Kostaive : Periodic safety update report assessment

28th November 2024 to 27th May 2025

This document consists of:

1. The PRAC assessment report of the EMA/PSUR/0000296565 periodic safety update report (PSUR) covering the period 28th November 2024 to 27th May 2025, and;
2. The EMA/PSUR/0000296565 PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMADOC-1700519818-2457701
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000296565

PRAC PSUR assessment report

EURD list no.: PSUSA/00011115/202505

Active substance: Zapomeran

Period covered by the PSUR: 28 Nov 2024 to 27 May 2025

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
Kostaive	Seqirus Netherlands B.V.

Status of this report and steps taken for the assessment

Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	11 September 2025	11 September 2025
☐	Start date	18 September 2025	18 September 2025
☐	PRAC Rapporteur AR	17 November 2025	07 November 2025
☐	PRAC/MAH comments	17 December 2025	N/A
☐	Updated PRAC Rapporteur AR	1 January 2026	22 December 2025
☒	PRAC outcome	15 January 2026	15 January 2026

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for Kostaive (zapomeran).

2. Assessment conclusions and actions

Kostaive is a COVID-19 self-amplifying messenger RNA (sa-mRNA) vaccine. The active pharmaceutical ingredient is a single-stranded, 5'-capped sa-mRNA replicon, produced using a cell-free in vitro transcription from the corresponding deoxyribonucleic acid (DNA) templated encoding a replicase and the prefusion-stabilised, furin cleavage site-inactivated spike glycoprotein (S glycoprotein) of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-2).

To generate the vaccine, the mRNA is encapsulated in lipid nanoparticles (LNP). The lipids serve to protect the sa-mRNA from degradation and enable delivery of the sa-mRNA into the host cell. The sa-mRNA consists of a series of ribonucleotides encoding the replicase and a RNA sequence encoding the SARS-CoV-2 S glycoprotein.

Unlike the sa-mRNA in conventional sa-mRNA vaccines, Kostaive is designed to replicate within the body's own cells. After intramuscular delivery of Kostaive, it produces a protein called replicase that makes copies of the entire sa-mRNA as well as specifically amplifying the SARS-CoV-2 S glycoprotein RNA messenger. Thus, a lower dose of Kostaive can produce as much or more SARS-Cov-2 S glycoprotein than can be delivered by a higher dose of a conventional sa-mRNA vaccine.

The approved indication of Kostaive is active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Kostaive must be administered intramuscularly after reconstitution. A single dose contains 5 µg of sa-mRNA in 0.5 mL.

At the time of the DLP of the PSUR, Kostaive was authorised in 31 countries worldwide.

Cumulative, around 21,235 participants have been exposed to Kostaive in MAH-sponsored and Partner-sponsored clinical trials (completed and ongoing) since the development international birth date (DIBD) on 20 July 2020.

During the reporting period, the marketing exposure to Kostaive was estimated at [redacted] standard doses sold. Cumulatively, the marketing exposure was estimated at 136,816 standard doses sold. After DLP on 27 May 2025, 7,386 vials were returned from stock. Therefore, the corrected cumulative exposure is 1,165 vials (18,640 standard doses).

During the reporting period, no significant actions for safety reasons were taken. No changes to the benefit-risk profile for Kostaive have been observed.

The overall benefit-risk balance for Kostaive remains unchanged.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing zapomeran remains unchanged and therefore recommends the maintenance of the marketing authorisation.

4. PSUR frequency

☒No changes to the PSUR frequency

The current **6**-month frequency for the submission of PSURs should remain unchanged.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the assessment of the third PSUR for Kostaive (Zapomeran) for the reporting period 28 November 2024 to 27 May 2025. It includes data from the marketing partner companies Meiji Seika Pharma and Arcturus Therapeutics. The IBD for Kostaive is 28 November 2023 in Japan.

Kostaive is a vaccine indicated for active immunisation to prevent COVID-19 disease. The active pharmaceutical ingredient is a single-stranded, 5'-capped self-amplifying messenger ribonucleic acid (sa-mRNA) replicon produced using a cell-free in vitro transcription from the corresponding DNA template, encoding a replicase and the spike glycoprotein (S glycoprotein) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To generate the vaccine, the sa-mRNA is encapsulated in lipid nanoparticles. The lipids serve to protect the mRNA from degradation and enable delivery of the sa-mRNA into the host cell. The sa-mRNA consists of a series of ribonucleotides encoding the replicase and an RNA sequence encoding the SARS-CoV-2 S glycoprotein. Unlike the sa-mRNA in conventional sa-mRNA vaccines, Kostaive is designed to replicate within the body's own cells. After intramuscular delivery of Kostaive, it produces a protein called replicase that makes copies of the entire sa-mRNA as well as specifically amplifying the SARS-CoV-2 S glycoprotein RNA messenger. Thus, a lower dose of Kostaive can produce as much or more SARS-CoV-2 S glycoprotein messenger than can be delivered by a higher dose of a conventional sa-mRNA vaccine. By promoting the expression of this viral S protein in vaccinated individuals, Kostaive is intended to promote SARS-CoV-2-specific immune responses to provide active immunisation to prevent COVID-19.

LUNAR-COV19 formulations are being developed for the prevention of COVID-19:

- ARCT-021: replicon (mRNA-2002) encodes for the ancestral strain S glycoprotein in the native conformation
- ARCT-154: replicon (mRNA-2105 [zapomeran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the G clade D614G variant of SARS-CoV-2
- ARCT-165: replicon (mRNA 2106) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Beta (B.1.351) variant of SARS-CoV-2 with the D614G mutation
- ARCT-2303: replicon (mRNA-2319 [lonpovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron XBB.1.5 variant of SARS-CoV-2
- ARCT-2301: contains 2 replicons:
    - one encoding for the prefusion-stabilised, furin cleavage site-inactivated S glyocoprotein of the G clade D614G variant of SARS-Cov-2 (mRNA-2318) and
    - the other encoding for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron BA.4/5 variants (mRNA-2317 [tagovameran]).
- CSL402: replicon (mRNA-2425 [quozovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron JN.1 variant

The approved indication for Kostaive according to the Reference Safety Information is for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Kostaive contains 5 µg of sa-mRNA in 0.5 mL and must be administered after reconstitution. The vaccine should not be mixed with any other vaccines or medicinal products in the same syringe. A

single dose must contain 0.5 mL of Kostaive. The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

The composition of Kostaive is presented in Table 1.

Table 1: Composition of Kostaive

Strains	**Per 0.5 mL Dose**
sa-mRNA	5.0 µg
Excipients	**Per 0.5 mL Dose**
ATX-126	[redacted]
DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)	
Cholesterol	
PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene)	
Tris (tris(hydroxymethyl)aminomethane)	
Sodium chloride	
Sucrose	
Potassium sorbate	
Kolliphor P 188 Bio[a]	

sa-mRNA = self-amplifying messenger ribonucleic acid
[a]also known as "Poloxamer 288"

No changes to the product information were proposed by the MAH.

1.2. Worldwide marketing authorisation status

Kostaive was first authorised on 28 November 2023 in Japan where it is marketed by Meiji Seika Pharma. The product is currently registered in 31 countries worldwide.

Kostaive was approved in the EU / EEA including Iceland, Liechtenstein and Norway on 12 February 2025. The Market Authorisation was transferred from Arcturus Therapeutics Europe B.V. to Seqirus Netherlands B.V. on 16 April 2025.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the reporting period, no actions for safety reasons were taken by the MAH, sponsors of clinical trials, regulatory authorities, data monitoring committees or ethics committees.

1.3.2. Changes to reference safety information

The Reference Safety Information (RSI) in effect at the start of the reporting period was the Company Core Data Sheet (CCDS) version 1.0, dated 05 November 2023. During the reporting period, the RSI was updated once to CCDS version 2.0, dated 15 May 2025, to include a general warning for myocarditis and pericarditis as events that may occur very rarely following administration of COVID-19 vaccines in section 4.4 (Warnings and Precautions) and to revise section 4.5 (Interactions), based on the completion of clinical study ARCT-2303-01, to include information on the concomitant administration of Kostaive with influenza vaccines.

Rapporteur assessment comment:

In the current PSUR interval, the CCDS has been updated to version 2.0 to include a warning regarding

the risk of myocarditis and pericarditis and to include information on the concomitant administration of Kostaive with influenza vaccines. The warning for myocarditis and pericarditis is already reflected in section 4.4 of the EU SmPC. An updated version of the SmPC which includes information on the concomitant information with influenza vaccines has been submitted by the MAH and is currently assessed in the ongoing procedure EMA/VR/0000284897.

1.3.3. Estimated exposure and use patterns

Cumulative subject exposure in clinical trials

Up to the Data Lock Point of the PBRER, 21,235 subjects have been exposed to Kostaive in completed and ongoing clinical trials. 29 subjects have been randomised to exclusively receive placebo (>18,000 participants received placebo either prior or after receiving Kostaive), 3,544 participants have been exposed to the comparator, which includes an estimated 1,499 participants who have received a co-administered or sequentially administered influenza vaccine.

Cumulative and interval patient exposure from marketing experience

- Post-authorisation (non-clinical trial) exposure

It is assumed that one dose of the vaccine accounts for one exposed patient.

Cumulative and interval sales volumes are presented in Table 2. It is to be noted that after DLP on 27 May 2025, 7,386 vials were returned from stock and therefore, the corrected cumulative exposure is 1,165 vials (18,640 standard doses).

Table 2: Estimated sales volume in vials

Previous period 28 May 2024 to 27 Nov 2024	Current period 28 Nov 2024 to 27 May 2025	Cumulatively 28 Nov 2023 to 27 May 2025	Cumulatively Correction after DLP
[redacted]		8,551	1,165

Table 3: Current period sales volume per country

Country	Sales Volume (Vials)
Japan	[redacted]

During the reporting period, 95,344 standard doses have been sold worldwide (5,959 vaccine vials shipped during the reporting period, each vial provided 16 doses of vaccine).

Cumulatively, 136,816 standard doses have been sold worldwide (8,551 vials shipped during the reporting period, each vial provides 16 doses of vaccine).

During the reporting period, exposure increased compared to the previous reporting period. Of note, Kostaive was commercially launched in October 2024. Thus, the previous post-marketing exposure only covers 2 months. The current reporting period includes a post-marketing exposure for 6 months. This explains the increase in post-marketing exposure if calculated on the interval only. See also Table 4.

Table 4: Estimated worldwide patient exposure for Kostaive

	Previous period 28 May 2024 to 27 Nov 2024	Current period 28 Nov 2024 to 27 May 2025	Cumulatively 28 Nov 2023 to 27 May 2025	Cumulatively Correction after DLP
Single-dose exposure	[redacted]		136,816	18,640

- Post-authorisation use in special populations

Other than its post-marketing data collection system, the MAH has no specific collection system in place to monitor exposure in special populations. Therefore, the available information regarding the cumulative and interval patient exposure in special populations was retrieved by searching the MAH's safety database for all valid cases received from post-marketing reporting regardless of causality. However, due to the nature of post-marketing reporting, it must be noted that a reliable exposure estimation cannot be drawn from these cases.

Use in paediatric population

Cumulatively, one case and during the reporting period, follow-up of this case was received from post-marketing reporting concerning exposure of an adolescent (12 to <18 years). No new significant information was received in this case. One foetal case was excluded from the number of cases as it is coded with foetal exposure during pregnancy and route of administration transplacental.

Review of cases concerning paediatric patient exposure did not change the current safety profile of the product.

Use in elderly population

During the reporting period, a total of 182 (172 initial and 10 follow-up) cases were retrieved from the MAH's Global Safety Database pertaining to use in elderly patients, aged 65 to >90 years (including 34 cases with unknown age). Of the 172 initial cases, 103 were reported from spontaneous sources and 69 from post-marketing safety study KO01 (Drug use-results survey, NIS-PVA159436).

Within the 172 initial cases, a total of 374 events were reported, of which 34 were serious (including 15 fatal events) and 340 were non-serious. The most frequently reported events were pyrexia (90), injection site pain (46), vaccination site pain (50), malaise (19), headache (16) and vaccination site swelling (13).

Out of the 10 fatal cases (with 15 fatal events), 8 cases were reported in patients with advanced elderly age (88 to 101 years). In most of these fatal cases, the patients had multiple underlying comorbidities which are considered as confounders for the reported events. None of these cases had autopsy results provided. Of note, 3 of the fatal cases were reported from non-intervention safety study KO01 and were assessed as unrelated both by the reporter and the Company.

During the reporting period, a total of 10 follow-up cases were received for Kostaive. All these cases did not include clinically significant follow-up information.

Cumulatively, 205 cases have been received pertaining to use in elderly patients. Among these cases, 136 cases were received from spontaneous reporting and 69 from post-marketing safety study KO01. These cases encompassed 422 events, of which 37 were serious and 385 were non-serious. The most frequently reported events included pyrexia (120), vaccination site pain (51), injection site pain (47), malaise (21), headache (16) and vaccination site swelling (13).

Use during pregnancy

During the reporting period and cumulatively, a total of 10 cases pertaining to exposure during pregnancy with Kostaive were received from post-marketing reporting. These 10 initial cases include one pregnancy with normal outcome (full term or live birth) and 8 cases with unknown outcome (lost to follow-up or outcome pending). In the above mentioned case (see section "use in paediatric population") with foetal exposure, the maternal outcome of live birth was considered.

Use of Kostaive during pregnancy is considered missing information.

Use during lactation

During the reporting period and cumulatively, 13 cases pertaining to lactation exposure with Kostaive were received from post-marketing reporting. Four of the cases also reported exposure during pregnancy and are included in the evaluation above. The remaining 9 maternal cases reported maternal exposure during breastfeeding. In one of these cases, no AEs were reported. The remaining 8 cases reported non-serious AEs (see also section 2.3 "Evaluation of risks"). No specific pattern of reported AEs was observed. No baby cases were reported.

Use of Kostaive during lactation is considered missing information.

Off-label use

A review of all post-authorisation experience pertaining to off-label use was performed by searching the MAH's Global Safety Database for all cases pertaining to off-label use in the post-marketing setting regardless of causality. During the reporting period, one follow-up case (no initial case) was received from post-marketing reporting. Cumulatively, one case pertaining to off-label use was received. This case concerns a [redacted]-year-old female patient who received Kostaive for COVID-19 prophylaxis (off-label use in unapproved age group) and experienced pyrexia (38.0 to 38.9 °C) on the same day as vaccination. The MAH assessed the event as related, outcome was resolved. Review of the case did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to off-label use per its routine pharmacovigilance procedures.

Drug interaction

A review of all post-authorisation cases pertaining to drug interaction was performed by searching the Global Safety Database for all cases containing at least one PT included in the High Level Term (HLT) Interactions.

During the reporting interval and cumulatively, no cases pertaining to drug interaction with Kostaive were received from post-marketing reporting, hence there was no new safety information relevant to the benefit-risk assessment. The MAH will continue to monitor all cases pertaining to drug interaction per its routine pharmacovigilance procedures.

Rapporteur assessment comment: There is no significant new safety information from the evaluation of use in special populations.

1.3.4. Data in summary tabulations

Table 5 presents an overview of Adverse Drug Reactions included in the Summary tabulations:

Table 5: Overview of Adverse Drug Reaction Data

Source	**Reporting period N / Reporting rate**	**Cumulative period N / Reporting rate**
Non-serious ADRs – spontaneous	330 / 346.12	374 / 273.36
Serious ADRs – spontaneous	25 / 26.22	25 / 18.27
Serious ADRs – non-interventional studies and other solicited	10 / 10.49	10 / 7.31
Total ADRs	**365 / 382.82**	**409 / 298.94**

Rapporteur assessment comment:

No new important safety information is identified from the summary tabulations of cumulative clinical trial exposure and cumulative and interval exposure from post-marketing.

1.3.5. Findings from clinical trials and other sources

- Completed clinical trials

During the reporting period, 2 clinical trials with Kostaive were completed: ARCT-165-01 and ARCT-2303-01.

Study ARCT-165-01 showed a higher frequency and severity of local and solicited AEs for the first-generation vaccine ARCT-021 compared with the next-generation vaccines ARCT-154 and ARCT-165 following a heterologous booster in licensed mRNA-primed participants. Data from this study confirm the improved tolerability of the next-generation vaccines. The clinical study report was finalised on 19 December 2024.

Study ARCT-2303-01 confirms the safe use of ARCT-2303 vaccine when administered concomitantly with influenza vaccines. Co-administration of ARCT-2303 with quadrivalent influenza vaccines (QIV; QIV in adults aged 18 to 64 years and adjuvanted QIV [aQIV] in adults aged 65 years and above) appeared not to affect the immunogenicity of the individual vaccines. There was no evidence of a significant impact on the safety and reactogenicity profiles for each vaccine when co-administered vs. stand alone. The clinical study report was finalised on 10 April 2025.

- Ongoing clinical trials

During the reporting period, one clinical trial with Kostaive was ongoing (CSL402-J01) in Japan. No new clinically important efficacy and safety findings have arisen from this clinical trial. Interim results showed [redacted] CSL402 5 µg. [redacted]

- Long-term follow-up

Up to 12 months long-term safety data have been collected in ARCT-154-01, ARCT-154-J01 and ARCT-165-01 clinical studies in participants who have been exposed to either a primary series 2-dose regimen or a single-dose booster vaccination. No new clinically important safety findings have arisen from these clinical trials up to 12 months post vaccination.

- Other therapeutic use of medicinal product

No other programmes following a specific protocol with solicited reporting for Kostaive were ongoing or completed during the reporting period.

- New safety data related to fixed combination therapies

Kostaive is not authorised or under development as a component of a fixed dose combination product or a multidrug regimen.

- Findings from non-interventional studies

During the reporting period, no non-interventional studies were sponsored by CSL Seqirus.

One ongoing non-interventional safety study (KO01 Drug Use-results survey / NIS_RVA159436: to evaluate the safety of Kostaive intramuscular injection in clinical practice of the post-marketing setting, started in October 2024) was sponsored by Meiji Seika Pharma. No new significant safety information was received from this partner-sponsored non-interventional study.

- Other clinical trials

The MAH is not aware of any other clinical trials with Kostaive that were conducted during the reporting period. During the reporting period, two Meiji-Seika Pharma sponsored studies (VERSUS-R-

an observational case-control study and Tokyo Shinagawa Hospital – a prospective observational study) with Kostaive were ongoing. To date, no clinically important safety information has arisen from these sources.

- Medication errors

Search in the MAH's Global Safety Database for all cases containing at least one PT pertaining to the Medication Errors SMQ (narrow) and two additional PTs (needle issue and syringe issue) retrieved one spontaneous case reporting medication errors for Kostaive, including two medication errors (cumulatively one case). This case concerns an elderly female patient who received 2 doses of Kostaive (0.5 mL, intramuscularly) within 2 weeks (PTs *Accidental overdose* and *Extra dose administered*). There was no additional AE reported. The root cause of these events was unspecified. As per CCDS, version 2.0, the second dose was not aligned with the intended dosing schedule. The MAH assessed these events as not related.

MAH's conclusion: no patterns of medication errors have been identified relevant to the interpretation of safety data or the overall benefit-risk evaluation of Kostaive. Appropriate risk minimisation measures, in the form of the applicable label text, are currently in place to prevent medication errors. The MAH will continue to monitor all cases pertaining to medication errors per its routine pharmacovigilance procedures.

- Non-clinical data

During the reporting period, one non-clinical study (Study 31983371, ARC24-071), titled "A single dose study of ARCT-2303 by intramuscular administration in rabbits" was in the reporting phase and finalised (04 March 2025).

The objective of this GLP study was to compare the potential local and systemic toxicity of the test article, ADCT-2303 vaccine, in two formats: a single-dose liquid (ARCT-2303-1LIQ) and a 16-dose lyophilised (ARCT-2303-16LYO) format, when given via an intramuscular injection as a single dose to rabbits. The ARCT-2303 vaccine encodes the spike protein from the XBB1.5 SARS-Cov-2 virus, and the dose level (5 µg / rabbit) in this non-clinical study represents the full clinical dose in absolute terms. The following parameters and endpoints were evaluated in this study: mortality, clinical signs, body weights, body weight gains, food consumption, evaluation of skin reaction, body temperature, clinical pathology parameters (haematology, coagulation and clinical chemistry), cytokine, immunogenicity evaluation, organ weights and macroscopic and microscopic examinations. To summarise, following a single intramuscular injection of ARCT-2303-1LIQ and ARCT-2303-16LYO, no ARCT-2303-related adverse effect were noted in any parameter examined. In conclusion, no significant safety findings have been observed from non-clinical studies.

- Literature

A standardised search in the scientific literature databases MEDLINE and EMBASE was performed for articles relevant to Kostaive covering the reporting period. In addition, unpublished manuscripts when made available have been reviewed to identify new and significant safety findings. Review of published and unpublished literature retrieved during the reporting period yielded non-clinical and clinical articles that presented new and significant safety findings and/or significant lack of efficacy for Kostaive.

1. **Liu YL, Liao TY, Ho KW, Liu ES, Huang BC, Hong ST, et al. Impact of pre-existing anti-polyethylene glycol antibodies on the pharmacokinetics and efficacy of a COVID-19 mRNA vaccine (Comirnaty) in vivo. Biomater Res. 2024; 28: 0112. Doi: 10.34133/bmr.0112. PMID: 39665081; PMCID: PMC11633857.**

Summary: the presence of anti-PEG antibodies can hinder the therapeutic efficacy of PEGylated drugs. With the widespread use of a PEGylated coronavirus disease 2019 mRNA vaccine (Comirnaty), the impact of pre-existing anti-PEG antibodies on vaccine potency has become a point of debate. To investigate this, we established mouse models with pre-existing anti-PEG antibodies and divided them into 3 groups: group 1 with anti-PEG immunoglobulin G + immunoglobulin M concentrations of 0.76 to 27.41 μg/mL, group 2 with concentrations of 31.27 to 99.52 μg/mL and a naïve group with no detectable anti-PEG antibodies. Results indicated that anti-spike antibody concentrations significantly decreased in group 1 and group 2 after the second vaccine dose compared with those in the naïve group. Spearman's rank correlation analysis demonstrated a negative relationship between anti-spike antibody production and anti-PEG antibody levels at both the second and third doses (second dose: ρ = −0.5296, P = 0.0031, third dose: ρ = -0.387, P = 0.0381). Additionally, spike protein concentrations were 31.4-fold and 46.6-fold lower in group 1 and group 2, respectively, compared with those in the naïve group at 8h post-vaccination. The concentration of complement C3a in group 2 was significantly higher than that in the naïve group after the third dose. These findings confirm that pre-existing anti-PEG antibodies diminish vaccine efficacy, alter pharmacokinetics and elevate complement activation. Therefore, detecting pre-existing anti-PEG antibodies is crucial for optimising vaccine efficacy, ensuring patient safety and developing improved therapeutic strategies.

MAH comment: Potential impact of anti-PEG antibodies on vaccine efficacy.

2. **Cheng KL, Yu WS, Wang YH, Ibarburu GH, Lee HL, Wei JC. Long-term thyroid outcomes after COVID-19 vaccination: A cohort study of 2,333,496 patients from the TriNetX Network. J Clin Endocrinol Metab. 2025: dgaf064. doi: 10.1210/clinem/dgaf064. Epub ahead of print. PMID: 39883558.**

Context: Reports on long-term thyroid dysfunction following COVID-19 vaccination are limited. Understanding the risk of subacute thyroiditis, hyperthyroidism and hypothyroidism in vaccinated individuals is crucial for postvaccination monitoring. Objective: This study evaluated the risk of thyroid dysfunction in COVID-19 vaccinated individuals compared to unvaccinated individuals using a large cohort. Methods: The authors conducted a retrospective cohort study from 01 January 2022 to 31 December 2023, using the TriNetX database, including 1,166,748 vaccinated and 1,166,748 unvaccinated individuals. Propensity score matching was used to balance baseline characteristics. The primary outcomes were new diagnoses of subacute thyroiditis, hyperthyroidism and hypothyroidism. Results: The risk of subacute thyroiditis remained unchanged (95% confidence intervals included 1). A significant reduction in hyperthyroidism risk was observed from 3 to 9 months postvaccination (HRs: 0.65-0.89, all 95% CIs below 1), but this trend was not significant at 12 months (HR: 0.99, 95% CI: 0.92-1.06). In contrast, the risk of hypothyroidism significantly increased from 6 to 12 months postvaccination (HR: 1.14-1.30, all 95% CIs above 1). Among mRNA vaccine recipients, the risk of both hyperthyroidism and hypothyroidism was significantly elevated at 12 months (HR: 1.16-2.13). Conclusion: COVID-19 vaccination was associated with a reduced risk of hyperthyroidism and an increased risk of hypothyroidism, highlighting the need for ongoing thyroid function monitoring.

MAH Comment: Information relevant for subacute thyroiditis, event of special interest for Kostaive.

3. **Fraenza F, Cagnotta C, Gaio M, Sportiello L, Scavone C, Capuano A, et al. Disproportionality analysis of European safety reports on autoimmune and rheumatic diseases following COVID-19 vaccination. 20025 Sci Rep 15, 14740.**

The safety profile of COVID-19 vaccines is well-established, yet the widespread immunisation campaign has led to an increase in reported cases of IMDRs. This study aimed to assess the reporting of AEFIs related to IMDRs after COVID-19 vaccination. The authors analysed all ICSRs related to COVID-19 vaccines authorised in the European Union (ie, tozinameran, elasomeran, ChAdOx1-S NCoV-

19 and Ad26.Cov2.S) registered in the EudraVigilance database from 01 January 2021 to 23 October 2023. The authors' analysis identified ICSRs with events indicative of IMDRs and conducted disproportionality analysis (ie, ROR with 95% CI) to examine the frequency of different IMDR types linked to each vaccine. In total, 45,352 ICSRs reported at least 1 AEFI associated with rheumatic or autoimmune conditions, with 54% of them implicating tozinameran as the suspected vaccine. More than half of the reported AEFIs were classified as serious, with approximately 45% remaining unresolved. The most frequently reported conditions were other immune-mediated diseases, followed by arthritis, vasculitis, systemic lupus erythematosus and tendinopathies. The disproportionality analysis suggested that mRNA vaccines may be more frequently associated with new autoimmune rheumatic diseases. Real-world pharmacovigilance data suggest that autoimmune and rheumatic diseases may be under-reported following COVID-19 vaccination, highlighting the need for further research to better understand the underlying mechanisms. The findings from this disproportionality analysis suggest the need for further studies to investigate these results in greater depth.

MAH Comment: Safety of mRNA COVID-19 vaccines in individuals with autoimmune and inflammatory disorders.

4. **Jeong J, Jo H, Son Y, Park J, Oh J, Lee S, et al. Global and regional estimates of vaccine-associated herpes zoster and their related vaccines from 1969 to 2023. Sci Rep. 2025 Apr 17;15(1):13285. doi:10.1038/s41598-025-98106-9. PMID: 40247100; PMCID: PMC12006434.**

Vaccine-induced immunosuppression can reactivate the varicella-zoster virus, potentially leading to the development of herpes zoster. However, the literature on this topic is inconsistent, resulting in limited clarity. Therefore, authors aimed to enhance the understanding of vaccine-associated herpes zoster and establish guidelines for future research, utilising a global database to improve global public health. The authors investigated vaccine-associated AEs in herpes zoster using reports (~13 million reports) from the WHO international pharmacovigilance database. Data were analysed for the global number of reports, ROR and IC to determine the potential association between 18 vaccines and vaccine-associated herpes zoster reports in nearly 170 countries and territories from 1969 to 2023. Of 7,805,380 vaccine-associated adverse events, there were 51,985 herpes zoster reports. Vaccine-associated herpes zoster showed the highest strength of association with COVID-19 mRNA vaccines (ROR, 11.85 [95% CI, 11.70-12.01]; IC, 2.74 [IC0.25, 2.72]), followed by encephalitis (ROR, 4.07 [95% CI, 3.37–4.92]; IC, 2.00 [IC0.25, 1.68]), influenza (ROR, 3.44 [95% CI, 3.28–3.62]; IC, 1.77 [IC0.25, 1.69]) and ad5-vectored COVID-19 vaccines (ROR, 3.05 [95% CI, 2.97–3.14]; IC, 1.54 [IC0.25, 1.50]). The ROR and IC increased with advancing age. The authors findings emphasize the need to consider the immune status of vaccine recipients.

MAH Comment: Safety of mRNA COVID-19 vaccines in immunocompromised individuals.

5. **Lim E, Kim YH, Jeong NY, Kim SH, Won H, Bae JS, et al. The association between acute transverse myelitis and COVID-19 vaccination in Korea: Self-controlled case series study. Eur J Neurol. 2025; 32(1): e70020. doi: 10.1111/ene.70020. PMID: 39739424; PMCID: PMC11683473.**

Background: ATM has been reported as a potential association between COVID-19 vaccination. In this study, the authors aimed to investigate the association between the COVID-19 vaccination and ATM. Methods: A self-controlled case series study was performed using a large database that combined the COVID-19 vaccine registry and the national claims database. The COVID-19 vaccination data included information on individuals aged 18 and above who received COVID-19 vaccination from 26 February 2021 to 31 August 2022. The claims database covered the entire Korean population for the period between 01 January 2002 to 31 August 2022. Patients who develop ATM within 1-42 days following

COVID-19 vaccination were included. The observation period was 270 days after the first dose of the COVID-19 vaccine. The IRR and 95% CI were estimated using a conditional Poisson regression model. Results: A total of 159 ATM patients were included. Among them, 82 (51.6%) were male, and mean age was 55.4±17.4 years. The IRR was 2.41 (95% CI: 1.76-3.30) for the ATM risk within 1-42 days after COVID-19 vaccination. The IRR by vaccine product was 3.31 (95% CI: 1.81-6.05) for ChAdOx1-S; 1.99 (95% CI: 1.30-3.03) for BNT162b2; 2.57 (95% CI: 1.14-5.97) for mRNA-1273; and 3.33 (95% CI: 0.30-36.44) for Ad26.COV2.S. Conclusion: These findings indicated an increased risk of ATM following COVID-19 vaccination within 42 days. An association with the risk of ATM was found both for viral vector and mRNA vaccines.

MAH Comment: Information relevant for transverse myelitis, event of special interest for Kostaive.

6. **Perez-Campuzano V, Rautou PE, Marjot T, Praktiknjo M, Alvarado-Tapias E, Turco L, et al. ERN RARE-LIVER; a study of VALDIG, an EASL consortium and REHEVASC. Impact of SARS-CoV-2 vaccination in patients with vascular liver diseases: Observations from a VALDIG multicenter study. JHEP Rep. 2024; 6(12): 101191. doi: 10.1016/j.jhepr.2024.101191. PMID: 39583091; PMCID: PMC11582744.**

Background & aims: Patients with VLD are at higher risk of both severe courses of COVID-19 disease and thromboembolic events. The impact of SARS-CoV-2 vaccination in patients with VLD has not been described and represents the aim of the study. Methods: International, multicentre, prospective observational study in patients with VLD analysing the incidence of COVID-19 infection after vaccination, severity of side effects, occurrence of thromboembolic events and hepatic decompensation. In a subgroup of patients, the humoral and cellular responses to vaccination were also analysed. Results: A total of 898 patients from 14 European centres - part of the VALDIG network - were included, 872 (97.1%) patients received 2 vaccine doses (fully vaccinated) and 674 (75.1%) 3 doses. Of the total cohort, 151 / 898 had a COVID-19 infection prior to vaccination, of whom 9 / 151 (5.9%) were re-infected. Of the 747/898 patients who were not previously infected, 11.2% (84/747) were diagnosed with a COVID-19 infection during the study period. Two infected patients required intensive care unit admission and infection was fatal in 2 fully vaccinated patients. AEs were reported in around 40% of patients, with local side effects being the most frequent. During the study period, 31 (3.5%) patients had thromboembolic events and 21 (2.3%) hepatic decompensations. No cases of vaccine-induced thrombocytopenia were reported. Vaccine immunogenicity was assessed in 36 patients; seroconversion reached 100% and IFN-γ T-cell responses significantly increased post 2 mRNA-1273 vaccine doses. Conclusion: Patients with VLD seem to have a preserved immune response to SARS-CoV-2 vaccination, which appears to be safe and effective in preventing severe COVID-19 infection. Our study cannot definitively establish a direct link between vaccination and thrombotic events though the contribution of vaccination as a cofactor in VLD remains to be elucidated. Impact and implications: Patients with VLD are at increased risk of both SARS-CoV-2 infection and severe COVID-19 disease. The potential risks associated with vaccination against this infection need thorough investigation. The authors' research enhances the understanding of the effects of COVID-19 vaccination in patients with VLD, highlighting its good tolerability. Moreover, patients with VLD appear to have a preserved immune response to SARS-CoV-2 vaccination, providing protection against severe COVID-19 infection. The study cannot definitively establish a direct link between vaccination and thrombotic events, and no cases of vaccine-induced thrombocytopenia were reported.

MAH Comment: Information relevant for missing information use in patients with significant, unstable chronic medical conditions and important potential risk of thromboembolism.

7. **Rungjirajittranon T, Nakkinkun Y, Suwanawiboon B, Chinthammitr Y, Owattanapanich W, Ruchutrakool T. Hemostatic changes following COVID-19 vaccination: Do they promote a pro-thrombotic state? Hum Vaccin Immunother.**

2025; 21(1): 2439627. doi: 10.1080/21645515.2024.24396 27. Epub 2024 Dec 19. PMID: 39699990; PMCID: PMC11660298.

VITT is a unique thrombotic complication of COVID-19 immunisation, especially with adenovirus vector vaccines. However, non-VITT thrombotic events were seen in mRNA vaccines. The authors aimed to investigate haemostatic changes following COVID-19 vaccination and to compare these changes between the ChAdOx1 and BNT162b2 vaccines. The authors conducted a prospective study involving COVID-19 infection and vaccination-naïve participants aged over 18 years receiving the ChAdOx1 or BNT162b2 vaccines. Blood samples were collected at pre-vaccination, 7 and 21 days postvaccination. D-dimer levels, platelet counts and TGA parameters were collected. ChAdOx1-S group D-dimer levels did not change significantly throughout the study ($p = 0.51$). BNT162b2 group median D-dimer levels increased significantly on Day 7 (245 ng FEU/mL [IQR 155–384] at baseline; 315 ng FEU/mL [IQR 187.5–412] at Day 7; and 271 ng FEU/mL [IQR 166–400] at Day 21; $p = 0.021$). BNT162b2 group platelet counts increased significantly on Day 7 ($p = 0.010$). TGA parameters in the ChAdOx1-S group decreased significantly in ETP levels ($p = 0.007$) and peak concentrations ($p = 0.041$) over time, while those of the BNT162b2 group were stable (median ETP levels and peak concentrations; $p > 0.05$). Mean change in ETP levels from pre-vaccination between the vaccines were significantly different at Day 21 ($p = 0.001$). No antiplatelet factor 4 antibody positivity or clinical thrombosis occurred. Both vaccines showed low thrombosis risk without increased thrombin generation. However, BNT162b2 vaccine recipients exhibited a temporary inflammatory response, evidenced by a brief rise in D-dimer levels.

8. **Skinningsrud B, Vlaisavljevic K, Oppedal LS, Endresen J, Mohn V, Fladseth K, et al. COVID-19 vaccine associated myocarditis in Norway – a nationwide validation study. Eur Heart J. 2024; 45(Suppl 1). doi: 10.1093/eurheartj/ehae666. 1987.**

Background: The SARS-CoV-2 pandemic led to worldwide initiation of vaccination campaigns. The new mRNA vaccines were unexpectedly associated with VAM. The incidence and severity of VAM has not been validated in a nation-wide and well-defined population. From December 2020 onwards, the mRNA vaccines Comirnaty and Spikevax have been in widespread use in Norway. The NPR includes all hospital contacts with corresponding diagnostic codes (ICD-10), and all vaccinations are registered in the Norwegian Immunization Register (SYSVAK). Purpose: The authors aimed to identify and validate all cases of suspected COVID-19 VAM in Norway during the national vaccination campaign between 2020 and 2022. Methods: The authors identified all cases of myocarditis acquired within 90 days of a COVID-19 vaccination through linkage of diagnostic codes for myocarditis in NPR and vaccination data in SYSVAK. Cases were included from December 2020 through April 2022. The authors assessed medical records, cardiac imaging and biochemistry to retrospectively validate all myocarditis cases. The Brighton Criteria (international criteria for myocarditis diagnosis following immunisation with defining levels of diagnostic certainty) were used to confirm the VAM diagnosis. Results: From December 2020 to April 2022, 4,114,750 unique subjects (2,036,792 men and 2,077,958 women, median age first dose 47 years) above 16 years of age, received 10,915,098 unique doses of COVID-19 vaccines (8,651,703[79%] Comirnaty and 2,263,395[21%] Spikevax). Of 277 cases of myocarditis identified in NPR < 90 days after receiving a COVID-19 vaccine, 176 (64%) were validated as VAM (78 definite, 90 probable and 8 possible VAM). Among the patients with VAM, 137 (78%) were men with median age 30 (IQR 24-47) years and 39 (22%) were women with median age 54 (IQR 32-65) years. There were 4 cases of VAM per 100,000 vaccinated subjects: 7 per 100,000 men and 2 per 100,000 women. Sixty-three percent of VAM occurred after the second mRNA vaccine dose. There were 3.3 cases of VAM per 100,000 unique doses of Spikevax compared to 1.1 per 100,000 unique doses of Comirnaty. The most common time interval from vaccination to VAM was 3 days and occurred in 30 patients (17.3% of VAM, 93% men) and 34% of VAM (90% men) occurred during the first 5 days from vaccination. Median duration of hospital stay was 4 (IQR 3-5) days, with only 7 (4%) patients needing

intensive care and 1 myocarditis-related patient death during hospitalisation. Conclusions: In this unique nationwide study including all COVID-19 vaccinated subjects in Norway from 2020-22, the authors found 4 cases of VAM per 100,000 vaccinated subjects. The majority of VAM occurred in young men. Interestingly, women presented later than men with VAM and most frequently at middle to older age. The occurrence of this unexpected serious adverse event underscores the importance of large studies in broad populations in future vaccine programs.

MAH Comment: Information relevant to important potential risk of myocarditis / pericarditis / myopericarditis.

9. **Tariq M, Gondal A, Suhagiya GH, Dholakiya PM, Girish F, Kumar A, et al. COVID-19 vaccine-induced acute pancreatitis: a systematic review. Am J Gastroenterol. 2024; 119(10S): S37-8. doi: 10.14309/01.ajg.0001028568.6 0097.bd**

Introduction: Despite the remarkable efficacy of COVID-19 vaccines in preventing severe illness and death, concerns about potential GI AEs have emerged. Recent reports suggest a possible link between COVID-19 vaccine and AP, but large-scale characterisation of this patient group is lacking. The study aims to evaluate and summarise the evidence regarding COVID-19 vaccine-induced AP. Methods: The authors conducted a systemic literature search using PubMed, EMBASE and Google Scholar. The search strategy included the MeSH term and keywords for 'COVID-19 vaccine' and 'pancreatitis' from date of inception to 30 May 2024. Initial search yielded 361 articles. After excluding irrelevant studies, duplicates and review articles, we included 45 articles reporting the COVID-19 vaccine-induced AP. Data were extracted and analysed on patient demographics, vaccine type, time to onset of symptoms, clinical presentation and outcomes. Results: The study included 46 patients of COVID-19 vaccine-induced AP with a median age of 55±18.13 years (range: 14-84). Of those, 60.86% were female. Of COVID-19 vaccines, 71.74% were mRNA and Pfizer-BioNTech was the most common vaccine involved (41.30%), followed by Moderna (30.43%) and AstraZeneca (17.39%). Symptoms typically appeared with a median of 6±3.48 days postvaccine, predominantly after the second dose (45.65%). Common symptoms included vomiting (97.82%), abdominal pain (95.65%) and nausea (89.13%). Elevated serum lipase and amylase levels were observed in all cases. Imaging (computed tomography and ultrasound) confirmed AP in 71.73% of patients. Most cases were mild (60.87%) or moderately severe (30.43%), with peripancreatic fluid collection being the most frequent complication (23.91%). The median hospital stay was 7±5.20 days, and all patients recovered with supportive care albeit 19.56% required intensive care unit admission. Conclusion: Precise aetiology of COVID-19 vaccine-induced AP is unknown and is believed to be related to a complex interplay of molecular mimicry, autoimmune response, direct pancreatic injury by vaccine components or systemic inflammatory response. Albeit rare, AP is a life-threatening complication of the COVID-19 vaccine, warranting urgent evaluation and management. COVID-19 vaccine should be included in the aetiology of AP in patients presenting postvaccination abdominal pain and vomiting, requiring continued surveillance and standardised reporting of vaccine-related GI-AEs.

MAH Comment: Information relevant for AP, event of special interest for Kostaive.

- Other periodic reports

The MAH prepares only a single PBRER for Kostaive that covers all indications and formulations. The MAH is not aware of any PBRER prepared by other parties during the reporting period.

Rapporteur assessment comment:

There is no new relevant safety information from clinical trials and other sources, including literature.

1.3.6. Lack of efficacy in controlled clinical trials

No new data indicating lack of efficacy were identified from controlled clinical trials with Kostaive conducted during the reporting period.

1.3.7. Late-breaking information

After the DLP of this report, no important safety, efficacy and effectiveness findings were received that would alter the benefit-risk profile of the product.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 6: Summary of Safety concerns at the beginning of the reporting period

Important identified risk	None
Important potential risk	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)

Of note, the MAH proposes to remove the missing information topics Interaction with other vaccines and Long-term safety data in the updated RMP, version 1.1, with DLP 27 May 2025, which was submitted to EMA on 03 July 2025.

Rapporteur assessment comment: *Assessment of the updated RMP is currently ongoing in procedure EMA/VR/0000284897.*

2.2. Signal evaluation

During the reporting period, there were no newly identified, ongoing or closed signals.

2.3. Evaluation of risks and safety topics under monitoring

<u>New information relating to important potential risk: myocarditis and pericarditis</u>

During the reporting period, a total of 2 clinical study follow-up cases were retrieved from a search in the MAH's Global Safety Database. From these follow-up cases, there was no significant new safety information.

The previous PSUR included two blinded cases from study ARCT-2303-01: one case reporting pericarditis and one case reporting myopericarditis. Both cases were initially assessed as related to the blinded study vaccine. Upon unblinding during the reporting period, the pericarditis event in the first case was assessed as related to Quadrivalent Influenza Vaccine (QIV); the subject had not received ARCT-2303 and was withdrawn after the first vaccination. The myopericarditis event in the second case occurred 57 days after ARCT-2303 vaccination and 28 days after adjuvanted QIV (aQIV) vaccination. Due to a closer temporal relationship to aQIV, the sponsor considers the event unlikely related to ARCT-2303 but related to aQIV (temporal relationship falls outside the known 3- to 42-day risk window). It should be noted that no related cases for Kostaive were reported cumulatively.

Review of the cases pertaining to myocarditis / pericarditis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this risk per its routine pharmacovigilance procedures.

New information relating to important potential risk: thromboembolic events

During the reporting period, a total of 5 cases (1 initial, 4 follow-up) were retrieved concerning Kostaive. The initial case, received from spontaneous reporting, concerns a 97-year-old female patient with a history of atrial fibrillation and [redacted] who experienced cerebral infarction approximately 8 days after vaccination with Kostaive. The MAH assessed the event as possibly related to Kostaive due to plausible temporal relationship; however, diagnosis of cerebral infarction was suspected (not confirmed) and causality is confounded by the history of atrial fibrillation and elderly age. The four follow-up clinical trial cases did not report any new significant information during the reporting period. The reporting rates are displayed in Table 7.

Table 7: Thromboembolic events interval and cumulative reporting rates

	Previous interval	Current interval	Cumulative	Cumulative correction after DLP
No. of cases / RR (per 100,000 doses distributed) initially provided	0 / not applicable	1 / 1.049	1 / 0.731	1 / 5.364

Note: after DLP 27 May 2025, cumulative RR was updated to reflect corrected exposure data
DLP = Data Lock Point; RR = Reporting Rate

Review of the cases pertaining to thromboembolic events did not change the current safety profile of Kostaive. There was an increase in the interval reporting rate compared with the cumulative period. The MAH will continue to monitor all cases pertaining to this risk per its routine pharmacovigilance procedures.

New information on Missing information: use in pregnancy and while breastfeeding

The safety of Kostaive in pregnant women has not been assessed in clinical studies. The administration of Kostaive during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. It is unknown whether Kostaive 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 infant from Kostaive.

During the reporting period, a total of 43 cases (11 initial, 32 follow-up) pertaining to pregnancy exposure with Kostaive were retrieved. Of the 11 initial cases, 9 were received from post-marketing safety study KO01, one was received from spontaneous reporting and one was received from clinical trial. In four of the 11 initial cases, both pregnancy and breastfeeding exposures were reported.

Of the 11 initial cases, one post-marketing case reported foetal exposure during pregnancy along with serious event transient tachypnoea of the newborn. In this case, the mother had received Kostaive 6 weeks and 5 days before "normal" delivery. The newborn received oxygen inhalation and a drip infusion at the neonatal intensive care unit due to event transient tachypnoea of the newborn (seriousness criteria: hospitalization). The event resolved 15 days later, and the neonate was discharged. The MAH assessed the event as not related due to temporal and biological implausibility.

Of the remaining 9 maternal cases, one case was reported without AEs and 8 cases reported 52 non-serious AEs (most frequently reported AEs. 13x vaccination site pain, 5x pyrexia, 4x each chills, headache and malaise). No specific pattern of reported AEs was observed. The pregnancy outcomes of these 9 cases were reported as 5x outcome pending, 3x unknown and 1x live birth.

The 32 follow-up cases did not report any new significant information during the reporting period.

During the reporting period, a total of 13 initial cases (no follow-ups) pertaining to lactation exposure with Kostaive were retrieved from post-marketing safety study KO01. Conservative case coding convention currently in use includes proactive coding of 2 terms: exposure in pregnancy and exposure in lactation, if it was not clearly stated by the reporter that the exposure in pregnancy did not result in the mother breastfeeding the baby. Some cases, therefore, include both types of exposures.

Four of the 13 cases, including exposure during pregnancy, are included in the discussion above. Of the remaining 9 maternal cases reporting maternal exposure during breastfeeding, in one case, no AEs were reported. In the remaining 8 cases, the following non-serious AEs were reported: vaccination site pain (8), injection site pain and chills (5 each), arthralgia and malaise (4 each), pyrexia and vaccination site induration (3 each), headache and vaccination site swelling (2 each), injection site induration, myalgia, nausea, palpitations and vaccination site erythema (1 each). No specific pattern of the reported AEs was observed. No baby cases were reported.

Review of the cases pertaining to use in pregnancy and while breastfeeding did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

<u>New information on missing information: use in immunocompromised patients</u>

The safety and efficacy of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Kostaive may be lower in immunocompromised individuals.

During the reporting period, a total of 16 cases (15 initial, 1 follow-up) were retrieved concerning Kostaive. Of the 15 initial cases, one case was received from spontaneous reporting and 14 were derived from report from post-authorisation safety study KO01.

The 15 initial cases reported 89 events, of which 3 were serious (including 2 fatal events): 1x asthenia (fatal event), 1x marasmus (fatal event), 1x pneumonia aspiration. Both fatal events occurred in one case concerning a 94-year-old female patient who experienced marasmus and asthenia approximately 2 months after vaccination. The MAH assessed the events as not related due to biological implausibility. Moreover, the patient's underlying medical conditions of breast cancer, diabetes mellitus, angina pectoris and advanced age were considered more likely contributors to the fatal outcome. In another case, the serious event of pneumonia aspiration was reported, causality was confounded by the patient's elderly age and underlying dementia.

The remaining 86 events were non-serious, the most frequently reported events were vaccination site pain (20x), malaise and headache (7x each), myalgia (6x), arthralgia, chills, injection site pain and pyrexia (5x each). No specific pattern of reported AEs was observed in these events.

In one clinical trial follow-up case, no new significant information was received during the reporting period.

Review of the cases pertaining to use in immunocompromised patients did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

New information on missing information: interaction with other vaccines

This safety concern is classified as missing information based on Kostaive EU-RMP version 1.0. As per CCDS, Kostaive may be administered concomitantly with influenza vaccine. A review of all post-authorisation cases pertaining to interaction with other vaccines was performed by searching the MAH's Global Safety Database for all cases with Kostaive where another vaccine is reported as a co-suspect.

The results of study ARCT-2303-01 confirm the safe use of Kostaive when administered concomitantly with influenza vaccines. Co-administration of Kostaive with quadrivalent influenza vaccines appeared not to affect the immunogenicity of co-administered vaccines. All vaccines were well tolerated in young and older adults, both as standalone and when co-administered.

During the reporting period, 2 initial spontaneous cases pertaining to interaction of Kostaive with other vaccines were received. In the first, serious case, tozinameran was administered as co-suspect drug. However, this case lacks information when the co-suspect vaccine was administered resulting in an inconclusive assessment. In the second case (non-serious), Kostaive was co-administered with an influenza vaccine at the same time, and the patient experienced pyrexia.

The results of the ARCT-2303-01 study confirm the safe use of Kostaive when administered concomitantly with influenza vaccines. Review of the two post-marketing cases pertaining to interaction with other vaccines did not raise any safety concerns related to Kostaive. Hence, the MAH proposes to remove this missing information in the updated RMP, version 1.1, which was submitted to EMA on 03 July 2025.

New information on missing information: use in patients with autoimmune or inflammatory disorders

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases with a medical history containing at least one PT in the CMQ for Use in Patients with autoimmune or inflammatory disorders.

During the reporting period, a total of 18 cases (17 initial, 1 follow-up) were retrieved. All the 17 initial cases were received from post-authorisation safety study KO01. In these 17 cases, the relevant medical history included autoimmune thyroiditis, colitis ulcerative and Graves's disease (3 each), chronic gastritis (2) and chronic inflammatory demyelinating polyradiculoneuropathy, collagen disorder, Crohn's disease, eosinophilic granulomatosis with polyangiitis, inflammatory bowel disease, rheumatic disorder, rheumatoid arthritis, systemic lupus erythematosus and type 1 diabetes mellitus (1 each).

Within these 17 cases, a total of 85 events were reported, of which one was serious (no fatal events). The serious event melaena was assessed by the MAH as not related due to underlying Crohn's disease, ulcerative colitis and inflammatory bowel disease which are considered possible confounders. The most frequently reported non-serious events were vaccination site pain (15), injection site pain (15), malaise (9), myalgia (7), headache (7), chills (6) and pyrexia (5). No specific pattern of reported AEs was observed.

No cases reported exacerbation of autoimmune or inflammatory disorders events during the reporting period.

One case received significant follow-up information: chronic gastritis was added as relevant medical history during the reporting period although it is unclear if it is a confirmed autoimmune disorder. This spontaneous case reported serious events of cardiac failure high output, cardiac failure and infection. Pyrexia and bronchitis were reported as non-serious. This case did not report any exacerbation of autoimmune or inflammatory disorders events.

Review of the cases pertaining to autoimmune or inflammatory disorders did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

New information on missing information: long-term safety data

Up to 12 months long-term safety data have been collected in ARCT-154-01, ARCT-154-J01 and ARCT-165-01 clinical studies in participants who have been exposed to either a primary series 2-dose regimen or a single-dose booster vaccination. No new clinically important safety findings have arisen from these clinical trials up to 12 months post vaccination. Of note, in line with Centers for Disease Control and Prevention guidance, most adults are recommended to receive an updated COVID-19 vaccine at least annually, while additional booster may be needed for population at risk based on country-specific recommendations. Therefore, long-term safety data beyond 1-year will likely be confounded by the use of other COVID-19 vaccines as boosters.

The completion of studies ARCT-165-01, ARCT-154-01 and ARCT-154-J01 support the removal of the missing information long-term safety data as they provide 1-year post-vaccination follow-up safety information for participants who have been exposed to either a primary series 2-dose regimen or a single dose booster vaccination.

Review of long-term safety data collected from ARCT-165-01 and ARCT-2303-01 studies confirmed long-term safety data for Kostaive. Hence, the MAH proposes to remove this missing information in the updated RMP, version 1.1, which was submitted to EMA on 03 July 2025.

New information on missing information: use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurologic disease, cardiovascular disorders)

A review of all post-authorisation cases pertaining to "use in patients with significant, unstable chronic medical conditions" was performed by searching the MAH's Global safety database for all cases containing medical history of unstable chronic medical conditions such as chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders.

During the reporting period, 24 cases (23 spontaneous, one from KO01 study) reported potential unstable chronic medical conditions including dementia (13), cerebral infarction (4), atrial fibrillation, cardiac failure chronic, myocardial infarction, type 2 diabetes mellitus and unspecified diabetes mellitus (2 each), and cerebral haemorrhage, cerebrovascular accident, putamen haemorrhage, Parkinson's disease and vascular dementia (1 each). Within these cases, a total of 57 events were reported, of which 24 were serious. The most frequently reported events were pyrexia (14), pneumonia aspiration (3), decreased appetite, hepatic function abnormal, malaise and pneumonia (2 each). Reported serious events were largely representative of age-related comorbidities.

The follow-up case received during the reporting period did not report any new significant information.

Review of the data pertaining to "use in patients with significant, unstable chronic medical conditions" did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases of use in patients with significant, unstable chronic medical conditions per its routine pharmacovigilance procedures.

Safety topics under monitoring

The Adverse Events of Special Interest were agreed upon with EMA during the approval process of EU-RMP version 1.0, with a DLP of 27 March 2023, dated 02 December 2024. The MAH was requested to monitor the AEs of special interest listed below and present in PSURs if new important information will arise.

- Acute disseminated encephalomyelitis
- Acute pancreatitis
- Anaphylaxis
- Anosmia
- Bell's palsy
- Delayed hypersensitivity
- Erythema multiforme
- Extensive limb swelling (ELS)
- Facial swelling in persons with dermal fillers
- Generalised convulsion
- Guillain-Barré syndrome
- Multisystem inflammatory syndrome in adults
- Myocarditis, myopericarditis and pericarditis
- Rhabdomyolysis
- Subacute thyroiditis
- Thrombocytopenia
- Thrombosis / thromboembolism
- Transverse myelitis

Acute disseminated encephalomyelitis

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the Customised MedDRA Query (CMD) for Acute disseminated encephalomyelitis. No cases pertaining to acute disseminated encephalomyelitis with Kostaive were retrieved during the reporting period and cumulatively, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of data pertaining to acute disseminated encephalomyelitis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases of acute disseminated encephalomyelitis per its routine pharmacovigilance procedures.

Acute pancreatitis

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Acute pancreatitis. During the reporting period, no initial cases concerning Kostaive were retrieved. Cumulatively, eight clinical trial cases were received, all of which reported pancreatitis acute. All cases were assessed as not related. Review of the data pertaining to acute pancreatitis did not change the

current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to acute pancreatitis per its routine pharmacovigilance procedures.

Anaphylaxis

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Anaphylaxis. During the reporting period, no initial cases concerning Kostaive were retrieved. Cumulatively, one clinical trial case was retrieved. This serious case concerns a 40-year-old female participant in the ARCT-154-01 study, who experienced an anaphylactic reaction one day after receiving ARCT-154 vaccine. The case met level 1 of Brighton collaboration diagnostic certainty for anaphylaxis. The event was assessed as related. Review of the data pertaining to anaphylaxis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to anaphylaxis per its routine pharmacovigilance procedures.

Anosmia

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Anosmia. During the reporting period and cumulatively, no cases pertaining to anosmia with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of data pertaining to anosmia did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to anosmia per its routine pharmacovigilance procedures.

Bell's palsy

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Bell's palsy. During the reporting period and cumulatively, no cases pertaining to Bell's palsy with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of data pertaining to Bell's palsy did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to Bell's palsy per its routine pharmacovigilance procedures.

Delayed Hypersensitivity

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Delayed hypersensitivity. For further analysis, relevant potential cases of delayed hypersensitivity are considered as those with a reported time to onset of more than 72 hours (≥3 days) following Kostaive vaccination. A delayed local reaction secondary to COVID-19 vaccination (also known as "COVID arm") is an immune-mediated reaction characterized by the development of a well-demarcated, inflamed plaque, cellulitis like reactions near the site of vaccination. All these cases were further reviewed to identify those consistent with delayed hypersensitivity reaction. During the reporting period, a total of 266 initial cases (no follow-up) were retrieved concerning Kostaive. Of the 266, 263 were reported from the postmarketing safety study (KO01 Drug Use-results Survey) and 3 were spontaneous reports. Upon review, 8 cases reported time to onset of more than 72 hours. Of these 8 cases, no cases were consistent with delayed hypersensitivity reaction. Cumulatively, 268 cases concerning Kostaive were retrieved. None of these cases were consistent with delayed hypersensitivity reaction. Review of the data pertaining to delayed hypersensitivity did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to delayed hypersensitivity per its routine pharmacovigilance procedures.

Erythema multiforme

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Erythema multiforme. During the reporting period and cumulatively, no cases pertaining to erythema multiforme with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of data pertaining to erythema multiforme did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to erythema multiforme per its routine pharmacovigilance procedures.

Extensive Limb Swelling

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Extensive limb swelling (ELS). All cases were then medically reviewed to identify potential ELS (i.e., swelling of the vaccinated limb > 100 mm or where there is a similar description indicating that there is a significant area of the limb involved, lasting more than one week) before further analysis was performed. During the reporting period, a total of 187 initial cases (no follow-up) were retrieved concerning Kostaive. Of the 187 cases, 185 were reported from postmarketing safety study KO01 and two were spontaneous reports. None of the 187 cases was consistent with ELS. Cumulatively, 189 cases were retrieved. None of these cases was consistent with ELS. Review of the data pertaining to ELS did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to ELS per its routine pharmacovigilance procedures.

Facial swelling in persons with dermal fillers

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Facial swelling in persons with dermal fillers. For further analysis, relevant potential cases of dermal filler reactions are considered as those with facial dermal fillers injections in medical history. During the reporting period and cumulatively, one initial case (no follow-up) concerning Kostaive was reported from postmarketing safety study KO01. This non-serious case reported face swelling, however, no medical history of facial dermal fillers injection was reported. Review of the data pertaining to facial swelling in persons with dermal fillers did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to facial swelling in persons with dermal fillers per its routine pharmacovigilance procedures.

Generalised convulsions

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Convulsions. During the reporting period and cumulatively, one initial case (no follow-up) was retrieved concerning Kostaive from postmarketing safety study KO01. This case concerns an 82-year elderly female with a complex medical history including cancer surgery, cerebral infarction, epilepsy and depression who experienced convulsion 23 days after receiving Kostaive. The event convulsion was assessed as not related. The case met level 4 Brighton collaboration diagnostic certainty for generalised convulsion based on limited information provided. Review of the data pertaining to generalised convulsions did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to generalised convulsions per its routine pharmacovigilance procedures.

Guillain-Barré syndrome

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Guillain-Barré

syndrome. During the reporting period and cumulatively, no cases pertaining to GBS with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of the data pertaining to GBS did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to GBS per its routine pharmacovigilance procedures.

Multisystem inflammatory syndrome in adults

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Multisystem inflammatory syndrome in adults. During the reporting period and cumulatively, no cases pertaining to multisystem inflammatory syndrome in adults with Kostaive were retrieved. Hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of the did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to multisystem inflammatory syndrome in adults per its routine pharmacovigilance procedures.

Myocarditis, Myopericarditis, Pericarditis

Myocarditis, myopericarditis and pericarditis is considered as an important potential risk. Evaluation can be found above.

Rhabdomyolysis

Review of new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for rhabdomyolysis. During the reporting period and cumulatively, no cases pertaining to rhabdomyolysis with Kostaive were retrieved. Hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of the data pertaining to rhabdomyolysis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to rhabdomyolysis per its routine pharmacovigilance procedures.

Subacute Thyroiditis

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Subacute thyroiditis. During the reporting period and cumulatively, no cases pertaining to subacute thyroiditis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of the data pertaining to subacute thyroiditis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to subacute thyroiditis per its routine pharmacovigilance procedures.

Thrombocytopenia

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Thrombocytopenia and Haemorrhage. During the reporting period, a total of 8 cases (6 initial, 2 follow-up) were retrieved which concerned Kostaive. Of the 6 initial cases, 3 were reported from postmarketing safety study KO01 and 3 were spontaneous reports. Within these 6 initial cases, a total of 7 events were reported, of which 3 were serious (including one fatal event) and 4 were non-serious. See also Table 6.

Table 8: Thrombocytopenia events by Preferred Terms

Preferred Term	Non-serious	Serious	Total

Haematuria	2	-	2
Gastrointestinal haemorrhage	-	1	1
Haematemesis	-	1	1
Haemorrhage subcutaneous	1	-	1
Injection site bruising	1	-	1
Melaena	-	1	1
Total	4	3	7

None of the cases reported thrombocytopenia during the reporting period. Hence, the Brighton Collaboration criteria level of diagnostic certainty for thrombocytopenia is not applicable. Causality for the events of haematuria, gastrointestinal haemorrhage, haematemesis and melaena were confounded by underlying medical history.

Of the 6 cases, one case reported a fatal event: this case concerns a [redacted]-year-old elderly female patient with underlying history of chronic cardiac failure and progressive dementia, who experienced fatal haematemesis (suspected haemorrhage of digestive tract) on an unknown date after vaccination with Kostaive. No autopsy was performed. Causality assessment was confounded by patient's advanced age and underlying medical history.

None of the follow-up cases received significant new information during the reporting period.

Cumulatively, 17 cases concerning Kostaive were retrieved. Of these, 6 initial cases were discussed above. The remaining 11 cases were received from clinical trials with a total of 11 serious events reported. The reported events included gastrointestinal haemorrhage (n=3) and single occurrences of abdominal wall haematoma, cerebral haemorrhage, duodenal ulcer haemorrhage, haemorrhoidal haemorrhage, haemorrhage subcutaneous, haemoptysis, menometrorrhagia and upper gastrointestinal haemorrhage. The events were assessed as not related to Kostaive. None of the cases reported thrombocytopenia.

Review of the data pertaining to thrombocytopenia and haemorrhage did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to thrombocytopenia per its routine pharmacovigilance procedures.

Thrombosis / Thromboembolism

Thrombosis / thromboembolism is considered as an important potential risk. An evaluation can be found above.

Transverse myelitis

Review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Transverse myelitis. During the reporting period and cumulatively, no cases pertaining to transverse myelitis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. Review of the data pertaining to transverse myelitis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to transverse myelitis per its routine pharmacovigilance procedures.

Special vaccine-related topics

- Issues related to batches:

No batch-related safety signals were identified during the reporting period.

- Age-related adverse reactions:

A review of reports received during the reporting period of the PBRER did not reveal any age-related specific AEs that would impact the benefit-risk profile of Kostaive.

- Reports of vaccination failure / lack of efficacy:

As per CCDS, vaccination with Kostaive may not protect all vaccine recipients. A search in the MAH's Global Safety Database for all cases containing at least one PT in the CMQ for Vaccination failure / lack of efficacy retrieved 5 initial cases received during the reporting period. One of these cases was from spontaneous reporting and 4 cases from study KO01. In one of the cases, the patient tested SARS-CoV-2 positive within 8 days after vaccination. Therefore, this case is not considered as vaccination failure (biological / chronological implausibility). Within the remaining 4 cases, a total of 6 serious events were reported with the PTs COVID-19 (1x), SARS-CoV-2 test positive (1x), vaccination failure (4x). The four cases were assessed as related considering a plausible temporal relationship (ranging from 15 days to 2 months and 25 days). The cumulative and interval reporting rates are provided in Table 9.

Table 9: Vaccination failure interval and cumulative reporting rates

	Previous interval	Current interval	Cumulative	Cumulative correction after DLP
No. of cases / RR (per 100,000 doses distributed) initially provided	0 / not applicable	4 / 4.195	4 / 2.924	4 / 21.459

Note 1: one case is not considered as vaccination failure and therefore not included in RR calculations
Note 2: after DLP 27 May 2025, cumulative RR was updated to reflect corrected exposure data
DLP = Data Lock Point; RR = Reporting Rate

A review of reports of vaccination failure did not reveal any new safety information relevant to the benefit-risk assessment of Kostaive. There was an increase in the interval RR compared with the cumulative reporting period due to cases reported from the KO01 Drug Use-results survey, where "novel Coronavirus infection" was one of the outcomes collected in the study. The MAH will continue to monitor all cases pertaining to vaccination failure per its routine pharmacovigilance procedures.

- Immunisation stress-related response reactions

As per CCDS, anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection.

For further analysis, relevant potential cases of immunisation stress-related response reactions are considered as those with a reported time-to-onset within 30 minutes following Kostaive vaccination. Cases that did not specify an exact time-to-onset but did specify that the event occurred while the patient was in the vaccination room or still onsite at the vaccination clinic were assumed to have occurred within 30 minutes. Cases with time-to-onset of >30 minutes, cases that occurred on the same day but did not clearly specify the location at which the events occurred and cases for which time-to-onset was unknown / not reported were not further evaluated.

During the reporting period, a total of 3 initial non-serious cases were retrieved concerning Kostaive. All 3 cases were reported from study KO01. The reported events were palpitations (n=2) and vision blurred (n=1). These cases were not further evaluated as the time to onset was >30 minutes (one day) post-vaccination.

A review of reports of immunisation stress-related response did not reveal any new safety information relevant to the benefit-risk assessment of Kostaive. The MAH will continue to monitor all cases pertaining to vaccination failure per its routine pharmacovigilance procedures.

Rapporteur assessment comment: There is no significant new information from the evaluation of risks and safety topics under monitoring.

2.4. Characterisation of risks

Rapporteur assessment comment:

The MAH provides a comprehensive overview of the important potential risks and missing information for Kostaive. The safety concerns remain unchanged.

3. Benefit evaluation

Kostaive has demonstrated benefits as a primary vaccination series in individuals ≥ 18 years of age in terms of efficacy and/or immunogenicity and as a heterologous booster based on a robust immune response and non-inferiority versus the licensed mRNA vaccine (Comirnaty). In addition, a higher immune response was observed after a homologous booster dose relative to post primary series. The potential of Kostaive to protect against a wide range of SARS-Cov-2 variants, including Omicron lineages, was supported by robust and broadly cross neutralising immune responses after booster vaccination.

The vaccine efficacy of Kostaive for the prevention of any COVID-19 was demonstrated in the pivotal phase 1 / 2 / 3 efficacy, safety and immunogenicity study ARCT-154-01. The primary efficacy endpoint, prevention of COVID-19 of any severity between day 36 and 92 in adult participants, was met. The key secondary efficacy objectives were also achieved as the lower limit of the CI met the prespecified success threshold of >0%, demonstrating significant vaccine efficacy of 95.3% (95% CI: 80.5%, 98.9%) after two doses of Kostaive against severe COVID-19 and vaccine efficacy of 56.7% (95% CI: 49.3%, 63.1%) against any COVID-19 reported between day 1 and day 92 in participants without evidence of COVID-19 prior to vaccination.

Immunogenicity data from the booster study ARCT-154-J01 demonstrated that the level of neutralising antibodies against ancestral SARS-CoV-2 induced at 18 days after a heterologous booster dose of Kostaive was non-inferior to the level induced by the approved COVID-19 mRNA vaccine (Comirnaty). Both geometric mean titre (GMT) and seroresponse rate were higher after Kostaive administration than after Comirnaty. The results of the study support favourable benefit of ARCT-154 vaccine when administered as a booster dose in adult individuals who previously received the primary vaccination with other mRNA COVID-19 vaccines.

In study ARCT-2301-J01, a phase 3 randomised, observer-blind, active-controlled study, the safety and immunogenicity of Kostaive versus Comirnaty given as a booster dose in adults was evaluated. When ARCT-2301 (bivalent, ancestral strain and Omicron BA.4/5) was administered as a booster who had received 3 to 5 doses of the authorised mRNA COVID-19 vaccine with the last dose 11.1 months prior (median time, range 4.0 to 13.7 months), the immunogenicity of ARCT-2301 was superior to that

of Comirnaty (bivalent, ancestral strain and Omicron BA.4/5) against Omicron BA.4/5 variant and ancestral strain for both the GMT ratio and the serious RR difference.

New information on the efficacy and effectiveness of Kostaive has become available during the reporting period from completed immunogenicity studies ARCT-165-01 and ARCT-2303-01:

ARCT-165-01: a phase 1/2 randomised, observer-blind, 2-cohort study evaluating the safety, reactogenicity and immunogenicity of three investigational SARS-CoV-2 sa-RNA vaccines. The study enrolled 72 adult participants 21-65 years of age divided into two cohorts of 36 participants selected based on previous vaccination status against SARS-CoV-2. Immunogenicity data from ARCT-165-01 support the benefits of Kostaive in seropositive vaccine-naïve subjects and as a booster dose in subjects previously vaccinated with the Comirnaty vaccine.

ARCT-2303-01: The study met the statistically powered 4 primary objectives and 2 secondary objectives and showed that a single booster dose of ARCT-2303 that encodes the Omicron XBB.1.5 variant was superior in the induction of neutralizing antibodies to ARCT-154 that encodes the ancestral / Wuhan strain and that co-administration of ARCT-2303 with quadrivalent influenza vaccine in adults was immunologically non-inferior to stand-alone administration of each vaccine in terms of the induction of neutralizing antibodies against the Omicron XBB.1.5 variant and haemagglutination inhibition antibodies specific for the 4 QIV strains. The study also showed that the co-administration of ARCT-2303 with adjuvanted QIV appeared not to affect the immunogenicities of the respective standalone vaccines and that a single booster dose of ARCT-2303 appeared to induce durable neutralizing antibody titres against Omicron XBB.1.5 for up to 6 months in both younger (18 to 64 years) and older (above 64 years) adults.

No new relevant benefit data for Kostaive have become available during the reporting period.

4. Benefit-risk balance

During the reporting interval, new information on the efficacy and effectiveness of Kostaive has become available from two completed studies that support the pre-existing benefit data. There were no new safety issues or signals that could have an impact on the benefit-risk ratio and no new information concerning the established risks for Kostaive.

The benefit-risk balance for Kostaive remains unchanged.

5. Rapporteur Request for supplementary information

None.

Periodic Benefit-Risk Evaluation Report

Active Substance: Lipid Nanoparticle Formulated Self-amplifying mRNA encoding for Spike SARS-CoV-2 Glycoprotein

ATC-Code: J07BN01

Medicinal Products Covered:

Invented Name of the Medicinal Product(s)[a]	Marketing Authorisation Number(s)	Date(s) of Authorisation	Marketing Authorisation Holder[b]
Kostaive	30500AMX00282000	28 November 2023	Meiji Seika Pharma
Kostaive	EU/1/24/1873/001	12 February 2025	Seqirus Netherlands B.V.

[a] Data for product in country of Internation Birth Date

[b] First Marketing Authorisation Holder; full list available in Section 2.

Authorisation Procedure in the EU: Centralised

International Birth Date (IBD): 28 November 2023

European Union Reference Date (EURD): 28 November 2023

Interval Covered by this Report:

28 November 2024 to 27 May 2025

Date of this Report:

29 July 2025

Report Number:

3

Marketing Authorisation Holder's Name and Address:

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Approved by (QPPV OR Delegate): e-signature (see last page)

[redacted]
Global Safety Lead

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Executive Summary

Introduction:

This is the third Periodic Benefit-Risk Evaluation Report (PBRER) for Kostaive. This PBRER summarises the safety data collected by the Marketing Authorisation Holder (MAH) during the reporting period between 28 November 2024 up to and including the Data Lock Point (DLP) of 27 May 2025. This PBRER is written in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2C (R2) and the European Medicines Agency Good Pharmacovigilance Practices Module VII (Revision 1) guidelines.

Reports and other data from the marketing partner companies Meiji Seika Pharma (clinical and postmarketing data) and Arcturus Therapeutics (only clinical data) are included.

Description of Product:

Kostaive is a coronavirus disease 2019 (COVID-19) self-amplifying messenger RNA (sa-mRNA) vaccine. The active pharmaceutical ingredient is a single-stranded, 5'-capped sa-mRNA replicon, produced using a cell-free in vitro transcription from the corresponding deoxyribonucleic acid templates encoding a replicase and the prefusion-stabilised, furin cleavage site-inactivated spike glycoprotein (S glycoprotein) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To generate the vaccine, the messenger ribonucleic acid (mRNA) is encapsulated in lipid nanoparticles. The lipids serve to protect the sa-mRNA from degradation and enable delivery of the sa-mRNA into the host cell. The sa-mRNA consists of a series of ribonucleotides encoding the replicase and a ribonucleic acid (RNA) sequence encoding the SARS-CoV-2 S glycoprotein. Unlike the sa-mRNA in conventional sa-mRNA vaccines, Kostaive is designed to replicate within the body's own cells. After intramuscular delivery of Kostaive, it produces a protein called replicase that makes copies of the entire sa-mRNA as well as specifically amplifying the SARS-CoV-2 S glycoprotein RNA messenger. Thus, a lower dose of Kostaive can produce as much or more SARS-CoV-2 S glycoprotein messenger than can be delivered by a higher dose of a conventional sa-mRNA vaccine. By promoting the expression of this viral S protein in vaccinated individuals, Kostaive is intended to promote SARS-CoV-2-specific immune responses to provide active immunisation to prevent COVID-19 in adults 18 years of age and older.

LUNAR-COV19 formulations ARCT-021, ARCT-154, ARCT-165, ARCT-2303, ARCT-2301 and CSL402 are developed for the prevention of COVID-19 caused by specific variants of concern. In ARCT-021, the replicon (mRNA-2002) encodes for the ancestral strain S glycoprotein in the native conformation; the ARCT-154 replicon (mRNA2105 [zapomeran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the G clade D614G variant of SARS-CoV-2; and the ARCT-165 replicon (mRNA-2106) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Beta (B.1.351) variant of SARS-CoV-2 with the D614G mutation. The ARCT-2303 replicon (mRNA- 2319 [lonpovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron XBB.1.5 variant of SARS-CoV-2. ARCT-2301 contains 2 replicons – 1 encoding for the prefusion-stabilised, furin cleavage site-inactivated, S glycoprotein of the G clade D614G variant of SARS-CoV-2 (mRNA-2318), the other encoding for the prefusion-stabilised, furin cleavage site-inactivated, S glycoprotein of the Omicron BA.4/5 variants (mRNA-2317 [tagovameran]). The CSL402 replicon (mRNA-2425 [quozovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated, S glycoprotein of the Omicron JN.1 variant.

The approved indication for Kostaive according to the Reference Safety Information is for 'active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older'. Kostaive must be administered intramuscularly after reconstitution. The vaccine should not be mixed with any other vaccines or medicinal products in the same syringe. A single dose contains 5 mcg of sa-mRNA in 0.5 mL. The preferred site for intramuscular injection is the deltoid muscle of the upper arm.

Estimated Exposure:

Cumulatively, around 21,235 participants have been exposed to Kostaive in MAH-sponsored and Partner-sponsored clinical trials (completed and ongoing) since the Development International Birth Date of 20 July 2020.

During the reporting period, the marketing exposure to Kostaive was estimated at [redacted] standard doses sold. Cumulatively, the marketing exposure of Kostaive was estimated at 136,816 standard doses sold. Note: After DLP 27 May 2025, 7386 vials were returned from stock. Therefore, the corrected cumulative exposure is 1165 vials (18,640 standard doses).

Worldwide Marketing Authorisation Status:

At the time of the DLP of this report, Kostaive was authorised in 31 countries worldwide. During the reporting period, Kostaive was approved in the European Union / European Economic Area including Iceland, Liechtenstein and Norway on 12 February 2025 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The Market Authorisation was transferred from Arcturus Therapeutics Europe B.V. to Seqirus Netherlands B.V. on 16 April 2025.

Actions Taken and Proposed for Safety Reasons:

During the reporting period, no significant actions for safety reasons were taken for Kostaive.

Benefit-Risk Analysis:

Review of the data received during the reporting period of this PBRER did not change the current benefit-risk profile of Kostaive for its authorised indication and population. Overall, the data received are in line with previously known safety and efficacy data of Kostaive.

Conclusions:

Based on the evaluation of information collected during this reporting period in context of the available cumulative data, no changes in the benefit-risk profile for Kostaive have been observed. The overall benefit-risk balance for Kostaive remains favourable. The MAH proposes to remove the missing information topics Interaction with other vaccines and Long-term safety data in the updated RMP, version 1.1, with DLP 27 May 2025 which was submitted to European Medicines Agency on 03 July 2025.

The safety profile of Kostaive is considered adequately reflected in the current Reference Safety Information, and no safety amendments are warranted at present.

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List of Abbreviations

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or Special Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
CCDS	Company Core Data Sheet
CMQ	Customised Medical Dictionary for Regulatory Activities Query
COVID-19	Coronavirus Disease 2019
CI	Confidence Interval
DLP	Data Lock Point
ELS	Extensive Limb Swelling
EMA	European Medicines Agency
EU	European Union
GMT	Geometric Mean Titre
HLT	High Level Terms
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
nAb	Neutralizing Antibody
PBRER	Periodic Benefit-Risk Evaluation Report
PT	Preferred Term
QIV	Quadrivalent Influenza Vaccine
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RR	Reporting Rate
RSI	Reference Safety Information
SAE	Serious Adverse Event
sa-mRNA	Self-amplifying Messenger Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Abbreviation or Special Term	Definition
S glycoprotein	Spike Glycoprotein
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
TTO	Time to Onset

1 Introduction

This is the third Periodic Benefit-Risk Evaluation Report (PBRER) for Kostaive. This PBRER summarises the safety data collected by the Marketing Authorisation Holder (MAH) during the reporting period between 28 November 2024 up to and including the Data Lock Point (DLP) of 27 May 2025. This PBRER is written in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2C (R2) and the European Medicines Agency (EMA) Good Pharmacovigilance Practices Module VII (Revision 1) guidelines. The International Birth Date for Kostaive is 28 November 2023 in Japan.

Reports and other data from the marketing partner companies Meiji Seika Pharma (clinical and postmarketing data) and Arcturus Therapeutics (only clinical data) are included.

Kostaive is a vaccine indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19); the active pharmaceutical ingredient is a single-stranded, 5'-capped self-amplifying messenger ribonucleic acid (sa-mRNA) replicon produced using a cell-free in vitro transcription from the corresponding deoxyribonucleic acid templates encoding a replicase and the spike glycoprotein (S glycoprotein) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To generate the vaccine, the sa-mRNA is encapsulated in lipid nanoparticles. The lipids serve to protect the messenger ribonucleic acid (mRNA) from degradation and enable delivery of the sa-mRNA into the host cell. The sa-mRNA consists of a series of ribonucleotides encoding the replicase and a ribonucleic acid (RNA) sequence encoding the SARS-CoV-2 S glycoprotein. Unlike the sa-mRNA in conventional sa-mRNA vaccines, Kostaive is designed to replicate within the body's own cells. After intramuscular delivery of Kostaive, it produces a protein called replicase that makes copies of the entire sa-mRNA as well as specifically amplifying the SARS-CoV-2 S glycoprotein RNA messenger. Thus, a lower dose of Kostaive can produce as much or more SARS-CoV-2 S glycoprotein messenger than can be delivered by a higher dose of a conventional sa-mRNA vaccine. By promoting the expression of this viral S protein in vaccinated individuals, Kostaive is intended to promote SARS-CoV-2-specific immune responses to provide active immunisation to prevent COVID-19 for adults 18 years of age and older (Anatomical Therapeutic Chemical Code: J07BN01).

LUNAR-COV19 formulations ARCT-021, ARCT-154, ARCT-165, ARCT-2303, ARCT-2301 and CSL402 are being developed for the prevention of COVID-19. In ARCT-021, the replicon (mRNA-2002) encodes for the ancestral strain S glycoprotein in the native

conformation; the ARCT-154 replicon (mRNA-2105 [zapomeran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the G clade D614G variant of SARS-CoV-2 and the ARCT-165 replicon (mRNA-2106) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Beta (B.1.351) variant of SARS-CoV-2 with the D614G mutation. The ARCT-2303 replicon (mRNA-2319 [lonpovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron XBB.1.5 variant of SARS-CoV-2. ARCT-2301 contains 2 replicons – 1 encoding for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the G clade D614G variant of SARS-CoV-2 (mRNA-2318) and the other encoding for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron BA.4/5 variants (mRNA-2317 [tagovameran]). The CSL402 replicon (mRNA-2425 [quozovameran]) encodes for the prefusion-stabilised, furin cleavage site-inactivated S glycoprotein of the Omicron JN.1 variant.

The approved indication for Kostaive according to the Reference Safety Information (RSI) is for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Kostaive contains 5 mcg of sa-mRNA in 0.5 mL and must be administered after reconstitution. The vaccine should not be mixed with any other vaccines or medicinal products in the same syringe. A single dose must contain 0.5 mL of Kostaive. The preferred site for intramuscular injection is the deltoid muscle of the upper arm. Information regarding the posology can be found in the RSI presented in Appendix 1.

This PBRER is prepared on behalf of all MAH partner companies in accordance with relevant Pharmacovigilance agreements.

The composition of Kostaive presented in Table 1-1.

Table 1-1: Composition of Kostaive

Strains	**Per (0.5) mL Dose**
sa-mRNA	5.0 mcg
Excipients	**Per (0.5) mL Dose**
ATX-126	[redacted]
DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)	
Cholesterol	
PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene)	
Tris (tris(hydroxymethyl)aminomethane)	
Sodium chloride	
Sucrose	
Potassium sorbate	
Kolliphor P 188 Bio[a]	

sa-mRNA = self-amplifying messenger ribonucleic acid

[a] Also known as 'Poloxamer 188'

2 Worldwide Marketing Authorisation Status

Kostaive was first authorised on 28 November 2023 in Japan where it is marketed by Meiji Seika Pharma. The product is currently registered in 31 countries worldwide. The approved indication for Kostaive according to the RSI is for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The approved dose of vaccine contains 5 mcg of sa-mRNA in 0.5 mL.

During the reporting period, Kostaive was approved in the European Union (EU) / European Economic Area including Iceland, Liechtenstein and Norway on 12 February 2025 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The Market Authorisation was transferred from Arcturus Therapeutics Europe B.V. to Seqirus Netherlands B.V. on 16 April 2025.

A detailed overview of the current worldwide registration status for Kostaive can be found in Appendix 6.

3 Actions Taken in the Reporting Interval for Safety Reasons

During the reporting period, no actions for safety reasons were taken by the MAH, sponsors of clinical trials, regulatory authorities, data monitoring committees or ethics committees.

4 Changes to Reference Safety Information

The RSI in effect at the start of the reporting period was the Company Core Data Sheet (CCDS) version 1.0, dated 05 November 2023.

During the reporting period, the RSI was updated once to CCDS, version 2.0, dated 15 May 2025. An overview of the most significant safety-related changes to the RSI is presented in Table 4-1.

Table 4-1: Overview of Significant Safety-related Changes to the Reference Safety Information

CCDS Version	Updated Section	Justification for Change
2.0	Section 4.4 (Warnings and Precautions)	Addition of a general warning for myocarditis and pericarditis as events that may occur very rarely following administration of COVID-19 vaccines.
2.0	Section 4.5 (Interactions)	Revised based on the completion of clinical study ARCT-2303-01 to include the concomitant administration of Kostaive with influenza vaccines.

CCDS = Company Core Data Sheet; COVID-19 = coronavirus disease 2019

A copy of the RSI versions in effect at the start and end of the reporting period can be found in Appendix 1.

5 Estimated Exposure and Use Patterns

5.1 Cumulative Subject Exposure in Clinical Trials

Up to the DLP of this PBRER, 21,235 subjects have been exposed to Kostaive in completed and ongoing clinical trials, 29 subjects have been randomised to exclusively receive placebo (> 18,000 participants received placebo either prior or after receiving Kostaive), 3544 participants have been exposed to the comparator, which includes an estimated 1499 participants who have received a coadministered or sequentially administered influenza vaccine.

Summaries of the estimated cumulative subject exposure are presented in Table 5-1, Table 5-2, Table 5-3 and Table 5-4.

Table 5-1: Estimated Cumulative Subject Exposure from all Completed and Ongoing Clinical Trials[a]

Treatment	Number of Subjects
Kostaive	21,235
Comparator	3544
Placebo (ie, randomised to exclusively receiving placebo)	29

[a] Estimates of cumulative subject exposure based upon actual exposure data from completed clinical trials (see Table 5-2) and the current enrolment for ongoing trial (CSL402-J01) as of 27 May 2025.

Table 5-2: Estimated Cumulative Subject Exposure to Kostaive from Completed Clinical Studies by Age Study and Age Range

Study and Age Range	Total[a,b]
ARCT-021-01	
≥ 21 years	78
ARCT-021-02	
Cohort 1a: 23-68 years	12
Cohort 1b: 25-71 years	12
Cohort 2: 25-55 years	25
Cohort 2: 56-80 years	16
ARCT-021-04	
≥ 18 years	580
ARCT-154-01	
≥ 18 - < 60 years	14,470
≥ 60 years	3112

Study and Age Range	Total[a,b]
ARCT-165-01	
≥ 21 - ≤ 65 years	72
ARCT-154-J01	
≥ 18 - < 65 years	408
≥ 65 years	12
ARCT-2301-J01	
≥ 18 - < 65 years	429
≥ 65 years	34
ARCT-2303-01[c]	
≥ 18 - < 65 years	1204
≥ 65 years	295
Total	**20,759**

[a] Data from completed studies as of 27 May 2025. Cumulative subject exposure based upon actual exposure data from completed clinical trials.

[b] Subjects who participated in more than 1 study have been counted more than once.

[c] Based on total number of subjects exposed on Day 1. Subjects were randomised 1:1:1 to receive either ARCT-2303, a flu vaccine or both. On Day 29, participants were planned to receive the vaccine they had not been exposed to on Day 1; however, 10 participants did not receive the Day 29 vaccination.

Table 5-3: Cumulative Exposure to Kostaive from Completed Clinical Studies by Gender[a]

	Number of Subjects	
	Male	**Female**
ARCT-021-01	57	21
ARCT-021-02	47	18
ARCT-021-04	314	266
ARCT-154-01	8677	8905
ARCT-165-01	30	42
ARCT-154-J01	172	248
ARCT-2301-J01	223	240
ARCT-2303-01[b]	547	952
Total	**10,067**	**10,692**

[a] Data from completed studies as of 27 May 2025.

[b] Based on total number of subjects exposed on Day 1. Subjects were randomised 1:1:1 to receive either ARCT-2303, a flu vaccine or both. On Day 29, participants were planned to receive the vaccine they had not been exposed to on Day 1; however, 10 participants did not receive the Day 29 vaccination.

Table 5-4: Estimated Cumulative Subject Exposure to Kostaive from Completed Clinical Studies by Ethnic Origin[a]

Ethnic Origin	Number of Subjects
ARCT-021-01	
Asian	74
Black	0
Caucasian	2
Other	1
American Indian or Alaska Native	1
Study total	**78**
ARCT-021-02	
Asian	61
Black	0
Caucasian	2
Other	1
American Indian or Alaska Native	1
Study total	**65**
ARCT-021-04	
Asian	93
Black	34
Caucasian	429
Other	10
Unknown	14
Study total	**580**
ARCT-154-01	
Asian	17,582
Black	0
Caucasian	0
Other	0
Unknown	0
Study total	**17,582**
ARCT-165-01	
American Indian and Alaskan Native	0
Asian	10
Black or African American	29
Native Hawaiian or Other Pacific Islander	0
White	35
Other	0
Study total	**72[b]**

Ethnic Origin	Number of Subjects
ARCT-154-J01	
Asian	420
Black	0
Caucasian	0
American Indian or Alaska Native	0
Other	0
Study total	**420**
ARCT-2301-J01	
Asian	463
Black	0
Caucasian	0
American Indian or Alaska Native	0
Other	0
Study total	**463**
ARCT-2303-01[c]	
Asian	700
Black	3
Caucasian	537
American Indian or Alaska Native	60
Other	199
Study total	**1499**
Total	**20,759**

[a] Data from completed studies as of 27 May 2025.

[b] Subjects may be included in more than 1 category

[c] Based on total number of subjects exposed on Day 1. Subjects were randomised 1:1:1 to receive either ARCT-2303, a flu vaccine or both. On Day 29, participants were planned to receive the vaccine they had not been exposed to on Day 1; however, 10 participants did not receive the Day 29 vaccination.

5.2 Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1 Postauthorisation (Nonclinical Trial) Exposure

It is assumed that 1 dose of the vaccine accounts for 1 exposed patient.

Cumulative and interval sales volumes are presented in Table 5-5. In addition, a summary of the interval sales data by country can be found in Table 5-6. Estimated interval and cumulative worldwide patient exposure is presented in Table 5-7. To be noted, after DLP 27 May 2025, 7386 vials were returned from stock. Therefore, the corrected cumulative exposure is 1165 vials (18,640 standard doses).

Table 5-5: Estimated Sales Volume in Vials

Previous Period 28 May 2024 to 27 November 2024	Current Period 28 November 2024 to 27 May 2025	Cumulatively 28 November 2023 to 27 May 2025	Cumulatively Correction after DLP
[redacted]		8551	1165

DLP = data lock point

Table 5-6: Current Period Sales Volume by Country

Country	Sales Volume (Vials)
Japan	[redacted]

Note: Each vial contains 16 doses.

During the reporting period, 95,344 standard doses have been sold worldwide (5959 vaccine vials shipped during the reporting period; each vial provides 16 doses of vaccine). Cumulatively, 136,816 standard doses have been sold worldwide (8551 vaccine vials shipped during the reporting period; each vial provides 16 doses of vaccine).

During the reporting period, exposure increased compared to the previous reporting period. Of note, Kostaive was commercially launched in October 2024; thus, the previous postmarketing exposure only covers 2 months. The current reporting period includes a postmarketing exposure for 6 months. This explains the increase in postmarketing exposure if calculated on the interval only.

Table 5-7: Estimated Worldwide Patient Exposure for Kostaive

	Previous Period 28 May 2024 to 27 November 2024	Current Period 28 November 2024 to 27 May 2025	Cumulatively 28 November 2023 to 27 May 2025	Cumulatively Correction after DLP
Single-dose Exposure	[redacted]		136,816	18,640

DLP = data lock point

5.2.2 Postauthorisation Use in Special Populations

Other than its postmarketing data collection system, the MAH has no specific collection system in place to monitor exposure in special populations. Therefore, the available information regarding the cumulative and interval patient exposure in special populations was retrieved by searching the MAH's safety database for all valid cases received from postmarketing reporting regardless of causality. However, due to the nature of postmarketing

reporting, it must be noted that a reliable exposure estimation cannot be drawn from these cases.

5.2.2.1 Use in Paediatric Patient Population

The number of postauthorisation paediatric cases is presented in Table 5-8.

Table 5-8: Number of Postauthorisation Paediatric Cases

Age Group	Interval Number of Cases	Cumulative Number of Cases
Neonate (< 1 month)	0	0
Infant (1 month to < 2 years)	0	0
Child (2 years to < 12 years)	0	0
Adolescent (12 years to < 18 years)	1	1
Total	**1**	**1**

Note: One foetal case ([redacted]) was excluded from the interval and cumulative number of cases as it is coded with foetal exposure during pregnancy and route of administration as transplacental. This case is discussed under Section 16.3.5.1.

Cumulatively, 1 case and during the reporting period, follow-up of this case was received from postmarketing reporting. No new significant information was received in this case.

Review of the cases concerning paediatric patient exposure did not change the current safety profile of the product.

5.2.2.2 Use in Elderly Patient Population

An overview of the estimated postauthorisation cases in elderly patients is presented in Table 5-9.

Table 5-9: Number of Postauthorisation Cases

Age Group	Interval Number of Cases	Cumulative Number of Cases
65 to 69 years	22	23
70 to 79 years	44	45
80 to 89 years	43	44
90 years and older	39	42
Unknown	34	51
Total	**182**	**205**

During the reporting period, a total of 182 (172 initial and 10 follow-up) cases were retrieved from the MAH's Global Safety Database pertaining to use in elderly patients. Of the 172 initial cases received, 103 cases were reported from spontaneous sources and 69 were

reported from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436).

Within these 172 initial cases, a total of 374 events were reported, of which 34 were serious (including 15 fatal events) and 340 were nonserious. The most frequently reported events (≥ 10) were Pyrexia (90), Injection site pain (46), Vaccination site pain (50), Malaise (19), Headache (16) and Vaccination site swelling (13).

Out of 10 fatal cases (15 fatal events), 8 cases were reported in patients with advanced elderly age (88 to 101 years). In most of these fatal cases, the patients had multiple underlying comorbidities which are considered as confounders for the reported events. None of the cases had autopsy results provided. Of note, 3 of the fatal cases were reported from noninterventional safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and were assessed as unrelated by both the reporter and the Company.

During the reporting period, a total of 10 follow-up cases were received for Kostaive. All these cases did not receive clinically significant follow-up information.

Cumulatively, 205 cases have been received pertaining to use in elderly patients. Among these cases, 136 cases were received from spontaneous reporting and 69 were reported from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436). These cases encompassed 422 events, of which 37 were serious and 385 were nonserious. The most frequently reported events (n ≥ 10) included Pyrexia (120), Vaccination site pain (51), Injection site pain (47), Malaise (21), Headache (16) and Vaccination site swelling (13).

Review of the cases concerning elderly patient exposure did not change the current safety profile of Kostaive.

5.2.2.3 Pregnancy and Lactation

5.2.2.3.1 Use during Pregnancy

During the reporting period and cumulatively, a total of 10 cases pertaining to exposure during pregnancy with Kostaive were received from postmarketing reporting. These 10 initial cases received during the reporting period are discussed in detail in Section 16.3.5.1.

An overview of the reported pregnancy outcomes during the cumulative and interval period is provided in Table 5-10.

Table 5-10: Reported Pregnancy Outcomes during Interval and Cumulative Period

Outcome	Interval Period	Cumulative Period
Normal (full term or live birth)	1	1
Postmature	0	0
Premature	0	0
Spontaneous abortion	0	0
Elective termination	0	0
Intrauterine death	0	0
Stillbirth	0	0
Unknown, lost to follow-up or outcome pending	8	8
Total	**9**	**9**

Note: The case with foetal exposure was excluded from the outcome as the maternal outcome of live birth was considered.

Use of Kostaive during pregnancy is considered missing information. An evaluation of the new information received during the reporting period can be found in Section 16.3.5.1. A characterisation of the use in pregnancy and while breastfeeding is presented in Section 16.4.3.1.

5.2.2.3.2 Use during Lactation

During the reporting period and cumulatively, 13 cases pertaining to lactation exposure with Kostaive were received from postmarketing reporting. These 13 initial cases received during the reporting period are discussed in detail in Section 16.3.5.1.

Use of Kostaive during lactation is considered missing information. An evaluation of the new information received during the reporting period can be found in Section 16.3.5.1. A characterisation of the use in pregnancy and while breastfeeding is presented in Section 16.4.3.1.

5.2.3 Other Postauthorisation Use

5.2.3.1 Off-label Use

A review of all postauthorisation experience pertaining to off-label use was performed by searching the MAH's Global Safety Database for all cases (valid and invalid) pertaining to off-label use in the postmarketing setting regardless of causality.

During the reporting period, 1 follow-up case (no initial case) pertaining to off-label use with Kostaive was received from postmarketing reporting.

Cumulatively, 1 case pertaining to off-label use with Kostaive was received from postmarketing reporting. This case concerns a [redacted]-year-old female patient who received Kostaive for COVID-19 prophylaxis (Off label use in unapproved age group [redacted] and experienced pyrexia (38.0 to 38.9 °C) on the same day as vaccination. The MAH assessed the event as related, and the event outcome was resolved.

Review of the case pertaining to off-label use did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to off-label use per its routine pharmacovigilance procedures.

5.2.3.2 Drug Interaction

A review of all postauthorisation cases pertaining to drug interaction was performed by searching the global safety database for all cases containing at least 1 Preferred Term (PT) included in the High Level Term (HLT) Interactions.

During reporting interval and cumulatively, no cases pertaining to drug interaction with Kostaive were received from postmarketing reporting; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive. The MAH will continue to monitor all cases pertaining to drug interaction per its routine pharmacovigilance procedures.

6 Data in Summary Tabulations

The data in the summary tabulations appended to this report are based on the Individual Case Safety Reports (ICSRs) that have been received by the MAH at the time of DLP and meet the 4 minimal criteria of a valid case, as specified in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E2D guideline. The adverse drug reaction (ADR) / adverse event (AE) terms in the summary tabulations are arranged alphabetically by primary System Organ Class (SOC) and PT. A single ICSR can include more than 1 event. Therefore, the total number of events may be greater than the total number of case reports presented.

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), version 28.0, has been used for the presentation and analysis of AEs in this report.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative summary tabulation of all serious AEs (SAEs) from all MAH- and partner-sponsored clinical studies since the Development International Birth Date is presented in Appendix 2.1.

Note: The cumulative summary tabulation of SAEs will only have studies listed if at least 1 SAE was reported in the study. Studies with no SAEs will not be listed.

6.3 Cumulative and Interval Summary Tabulations from Postmarketing Data Sources

Cumulative and interval summary tabulations of all spontaneous ICSRs and serious ADRs derived from noninterventional studies and other solicited sources are listed in Appendix 2.2.

An overview of the interval and cumulative ADR data is presented in Table 6-1.

Table 6-1: Overview of Adverse Drug Reaction Data

Source	**Reporting Period** **N / Reporting Rate**	**Cumulative Period** **N / Reporting Rate**
Nonserious ADRs - spontaneous	330 / 346.12	374 / 273.36
Serious ADRs - spontaneous	25 / 26.22	25 / 18.27
Serious ADRs – noninterventional studies and other solicited	10 / 10.49	10 / 7.31
Total ADRs	365 / 382.82	409 / 298.94

ADR = adverse drug reaction; N = number

7 Summaries of Significant Findings from Clinical Trials During the Reporting Interval

Safety and efficacy concerns obtained during the reporting period of this PBRER from information from MAH- and partner-sponsored (Meiji Seika Pharma and Arcturus Therapeutics) interventional trials are presented in this section.

An overview of all MAH-sponsored interventional studies with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting period is presented in Appendix 4.

7.1 Completed Clinical Trials

During the reporting period, 2 clinical trials with Kostaive were completed (ARCT-165-01 and ARCT-2303-01).

Study ARCT-165-01 showed a higher frequency and severity of local and solicited AEs for the first-generation vaccine ARCT-021 compared with the next-generation vaccines ARCT-154 and ARCT-165 following a heterologous booster in licensed mRNA-primed participants. Data from this study confirm the improved tolerability of the next-generation vaccines. The clinical study report was finalised on 19 December 2024.

Study ARCT-2303-01 confirms the safe use of ARCT-2303 vaccine when administered concomitantly with influenza vaccines. Coadministration of ARCT-2303 with quadrivalent influenza vaccines (QIV; QIV in adults aged 18 to 64 years and adjuvanted QIV [aQIV] in adults aged 65 years and above) appeared not to affect the immunogenicity of the individual vaccines. There was no evidence of a significant impact on the safety and reactogenicity profiles for each vaccine when coadministered vs. standalone. The clinical study report was finalised 10 April 2025.

No new clinically important efficacy and safety findings have arisen from these clinical trials.

7.2 Ongoing Clinical Trials

During the reporting period, 1 clinical trial with Kostaive was ongoing (CSL402-J01) in Japan. No new clinically important efficacy and safety findings have arisen from this clinical trial. Interim results showed [redacted]

[redacted]
CSL402 5 mcg; [redacted]

7.3 Long-term Follow-up

Up to 12 months long-term safety data have been collected in ARCT-154-01, ARCT-154-J01 and ARCT-165-01 clinical studies in participants who have been exposed to either a primary series 2-dose regimen or a single-dose booster vaccination. No new clinically important safety findings have arisen from these clinical trials up to 12 months post vaccination (see Section 16.3.5.5).

7.4 Other Therapeutic Use of Medicinal Product

No other programmes following a specific protocol with solicited reporting for Kostaive were ongoing or completed during the reporting period.

7.5 New Safety Data Related to Fixed Combination Therapies

Kostaive is not authorised or under development as a component of a fixed dose combination product or a multidrug regimen.

8 Findings from Noninterventional Studies

During the reporting period, no noninterventional studies were sponsored by CSL Seqirus.

During the reporting period, 1 ongoing noninterventional safety study (KO01 Drug Use-results Survey, NIS_PVA159436) was sponsored by Meiji Seika Pharma. No new significant safety information was received from this partner-sponsored noninterventional study.

An overview of all MAH-sponsored noninterventional studies with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting period is presented in Appendix 4.

9 Information from Other Clinical Trials and Sources

9.1 Other Clinical Trials

The MAH is not aware of any other clinical trials with Kostaive that were conducted during the reporting period of this PBRER.

During the reporting period, 2 Meiji Seika Pharma sponsored studies (VERSUS-R- an observational case-control study and Tokyo Shinagawa Hospital -a prospective observational study) with Kostaive were ongoing.

To date, no clinically important safety information has arisen from these sources.

9.2 Medication Errors

Based on the experience with vaccines in general, there are different types of medication error that can occur. The most common medication errors are these related to errors in product administration and storage, administration of additional dose(s) and administration to persons of inappropriate age. Experience with Kostaive appears to confirm the nature of these types of errors.

The relevant information on patterns of medication errors was obtained by searching the MAH's Global Safety Database for all cases containing at least 1 PT pertaining to the Medication errors (Standardised MedDRA Query [SMQ]; Narrow) and 2 additional PTs: Needle issue and Syringe issue.

During the reporting period, 1 spontaneous case reporting medication errors was received for Kostaive that reported a total of 2 medication errors. This case concerned an elderly female patient who received 2 doses of Kostaive (0.5 mL intramuscularly) within 2 weeks (PTs Accidental overdose and Extra dose administered). There was no additional AE reported. The root cause of these events was unspecified. As per CCDS, version 2.0, dated 15 May 2025, the second dose was not aligned with the intended dosing schedule. The MAH assessed these events as not related.

The cumulative and interval reporting rates (RRs) are provided in Table 9-1.

Table 9-1: Medication Error Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative	Cumulative Correction After DLP
No cases/RR (per 100,000 doses distributed) initially provided	0/Not applicable	1/1.049	1/0.731	1/5.364

Note: After DLP 27 May 2025, cumulative RR was updated to reflect corrected exposure data.

DLP = data lock point; RR = reporting rate

Conclusion

No patterns of medication errors have been identified relevant to the interpretation of safety data or the overall benefit-risk evaluation of Kostaive. Appropriate risk minimisation measures, in the form of the applicable label text, are currently in place to prevent medication errors. There was an increase in the interval RR compared with the cumulative reporting period. The MAH will continue to monitor all cases pertaining to medication errors per its routine pharmacovigilance procedures.

10 Nonclinical Data

During the reporting period, 1 nonclinical study (Study 31983371, ARC24-071) titled 'A Single Dose Study of ARCT-2303 by Intramuscular Administration in Rabbits' was in the reporting phase and finalised (04 March 2025).

The objective of this Good Laboratory Practice study was to compare the potential local and systemic toxicity of the test article, ARCT-2303 vaccine, in 2 formats, a single-dose liquid (ARCT-2303-1LIQ) and a 16-dose lyophilised (ARCT-2303-16LYO) format, when given via an intramuscular injection as a single dose to rabbits. The ARCT-2303 vaccine encodes the spike protein from the XBB1.5 SARS-CoV-2 virus, and the dose level (5 µg/rabbit) in this nonclinical study represents the full clinical dose in absolute terms. The following parameters and endpoints were evaluated in this study: mortality, clinical signs, body weights, body weight gains, food consumption, evaluation of skin reaction, body temperature, clinical pathology parameters (haematology, coagulation and clinical chemistry), cytokine, immunogenicity evaluation, organ weights and macroscopic and microscopic examinations. To summarise, following a single intramuscular injection of ARCT-2303-1LIQ and ARCT-2303-16LYO, no ARCT-2303-related adverse effects were noted in any parameter examined.

In conclusion, no significant safety findings have been observed from nonclinical studies.

11 Literature

A standardised search in the scientific literature databases MEDLINE and EMBASE was performed for articles relevant to Kostaive covering the reporting period. In addition, unpublished manuscripts when made available have been reviewed to identify new and significant safety findings. The retrieved abstracts and / or full texts were reviewed for important safety findings. Adverse reactions deriving from published individual case reports are included in the summary tabulations in Appendix 2.2.

The review of the published and unpublished literature retrieved during the reporting period yielded nonclinical and clinical articles that presented new and significant safety findings and / or significant lack of efficacy for Kostaive. These articles are presented below.

Table 11-1: Summary of Nonclinical Literature Received

Reference	Summary
Liu YL, Liao TY, Ho KW, Liu ES, Huang BC, Hong ST, et al. Impact of pre-existing anti-polyethylene glycol antibodies on the pharmacokinetics and efficacy of a COVID-19 mRNA vaccine (Comirnaty) in vivo. Biomater Res. 2024; 28: 0112. doi: 10.34133/bmr.0112. PMID: 39665081; PMCID: PMC11633857.	The presence of anti-PEG antibodies can hinder the therapeutic efficacy of PEGylated drugs. With the widespread use of a PEGylated coronavirus disease 2019 mRNA vaccine (Comirnaty), the impact of pre-existing anti-PEG antibodies on vaccine potency has become a point of debate. To investigate this, we established mouse models with pre-existing anti-PEG antibodies and divided them into 3 groups: Group 1 with anti-PEG immunoglobulin G + immunoglobulin M concentrations of 0.76 to 27.41 μg/mL, Group 2 with concentrations of 31.27 to 99.52 μg/mL, and a naïve group with no detectable anti-PEG antibodies. Results indicated that antispike antibody concentrations significantly decreased in Group 1 and Group 2 after the second vaccine dose compared with those in the naïve group. Spearman's rank correlation analysis demonstrated a negative relationship between antispike antibody production and anti-PEG antibody levels at both the second and third doses (second dose: $\rho = -0.5296$, $P = 0.0031$; third dose: $\rho = -0.387$, $P = 0.0381$). Additionally, spike protein concentrations were 31.4-fold and 46.6-fold lower in Group 1 and Group 2, respectively, compared with those in the naïve group at 8 h postvaccination. The concentration of complement C3a in Group 2 was significantly higher than that in the naïve group after the third dose. These findings confirm that pre-existing anti-PEG antibodies diminish vaccine efficacy, alter pharmacokinetics and elevate complement activation. Therefore, detecting pre-existing anti-PEG antibodies is crucial for optimising vaccine efficacy, ensuring patient safety and developing improved therapeutic strategies. **MAH Comment:** Potential impact of anti-PEG antibodies on vaccine efficacy.

MAH = marketing authorisation holder; mRNA = messenger ribonucleic acid; PEG = polyethylene glycol

Table 11-2: Summary of Clinical Literature Received

Reference	Summary
Cheng KL, Yu WS, Wang YH, Ibarburu GH, Lee HL, Wei JC. Long-term thyroid outcomes after COVID-19 vaccination: A cohort study of 2,333,496 patients from the TriNetX Network. J Clin Endocrinol Metab. 2025: dgaf064. doi: 10.1210/clinem/dgaf064. Epub ahead of print. PMID: 39883558.	Context: Reports on long-term thyroid dysfunction following COVID-19 vaccination are limited. Understanding the risk of subacute thyroiditis, hyperthyroidism and hypothyroidism in vaccinated individuals is crucial for postvaccination monitoring. Objective: This study evaluated the risk of thyroid dysfunction in COVID-19 vaccinated individuals compared to unvaccinated individuals using a large cohort. Methods: The authors conducted a retrospective cohort study from 01 January 2022 to 31 December 2023, using the TriNetX database, including 1,166,748 vaccinated and 1,166,748 unvaccinated individuals. Propensity score matching was used to balance baseline characteristics. The primary outcomes were new diagnoses of subacute thyroiditis, hyperthyroidism and hypothyroidism. Results: The risk of subacute thyroiditis remained unchanged (95% confidence intervals included 1). A significant reduction in hyperthyroidism risk was observed from 3 to 9 months postvaccination (HRs: 0.65-0.89, all 95% CIs below 1), but this trend was not significant at 12 months (HR: 0.99, 95% CI: 0.92-1.06). In contrast, the risk of hypothyroidism significantly increased from 6 to 12 months postvaccination (HR: 1.14-1.30, all 95% CIs above 1). Among mRNA vaccine recipients, the risk of both hyperthyroidism and hypothyroidism was significantly elevated at 12 months (HR: 1.16-2.13). Conclusion: COVID-19 vaccination was associated with a reduced risk of hyperthyroidism and an increased risk of hypothyroidism, highlighting the need for ongoing thyroid function monitoring. **MAH Comment:** Information relevant for subacute thyroiditis, event of special interest for Kostaive.
Fraenza F, Cagnotta C, Gaio M, Sportiello L, Scavone C, Capuano A, et al. Disproportionality analysis of European safety reports on autoimmune and rheumatic diseases following COVID-19 vaccination. 20025 Sci Rep 15, 14740.	The safety profile of COVID-19 vaccines is well-established, yet the widespread immunisation campaign has led to an increase in reported cases of IMDRs. This study aimed to assess the reporting of AEFIs related to IMDRs after COVID-19 vaccination. The authors analysed all ICSRs related to COVID-19 vaccines authorised in the European Union (ie, tozinameran, elasomeran, ChAdOx1-S NCoV-19 and Ad26.Cov2.S) registered in the EudraVigilance database from 01 January 2021 to 23 October 2023. The authors' analysis identified ICSRs with events indicative of IMDRs and conducted disproportionality analysis (ie, ROR with 95% CI) to examine the frequency of different IMDR types linked to each vaccine. In total, 45,352 ICSRs reported at least 1 AEFI associated with rheumatic or autoimmune conditions, with 54% of them implicating tozinameran as the suspected vaccine. More than half of the reported AEFIs were classified as serious, with approximately 45% remaining unresolved. The most frequently reported conditions were other immune-mediated diseases, followed by arthritis, vasculitis, systemic lupus erythematosus and tendinopathies. The disproportionality analysis

Reference	Summary
	suggested that mRNA vaccines may be more frequently associated with new autoimmune rheumatic diseases. Real-world pharmacovigilance data suggest that autoimmune and rheumatic diseases may be under-reported following COVID-19 vaccination, highlighting the need for further research to better understand the underlying mechanisms. The findings from this disproportionality analysis suggest the need for further studies to investigate these results in greater depth. **MAH Comment:** Safety of mRNA COVID-19 vaccines in individuals with autoimmune and inflammatory disorders.
Jeong J, Jo H, Son Y, Park J, Oh J, Lee S, et al. Global and regional estimates of vaccine-associated herpes zoster and their related vaccines from 1969 to 2023. Sci Rep. 2025 Apr 17;15(1):13285. doi: 10.1038/s41598-025-98106-9. PMID: 40247100; PMCID: PMC12006434.	Vaccine-induced immunosuppression can reactivate the varicella-zoster virus, potentially leading to the development of herpes zoster. However, the literature on this topic is inconsistent, resulting in limited clarity. Therefore, authors aimed to enhance the understanding of vaccine-associated herpes zoster and establish guidelines for future research, utilising a global database to improve global public health. The authors investigated vaccine-associated AEs in herpes zoster using reports (~13 million reports) from the WHO international pharmacovigilance database. Data were analysed for the global number of reports, ROR and IC to determine the potential association between 18 vaccines and vaccine-associated herpes zoster reports in nearly 170 countries and territories from 1969 to 2023. Of 7,805,380 vaccine-associated adverse events, there were 51,985 herpes zoster reports. Vaccine-associated herpes zoster showed the highest strength of association with COVID-19 mRNA vaccines (ROR, 11.85 [95% CI, 11.70-12.01]; IC, 2.74 [IC0.25, 2.72]), followed by encephalitis (ROR, 4.07 [95% CI, 3.37–4.92]; IC, 2.00 [IC0.25, 1.68]), influenza (ROR, 3.44 [95% CI, 3.28–3.62]; IC, 1.77 [IC0.25, 1.69]) and ad5-vectored COVID-19 vaccines (ROR, 3.05 [95% CI, 2.97–3.14]; IC, 1.54 [IC0.25, 1.50]). The ROR and IC increased with advancing age. The authors findings emphasize the need to consider the immune status of vaccine recipients. **MAH Comment:** Safety of mRNA COVID-19 vaccines in immunocompromised individuals.
Lim E, Kim YH, Jeong NY, Kim SH, Won H, Bae JS, et al. The association between acute transverse myelitis and COVID-19 vaccination in Korea: Self-controlled case series study. Eur J Neurol. 2025; 32(1): e70020. doi: 10.1111/ene.70020. PMID: 39739424; PMCID: PMC11683473.	Background: ATM has been reported as a potential association between COVID-19 vaccination. In this study, the authors aimed to investigate the association between the COVID-19 vaccination and ATM. Methods: A self-controlled case series study was performed using a large database that combined the COVID-19 vaccine registry and the national claims database. The COVID-19 vaccination data included information on individuals aged 18 and above who received COVID-19 vaccination from 26 February 2021 to 31 August 2022. The claims database covered the entire Korean population for the period between 01 January 2002 to 31 August 2022. Patients who develop ATM within 1-42 days following COVID-19 vaccination were included. The observation period was 270 days after the first dose of the COVID-19 vaccine. The IRR and 95% CI were estimated using a conditional Poisson regression model.

Reference	Summary
	Results: A total of 159 ATM patients were included. Among them, 82 (51.6%) were male, and mean age was 55.4±17.4 years. The IRR was 2.41 (95% CI: 1.76-3.30) for the ATM risk within 1-42 days after COVID-19 vaccination. The IRR by vaccine product was 3.31 (95% CI: 1.81-6.05) for ChAdOx1-S; 1.99 (95% CI: 1.30-3.03) for BNT162b2; 2.57 (95% CI: 1.14-5.97) for mRNA-1273; and 3.33 (95% CI: 0.30-36.44) for Ad26.COV2.S. Conclusion: These findings indicated an increased risk of ATM following COVID-19 vaccination within 42 days. An association with the risk of ATM was found both for viral vector and mRNA vaccines. **MAH Comment:** Information relevant for transverse myelitis, event of special interest for Kostaive.
Perez-Campuzano V, Rautou PE, Marjot T, Praktiknjo M, Alvarado-Tapias E, Turco L, et al. ERN RARE-LIVER; a study of VALDIG, an EASL consortium and REHEVASC. Impact of SARS-CoV-2 vaccination in patients with vascular liver diseases: Observations from a VALDIG multicenter study. JHEP Rep. 2024; 6(12): 101191. doi: 10.1016/j.jhepr.2024.101191. PMID: 39583091; PMCID: PMC11582744.	Background & aims: Patients with VLD are at higher risk of both severe courses of COVID-19 disease and thromboembolic events. The impact of SARS-CoV-2 vaccination in patients with VLD has not been described and represents the aim of the study. Methods: International, multicentre, prospective observational study in patients with VLD analysing the incidence of COVID-19 infection after vaccination, severity of side effects, occurrence of thromboembolic events and hepatic decompensation. In a subgroup of patients, the humoral and cellular responses to vaccination were also analysed. Results: A total of 898 patients from 14 European centres - part of the VALDIG network - were included, 872 (97.1%) patients received 2 vaccine doses (fully vaccinated) and 674 (75.1%) 3 doses. Of the total cohort, 151 / 898 had a COVID-19 infection prior to vaccination, of whom 9 / 151 (5.9%) were re-infected. Of the 747/898 patients who were not previously infected, 11.2% (84/747) were diagnosed with a COVID-19 infection during the study period. Two infected patients required intensive care unit admission and infection was fatal in 2 fully vaccinated patients. AEs were reported in around 40% of patients, with local side effects being the most frequent. During the study period, 31 (3.5%) patients had thromboembolic events and 21 (2.3%) hepatic decompensations. No cases of vaccine-induced thrombocytopenia were reported. Vaccine immunogenicity was assessed in 36 patients; seroconversion reached 100% and IFNγ T-cell responses significantly increased post 2 mRNA-1273 vaccine doses. Conclusion: Patients with VLD seem to have a preserved immune response to SARS-CoV-2 vaccination, which appears to be safe and effective in preventing severe COVID-19 infection. Our study cannot definitively establish a direct link between vaccination and thrombotic events though the contribution of vaccination as a cofactor in VLD remains to be elucidated. Impact and implications: Patients with VLD are at increased risk of both SARS-CoV-2 infection and severe COVID-19 disease. The potential risks associated with vaccination against this infection need thorough

Reference	Summary
	investigation. The authors' research enhances the understanding of the effects of COVID-19 vaccination in patients with VLD, highlighting its good tolerability. Moreover, patients with VLD appear to have a preserved immune response to SARS-CoV-2 vaccination, providing protection against severe COVID-19 infection. The study cannot definitively establish a direct link between vaccination and thrombotic events, and no cases of vaccine-induced thrombocytopenia were reported. **MAH Comment:** Information relevant for missing information use in patients with significant, unstable chronic medical conditions and important potential risk of thromboembolism.
Rungjirajittranon T, Nakkinkun Y, Suwanawiboon B, Chinthammitr Y, Owattanapanich W, Ruchutrakool T. Hemostatic changes following COVID-19 vaccination: Do they promote a pro-thrombotic state? Hum Vaccin Immunother. 2025; 21(1): 2439627. doi: 10.1080/21645515.2024.2439627. Epub 2024 Dec 19. PMID: 39699990; PMCID: PMC11660298.	VITT is a unique thrombotic complication of COVID-19 immunisation, especially with adenovirus vector vaccines. However, non-VITT thrombotic events were seen in mRNA vaccines. The authors aimed to investigate haemostatic changes following COVID-19 vaccination and to compare these changes between the ChAdOx1 and BNT162b2 vaccines. The authors conducted a prospective study involving COVID-19 infection- and vaccination-naïve participants aged over 18 years receiving the ChAdOx1 or BNT162b2 vaccines. Blood samples were collected at prevaccination, 7 and 21 days postvaccination. D-dimer levels, platelet counts and TGA parameters were collected. ChAdOx1-S group D-dimer levels did not change significantly throughout the study ($p = 0.51$). BNT162b2 group median D-dimer levels increased significantly on Day 7 (245 ng FEU/mL [IQR 155–384] at baseline; 315 ng FEU/mL [IQR 187.5–412] at Day 7; and 271 ng FEU/mL [IQR 166–400] at Day 21; $p = 0.021$). BNT162b2 group platelet counts increased significantly on Day 7 ($p = 0.010$). TGA parameters in the ChAdOx1-S group decreased significantly in ETP levels ($p = 0.007$) and peak concentrations ($p = 0.041$) over time, while those of the BNT162b2 group were stable (median ETP levels and peak concentrations; $p > 0.05$). Mean change in ETP levels from prevaccination between the vaccines were significantly different at Day 21 ($p = 0.001$). No antiplatelet factor 4 antibody positivity or clinical thrombosis occurred. Both vaccines showed low thrombosis risk without increased thrombin generation. However, BNT162b2 vaccine recipients exhibited a temporary inflammatory response, evidenced by a brief rise in D-dimer levels. **MAH Comment:** Information relevant for important potential risk of thromboembolism.
Skinningsrud B, Vlaisavljevic K, Oppedal LS, Endresen J, Mohn V, Fladseth K, et al. COVID-19 vaccine associated myocarditis in Norway - a nationwide validation study. Eur Heart J. 2024; 45(Suppl 1).	Background: The SARS-CoV-2 pandemic led to worldwide initiation of vaccination campaigns. The new mRNA vaccines were unexpectedly associated with VAM. The incidence and severity of VAM has not been validated in a nation-wide and well-defined population. From December 2020 onwards, the mRNA vaccines Comirnaty and Spikevax have been in widespread use in Norway. The NPR includes all hospital contacts with corresponding diagnostic codes (ICD-10), and all

Reference	Summary
doi: 10.1093/eurheartj/ehae666. 1987.	vaccinations are registered in the Norwegian Immunization Register (SYSVAK). Purpose: The authors aimed to identify and validate all cases of suspected COVID-19 VAM in Norway during the national vaccination campaign between 2020 and 2022. Methods: The authors identified all cases of myocarditis acquired within 90 days of a COVID-19 vaccination through linkage of diagnostic codes for myocarditis in NPR and vaccination data in SYSVAK. Cases were included from December 2020 through April 2022. The authors assessed medical records, cardiac imaging and biochemistry to retrospectively validate all myocarditis cases. The Brighton Criteria (international criteria for myocarditis diagnosis following immunisation with defining levels of diagnostic certainty) were used to confirm the VAM diagnosis. Results: From December 2020 to April 2022, 4,114,750 unique subjects (2,036,792 men and 2,077,958 women, median age first dose 47 years) above 16 years of age, received 10,915,098 unique doses of COVID-19 vaccines (8,651,703[79%] Comirnaty and 2,263,395[21%] Spikevax). Of 277 cases of myocarditis identified in NPR < 90 days after receiving a COVID-19 vaccine, 176 (64%) were validated as VAM (78 definite, 90 probable and 8 possible VAM). Among the patients with VAM, 137 (78%) were men with median age 30 (IQR 24-47) years and 39 (22%) were women with median age 54 (IQR 32-65) years. There were 4 cases of VAM per 100,000 vaccinated subjects: 7 per 100,000 men and 2 per 100,000 women. Sixty-three percent of VAM occurred after the second mRNA vaccine dose. There were 3.3 cases of VAM per 100,000 unique doses of Spikevax compared to 1.1 per 100,000 unique doses of Comirnaty. The most common time interval from vaccination to VAM was 3 days and occurred in 30 patients (17.3% of VAM, 93% men) and 34% of VAM (90% men) occurred during the first 5 days from vaccination. Median duration of hospital stay was 4 (IQR 3-5) days, with only 7 (4%) patients needing intensive care and 1 myocarditis-related patient death during hospitalisation. Conclusions: In this unique nationwide study including all COVID-19 vaccinated subjects in Norway from 2020-22, the authors found 4 cases of VAM per 100,000 vaccinated subjects. The majority of VAM occurred in young men. Interestingly, women presented later than men with VAM and most frequently at middle to older age. The occurrence of this unexpected serious adverse event underscores the importance of large studies in broad populations in future vaccine programs. **MAH Comment:** Information relevant to important potential risk of myocarditis / pericarditis / myopericarditis.
Tariq M, Gondal A, Suhagiya GH, Dholakiya PM, Girish F, Kumar A, et al. COVID-19 vaccine-induced acute	Introduction: Despite the remarkable efficacy of COVID-19 vaccines in preventing severe illness and death, concerns about potential GI AEs have emerged. Recent reports suggest a possible link between COVID-19 vaccine and AP, but large-scale characterisation of this patient group is

Reference	Summary
pancreatitis: a systematic review. Am J Gastroenterol. 2024; 119(10S): S37-8. doi: 10.14309/01.ajg.0001028568.60097.bd	lacking. The study aims to evaluate and summarise the evidence regarding COVID-19 vaccine-induced AP. Methods: The authors conducted a systemic literature search using PubMed, EMBASE and Google Scholar. The search strategy included the MeSH term and keywords for 'COVID-19 vaccine' and 'pancreatitis' from date of inception to 30 May 2024. Initial search yielded 361 articles. After excluding irrelevant studies, duplicates and review articles, we included 45 articles reporting the COVID-19 vaccine-induced AP. Data were extracted and analysed on patient demographics, vaccine type, time to onset of symptoms, clinical presentation and outcomes. Results: The study included 46 patients of COVID-19 vaccine-induced AP with a median age of 55±18.13 years (range: 14-84). Of those, 60.86% were female. Of COVID-19 vaccines, 71.74% were mRNA and Pfizer-BioNTech was the most common vaccine involved (41.30%), followed by Moderna (30.43%) and AstraZeneca (17.39%). Symptoms typically appeared with a median of 6±3.48 days postvaccine, predominantly after the second dose (45.65%). Common symptoms included vomiting (97.82%), abdominal pain (95.65%) and nausea (89.13%). Elevated serum lipase and amylase levels were observed in all cases. Imaging (computed tomography and ultrasound) confirmed AP in 71.73% of patients. Most cases were mild (60.87%) or moderately severe (30.43%), with peripancreatic fluid collection being the most frequent complication (23.91%). The median hospital stay was 7±5.20 days, and all patients recovered with supportive care albeit 19.56% required intensive care unit admission. Conclusion: Precise aetiology of COVID-19 vaccine-induced AP is unknown and is believed to be related to a complex interplay of molecular mimicry, autoimmune response, direct pancreatic injury by vaccine components or systemic inflammatory response. Albeit rare, AP is a life-threatening complication of the COVID-19 vaccine, warranting urgent evaluation and management. COVID-19 vaccine should be included in the aetiology of AP in patients presenting postvaccination abdominal pain and vomiting, requiring continued surveillance and standardised reporting of vaccine-related GI-AEs. **MAH Comment:** Information relevant for AP, event of special interest for Kostaive.

AE = adverse event; AEFI = adverse event following immunisation; AP = acute pancreatitis; ATM = acute transverse myelitis; CI = confidence interval; COVID-19 = coronavirus disease 2019; ETP = endogenous thrombin potential; GI = gastrointestinal; HR = hazard ratio; IC = information component; ICD = international classification of diseases; ICSR = individual case safety report; IMDR = Immune-mediated and Rheumatic Diseases; IFNy = interferon gamma; IQR = inter-quartile range; IRR = incidence rate ratio; MAH = marketing authorization holder; mRNA = messenger ribonucleic acid; NPR = National Patient Register; ROR = reporting odds ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TGA = thrombin generation assay; VAM = vaccine-associated myocarditis; VITT = vaccine-induced thrombotic thrombocytopenia; VLD = vascular liver disease; WHO = World Health Organization

Review of the published literature retrieved during the reporting period largely confirmed favourable safety profile of sa-mRNA COVID-19 vaccines in populations considered missing information for Kostaive.

12 Other Periodic Reports

The MAH prepares only a single PBRER for Kostaive that covers all indications and formulations. The MAH is not aware of any PBRERs prepared by other parties during the reporting period.

13 Lack of Efficacy in Controlled Clinical Trials

No new data indicating lack of efficacy were identified from controlled clinical trials with Kostaive conducted during the reporting period.

14 Late-breaking Information

After the DLP of this report, no important safety, efficacy and effectiveness findings were received that would alter the benefit-risk profile of the product.

15 Overview of Signals: New, Ongoing or Closed

15.1 Signals

During the reporting period, no signal evaluation was ongoing or completed for Kostaive.

Appendix 3 lists signals that are new, ongoing or were closed during the reporting interval.

15.2 Monitored Topics

The AEs of special interest were agreed upon with EMA during the approval process of EU-Risk Management Plan (RMP), version 1.0, with a DLP of 27 March 2023, dated 02 December 2024. The MAH was requested to monitor the AEs of special interest listed below and present in Periodic Safety Update Reports if new important information will arise.

- Acute disseminated encephalomyelitis
- Acute pancreatitis
- Anaphylaxis
- Anosmia
- Bell's palsy
- Delayed hypersensitivity
- Erythema multiforme
- Extensive limb swelling (ELS)
- Facial swelling in persons with dermal fillers
- Generalised convulsion
- Guillain-Barre syndrome
- Multisystem inflammatory syndrome in adults
- Myocarditis, myopericarditis and pericarditis
- Rhabdomyolysis
- Subacute thyroiditis
- Thrombocytopenia
- Thrombosis / thromboembolism
- Transverse myelitis

15.2.1 Acute Disseminated Encephalomyelitis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the Customised MedDRA Query (CMQ) for Acute disseminated encephalomyelitis (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to acute disseminated encephalomyelitis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to acute disseminated encephalomyelitis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to acute disseminated encephalomyelitis per its routine pharmacovigilance procedures.

15.2.2 Acute Pancreatitis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Acute pancreatitis (see Appendix 5.2 for more details).

Result and Discussion

During the reporting period, no initial cases concerning Kostaive were retrieved.

Cumulatively, 8 clinical trial cases were retrieved, all of which reported pancreatitis acute (n = 8). All cases were assessed as not related.

Conclusion

Review of the data pertaining to acute pancreatitis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to acute pancreatitis per its routine pharmacovigilance procedures.

15.2.3 Anaphylaxis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for anaphylaxis (see Appendix 5.2 for more details).

Result and Discussion

During the reporting period, no initial cases concerning Kostaive were retrieved.

Cumulatively, 1 clinical trial case concerning Kostaive was retrieved. This serious case concerns a 40-year-old female participant in the ARCT-154-01 study, who experienced an anaphylactic reaction 1 day after receiving ARCT-154 vaccine. The case met level 1 of Brighton collaboration diagnostic certainty for anaphylaxis. The event was assessed as related.

Conclusion

Review of the data pertaining to anaphylaxis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to anaphylaxis per its routine pharmacovigilance procedures.

15.2.4 Anosmia

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Anosmia (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to anosmia with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to anosmia did not change the current safety profile of the product. The MAH will continue to monitor all cases pertaining to anosmia per its routine pharmacovigilance procedures.

15.2.5 Bell's Palsy

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Bell's palsy (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to Bell's palsy with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to Bell's palsy did not change the current safety profile of the product. The MAH will continue to monitor all cases pertaining to Bell's palsy per its routine pharmacovigilance procedures.

15.2.6 Delayed Hypersensitivity

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Delayed hypersensitivity (see Appendix 5.2 for more details).

For further analysis, relevant potential cases of delayed hypersensitivity are considered as those with a reported time to onset (TTO) more than 72 hours (≥ 3 days) following Kostaive vaccination. A delayed local reaction secondary to COVID-19 vaccination (also known as 'COVID arm') is an immune-mediated reaction characterized by the development of a well-demarcated, inflamed plaque, cellulitis like reactions near the site of vaccination. All these cases were further reviewed to identify those consistent with delayed hypersensitivity reaction.

Result and Discussion

During the reporting period, a total of 266 initial cases (no follow-up) were retrieved concerning Kostaive. Of the 266 cases, 263 were reported from the postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 3 were spontaneous reports.

Upon review, 8 cases reported TTO of more than 72 hours (≥ 3 days). Of these 8 cases, no cases were consistent with delayed hypersensitivity reaction.

Cumulatively, 268 cases concerning Kostaive were retrieved during the reporting period. None of these cases were consistent with delayed hypersensitivity reaction.

Conclusion

Review of the data pertaining to delayed hypersensitivity did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to delayed hypersensitivity per its routine pharmacovigilance procedures.

15.2.7 Erythema Multiforme

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Erythema multiforme (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to erythema multiforme with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to erythema multiforme did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to erythema multiforme per its routine pharmacovigilance procedures.

15.2.8 Extensive Limb Swelling

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Extensive limb swelling (ELS) (see Appendix 5.2 for more details).

All cases were then medically reviewed to identify potential ELS (ie, swelling of the vaccinated limb > 100 mm or where there is a similar description indicating that there is a significant area of the limb involved, lasting more than 1 week) before further analysis was performed.

Result and Discussion

During the reporting period, a total of 187 initial cases (no follow-up) were retrieved concerning Kostaive. Of the 187 cases received, 185 were reported from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 2 were spontaneous reports. Of these 187 cases, none were consistent with ELS.

Cumulatively, 189 cases were retrieved concerning Kostaive during the reporting period. None of these cases were consistent with ELS.

Conclusion

Review of the data pertaining to ELS did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to ELS per its routine pharmacovigilance procedures.

15.2.9 Facial Swelling in Persons with Dermal Fillers

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Facial swelling in persons with dermal fillers (see Appendix 5.2 for more details).

For further analysis, relevant potential cases of dermal filler reactions are considered as those with facial dermal fillers injections in medical history.

Result and Discussion

During the reporting period and cumulatively, 1 initial case (no follow-up) concerning Kostaive was reported from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436). This nonserious case reported face swelling, however, no medical history of facial dermal fillers injection was reported.

Conclusion

Review of the data pertaining to facial swelling in persons with dermal fillers did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to facial swelling in persons with dermal fillers per its routine pharmacovigilance procedures.

15.2.10 Generalised Convulsions

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Convulsions (see Appendix 5.2 for more details).

Result and Discussion

During the reporting period and cumulatively, 1 initial case (no follow-up) was retrieved concerning Kostaive from postmarketimg safety study (KO01 Drug Use-results Survey, NIS_PVA159436).

This case concerns an 82-year elderly female with a complex medical history including cancer surgery, cerebral infarction, epilepsy and depression who experienced convulsion

23 days after receiving Kostaive. The event convulsion was assessed as not related. The case met level 4 Brighton collaboration diagnostic certainty for generalised convulsion based on limited information provided.

Conclusion

Review of the data pertaining to generalise convulsions did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to generalised convulsions per its routine pharmacovigilance procedures.

15.2.11 Guillain-Barre Syndrome

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Guillain-Barre syndrome (GBS) (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to GBS with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to GBS did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to GBS per its routine pharmacovigilance procedures.

15.2.12 Multisystem Inflammatory Syndrome in Adults

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Multisystem inflammatory syndrome in adults (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to multisystem inflammatory syndrome in adults with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to multisystem inflammatory syndrome in adults did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to multisystem inflammatory syndrome in adults per its routine pharmacovigilance procedures.

15.2.13 Myocarditis, Myopericarditis and Pericarditis

Myocarditis, myopericarditis and pericarditis is considered as an important potential risk. An evaluation of the new information received during the reporting period can be found in Section 16.3.1.1.

15.2.14 Rhabdomyolysis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for rhabdomyolysis (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to rhabdomyolysis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to rhabdomyolysis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to rhabdomyolysis per its routine pharmacovigilance procedures.

15.2.15 Subacute Thyroiditis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Subacute thyroiditis (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to subacute thyroiditis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to subacute thyroiditis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to subacute thyroiditis per its routine pharmacovigilance procedures.

15.2.16 Thrombocytopenia

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Thrombocytopenia and Haemorrhage (see Appendix 5.2 for more details).

Result and Discussion

During the reporting period, a total of 8 cases (6 initial; 2 follow-up) were retrieved which concerned Kostaive. Of the 6 initial cases, 3 were reported from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 3 were spontaneous reports.

Within these 6 initial cases, a total of 7 events were reported, of which 3 were serious (including 1 fatal event) and 4 were nonserious (see Table 15-1).

Table 15-1: Thrombocytopenia Events by Preferred Terms

Preferred Term	Nonserious	Serious	Total
Haematuria	2	-	2
Gastrointestinal haemorrhage	-	1	1
Haematemesis	-	1	1
Haemorrhage subcutaneous	1	-	1
Injection site bruising	1	-	1
Melaena	-	1	1
Total	4	3	7

Note: One case may report more than 1 PT.

PT = preferred term

None of the cases reported thrombocytopenia during the reporting period. Hence, the Brighton collaboration criteria level of diagnostic certainty for thrombocytopenia is not applicable. Causality for the events of haematuria, gastrointestinal haemorrhage, haematemesis and melaena were confounded by underlying medical history.

Of these 6 cases, 1 case reported fatal event is discussed below.

This fatal case concerns a 101-year-old elderly female patient with underlying history of chronic cardiac failure and progressive dementia, who experienced fatal haematemesis (suspected haemorrhage of digestive tract) on an unknown date after vaccination with Kostaive. No autopsy was performed. Causality assessment was confounded by patient's advanced age and underlying medical history. This case is also included in Section 5.2.2.2.

None of the follow-up cases received significant new information during the reporting period.

Cumulatively, 17 cases concerning Kostaive were retrieved. Of these, 6 initial cases were discussed above. The remaining 11 cases were received from clinical trials with a total of 11 serious events reported. The reported events included gastrointestinal haemorrhage (n = 3) and single occurrences of abdominal wall haematoma, cerebral haemorrhage, duodenal ulcer haemorrhage, haemorrhoidal haemorrhage, haemorrhage subcutaneous, haemoptysis, menometrorrhagia and upper gastrointestinal haemorrhage. The events were assessed as not related to Kostaive. None of the cases reported thrombocytopenia.

Conclusion

Review of the data pertaining to thrombocytopenia and haemorrhage did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to thrombocytopenia per its routine pharmacovigilance procedures.

15.2.17 Thrombosis / Thromboembolism

Thrombosis / thromboembolism is considered as an important potential risk. An evaluation of the new information received during the reporting period can be found in Section 16.3.1.2.

15.2.18 Transverse Myelitis

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Transverse myelitis (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period and cumulatively, no cases pertaining to Transverse myelitis with Kostaive were retrieved; hence, there was no new safety information relevant to the benefit-risk assessment for Kostaive.

Conclusion

Review of the data pertaining to transverse myelitis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to transverse myelitis per its routine pharmacovigilance procedures.

16 Signal and Risk Evaluation

16.1 Summary of Safety Concerns

The summary of the important safety concerns in effect at the start of the reporting period of this PBRER is presented in Table 16-1. The summary is derived from the safety specification described in the following:

- EU-RMP, version 1.0, dated 02 December 2024

Table 16-1: Summary of Important Safety Concerns at the Start of the Reporting Period

Important identified risk	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 (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

EU = European union; RMP = risk management plan

Source: EU-RMP, version 1.0, dated 02 December 2024

Of note, the MAH proposes to remove the missing information topics Interaction with other vaccines and Long-term safety data in the updated RMP, version 1.1 with DLP 27 May 2025 which was submitted to EMA on 03 July 2025.

16.2 Signal Evaluation

During the reporting period, no signal evaluations were closed.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Potential Risks

16.3.1.1 New Information Relating to Important Potential Risk: Myocarditis and Pericarditis

Introduction

This safety concern is classified as important potential risk based on Kostaive EU-RMP, version 1.0, dated 2 December 2024. Characterisation of this risk is provided in Section 16.4.2.

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for myocarditis / pericarditis (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period, a total of 2 clinical study follow-up cases were retrieved concerning Kostaive. The follow-up cases did not receive any new significant information during the reporting period.

The previous PSUR included 2 blinded cases from the ARCT-2303-01 study, 1 case reporting pericarditis and the second case reporting myopericarditis. Both cases were initially assessed as related to the blinded study vaccine. Upon unblinding during the reporting period, the pericarditis event in the first case was assessed as related to QIV; the subject had not received ARCT--2303 and was withdrawn after the first vaccination. The myopericarditis event in the second case occurred 57 days after ARCT-2303 vaccination and 28 days after aQIV vaccination. Due to a closer temporal relationship to aQIV, the sponsor considers the event unlikely related to ARCT-2303 but related to aQIV (temporal relationship falls outside the known 3- to 42-day risk window). It should be noted that no related cases for Kostaive were

reported cumulatively.

Conclusion

Review of the cases pertaining to myocarditis / pericarditis did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this risk per its routine pharmacovigilance procedures.

16.3.1.2 New Information Relating to Important Potential Risk: Thromboembolic Events

Introduction

Thromboembolic events are classified as an important potential risk based on Kostaive EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this risk is provided in Section 16.4.2.

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Thromboembolic Events (see Appendix 5.2 for more details).

Results / Discussion

During the reporting period, a total of 5 cases (1 initial; 4 follow-up) were retrieved concerning Kostaive. Of these, 1 initial case received from spontaneous reporting is discussed below.

This spontaneous case concerns a 97-year-old female patient with a history of atrial fibrillation and [redacted] who experienced cerebral infarction approximately 8 days after vaccination with Kostaive. The MAH assessed the event as possibly related to Kostaive due plausible temporal relationship; however, diagnosis of cerebral infarction was suspected (not confirmed) and causality is confounded by the history of atrial fibrillation and elderly age.

The cumulative and interval RRs are provided in Table 16-2.

Table 16-2: Thromboembolic Events Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative	Cumulative Correction After DLP
No cases/RR (per 100,000 doses distributed) initially provided	0/Not applicable	1/1.049	1/0.731	1/5.364

Note: After DLP 27 May 2025, cumulative RR was updated to reflect corrected exposure data.
DLP = data lock point; RR = reporting rate

The 4 follow-up clinical trial cases did not report any new significant information during the reporting period.

Conclusion

Review of the cases pertaining to thromboembolic events did not change the current safety profile of Kostaive. There was an increase in the interval RR compared with the cumulative reporting period. The MAH will continue to monitor all cases pertaining to this risk per its routine pharmacovigilance procedures.

16.3.2 New Information on Important Identified Risks

As described in Section 16.1, no important identified risks have been recognised for Kostaive.

16.3.3 New Information on Other Potential Risks Not Categorised as Important

No new safety relevant information for Kostaive was received on any other potential risks not categorised as important during the reporting period.

16.3.4 New Information on Other Identified Risks Not Categorised as Important

No new safety relevant information for Kostaive was received on any other identified risks not categorised as important during the reporting period.

16.3.5 Update on Missing Information

16.3.5.1 New Information on Missing Information: Use in Pregnancy and While Breastfeeding

Introduction

According to CCDS, version 2.0, dated 15 May 2025, the safety of Kostaive in pregnant women has not been assessed in clinical studies. The administration of Kostaive during pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

It is unknown whether Kostaive 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 infant from Kostaive.

This safety concern is classified as missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's global safety database for all cases concerning pregnant and / or lactating patients.

Results and Discussion

During the reporting period, a total of 43 cases (11 initial; 32 follow-up) pertaining to pregnancy exposure with Kostaive were retrieved. Of the 11 initial cases received, 9 were received from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436), 1 was received from spontaneous reporting and 1 was received from clinical trial. In 4 of the 11 initial cases, both pregnancy and breastfeeding exposures were reported and are discussed below.

Of the 11 initial cases, 10 were postmarketing cases, of which 1 case reported foetal exposure during pregnancy along with serious event transient tachypnoea of the newborn.

In the case involving a foetus, the mother had received Kostaive 6 weeks and 5 days before 'normal' delivery. The newborn received oxygen inhalation and a drip infusion at the neonatal intensive care unit due to event transient tachypnoea of the newborn (seriousness criteria: hospitalization). The event resolved 15 days later, and the neonate was discharged. The MAH assessed event as not related due to temporal and biological implausibility.

Of the remaining 9 maternal cases, 1 case was reported without AEs and 8 cases reported the following 52 nonserious AEs: vaccination site pain (13); pyrexia (5); chills, headache and malaise (4 each); arthralgia, diarrhoea, nausea, vaccination site induration and vaccination site swelling (3 each); myalgia and vaccination site erythema (2 each); and dyspnoea, mastitis and muscular weakness (1 each). No specific pattern of reported AEs was observed. The pregnancy outcome of these 9 cases were reported as outcome pending (5), unknown (3) and live birth (1).

One initial clinical trial maternal case reported no AEs. The outcome was a live birth with no complications.

The 32 follow-up cases did not report any new significant information during the reporting period.

During the reporting period, a total of 13 initial cases (no follow-up) pertaining to lactation exposure with Kostaive were retrieved from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436). Conservative case coding convention currently in use includes proactive coding of 2 terms: exposure in pregnancy and exposure in lactation, if it was not clearly stated by the reporter that the exposure in pregnancy did not result in the mother breastfeeding the baby. Some cases, therefore, include both types of exposures.

Of these 13 cases, 4 cases reporting exposure during pregnancy are discussed above. The remaining 9 maternal cases reporting maternal exposure during breastfeeding are discussed below.

In 1 of the 9 maternal cases, no AEs were reported. In the remaining 8 cases, the following nonserious AEs were reported: vaccination site pain (8); injection site pain and chills (5 each); arthralgia and malaise (4 each); pyrexia and vaccination site induration (n = 3 each); headache and vaccination site swelling (2 each); and injection site induration, myalgia, nausea, palpitations and vaccination site erythema (1 each). No specific pattern of reported AEs was observed. No baby cases were reported.

Conclusion

Review of the cases pertaining to use in pregnancy and while breastfeeding did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

16.3.5.2 New Information on Missing Information: Use in Immunocompromised Patients

Introduction

According to CCDS, version 2.0, dated 15 May 2025, the safety and efficacy of the vaccine have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Kostaive may be lower in immunocompromised individuals.

This safety concern is classified as missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

Methodology

A review of all postauthorisation cases pertaining to 'use in immunocompromised patients' was performed by searching the MAH's Global Safety Database for all cases in which the medical history containing at least 1 PT in the CMQ for Use in Immunocompromised Patients (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period, a total of 16 cases (15 initial; 1 follow-up) were retrieved concerning Kostaive. Of the 15 initial cases received, 1 case was received from spontaneous reporting and 14 were derived from report from postauthorisation safety study (KO01 Drug Use-results Survey, NIS_PVA159436).

Within these 15 initial cases, a total of 89 events were reported, of which 3 were serious (including 2 fatal events). An overview of the most reported events is presented in Table 16-3.

Table 16-3: Use in Immunocompromised Patients Events by Preferred Terms

Reported Preferred Term	Nonserious	Serious	Total
Vaccination site pain	20	-	20
Malaise	7	-	7
Headache	7	-	7
Myalgia	6	-	6
Arthralgia	5	-	5
Chills	5	-	5
Injection site pain	5	-	5
Pyrexia	5	-	5
Diarrhoea	3	-	3
Axillary pain	2	-	2
Injection site swelling	2	-	2
Loss of personal independence in daily activities	2	-	2
Nausea	2	-	2
Somnolence	2	-	2
Vaccination site erythema	2	-	2
Vaccination site swelling	2	-	2
Asthenia	-	1[a]	1
Condition aggravated	1	-	1
Dehydration	1	-	1
Dysphagia	1	-	1
Hypophagia	1	-	1
Injection site erythema	1	-	1
Marasmus	-	1[a]	1
Oral herpes	1	-	1
Pneumonia aspiration	-	1	1
Pruritus	1	-	1
Walking disability	1	-	1
Wheelchair user	1	-	1
Total	**86**	**3**	**89**

[a] Fatal event

Among the 3 serious events reported, 2 were fatal events and occurred in 1 case concerning a 94-year-old female patient, who experienced marasmus and asthenia approximately 2 months of postvaccination. The MAH assessed the events as not related due to biological implausibility. Moreover, the patient's underlying medical conditions of breast cancer, diabetes mellitus, angina pectoris and advanced age were considered more likely contributors to the fatal outcome. This case is also included in Section 5.2.2.2.

In another case, a serious event pneumonia aspiration was reported, causality was confounded by the patient's elderly age and underlying dementia.

No specific pattern of reported AEs was observed in the remaining 86 nonserious events.

In 1 clinical trial follow-up case, no new significant information was received during the reporting period.

Conclusion

Review of the cases pertaining to 'use in immunocompromised patients' did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

16.3.5.3 New Information on Missing Information: Interaction with Other Vaccines

Introduction

This safety concern is classified as missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

As per CCDS, version 2.0, dated 15 May 2025, Kostaive may be administered concomitantly with influenza vaccine.

Methodology

A review of all postauthorisation cases pertaining to interaction with other vaccines was performed by searching the MAH's Global Safety Database for all cases with Kostaive where another vaccine is reported as a cosuspect (eg, influenza vaccine).

Results and Discussion

The results of the ARCT-2303-01 study confirms the safe use of Kostaive when administered concomitantly with influenza vaccines. Coadministration of Kostaive with quadrivalent influenza vaccines appeared not to affect the immunogenicity of coadministered vaccines. All vaccines were well tolerated in young and older adults, both as standalone and when coadministered.

During reporting period, 2 initial spontaneous cases pertaining to Interaction of Kostaive with other vaccines were received.

In the first serious case, tozinameran was administered as cosuspect drug. However, this case lacks information when the cosuspect vaccine was administered resulting in an inconclusive assessment. In the second case (nonserious), Kostaive was coadministered with an influenza vaccine at same time, and the patient experienced pyrexia.

Conclusion

The results of the ARCT-2303-01 study confirms the safe use of Kostaive when administered concomitantly with influenza vaccines. Review of the 2 postmarketing cases pertaining to interaction with other vaccines did not raise any safety concerns related to Kostaive. Hence, the MAH proposes to remove this missing information in the updated RMP, version 1.1, with DLP 27 May 2025 was submitted to EMA on 03 July 2025.

16.3.5.4 New Information on Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

Introduction

This safety concern is classified as missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

Methodology

A review of the new information received during the reporting period was performed by searching the MAH's Global Safety Database for all cases in which the medical history containing at least 1 PT in the CMQ for Use in Patients with Autoimmune or Inflammatory Disorders (see Appendix 5.2 for more details).

Results and Discussion

During the reporting period, a total of 18 cases (17 initial; 1 follow-up) were retrieved concerning Kostaive. All these 17 initial cases were received from report from postauthorisation safety study (KO01 Drug Use-results Survey, NIS_PVA159436).

Of the 17 initial cases, the relevant medical history included autoimmune thyroiditis, colitis ulcerative and Graves' disease (3 each); chronic gastritis (2); and chronic inflammatory demyelinating polyradiculoneuropathy, collagen disorder, Crohn's disease, eosinophilic

granulomatosis with polyangiitis, inflammatory bowel disease, rheumatic disorder, rheumatoid arthritis, systemic lupus erythematosus and type 1 diabetes mellitus (1 each).

Within these 17 cases, a total of 85 events were reported, of which 1 was serious (no fatal events). The serious event melaena was assessed by the MAH as not related due to underlying Crohn's disease, ulcerative colitis and inflammatory bowel disease which are considered possible confounders. The most frequently reported (≥ 5) nonserious events were vaccination site pain (15), injection site pain (15), malaise (9), myalgia (7), headache (7), chills (6) and pyrexia (5). No specific pattern of reported AEs was observed.

No cases reported exacerbation of autoimmune or inflammatory disorders events during the reporting period.

One case received significant follow-up information; chronic gastritis was added as relevant medical history during the reporting period although it is unclear if it is a confirmed autoimmune disorder. This spontaneous case reported serious events of cardiac failure high output, cardiac failure and infection. Pyrexia and bronchitis were reported as nonserious. This case did not report any exacerbation of autoimmune or inflammatory disorders events.

Conclusion

Review of the cases pertaining to autoimmune or inflammatory disorders did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to this missing information per its routine pharmacovigilance procedures.

16.3.5.5 New Information on Missing Information: Long-term Safety Data

This safety concern is classified as a missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

Up to 12 months long-term safety data have been collected in ARCT-154-01, ARCT-154-J01 and ARCT-165-01 clinical studies in participants who have been exposed to either a primary series 2-dose regimen or a single-dose booster vaccination. No new clinically important safety findings have arisen from these clinical trials up to 12 months post vaccination.

Of note, in line with Centers for Disease Control and Prevention guidance, most adults are recommended to receive an updated COVID-19 vaccine at least annually, while additional booster may be needed for population at risk based on country-specific recommendations. Therefore, long-term safety data beyond 1-year will likely be confounded by the use of other COVID-19 vaccines as boosters.

The completion of studies ARCT-165-01, ARCT-154-01 and ARCT-154-J01 support the removal of the missing information long term safety data as they provide 1-year postvaccination follow-up safety information for participants who have been exposed to either a primary series 2-dose regimen or a single dose booster vaccination.

Conclusion

Review of long-term safety data collected from ARCT-165-01 and ARCT-2303-01 studies confirmed long term safety data for Kostaive. Hence, the MAH proposes to remove this missing information in the updated RMP, version 1.1, with DLP 27 May 2025 which was submitted to EMA on 03 July 2025.

16.3.5.6 New Information on Missing Information: Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Introduction

This safety concern is classified as a missing information based on Kostaive in EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in Section 16.4.3.

Methodology

A review of all postauthorisation cases pertaining to 'Use in Patients with Significant, Unstable Chronic Medical Conditions' was performed by searching the MAH's Global safety database for all cases containing medical history of unstable chronic medical conditions such as chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders.

Result and Discussion

During the reporting period 24 cases (23 spontaneous and 1 from KO01 Drug Use-results Survey, NIS_PVA159436) reported potential unstable chronic medical conditions including dementia (13); cerebral infarction (4); atrial fibrillation, cardiac failure chronic, myocardial infarction, type 2 diabetes mellitus and unspecified diabetes mellitus (2 each); and cerebral haemorrhage, cerebrovascular accident, putamen haemorrhage, Parkinson's disease and vascular dementia (1 each).

Within these cases, a total of 57 events were reported, of which 24 were serious. The most frequently reported (≥ 2) events were pyrexia (14); pneumonia aspiration (3), decreased appetite, hepatic function abnormal, malaise and pneumonia (2 each). Reported serious events were largely representative of age-related comorbidities.

The follow-up case received during the reporting period did not report any new significant information.

Conclusion

Review of the data pertaining to 'Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)' did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders) per its routine pharmacovigilance procedures.

16.3.6 Special Vaccine-related Topics

16.3.6.1 Issues Related to Batch(es)

No batch-related safety signals were identified during the reporting period.

16.3.6.2 Age-related Adverse Reactions

A review of reports received during the reporting period of the PBRER did not reveal any age-related specific AEs that would impact the benefit-risk profile of Kostaive. Cases relating to the elderly age group are included in Section 5.2.2.2.

16.3.6.3 Reports of Vaccination Failure / Lack of Efficacy

Introduction

As per the CCDS, version 2.0, dated 15 May 2025, vaccination with Kostaive may not protect all vaccine recipients.

Methodology

A search of the MAH's Global Safety Database for all cases containing at least 1 PT in the CMQ for Vaccination Failure / Lack of Efficacy (see Appendix 5.2 for more details).

Result and Discussion

During the reporting period, a total of 5 initial cases were retrieved. Of the 5 cases received, 1 case was received from spontaneous reporting and 4 cases were reported from postauthorisation safety study (KO01 Drug Use-results Survey, NIS_PVA159436). In 1 out of the 5 cases, the patient tested SARS-CoV-2 positive within 8 days after vaccination. Therefore, this case is not considered as vaccination failure (biological/chronological implausibility), and the remaining relevant cases are discussed below.

Within these 4 cases, a total of 6 serious events were reported (see Table 16-4).

Table 16-4: Vaccination Failure / Lack of Efficacy Events by Preferred Terms

Preferred Term	Nonserious	Serious	Total
COVID-19	-	1	1
SARS-CoV-2 test positive	-	1	1
Vaccination failure	-	4	4
Total	-	6	6

Note 1: One case may report more than 1 PT.
Note 2: Following the DLP, corrections were made for 2 cases: in case [redacted] the event SARS-CoV-2 test positive was reclassified from symptom to diagnosis, and in case [redacted] the coding for the event Coronavirus test positive was updated to more specific term SARS-CoV-2 test positive.
DLP = data lock point; PT = preferred term; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Four cases were assessed as related considering a plausible temporal relationship (ranging from 15 days to 2 months and 25 days).

The cumulative and interval RRs are provided in Table 16-5.

Table 16-5: Vaccination Failure Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative	Cumulative Correction After DLP
No. cases/RR (per 100,000 doses distributed) initially provided	0/Not applicable	4/4.195	4/2.924	4/21.459

Note 1: One case is not considered as vaccination failure therefore not included in RR calculations.
Note 2: After DLP 27 May 2025, cumulative RR was updated to reflect corrected exposure data.
DLP = data lock point; RR = reporting rate

Conclusion

A review of reports of vaccination failure did not reveal any new safety information relevant to the benefit-risk assessment of Kostaive. There was an increase in the interval RR compared with the cumulative reporting period due to cases reported from the KO01 Drug Use-results Survey, where 'Novel Coronavirus Infection' was one of the outcomes collected in the study. The MAH will continue to monitor all cases pertaining to vaccination failure per its routine pharmacovigilance procedures.

16.3.6.4 Immunisation Stress-related Response Reactions

Introduction

As per CCDS, version 2.0, dated 15 May 2025, anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection.

Methodology

A search of the MAH's Global Safety Database using at least 1 PT in the CMQ for Immunisation Stress-related Response Reactions (see Appendix 5.2 for more details).

For further analysis, relevant potential cases of immunisation stress-related response reactions are considered as those with a reported time-to-onset within 30 minutes following Kostaive vaccination. Cases that did not specify an exact time-to-onset but did specify that the event occurred while the patient was in the vaccination room or still onsite at the vaccination clinic were assumed to have occurred within 30 minutes. Cases with TTO (> 30 mins), cases that occurred on the same day but did not clearly specify the location at

which the events occurred and cases for which TTO was unknown / not reported were not further evaluated.

Result and Discussion

During the reporting period, a total of 3 initial nonserious cases were retrieved concerned Kostaive. All 3 cases were reported from study (KO01 Drug Use-results Survey, NIS_PVA159436). The reported events were palpitations (n = 2) and vision blurred (n = 1). These cases were not further evaluated as the time to onset was > 30 minutes (1 day) postvaccination.

The cumulative and interval RRs are provided in Table 16-6.

Table 16-6: Immunisation Stress-related Response Reactions Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative
No. cases/RR (per 100,000 doses distributed) initially provided	0/Not applicable	0/Not applicable	0/Not applicable

Note: Three cases reported time to onset > 30 minutes (1 day) postvaccination; therefore, it is not considered in RR calculations.
RR = reporting rate

Conclusion

A review of reports of immunisation stress-related response did not reveal any new safety information relevant to the benefit-risk assessment of Kostaive. The MAH will continue to monitor all cases pertaining to vaccination failure per its routine pharmacovigilance procedures.

16.4 Characterisation of Risks

16.4.1 Important Identified Risks

There are no important identified risks for Kostaive.

16.4.2 Important Potential Risks

16.4.2.1 Important Potential Risk: Myocarditis and Pericarditis

Table 16-7: Characterisation of the Important Potential Risk of Myocarditis and Pericarditis

Important Potential Risk	Myocarditis and Pericarditis
Potential Mechanism	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	Myocarditis and pericarditis have been reported in postmarketing surveillance of other mRNA COVID-19 vaccines.
Characterisation of the Risk	With respect to Kostaive, the following cases have been received: **Clinical Trials:** Cumulatively up to the DLP, no cases for myocarditis / pericarditis that were related to Kostaive were received from clinical studies. **Postmarketing:** Cumulatively up to the DLP, no cases were received for Kostaive from postmarketing use.
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	According to the CCDS, version 2, healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis in vaccine recipients. Vaccine recipients should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis.
Impact on the Risk-Benefit Balance of the Biologic Product	While the data available from other mRNA COVID-19 vaccine manufacturers suggest the rare risk of primarily mild myocarditis or pericarditis without sequelae following vaccination, no related cases have been observed to date with Kostaive. 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 postvaccination myocarditis and pericarditis is minimal.
MedDRA Terms	SMQ Noninfectious myocarditis/pericarditis (Narrow)

CCDS = Company Core Data Sheet; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; DLP = data lock point; ECDC = European Centers for Disease Control and Prevention; FDA = Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory

Activities; mRNA = messenger ribonucleic acid; MOA = mechanism of action; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMQ = Standardised Medical Dictionary for Regulatory Activities Query; US =United States

16.4.2.2 Important Potential Risk: Thromboembolic Events

Table 16-8: Characterisation of the Important Potential Risk of Thromboembolic Events

Important Potential Risk	Thromboembolic Events
Potential Mechanism	The mechanism by which Kostaive may cause thromboembolic events has not yet been elucidated.
Evidence Source	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 et al, 2022).
Characterisation of the Risk	With respect to Kostaive, the following cases have been received: **Clinical Trials:** Cumulatively up to the DLP, 3 cases for thromboembolic events related to Kostaive were received from clinical studies. **Postmarketing:** Cumulatively up to the DLP, 1 case was received for Kostaive from postmarketing use that was considered as related to Kostaive by the company.
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 ischaemic attack and heart failure requiring hospitalisation.
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 postvaccination thromboembolic events is minimal.
MedDRA Terms	SMQ Embolic and thromboembolic events (sub-SMQ Embolic and thromboembolic events, arterial; sub-SMQ Embolic and thromboembolic events, venous: sub-SMQ Embolic and thromboembolic events, vessel type unspecified and mixed arterial and venous)

CI = confidence interval; COVID-19 = coronavirus disease 2019; DLP = data lock point; MedDRA = Medical Dictionary for Regulatory Activities; RR = reporting rate; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SMQ = Standardised Medical Dictionary for Regulatory Activities Query

16.4.3 Missing Information

16.4.3.1 Missing Information: Use in Pregnancy and While Breastfeeding

Table 16-9: Missing Information: Use in Pregnancy and While Breastfeeding

Missing Information:	Use in Pregnancy and While Breastfeeding
Evidence Source: The safety profile of the vaccine is not yet fully known in pregnant or breast-feeding women due to their exclusion from the clinical studies of Kostaive to date. Limited data are available from individuals vaccinated with Kostaive or the 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).	

COVID-19 = coronavirus disease 2019; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

16.4.3.2 Missing Information: Use in Immunocompromised Patients

Table 16-10: Missing Information: Use in Immunocompromised Patients

Missing Information:	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.	

16.4.3.3 Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

Table 16-11: Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

Missing Information:	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.	

16.4.3.4 Missing Information: Interaction with Other Vaccines

Table 16-12: Missing Information: Interaction with Other Vaccines

Missing Information:	Interaction with Other Vaccines
Evidence Source: Kostaive may be administered concomitantly with influenza vaccine.	
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 vaccine in an adult population has been collected in the completed clinical study ARCT-2303-01. There was no evidence of an impact on the safety and reactogenicity profiles for each vaccine when coadministered vs. standalone. Please refer to Section 7.1 and Section 17.2.	

COVID-19 = coronavirus disease 2019

16.4.3.5 Missing Information: Long-term Safety Data

Table 16-13: Missing Information: Long-term Safety Data

Missing Information:	Long-term Safety Data
Evidence Source: The completion of studies ARCT-165-01, ARCT-154-01 and ARCT-154-J01 support the removal of the missing information long-term safety data as they provide 1-year postvaccination follow-up safety information for participants who have been exposed to either a primary series 2-dose regimen or a single dose booster vaccination. No new clinically important safety findings have arisen from these clinical trials up to 12 months postvaccination Please refer Section 7.3	
Population in Need of Further Characterisation: Not applicable	

16.4.3.6 Missing Information: Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Table 16-14: Missing Information: Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Missing Information:	**Use in Patients with Significant, Unstable Chronic Medical Conditions (eg, Chronic Obstructive Pulmonary Disease, Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)**
Evidence Source: The vaccine has been studied in individuals with stable chronic diseases (eg, hypertension, obesity); however, it has not been studied in individuals with significant, unstable chronic medical conditions (eg, 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 (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) through routine pharmacovigilance activities.	

16.5 Effectiveness of Risk Minimisation

Besides the routine pharmacovigilance risk minimisation measures, such as the information described in the Summary of Product Characteristics, no additional risk minimisation measures are in place for Kostaive.

17 Benefit Evaluation

17.1 Important Baseline Efficacy and Effectiveness Information

As of 04 May 2025, over 775,750,000 cases of COVID-19 been confirmed worldwide and over 7 million people have died (WHO, 2025). Of these, over 193 million cases have been confirmed in the Americas and over 3 million people have died. A critical component of addressing morbidity and mortality due to SARS-CoV-2 is the development of vaccines to prevent COVID-19 disease, the transmission of SARS-CoV-2 infection and limit the emergence of resistant strains. In late 2020 and early 2021, multiple companies shared the results of pivotal studies examining vaccine candidates intended to prevent COVID-19. This has led to the approvals of several COVID-19 vaccines throughout the world using different platforms including mRNA, adenoviral vector, protein and inactivated approaches. However, variant strains of SARS-CoV-2 have since displaced the ancestral (Wuhan Hu1) strain and have shown varying levels of resistance to antibodies induced by vaccines encoding or containing ancestral strain antigens. The D614G variant, which appeared soon after the emergence of the ancestral strain and is associated with a point mutation of the S protein, became a globally dominant variant of SARS-CoV-2 (Korber et al, 2020). Following this, a succession of other variants emerged on a global scale, including the Alpha, Beta, Gamma, Delta and Omicron variants. Within the Omicron variant, multiple subvariants have swiftly replaced previously circulating strains variants, displaying higher transmissibility and an elevated risk of breakthrough infections among the vaccinated. Due to reduced immunity against these newer variants, the United States Food and Drug Administration (FDA, 2023) The Vaccines and Related Biological Products Advisory Committee has advised using updated COVID-19 vaccines tailored to better combat the current circulating strains. For the 2024 to 2025 season, the World Health Organization recommended on 26 April 2024 (WHO, 2024) to update the vaccines to include a monovalent component that corresponds to the Omicron variant JN.1.

Given the global spread of SARS-CoV-2 and the emergence of variant SARS-CoV-2 strains, there is a demand for the development of new vaccines that are not only capable of conferring strong immunity against the current circulating strains but also possess the flexibility to adapt to future variants. Kostaive has demonstrated benefits as a primary vaccination series in individuals ≥ 18 years of age in terms of efficacy and / or immunogenicity and as a heterologous booster based on a robust immune response and noninferiority versus the licensed mRNA vaccine (Comirnaty). In addition, a higher immune response was observed

after a homologous booster dose relative to post primary series. The potential of Kostaive to protect against a wide range of SARS-CoV-2 variants, including Omicron lineages, was supported by robust and broadly cross neutralising immune responses after booster vaccination.

17.1.1 Benefits of Kostaive as a Primary Vaccination Series

ARCT-154-01:

The vaccine efficacy of Kostaive for the prevention of any COVID-19 was demonstrated in the pivotal phase 1 / 2 / 3 efficacy, safety and immunogenicity study (ARCT-154-01). The primary efficacy endpoint in Study ARCT-154-01 was met: Kostaive demonstrated the prevention of COVID-19 of any severity between Day 36 (7 days after the second dose) and Day 92 in adult participants based on a total of 640 accrued cases (200 cases in the ARCT-154 vaccine group; 440 cases in the placebo group). The vaccine efficacy was 56.7% (95% confidence interval [CI]: 48.8%, 63.4%).

The key secondary efficacy objectives were also achieved as the lower limit of the CI met the prespecified success threshold of > 0%, demonstrating significant vaccine efficacy of 95.3% (95% CI: 80.5%, 98.9%) after 2 doses of Kostaive against severe COVID-19 and vaccine efficacy of 56.7% (95% CI: 49.3%, 63.1%) against any COVID-19 reported between Day 1 and Day 92 in participants without evidence of COVID-19 prior to vaccination. The vaccine used in ARCT-154-01 was targeting ancestral strain, however most cases were caused by the Delta variant. Vaccine efficacy against COVID-19 of any severity caused by the Delta variant was 50.0% (95% CI: 39.6%, 58.6%) and against severe COVID-19 was 94.3% (95% CI: 57.4%, 99.2%). For approximately 8.6% of isolated SARS-CoV-2 variants, sequencing was not able to detect lineage; vaccine efficacy of Kostaive against these cases was 67.7% (95% CI: 40.7%, 82.4%) and 100% (95% CI not estimated) for any COVID-19 and severe COVID-19, respectively.

The relative efficacy of 2 doses of Kostaive versus 2 doses of ChAdOx1 was evaluated in phase 3c part of the study when the Delta variant, followed by Omicron BA.1 and BA.2 variants, were circulating in Vietnam. From 7 days post Dose 2 to the end of the study over 1 year later, the relative efficacy against COVID-19 was 19.8% (95% CI: 4.0% to 33.0%), suggesting that Kostaive is more efficacious than the ChAdOx1 vaccine in preventing COVID-19 over a 1-year period. Pivotal immunogenicity data to Day 57 obtained in Study ARCT-154-01 support the observed efficacy of Kostaive to prevent COVID-19. In

conclusion, the data presented herein demonstrate that Kostaive as a 2-dose primary vaccination series offers active immunisation to prevent COVID-19 disease of any severity caused by ancestral SARS-CoV-2 and various variants (mainly Delta) following 2 doses given at least 28 days apart in individuals 18 years of age and older.

17.1.2 Benefits of Kostaive as a Booster

ARCT-154-J01:

Immunogenicity data from the booster study ARCT-154-J01 demonstrated that the level of neutralising antibodies against ancestral SARS-CoV-2 (targeted with the vaccine) induced at 28 days after a heterologous booster dose of Kostaive was noninferior to the level induced by the approved COVID-19 mRNA vaccine (Comirnaty). Both geometric mean titre (GMT) and seroresponse rate were higher after Kostaive administration than after Comirnaty.
Immune responses of the Kostaive booster dose against the Omicron BA.4/5 variant were higher than those observed after administration of Comirnaty. The prespecified noninferiority and superiority criteria for both GMT ratio and seroresponse rate differences were met for the Omicron BA.4/5 variant assay. A booster dose of Kostaive, administered ≥ 5 months after the previous COVID-19 vaccine dose in majority of participants, induced a 6.7- and 8.0-fold increase against the ancestral strain and Omicron BA.4/5 variant, respectively, at Day 29. In contrast, the magnitude of the booster response for both assays after the Comirnaty dose was 4.4- and 5.7-fold increase, respectively. The antibody persistence data in
Study ARCT-154-J01 at Day 91, 181 and at 12 months (Oda et al, 2024) postvaccination suggest improved durability and broader immune responses following Kostaive vaccination compared with those after conventional mRNA vaccine.

The results of the study support favourable benefit of ARCT-154 vaccine when administered as a booster dose in adult individuals who previously received the primary vaccination with other mRNA COVID-19 vaccines.

ARCT-2301-J01:

ARCT-2301-J01, a phase 3 randomised, observer-blind, active-controlled study, evaluated the safety and immunogenicity of Kostaive (bivalent; 0.5 mL [5 µg]) versus COMIRNATY (BA.4/5; bivalent: Wuhan strain/Omicron strain BA.4/5) given as a booster dose in persons 18 years of age and older. The study was conducted when the Omicron strains XBB.1.5, XBB.1.16, EG.5.1, HK.3 and JN.1 were prevalent in Japan where the study was conducted.

When ARCT-2301 (bivalent, ancestral strain and Omicron BA.4/5) was administered intramuscularly as a booster dose in participants who had received 3 to 5 doses of the authorised mRNA COVID-19 vaccine, with the last dose 11.1 months (median time, range 4.0 to 13.7 months) prior, the immunogenicity of ARCT-2301 was superior to that of Comirnaty (bivalent, ancestral strain and Omicron BA.4/5) against Omicron BA.4/5 variant and ancestral strain for both the GMT ratio and the serious RR difference.

17.2 Newly Identified Information on Efficacy and Effectiveness

Information on the benefit of Kostaive has become available during the reporting period from completed immunogenicity studies ARCT-165-01 and ARCT-2303-01.

ARCT-165-01

ARCT-165-01 is a phase 1 / 2 randomised, observer-blind, 2-cohort study evaluating the safety, reactogenicity and immunogenicity of 3 investigational SARS-CoV-2 sa-RNA vaccines.

The study enrolled 72 adult participants ≥ 21 to ≤ 65 years of age divided into 2 cohorts (A and B) of 36 participants selected based on previous vaccination status against SARS-CoV-2.

Cohort A of vaccine-naïve participants was subdivided into 2 subcohorts: Subcohort A1, of 12 participants who were seronegative at screening and received two 5-µg doses of ARCT-165, ARCT-154, or ARCT-021 (4 participants each) on Days 1 and 29; Subcohort A2 of 24 participants who were seropositive at screening and randomized 3:1 to receive two 5-µg doses of ARCT-154 or ARCT-021 on Days 1 and 29. Immunogenicity results from Cohort A2 showed that a single dose of ARCT-154 appeared to be immunogenic in seropositive subjects who had not received a COVID-19 vaccine previously, with a geometric mean fold rise of 4.4 (95% CI: 2.7-7) from baseline to 28 days after the first dose. The immune response further increased after the second dose to a geometric mean fold rise (Day 57/Day 1) of 6.2 (95% CI: 3.8-10). The same trend was seen whether immune response was measured against the ancestral strain or against the Beta variant.

Cohort B included 36 adult participants who were previously vaccinated (5 months or longer prior to study enrolment) with the Comirnaty vaccine and randomised to receive ARCT-021, ARCT-154 or ARCT-165 (12 participants each) on Day 1. Results from Cohort B demonstrated that a booster dose of ARCT-154 (ancestral strain) or ARCT-165 (Beta variant) induced a higher immune response compared to ARCT-021 (first generation vaccine). Both

ARCT-154 and ARCT-165 demonstrated a robust immune response that was well maintained for a year post vaccination.

Overall, ARCT-165-01 immunogenicity data support the benefits of Kostaive in seropositive vaccine-naïve subjects and as a booster dose in subjects previously vaccinated with the Comirnaty vaccine.

ARCT-2303-01

The study met the statistically powered 4 primary objectives and 2 secondary objectives.

Hence the study demonstrated the following:

- A single booster dose of ARCT-2303 that encodes the Omicron XBB.1.5 variant was superior in the induction of neutralizing antibