deep vein thrombosis to severe life-threatening pulmonary embolism. Thromboembolic events may have a marked impact on a person's quality of life.

Public health impact	Considering the low rates of thromboembolic events reported following vaccination, balanced with the risk of death and illness caused by SARS-CoV-2, the public health impact of post-vaccination thromboembolic events is minimal.

Abbreviations: COVID-19, coronavirus disease 2019, RR, risk ration; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

SVII.3.2. Presentation of the missing information

Missing information is presented in Table 16, Table 17, Table 18, Table 19, Table 20, and Table 21.

Table 16 Use in Pregnancy and While Breastfeeding

Evidence source: The safety profile of the vaccine is not yet fully known in pregnant or breastfeeding women due to their exclusion from the clinical studies of Kostaive to date. Limited data are available from individuals vaccinated with Kostaive or placebo who became pregnant after study vaccination. A preclinical reproductive toxicity study demonstrated no vaccine-related effects on female fertility, foetal development, and neonatal outcomes. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy are not yet fully understood but some data have suggested that pregnant women have an increased risk of severe disease and complications when affected by COVID-19. Experience with other mRNA COVID-19 vaccines suggests a favourable risk-benefit balance when weighing the increased risks of COVID-19 in pregnant women.
Population in need of further characterisation: The lack of data is communicated in product labelling;III.2III.3 information about Kostaive use in this population will continue to be sought via pregnancy report and outcomes tracking for upcoming clinical trials, participation in a pregnancy exposure study, and commercial experience (as relevant).

Table 17 Use in Immunocompromised Patients

Evidence source: Kostaive has not been studied in individuals with overt immunocompromised conditions. Therefore, this population will be further studied in the postmarketing setting.
Population in need of further characterisation: A postauthorisation safety study to collect additional safety data in immunocompromised individuals, individuals with autoimmune disease, and patients who are on immunosuppressive therapies is planned.

Table 18 Use in Patients with Autoimmune or Inflammatory Disorders

Evidence source: Limited information is available on the safety of the vaccine in patients with autoimmune or inflammatory disorders.
Population in need of further characterisation: Adverse events in individuals with a medical history significant for autoimmune or inflammatory disorders will be monitored on an aggregate level. A postauthorisation safety study to collect additional safety data in immunocompromised individuals, individuals with autoimmune disease, and patients who are on immunosuppressive therapies is planned.

Table 19 Interaction with Other Vaccines

Evidence source: No data are available on interaction of Kostaive with other vaccines at this time.
Population in need of further characterisation: All reports describing interactions of COVID-19 vaccine with other vaccines per national recommendations in individuals will be collected and analysed as per routine pharmacovigilance activities. Additional safety information on the combination of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population is planned.

Table 20 Long-term Safety Data

Evidence source: At this time, 12-month post vaccination safety data are available for participants in the ARCT-154-01 and ARCT-154-J01 studies.
Population in need of further characterisation: Further safety data will be collected in studies including, ARCT-2301-J01 (6-month follow-up period) and ARCT-2303-01 (6-month follow-up period).

Table 21 Use in Patients with Significant, Unstable Chronic Medical Conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Evidence source: No data are available on interaction of Kostaive with other vaccines at this time. The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity); however, it has not been studied in individuals with significant, unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) that may compromise the immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population.
Population in need of further characterisation: Safety data will be collected in individuals with unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) through routine pharmacovigilance activities.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 19 Summary of the Safety Concerns

Important Identified Risks	None
Important Potential Risks	Myocarditis and pericarditis
	Thromboembolic events
Missing Information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data
	Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities for the lifecycle of a product are critical components to the detection, assessment, understanding, and mitigation of risks. Routine pharmacovigilance includes the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate safety data review, in accordance with Arcturus Global Patient Safety Standard Operating Procedures and applicable laws, regulations, and guidances.

Arcturus monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations. Signal detection activities for the lifecycle of vaccines consist of individual AE assessment at case receipt and regular aggregate review of events for trends. Safety signal evaluation requires the collection, analysis, and assessment of information to evaluate potential causal associations between an event and the Arcturus product and includes subsequent qualitative and quantitative characterisation of the relevant risk to determine appropriate actions in accordance with Arcturus Global Patient Safety standard operating procedures. Safety data are collected from multiple sources for signal detection and evaluation including the global safety database, the clinical database, routine published scientific literature surveillance, product quality complaints, business partner clinical studies, and commercial experience (as relevant) commensurate with product characteristics. As part of routine signal management, comparator sources of data are sought including EudraVigilance and other publicly available sources of information.

Signal detection activities for Kostaive occur every 2 weeks. Upon the identification of a potential signal, evaluation is performed to determine if the signal is valid or refuted.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine pharmacovigilance activities beyond the receipt and clinical review of individual AE reports include the use of event specific follow-up questionnaires called Data Capture Aids (DCAs) to monitor AEs of special interest. DCAs have been created for all items marked with an * and are intended to facilitate the capture of clinical details about the following AEs of special interest:

- Acute disseminated encephalomyelitis*
- Acute pancreatitis
- Anaphylaxis*
- Anosmia
- Bell’s Palsy*
- Delayed hypersensitivity
- Erythema multiforme
- Extensive limb swelling
- Facial swelling in persons with dermal fillers

- Generalized convulsion*
- Guillain-Barré Syndrome*
- Rhabdomyolysis
- Thrombocytopenia*
- Thrombosis/thromboembolism*
- Subacute thyroiditis
- Transverse myelitis*
- Multisystem inflammatory syndrome in adults*
- Myocarditis, myopericarditis, and pericarditis*

The updated version of the data capture aids is provided in Annex 4.

The DCA tool will be assessed for effectiveness, as applicable, and may be updated to incorporate and/or remove questions to ensure the form is value added.

Other forms of routine pharmacovigilance activities for: *Potential Medication Errors*

Large-scale public health approaches for mass vaccination may represent changes to standard vaccine treatment process, thereby potentially introducing the risk of medication errors related to reconstitution and administration, vaccination scheme, storage conditions, errors associated with a multi-dose vial, and confusion with other COVID vaccines. These potential medication errors are mitigated through the information in the Summary of Product Characteristics (SmPC).

- SmPC (Section 6.6) contains instructions for reconstitution and administration, vaccination scheme, and storage conditions of Kostaive.

The SmPC will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication error in the context of amass vaccination campaign. Further, risks of potential medical errors will be minimised through routine pharmacovigilance activities with a summary of data and analyses presented in the PSUR.

Traceability

Upon approval, pre-printed batch/lot stickers for traceability will be developed in accordance with the coreRMP19 guidance and will be available to co-ship with each vaccine shipment.

Traceability is available for every shipping container of Kostaive, which is outfitted with a unique device that provides real-time monitoring of temperature 24 hours per day, 7 days per week. A shipment quality report that indicates if the product is acceptable for immediate use is generated by Arcturus and transmitted to the vaccinator's practice site upon pressing of the stop button on the data logger, or arrival notification from the carrier in combination with the data loggers' location and/or light signal. Additionally, alarms and escalation/notification for excursions (per pre-defined specifications) are programmed into the device. These data may be used for the assessment of a safety signal.

Cold-Chain Handling and Storage

Multiple modalities will be used for quality assurance throughout shipment due to the required cold storage for Kostaive.

- Joint AE and product complaint (including available batch/lot information) trending reviews occur routinely with Global Product Quality.
- Additionally, available resources and reference materials for vaccinators will include information regarding proper handling of the shipment container as temporary storage and handling/disposal of dry ice until the received shipment is either placed into a low temperature freezer or is maintained in accord with pre-defined specifications in the shipment container as temporary storage (i.e., upon receipt of the shipment quality report noted above), as appropriate.

III.2 Additional Pharmacovigilance Activities

For the majority of safety concerns, routine pharmacovigilance activities including continuation of safety surveillance from the ongoing clinical trials are considered to be sufficient. In addition, the following additional pharmacovigilance activities are proposed:

Myocarditis/pericarditis and thromboembolic events summary

V206_06: A postauthorization safety surveillance study is proposed to be conducted.

Study short name and title:

A retrospective post-authorisation safety study to assess the risk of cardiac inflammatory and thromboembolic events following vaccination with sa-mRNA COVID-19 vaccine in adult individuals.

Rationale and study objectives:

Assess the risk of cardiac inflammatory and thromboembolic events following vaccination with sa-mRNA COVID-19 vaccine in adults aged 18 years and older in the real-world setting.

To evaluate the risk of myocarditis, myopericarditis, pericarditis, and thromboembolic events following vaccination with Kostaive using a self-controlled risk interval design among individuals aged 18 years and older.

To characterise the occurrence of myocarditis, myopericarditis, pericarditis, and thromboembolic events following vaccination with Kostaive in the following subgroups: age groups (<30, 30-59 and ≥60 years), sex (male, female), other characteristics, as applicable.

Study design:

The study is an observational retrospective post-authorisation safety study of Kostaive in the real-world setting.

This study will use a self-controlled risk interval design to compare the incidence of prespecified safety outcomes within a prespecified risk period (28-day risk window following Kostaive vaccination) with the incidence during the control period within the same individual. The incidence of each prespecified safety outcome during the risk window will be compared with the self-matched control window, used to determine the baseline risk of the outcome. Safety outcomes of interest will include incidence of myocarditis, myopericarditis, pericarditis and thromboembolic events.

Study population:

The source population will comprise of individuals ≥18 years of age with Kostaive exposure in the selected (linked) data source during the study period.

The study population will comprise all persons in the source population who experienced an event of any outcome of interest and met specific inclusion and exclusion criteria (such as study period, design requirements, and occurrence of prior events). Eligible individuals will be identified from electronic database(s) that link vaccination data to health outcomes using a prespecified selection process and/or algorithms. These data sources may capture AE outcomes from inpatient, emergency, or outpatient settings.

Milestones:

The draft study protocol will be submitted within 6 months following receipt of the marketing authorization approval.

Study start:

To be commenced 6 months following first post-authorisation exposure.

Clinical study report:

A final study report is planned for submission 6 months following completion of the data collection.

Note: Modifications to the study design may be applied at the time of the full protocol, depending on current vaccination recommendations, vaccine coverage, and other real-world conditions. Additionally, the study design may evolve based on new scientific evidence and methodological advancements.

Interactions with other vaccines summary

Safety data to address missing information “Interaction with other vaccines” will be available following the completion of the study of the immunogenicity and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population (ARCT-2303-01).

Study short name and title:

ARCT-2303-01: Observer-blind, randomized controlled study to evaluate the immunogenicity, reactogenicity, and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in adults.

Rationale and study objectives:

Concomitant vaccination with both COVID-19 and influenza vaccines should reduce the burden on the healthcare services for vaccine delivery, allowing for timely vaccine administration and protection from COVID-19 and influenza for those in need.

To demonstrate that the immune responses against the ARCT-2303 vaccine and the quadrivalent influenza vaccine, when administered concomitantly, are noninferior to immune responses induced when administered separately.

Study design:

Multicenter, randomized, observer blind, controlled.

Study population:

Healthy participants or individuals with pre-existing stable medical conditions ≥18 years of age who received primary vaccination series and at least 1 booster dose of un-US authorized-mRNA COVID 19 vaccines, ≥5 months prior to enrollment.

Milestones:

Clinical study report: 30 April 2025

Long-term safety data summary

Studies ARCT-154-01, ARCT-154-J01, and ARCT-165-01 provide one-year post-vaccination follow-up information for participants to address missing information "Long-term safety data".

Study short name and title:

ARCT-165-01 - A phase 1/2 randomized, observer-blind study of the safety, reactogenicity, and immunogenicity of 3 SARS-CoV-2 RNA vaccine candidates in adults previously vaccinated and not previously vaccinated against SARS-CoV-2.

Rationale and study objectives:

Safety follow-up for all participants up to Day 394.

Study design:

Multicenter, randomized, observer blind.

Study population:

Healthy adults ≥21 to ≤65 years of age.

Milestones:

Study start – 30 August 2021

Clinical study report – 31 December 2024

Study short name and title:

ARCT-154-01: A randomized, observer-blind, controlled study to assess the safety, immunogenicity and efficacy of the SARS-CoV-2 self-amplifying RNA vaccine ARCT-154 in adults.

Rationale and study objectives:

Safety follow-up for all participants up to Day 394.

Study design:

Multicenter, randomized, observer blind, controlled.

Study population:

Healthy individuals and individuals at risk of severe COVID-19 (those with asthma, cancer, cerebrovascular disease, chronic kidney/liver/lung disease, cystic fibrosis, diabetes mellitus Type 1 or 2, cardiovascular conditions, mental health conditions, smoking, pulmonary fibrosis, Down syndrome, obesity, sickle cell disease, or substance abuse disorder), ≥18 years of age.

Milestones:

Study start: 11 August 2021

Clinical study report: 29 January 2024

Study short name and title:

ARCT-154-J01: A randomized, multicenter, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA COVID-19 vaccine) in healthy subjects.

Rationale and study objectives:

Safety follow-up for all participants up to Day 361.

Study design:

Multicenter, randomized, observer blind, active controlled.

Study population:

Individuals ≥18 years of age who had previously been vaccinated with mRNA COVID-19 vaccines and have received COMIRNATY at last dose. Healthy individuals and individuals requiring caution in vaccination which considers individuals with underlying diseases for which vaccination was considered with caution.

Milestones:

Study start: 13 December 2022

Clinical study report: 31 December 2024

Immunocompromised patients summary

To address missing information “Use in immunocompromised patients” and “Use in patients with autoimmune or inflammatory disorders” a postauthorisation safety study will be conducted. This study will include a broad population of patients with immunocompromising conditions (including autoimmune conditions), individuals with autoimmune disease, and patients who are on immunosuppressive therapies.

Study short name and title:

V206_05: A phase IIb, single-arm, open label study to evaluate the safety, tolerability and immunogenicity of Kostaive when administered to adults and elderly subjects with immunosuppressive disorders, or receiving immunosuppressive therapies, who are indicated for a booster dose of COVID-19 vaccine.

Rationale and study objectives:

Descriptive study to understand safety of Kostaive use in immunocompromised individuals, individuals with autoimmune disease, and individuals on immunosuppressive therapies who are indicated for a booster dose of COVID-19 vaccine.

To assess the safety and tolerability profile of Kostaive in adults and elderly subjects with immunosuppressive disorders or receiving immunosuppressive therapies.

To evaluate immunogenicity of Kostaive, as determined by virus neutralization assay for the SARS-CoV-2 variant recommended by WHO in adults and elderly subjects with immunosuppressive disorders or receiving immunosuppressive therapies.

Study design:

Single-arm, open label descriptive study.

Study population:

500 subjects, who have an immunosuppressive disorder, an autoimmune disease, or are on immunosuppressive therapies.

Current draft inclusion criteria are the following:

Immunosuppressed individuals 18 years of age and above who are non-institutionalized and mentally competent.

a. Individuals who are receiving chemotherapy, biological therapy, or radiation therapy.
b. Individuals with rheumatologic diseases.
c. Individuals undergoing hemodialysis or continuous ambulatory peritoneal dialysis.
d. Individuals receiving immunosuppressive drugs.
e. Individuals with confirmed diagnosis of advanced or metastatic solid tumor or hematological malignancies.
f. Individuals with documented HIV infection (serologically and/or virologically confirmed) and a CD4 count ≥200 and ≤500.
g. Individuals who have undergone renal, cardiac, liver, lung, or stem cell transplantation for any reason, more than 3 months prior to enrolment.

Milestones:

Final protocol: 01 February 2027

Clinical study report: 30 April 2029

Pregnancy exposure study summary

To address missing information for use of Kostaive in pregnancy, a noninterventional, prospective study (pregnancy exposure study) to monitor the safety of Kostaive when used during pregnancy will be conducted.

Study short name and title:

V206_03: A prospective observational safety study on pregnancy outcomes in persons immunized with Kostaive during pregnancy.

Rationale and study objectives:

To understand safety of Kostaive when exposed in pregnancy.

To evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with Kostaive during pregnancy.

Study design:

A prospective, observational cohort study.

Study population:

Approximately 300 pregnant persons will be enrolled who have been vaccinated during pregnancy with Kostaive through routine medical care.

Milestones:

Final protocol: 01 March 2028

Clinical study report: 30 April 2031

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
Category 1				
N/A	N/A	N/A	N/A	N/A
Category 2				
N/A	N/A	N/A	N/A	N/A
Category 3				
V206_06: A retrospective post-authorisation safety study to assess the risk of cardiac inflammatory and thromboembolic events following vaccination with sa-mRNA COVID-19 vaccine in adult individuals Planned	To evaluate the risk of myocarditis, myopericarditis, pericarditis, and thromboembolic events following vaccination with Kostaive using a self-controlled risk interval design among individuals aged 18 years and older. To characterise the occurrence of myocarditis, myopericarditis, pericarditis, and thromboembolic events following	Myocarditis and pericarditis Thromboembolic events	Draft protocol Clinical study report	6 months following MAA approval (17 August 2025) 6 months following the completion of data collection

Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
	vaccination with Kostaive in the following subgroups: age groups (<30, 30-59 and ≥60 years), sex (male, female), other characteristics, as applicable.			
V206_05: A phase IIb, single-arm, open label study to evaluate the safety, tolerability and immunogenicity of Kostaive when administered to adults and elderly subjects with immunosuppressive disorders, or receiving immunosuppressive therapies, who are indicated for a booster dose of COVID-19 vaccine. Planned	To assess the safety and tolerability profile of Kostaive in adults and elderly subjects with immunosuppressive disorders (including autoimmune conditions) or receiving immunosuppressive therapies. To evaluate immunogenicity of Kostaive, as determined by virus neutralization assay for the SARS-CoV-2 variant recommended by WHO in adults and elderly subjects with immunosuppressive disorders (including autoimmune conditions) or receiving immunosuppressive therapies.	Missing information: Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders	Final protocol Clinical study report	01 February 2027 30 April 2029
ARCT-2303-01: Observer-blind, randomized controlled study to evaluate the immunogenicity, reactogenicity, and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in adults Planned	To assess the safety, reactogenicity, and immunogenicity of the study vaccines when given in co-administration or standalone	Missing information: Interaction with other vaccines	Clinical study report	31 April 2025

Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
V206_03: A prospective observational safety study on pregnancy outcomes in persons immunized with Kostaive during pregnancy Planned	To evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with Kostaive during pregnancy	Missing information: Use in pregnancy and while breastfeeding	Final protocol Summary report	01 March 2028 30 April 2031
ARCT-165-01: A Phase 1/2 Randomized, Observer-blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2 Ongoing	To describe the safety and reactogenicity of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines through Final Visit, defined as 365 days after the last study vaccine dose	Missing information: Long-term safety data	Study start Clinical study report	30 August 2021 31 December 2024
ARCT-154-J01: A randomized, multicenter, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA COVID-19 vaccine) in healthy subjects Ongoing	To evaluate the safety and immunogenicity of ARCT-154 given as a booster dose in subjects 18 years of age and older who have received 3 doses of approved mRNA COVID-19 vaccine at least 3 months prior, for up to 12 months after vaccination	Missing information: Long-term safety data	Study start Clinical study report	13 December 2022 31 December 2024
ARCT-154-01: A Randomized, Observer-blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self-Amplifying	Safety follow-up for all participants up to Day 394.	Missing information: Long-term safety data	Study start Clinical study report	11 August 2021 29 January 2024

Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
RNA Vaccine ARCT-154 in Adults Ongoing				

Abbreviations: COVID-19, coronavirus disease 2019; MAA, marketing authorisation application; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

The product information is sufficient to mitigate the current identified and potential risks of Kostaive. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC. No additional measures for risk minimisation are considered necessary at this time. The proposed minimisation measures are summarised in Table 23 for each safety concern.

Table 23 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risk: None	
Important Potential Risk	
Myocarditis and pericarditis	Routine risk communication: SmPC Section 4.4 Special warnings and precautions for use PL Section 2. What you need to know before you receive Kostaive Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None
Thromboembolic events	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None

Table 23 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Missing Information	
Use in pregnancy and while breastfeeding	Routine risk communication: SmPC Section 4.6 Fertility, pregnancy and lactation PL Section 2. What you need to know before you receive Kostaive Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in immunocompromised patients	Routine risk communication: SmPC Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use; Section 5.1 Pharmacodynamic properties. PL Section 2. What you need to know before you receive Kostaive Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in patients with autoimmune or inflammatory disorders	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Table 23 Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Interaction with other vaccines	Routine risk communication: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Long-term safety data	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in PART V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 24 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC Section 4.4; PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A data capture aid for myocarditis/myopericarditis/pericarditis will be used to collect event specific follow-up information. Additional pharmacovigilance activities:

Table 24 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Observational retrospective post-authorisation safety study (V206_06)
Thromboembolic events	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A data capture aid for thrombosis/thromboembolism will be used to collect event specific follow-up information. Additional pharmacovigilance activities: Observational retrospective post-authorisation safety study (V206_06)
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC Section 4.6; PL Section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A noninterventional, prospective study (pregnancy exposure study) to monitor the safety of Kostaive when used during pregnancy (V206_03).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 5.1. PL Section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A postauthorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A postauthorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).

Table 24 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Interaction with other vaccines	Routine risk minimisation measures: SmPC Section 4.5 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A study of the immunogenicity and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population (ARCT-2303-01).
Long-term safety data	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: One-year post-vaccination follow-up of participants in studies ARCT-154-01, ARCT-154-J01, and ARCT-165-01.
Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR KOSTAIVE (ZAPOMERAN)

This is a summary of the RMP for Kostaive. The RMP details important risks of Kostaive, how these risks can be minimised, and how more information will be obtained about Kostaive's risks and uncertainties (missing information).

The Kostaive SmPC and its package leaflet give essential information to healthcare professionals and patients on how Kostaive should be used.

This summary of the RMP for Kostaive should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Kostaive's RMP.

I. The medicine and what it is used for

Kostaive is authorised for active immunisation to prevent COVID-19 in individuals ≥18 years of age (see SmPC for the full indication). It contains zapomeran as the active substance and it is given intramuscularly.

Further information about the evaluation of Kostaive's benefits can be found in Kostaive's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage www.ema.europa.eu/en/medicines/human/EPAR/Kostaive.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kostaive, together with measures to minimise such risks and the proposed studies for learning more about Kostaive's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Kostaive is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Kostaive are those that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kostaive. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Myocarditis and pericarditis
	Thromboembolic events
Missing information	Use in pregnancy and while breastfeeding
	Use in immunocompromised patients
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long-term safety data
	Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

II.B Summary of Important Risks

Important Potential Risk: Myocarditis and pericarditis	
Evidence for linking the risk to the medicine	Myocarditis and pericarditis have been reported in postmarketing surveillance of mRNA COVID-19 vaccines.
Risk factors and risk groups	Post-authorisation reports from other mRNA vaccine manufacturers, have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by the ECDC and US CDC and FDA has found reports to be most frequent in adolescent and young adult male patients following the second dose of vaccine, however, cases have also been observed in adult males and females of a broader age range following dose 1 and dose 2 of the vaccination.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4; PL Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Observational retrospective post-authorisation safety study (V206_06)

Important Potential Risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Several observational studies indicate an increased rate of coagulation disorders following COVID-19 vaccines (Vaxzevria: RR, 2.01 [95% CI, 1.75-2.31]; Comirnaty: RR, 1.12 [95% CI, 1.07-1.19]; and Spikevax: RR, 1.26 [95% CI, 1.07-1.47]) (Dag Berild 2022).
Risk factors and risk groups	Elderly age, prolonged hospitalisation/immobilisation, cancer, thyroid disease, oral contraceptive use, surgery, and pre-existing cardiovascular disease including prior deep vein thrombosis/ischaemia, phlebitis or cerebrovascular ischaemic attack, and hypertension. The risk of thromboembolism is also increased with inflammatory bowel disease. Lifestyle factors, including smoking, physical inactivity and increased weight.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Observational retrospective post-authorisation safety study (V206_06)

Missing Information: Use in Pregnancy and While Breastfeeding	
Evidence for linking the risk to the medicine	The safety profile of the vaccine is not fully known in pregnant or breastfeeding women

Missing Information: Use in Pregnancy and While Breastfeeding	
Risk factors and risk groups	Women of childbearing potential and lactating women.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6; PL Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A non-interventional, prospective study (pregnancy exposure study) to monitor the safety of Kostaive when used during pregnancy (V206_03)

Missing Information: Use in Immunocompromised Patients	
Evidence for linking the risk to the medicine	The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.
Risk factors and risk groups	Immunocompromised individuals and patients who are on immunosuppressive therapies.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 5.1. PL Section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A postauthorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).

Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders	
Evidence for linking the risk to the medicine	There is a theoretical concern that the vaccine may exacerbate their underlying disease.
Risk factors and risk groups	Individuals with autoimmune or inflammatory disorders.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A postauthorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).

Missing Information: Interaction with Other Vaccines	
Evidence for linking the risk to the medicine	There is a theoretical concern that the vaccine may interact with other vaccines.

Missing Information: Interaction with Other Vaccines	
Risk factors and risk groups	Individuals receiving additional vaccines.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A study of the immunogenicity and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population (ARCT-2303-01).

Missing Information: Long-term Safety Data	
Evidence for linking the risk to the medicine	The long-term safety profile of Kostaive is not fully known at present. Safety data has been collected for up to 12 months in studies.
Risk factors and risk groups	Individuals receiving Kostaive.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: One-year post-vaccination follow-up of participants in studies ARCT-154-01, ARCT-154-J01, and ARCT-165-01.

Missing Information: Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	
Evidence for linking the risk to the medicine	There is limited information in individuals with significant, unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders).
Risk factors and risk groups	Individuals with significant, unstable chronic medical conditions who are potentially at risk of severe COVID-19.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Kostaive.

II.C.2 Other studies in post-authorisation development plan

For the majority of safety concerns, routine pharmacovigilance activities including continuation of safety surveillance from the ongoing clinical trials are considered to be sufficient.

To address important potential risks myocarditis, pericarditis, and thromboembolic events, an observational safety surveillance study will be conducted (V206_06).

In addition, safety data to address missing information “Interaction with other vaccines” will be available following the completion of study of the immunogenicity and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population (ARCT-2303-01).

Studies ARCT-154-01, ARCT-154-J01, and ARCT-165-01 provide one-year post-vaccination follow-up information for participants to address missing information “Long-term safety data”.

To address missing information “Use in immunocompromised patients” and “Use in patients with autoimmune or inflammatory disorders” a postauthorisation safety study will be conducted. This study will include a broad population of patients with immunocompromising conditions (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).

To address missing information for use of Kostaive in pregnancy, a noninterventional, prospective study (pregnancy exposure study) to monitor the safety of Kostaive when used during pregnancy will be conducted (V206_03).

PART VII: ANNEXES

Annex 1 – Interface to the Eudravigilance System

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan

Annex 4 – Specific adverse drug reaction follow-up forms

Annex 5 – Protocols for proposed and ongoing studies in RMP Part IV

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Annex 7 – Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 4 – Specific adverse drug reaction follow-up forms

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1.1 Anaphylaxis Follow-up Form

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1.2 Bell's Palsy Follow-up Form

Link: Bell's Palsy Questionnaire

1.3 Guillain-Barré Syndrome Follow-up Form

Link: Guillain-Barré Syndrome Questionnaire

1.4 Multisystem Inflammatory Syndrome in Adults Follow-up Form

Link: Multisystem Inflammatory Syndrome in Adults

1.5 Myocarditis, Myopericarditis and Pericarditis Follow-up Form

Link: Myocarditis, Myopericarditis and Pericarditis Questionnaire

1.6 Thrombosis/Thromboembolism Follow-up Form

Link: Thrombosis/Thromboembolism Questionnaire

1.7 Transverse Myelitis Follow-up Form

Link: Transverse Myelitis Questionnaire

1.8 Acute Disseminated Encephalomyelitis Follow-up Form

Link: Acute Disseminated Encephalomyelitis Questionnaire

1.9 Thrombocytopenia Follow-Up Form

Link: Thrombocytopenia Questionnaire

1.10 Generalized Convulsion Follow-up Form

Link: Generalized Convulsion Questionnaire

Anaphylaxis Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s): ……

Symptoms / Signs: ……

1. What was the date and time of Kostaive last dose prior to onset of the EVENT(s)?

2. What was the date and time of onset of the EVENT(s)?

3. Please describe all the relevant signs and symptoms associated with the event (e.g. pruritis, urticaria, angioedema, lip oedema, conjunctivitis, dyspnea, tachypnoea, erythema, chest tightness, chills, rigors, cyanosis, tachycardia, numbness, laryngeal edema, hoarseness, stridor, bronchospasm, wheezing cough, fever, difficulty swallowing, taste disturbance, arrhythmia, tingling, flushing, hypotension, syncope, loss of consciousness, rash, myalgia, arthralgia, abdominal cramps, nausea, vomiting, diarrhea etc.):
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4. Relevant medical history – including prior anaphylaxis / hypersensitivity reactions, food allergies, drug allergies, recent insect bites, recent transfusion of blood or blood related products, recent vaccination, asthma, hay fever, urticaria, hives, recent contact with animals, history of infections (e.g. streptococcal throat, measles, ear infections, infected/abscessed tooth, mononucleosis, skin or wound infections/cellulitis, HIV, tuberculosis, sexually transmitted infections (e.g. syphilis), toxoplasmosis, cat scratch fever, etc.), immune-mediated diseases (e.g. lupus, rheumatoid arthritis, sarcoidosis, Sjogren's syndrome, etc.), etc.:
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5. Relevant concomitant medications (including dose and dates) – namely antibiotics (penicillins and cephalosporins), aspirin, NSAIDs, narcotic analgesics, herbal remedies, dietary supplements, radiocontrast media, etc.:
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Anaphylaxis Questionnaire

6. Family history of allergies/ anaphylaxis / hypersensitivity:
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7. Was the EVENT treated or managed?
☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. adrenaline, antihistamines, steroids, oxygen, etc.):
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8. What was the outcome of the EVENT?
☐ Resolved – date and time resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

9. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No If yes, please provide details: ……
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10. Was the patient examined by a specialist/consult (dermatologist, immunologist, intensivist)?
☐ Yes ☐ No
If yes, provide opinion/diagnosis.
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Investigations / Labs

11. Provide information concerning any investigations / labs / vitals performed with date and exact time (if available), including mast cell tryptase (MCT, serum/plasma), histamine (plasma) prostaglandin D2 (PGD2), temperature readings, blood pressure, blood chemistries (LFTs), CBC with differential, eosinophils, urinalysis, hepatitis serology, allergy testing, complete metabolic panel (CH50, C3, C4, C5a, Bb), antibodies (e.g. ANA, ANCA, anti-DNA, anti-SMA), immunoglobulins (IgE), skin biopsy, etc.:
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12. Please provide a brief summary of the event(s), include exact times if available:
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Anaphylaxis Questionnaire

Name of Reporter: ……
Profession: ……
Date: ……

Bell's Palsy Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of Kostaive last dose prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. Relevant medical history / concurrent illness – including cold sores and genital herpes (herpes simplex), chickenpox and shingles (herpes zoster), Epstein-Barr, CMV, respiratory illnesses (adenovirus), rubella, mumps, influenza, coxsackievirus, diabetes, sarcoidosis, Lyme's disease, inflammatory infections, immune-mediated diseases (e.g. RA, lupus, Guillain-Barré syndrome, Sjogren's syndrome, etc.), protein abnormalities, exposure to toxic chemicals (toxic neuropathy), exposure to cold temperature, poor nutrition / vitamin deficiencies, kidney failure, chronic alcoholism, etc.:
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4. (for female patients) Was the patient pregnant at the time of Bell's palsy?
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5. Vaccination history (received in last 6 weeks):
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6. Relevant concomitant medications (including dose and dates) – namely amiodarone, cancer therapies, chloramphenicol, chloroquine, colchicine, cytarabine, dapsone, disulfiram, etanercept, ethambutol, isoniazid, fluoroquinolones, gold, anti-hypertensive medications, hydroxychloroquine, infliximab, antibiotics, metronidazole, phenytoin, procainamide, statins, zalcitabine, etc.:
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Bell's Palsy Questionnaire

7. Please describe anatomic area involved (including ptosis), severity (including any stabbing pains), motor impact (location and extent of weakness), sensory impact (including tingling, numbness, loss of sensation, temperature sensation), findings from general examination (e.g. unable to or limited ability to wrinkle forehead, unable to or limited ability to raise eyebrows), etc.

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8. Other signs and symptoms associated with facial palsy (e.g. drooling, pain around the jaw or in or behind your ear, increased sensitivity to sound on the affected side, headache, loss of taste, changes in the amount of tears and saliva you produce, changes in hearing or vision, blood pressure, sexual dysfunction, GI problems, GU problems, excessive sweating, etc.):

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9. Family history of neuropathies (e.g. Charcot-Marie-Tooth disease, familial amyloidosis, Fabry disease, metachromatic leukodystrophy, etc.):

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10. Was the EVENT treated or managed?

☐ Yes ☐ No

If yes, provide details of treatments for the event(s) (e.g. corticosteroids, antiviral or antibacterial medication, pain medications, eye drops, antidepressants such as duloxetine or nortriptyline, antiseizure medicines such as gabapentin and pregabalin, topical patches and creams containing lidocaine or capsaicin, etc.):

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11. What was the outcome of the EVENT?

☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

12. Did the patient experience any EVENTs after previous dose(s) of Kostaive?

☐ Yes ☐ No ☐ N/A If yes, please provide details:

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13. Was the patient examined by a Neurologist? ☐ Yes ☐ No

If yes, provide opinion/diagnosis.

Bell's Palsy Questionnaire

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Investigations / Labs

14. Provide information concerning any investigations / labs / vitals performed, including (temperature (readings and dates), BMI, blood glucose, renal function, thyroid function, vitamins deficiency (E, B-1, B-6, and B-12), liver function, toxicology panel, MRI, electrodiagnostic assessment, nerve conduction study, needle electromyography, biopsy (nerve, muscle or skin), etc.:
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15. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: ……

Guillain Barre Syndrome Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of Kostaive last dose prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. Relevant medical history / concurrent illness – gastrointestinal infections (diarrhea), respiratory infections, septicemia, infections with Campylobacter jejuni, Cytomegalovirus, Epstein–Barr virus, Varicella zoster virus, Mycoplasma pneumoniae, Dengue fever, Zika virus, Hepatitis E virus, etc., any recent surgery, etc.:
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4. Vaccination history (received in last 6 weeks):
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5. Relevant concomitant medications (including dose and dates) – namely antibiotics, antipsychotics (risperidone) etc.:
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6. Please describe the extent of the GBS, including anatomic location(s), extent, severity, time to onset of symptoms, motor impact (location and extent of weakness), sensory impact (including tingling, numbness, loss of sensation, temperature sensation), etc.
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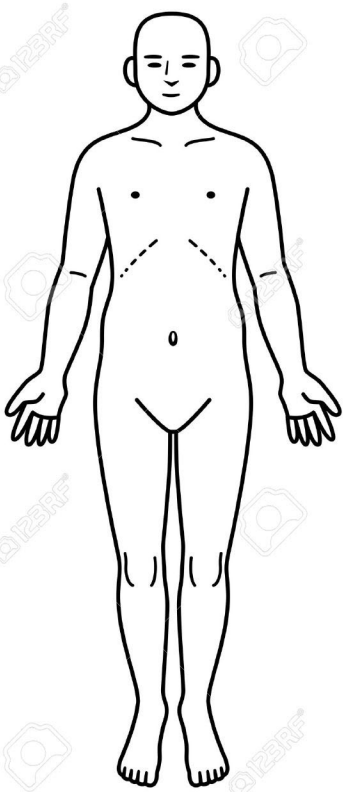
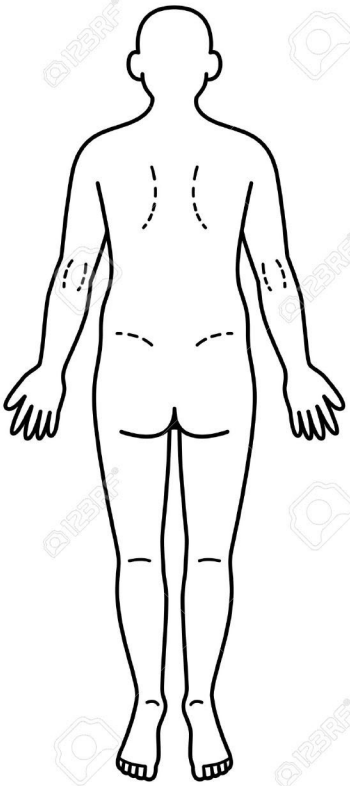
7. Please denote on the images below the anatomic areas impacted by the GBS:





8. Other signs and symptoms associated with GBS (e.g. numbness, tingling, muscle weakness, weakness of the legs and arms, weakness of the eye, face and neck muscles, swallowing difficulties, pain (back, head, neck), muscle pain, drowsiness, sleepiness, coma, cranial nerves involvement, hypo- or areflexia (reduced or absent tendon reflexes respectively), exaggerated reflexes, heart rate and blood pressure changes, sweating abnormalities, etc.):

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9. Family history of GBS:

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10. Was the EVENT treated or managed?

☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. immunotherapy (plasmapheresis, intravenous immunoglobulins), steroids, pain medication, oxygen, mechanical ventilation, anti-hypertensives, etc.):

Guillain Barre Syndrome Questionnaire

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11. What was the outcome of the EVENT?
☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

12. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No ☐ N/A If yes, please provide details:
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13. Was the patient examined by a Neurologist? ☐ Yes ☐ No
If yes, provide opinion/diagnosis.
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Investigations / Labs

14. Provide information concerning any investigations / labs / vitals performed, including (nerve conduction studies, cerebrospinal fluid analysis, antiganglioside antibodies, blood sodium and potassium, MRI spine), etc.:
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15. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: ……

Multisystem Inflammatory Syndrome in Adults

Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date of Kostaive last dose prior to onset of the diagnosis of Multisystem Inflammatory Syndrome in Adults (MIS-A)?

2. Provide details of Kostaive vaccine and other COVID-19 vaccine if available with dates and dose.

3. What was the date of diagnosis of MIS-A, which is described as a severe illness requiring hospitalization in a person aged 21 years or more, with laboratory evidence of current or previous (within 12 weeks) SARS-CoV-2 infection, severe extrapulmonary organ dysfunction (including thrombosis), laboratory evidence of severe inflammation, and absence of severe respiratory disease?

4. Please describe all the relevant signs, symptoms and lab values pertaining to MIS-A:

- Fever more than 3 consecutive days
- Clinical features: mucocutaneous (rash, erythema or cracking of the lips/mouth/pharynx, bilateral nonexudative conjunctivitis, erythema/edema of the hands and feet), gastrointestinal (abdominal pain, vomiting, diarrhea), shock/hypotension, neurologic (altered mental status, headache, weakness, paresthesiae, lethargy), thrombosis/thromboembolism, acute liver injury, multiorgan failure
- Laboratory confirmed SARS-CoV-2 infection
- Laboratory evidence of inflammation (elevated CRP, ESR, ferritin, or procalcitonin)
- Elevated BNP or NT-proBNP or troponin
- Neutrophilia, lymphopenia, or thrombocytopenia
- Evidence of cardiac involvement by echocardiography or physical stigmata of heart failure (gallop or rales, lower extremity edema, jugular venous distension, hepatosplenomegaly)
- ECG changes consistent with myocarditis/myopericarditis. pericarditis

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Multisystem Inflammatory Syndrome in Adults

Questionnaire

5. Please describe if other symptoms were present? (e.g., fever, shock, rash, conjunctivitis, abdominal symptoms (nausea, vomiting, diarrhea), hypotension, cardiac dysfunction, headache, respiratory symptoms, features of meningitis, cellulitis, etc.)

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6. Relevant medical history (e.g., immunocompromised status, cardiovascular risk factors, hepatic/renal disease, hypertension, diabetes, etc.)

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7. Was there an alternate explanation for MIS-A? (Please specify differential diagnosis)

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8. Relevant concomitant medications (including dose and dates):

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9. Family history of COVID-19/ MIS (Children or Adults):

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10. How was MIS-A treated or managed?
Provide details of treatments for the event(s) (e.g. antivirals, specific medications for COVID-19, adrenaline, antihistamines, steroids, antibiotics, etc.):

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11. What was the outcome of the EVENT?

☐ Resolved – date and time resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....……
☐ Not resolved (ongoing)

12. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?

☐ Yes ☐ No If yes, please provide details: ……
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13. Was the patient examined by a specialist/consult (pulmonologist, cardiologist, intensivist)?
☐ Yes ☐ No

If yes, provide opinion/diagnosis.
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Investigations / Labs

14. Provide information concerning any physiologic / laboratory testing performed with date and exact time if available
- SARS-CoV-2 infection
- Inflammation markers (elevated CRP, ESR, ferritin, or procalcitonin)
- BNP or NT-proBNP or troponin
- ECG / Echocardiography
- CBC (neutrophil, lymphocyte, thrombocyte counts)
- Coagulation profile
- Other relevant for multiorgan failure

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15. Please provide Adult severity scores

□ National Early Warning Score (NEWS)
□ APACHE II
□ Sequential Organ Failure Assessment (SOFA)
□ Glasgow Coma Score
□ Other adult score (describe)

□ Not available

16. Please provide a brief summary of the event(s), include exact times if available:
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Multisystem Inflammatory Syndrome in Adults

Questionnaire

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Name of Reporter: ……
Profession: ……
Date: …….

Myocarditis/Myopericarditis/Pericarditis Questionnaire

Subject Number (if applicable):

Age: ……..
Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of last dose of Kostaive prior to onset of the EVENT(s)?

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2. What was the date of onset of the EVENT(s)? ……..

3. Signs and symptoms associated with the event (e.g. chest pain, shortness of breath (at rest or during physical activity, please specify), fluid retention / edema (specify anatomic location – e.g. legs, ankles, feet, etc.), fatigue, signs and symptoms of a viral infection (such as a headache, body aches, joint pain, fever, sore throat, breathing difficulties, diarrhea, etc.):
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4. Relevant medical history / concurrent or recent illness (including month/ year):

- athletes/ history of intense physical exercise
- alcohol consumption (amount and frequency)
- chest trauma
- myocardial infarction, aneurysm, pleural and pulmonary disease
- viral infections (e.g. Coxsackie, Influenza, Rubella, Polio, Adenovirus, HIV, Hepatitis B and C, Parvovirus, Herpes simplex, etc.)
- bacterial infections (e.g. Staphylococcus, Streptococcus, Corynebacterium, Rickettsia, Chlamydia, Coxiella, Lyme's disease, etc.)
- protozoal infections (e.g. E histolytica, Leishmania, P. falciparum, N. fowleri, Toxoplasma gondii, Trypanasomomiasis/Chagas disease)
- fungal infections (e.g. Actinomyes aspergillis, Blastomyceses, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucor, Nocardia, Sporothrix)
- parasitic infections (Ascaris, Cysticercosis, Echinococcus granulosus, Trichinosis, Schistosomiasis, Visceral larva migrans, Wucheria bancrofti)
- radiation
- poisoning (e.g. lead, hydrocarbons, arsenic, etc.)
- immune-mediated diseases (e.g. systemic lupus erythematosus (SLE), Sjögren's syndrome, vasculitis, polymyositis, sarcoidosis, etc.)

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5. Relevant concomitant medications (including dose and dates) and any new drugs initiated in the previous 1 month

- Allergy and asthma medications (pyribenzamine, aminophylline, theophylline)
- Anti-arrhythmics (procainamide, quinidine, mexiletine)
- Antibacterials, antifungals & antivirals (penicillin, ampicillin, azithromycin, cephalosporins, tetracyclines, INH, tetracycline, sulfonamides, chloramphenicol, streptomycin, trimethoprim amphotericin B, dapsone, zidovudine)
- Anti-diabetic (chlorpropamide)
- Anti-hypertensives (reserpine, triamterene)
- Anti-inflammatory (indomethacin, diclofenac, colchicine, allopurinol, phenylbutazone)
- Antimigraine (methylsergide)
- Antineoplastic (anthracyclines, cyclophosphamide, doxorubicin, 5-FU, Immune checkpoint inhibitors, tyrosine kinase inhibitors, trastuzumab, TNF-antagonists, doxorubicin)
- Anti-seizure (phenytoin)
- Cardiac medications (digoxin, dobutamine, catecholamines)
- Diuretics (thiazide, hydrochlorothiazide, furosemide, spironolactone)
- Local anaesthetic (lidocaine)
- Psychiatric drugs (tricyclic antidepressants, benzodiazepines, clozapine, lithium, methyldopa)
- Recreational/illicit drugs (metamphetamine, cocaine)
- Other (Bites - scorpion, bee/wasp, black widow spider, snakes; Radiation; Heavy metal - Copper, lead, arsenical, iron)

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6. Any recent illegal substance use, such as cocaine, alcohol, etc. (please specify quantity):
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7. Please describe the extent of the EVENT(s), from a cardiology perspective (rapid or abnormal heart rhythms (arrhythmias), heart failure (please specify NYHA class), ventricular assist device, heart transplant, MI, stroke, sudden cardiac death:
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8. Was the EVENT treated or managed, including treatment at another institution?
☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. corticosteroids, antibiotics, antivirals, antifungals, anticoagulants, ACE inhibitors, ARBs, beta blockers, ventricular assist devices (VADs), intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), etc.):
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9. What was the outcome of the EVENT?
☐ Resolved – date resolved ……...…
☐ Sequelae ☐ Yes ☐ No If yes, describe ..…….....
☐ Not resolved (ongoing)

10. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No ☐ N/A If yes, please provide details:
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11. Was the patient examined by a Cardiologist? ☐ Yes ☐ No
If yes, provide opinion/diagnosis.
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Investigations / Labs

12. Provide information concerning any investigations / labs / vitals performed, including:
☐ ECG results (arrhythmias, AV conduction delays, segment abnormalities, PACs, PVCs, etc.)
☐ Chest X-ray
☐ Cardiac MRI (T2 study (edema); late gadolinium enhancement on T1 study (myocyte injury))
☐ Echocardiogram (cardiac abnormalities)
☐ Cardiac catheterization
☐ Troponin I and T, CK myocardial band
☐ Laboratory tests for inflammation (e.g. CRP, ESR)
☐ Laboratory tests for infections (including bacterial, viral, fungal and protozoal)
☐ Histopathology diagnosis of endo/myocardial tissue (biopsy)
☐ Cardiac Functional Status test results (pre and post myocarditis/pericarditis event)

Myocarditis/Myopericarditis/Pericarditis Questionnaire

Please provide details of any of these test results below:

13. Please provide a brief summary of the event(s):

Myocarditis/Myopericarditis/Pericarditis Questionnaire

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Name of Reporter: ………………………………………………………………………………
Profession: ………………………………………………………………………………………
Date: ……………………………………………………………………………………………

Thrombosis/Thromboembolism Questionnaire

Subject Number (if applicable):

Age: ……

Sex: ☐ Male ☐ Female

Reported Adverse EVENT(s):

1. What was the date of the most recent dose of Kostaive prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. What was the severity of the most severe EVENT?
☐ Mild ☐ Moderate ☐ Severe

4. Were any of the EVENT(s) serious and if so which one(s):
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5. Relevant medical history / concurrent illnesses: (e.g., hypertension, smoking, atrial fibrillation or other arrhythmias, cancer/ chemotherapy, congenital heart diseases, sickle cell disease, coagulation/bleeding disorders (thrombophilia, e.g., Factor V Leiden mutation, protein C and S deficiency, antithrombin III deficiency, hyper-homocystinuria), estrogen-based medications (oral contraceptives or hormone replacement therapy), immobility/critically ill patients, indwelling devices, trauma/surgery, and inherited predisposition, thrombosis (e.g. DVT, pulmonary embolism etc.), metabolic, endocrine, respiratory, acute infectious diseases; infections (including GI, E coli and shigella), inflammatory conditions, recent surgeries (including joint replacement), varicose veins with phlebitis, etc. (including dates):
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6. Relevant concomitant medications (including dose and dates) – namely nonsteroidal anti-inflammatory drugs (NSAIDs), estrogen-based medications (oral contraceptives or hormone replacement therapy), heparin, tamoxifen, thalidomide, erythropoietin, JAK-inhibitors, anti-coagulant medications, etc.:
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7. Vaccination history (received in last 6 weeks):
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Thrombosis/Thromboembolism Questionnaire

8. Ambulation history:
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9. Hydration status:
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10. If female, method of contraception (if any) and gestation history:
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11. History of smoking (including dates, quantity of smoking per day, etc.):
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12. Family history of thrombosis/thromboembolism:
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13. Was the EVENT treated or managed?
☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. anticoagulants, procedures, filters, compression stockings, etc.):
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14. What was the outcome of the EVENT?
☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

15. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No If yes, please provide details: ……
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16. Was the patient examined by a hematologist? ☐ Yes ☐ No
If yes, provide hematologist's opinion/diagnosis:
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17. Was the event venous or arterial?
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Investigations / Labs

18. Provide information concerning any investigations / labs performed, including (PT (and other coagulation test results), INR, D-dimer, fibrinogen, CBC and microscopy/smear, Factor V Leiden, antiphospholipid antibody, protein C/S deficiency, ATIII deficiency and any other abnormal factors that affect coagulation, homocysteine, imaging test results (e.g. VQ scan, CT/MRI, angiogram, carotid doppler, duplex ultrasound, venography, etc.)
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Thrombosis/Thromboembolism Questionnaire

19. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: …….

Transverse Myelitis Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of Kostaive last dose prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. Relevant medical history / concurrent illness – including viral infections (HIV, herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, Zika virus and West Nile virus), bacterial infections (Mycoplasma pneumoniae, Bartonella henselae, Lyme disease, Campylobacter jejuni, Tuberculosis, Actinomyces), schistosomiasis, sarcoidosis. immune system disorders, demyelinating diseases, multiple sclerosis, meningococcal meningitis, neuromyelitis optica (NMO), spinal cord injuries, vascular disorders affecting spinal cord, paraneoplastic syndrome), etc.:
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4. Vaccination history (received in last 6 weeks):
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5. Relevant concomitant medications (including dose and dates) – antivirals, antibiotics, etc.:
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6. Please describe the extent of the symptoms of TM, including anatomic location(s), extent, severity, time to onset of the symptoms, motor impact (location and extent of weakness), sensory impact (including tingling, numbness, loss of sensation, temperature sensation), etc.
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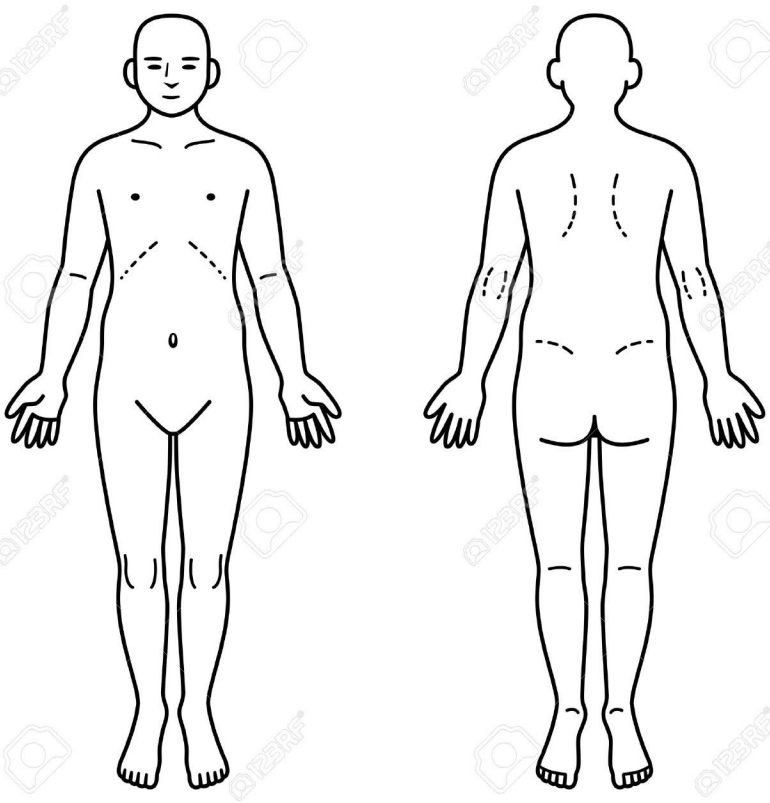
7. Please denote on the images below the anatomic areas impacted by the symptoms of TM:



8. Other signs and symptoms associated with the EVENT (e.g., pain, abnormal sensations, weakness, numbness and sensory/motor deficits in the limbs, disturbances in sensory nerves and motor nerves, dysfunction of the autonomic nervous system at the level or below the lesion, bladder and bowel dysfunction, erectile dysfunction, high blood pressure, pain, respiratory failure, etc.):

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9. Family history of any neurological disorders:

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10. Was the EVENT treated or managed?

☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. corticosteroids, plasmapheresis, supportive care, etc.):

Transverse Myelitis Questionnaire

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11. What was the outcome of the EVENT?
☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

12. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No ☐ N/A If yes, please provide details:
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13. Was the patient examined by a Neurologist? ☐ Yes ☐ No
If yes, provide opinion/diagnosis.
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Investigations / Labs

14. Provide information concerning any investigations / labs / vitals performed, including (CSF analysis, CT/MRI myelography), etc.:
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15. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: …….

Acute Disseminated Encephalomyelitis Questionnaire

Subject Number (if applicable):

Age: ……..

Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of Kostaive last dose prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. Relevant medical history / concurrent illness – including viral infections (e.g. HIV, herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, adenovirus, COVID-19), bacterial infections (e.g. Lyme disease, tuberculosis, meningococcus), immune-mediated conditions (e.g. demyelinating diseases (e.g. multiple sclerosis, neuromyelitis optica, neurologic Behcet's disease, neurosarcoidosis), systemic lupus erythematosus, anti NMDA receptor encephalitis, vasculitis), cerebral injuries, CNS malignancy, paraneoplastic syndrome, organ transplant, toxic or metabolic disorders (e.g. carbon dioxide poisoning, Vit B12/folate deficiency, mercury poisoning, Grave's disease, Hashimoto encephalopathy), etc.:
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4. Vaccination history (received in last 6 weeks):
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5. Relevant concomitant medications (including dose and dates) – antivirals, antibiotics, NSAID, immunosuppressants, radiological imaging agents, antiepileptics, blood transfusions, intravenous immunoglobulins, etc.:
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6. Please describe the symptoms of ADEM, including focal/multifocal CNS abnormalities (e.g. lethargy, depressed/altered level of consciousness, response to external stimuli, seizure, focal cortical signs, cranial nerve dysfunction, visual field defect, presence of primitive reflexes, cerebellar

dysfunction, etc.), motor impact (location and extent of weakness), sensory impact (including tingling, numbness, loss of sensation, temperature sensation), deep tendon reflexes impact, severity, time to onset of the symptoms, etc.

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7. Other signs and symptoms associated with the EVENT (e.g., myelopathy - sensory, motor or autonomic dysfunction attributable to spinal cord, including upper-and/or lower-motor neuron weakness, sensory deficit, dysfunction of the autonomic nervous system (bladder and/or bowel dysfunction, erectile dysfunction):

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8. Family history of any neurological disorders:

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9. Was the EVENT treated or managed?

☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. corticosteroids, plasmapheresis, intravenous immunoglobulins, supportive care, etc.):

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10. What was the outcome of the EVENT?

☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

11. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?

☐ Yes ☐ No ☐ N/A If yes, please provide details:

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12. Was the patient examined by a Neurologist? ☐ Yes ☐ No

If yes, provide opinion/diagnosis.

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Acute Disseminated Encephalomyelitis Questionnaire

Investigations / Labs

13. Provide information concerning any investigations / labs / vitals performed (e.g. CSF analysis (including bacterial culture, cytology and viral detection), CT/MRI, tissue biopsy with histopathology (brain, spinal cord), EEG, blood culture, serology for infectious agents, immune profile, etc.):

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14. Please provide a brief summary of the event(s):

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Name of Reporter: ……
Profession: ……
Date: …….

Thrombocytopenia Questionnaire

Subject Number (if applicable):

Age: ……

Sex: ☐ Male ☐ Female

Reported Adverse EVENT(s):

1. What was the date of the most recent dose of Kostaive prior to onset of the EVENT(s)?

2. What was the date of onset of the EVENT(s)?

3. Provide exact symptoms/signs with details (such as bruising, epistaxis, hematuria, hematemesis, purpura, petechiae, hematoma hematochezia, hemorrhagic oozing of skin lesion, occult bleeding from rectum, conjunctival bleeding, intracranial bleeding, non-menstrual vaginal bleeding, other bleeding)

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4. What was the severity of the most severe EVENT?
☐ Mild ☐ Moderate ☐ Severe

5. Were any of the EVENT(s) serious and if so which one(s):
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6. Relevant medical history / concurrent illnesses:

- Autoimmune diseases (systemic lupus erythematosus, Evans / Sjogren's / antiphospholipid syndromes), Hematologic malignancy: non-Hodgkin lymphoma, chronic lymphocytic leukemia, Primary immune deficiency: common variable immune deficiency, autoimmune lymphoproliferative syndrome, Vitamin B9 or B12 deficiency
- Non-immune thrombocytopenia (decreased production - bone marrow replacement, bone marrow failure, Increased consumption – Hypersplenism, Giant hemangioma/Kasabach-Merritt Syndrome)
- Infection (Viral: Hepatitis C, HIV, CMV, Helicobacter pylori; Dengue, bacterial sepsis)
- Genetic disorders (polymorphisms of several genes including MHC, Fc gamma receptor, transcription factors, chemokines, pro/anti-inflammatory cytokines and their receptors; human platelet antigens; Congenital thrombocytopenia, several syndromes - Absent Radius, DiGeorge, Wiskott-Aldrich, Bernard-Soulier, congenital megakaryocytic thrombocytopenia)
- Other: hypertension, smoking
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7. Vaccination history (received in last 6 weeks):
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8. Relevant concomitant medications (including dose and dates):
- Bone marrow myelosuppression: anticancer drugs, valproic acid
- Secondary thrombocytopenia due to several drugs

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9. Family history of thrombocytopenia:
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10. Was the EVENT treated or managed?
☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. anticoagulants, procedures, filters, compression stockings, etc.):
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11. What was the outcome of the EVENT?
☐ Resolved – date resolved ……
☐ Sequelae ☐ Yes ☐ No If yes, describe …….....
☐ Not resolved (ongoing)

12. Did the patient experience any EVENT(s) after previous dose(s) of Kostaive?
☐ Yes ☐ No If yes, please provide details: ……
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13. Was the patient examined by a hematologist? ☐ Yes ☐ No
If yes, provide hematologist's opinion/diagnosis:
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Investigations / Labs

14. Provide information concerning any investigations / labs performed, including (CBC, Platelet count, peripheral blood smear, other coagulation test results, INR, bone marrow cytology and

Thrombocytopenia Questionnaire

histology, anti-platelet antibodies, serum cytokine levels, etc.):
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15. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: …….

Generalised Convulsion Questionnaire

Subject Number (if applicable):

Age: ……..
Sex: ☐ Male ☐ Female

Reported Adverse Event(s):

1. What was the date and time of last dose of Kostaive prior to onset of the EVENT(s)?

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2. What was the date of onset of the EVENT(s)? ……..

3. Please describe the EVENT(s) (simple seizure (e.g. single, isolated occurrence, brief and symmetric in appearance) or complex seizure (repeated seizure activity, > 15 min in duration or focal features), psychogenic non-epileptic seizure (immunisation stress-related response), febrile/afebrile seizure, duration of seizure episode (time in minutes or seconds), sudden loss of consciousness, motor manifestation of seizure (e.g. generalised motor manifestations, tonic movements, clonic movements, tonic-clonic movements, atonic motor manifestations), etc.):
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4. Relevant medical history / concurrent illness (including drug withdrawal, stroke, cerebral hypoxia, head trauma, Parkinson's disease, CNS infection, neoplasm, metabolic disorders (e.g., uremia, hypoglycemia, and electrolyte disorders), psychiatric disorders (e.g. Alzheimer's disease, dementia), etc.):

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5. Previous history of seizures (e.g. febrile convulsion, epilepsy):
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6. Family history of seizures or epilepsy
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Generalised Convulsion Questionnaire

7. Vaccination history (received in last 6 weeks):
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8. Relevant concomitant medications (including dose and dates) – anticonvulsants, herbal or homeopathic medication, immunoglobulins, blood transfusion, etc.

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9. Any recent illegal substance use, such as cocaine, alcohol, etc. (please specify quantity):
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10. Was the EVENT treated or managed, including treatment at another institution?
☐ Yes ☐ No If yes, provide details of treatments for the event(s) (e.g. anticonvulsants, antipyretics, electrical stimulation, etc.):
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11. What was the outcome of the EVENT?
☐ Resolved – date resolved ……...…
☐ Sequelae ☐ Yes ☐ No If yes, describe ...…….....
☐ Not resolved (ongoing)

12. Was the patient examined by a Neurologist? ☐ Yes ☐ No
If yes, provide opinion/diagnosis.
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Investigations / Labs

13. Provide information concerning any investigations / labs / vitals performed, including head CT/MRI, CSF analysis, EEG:
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Generalised Convulsion Questionnaire

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14. Please provide a brief summary of the event(s):
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Name of Reporter: ……
Profession: ……
Date: ……

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable.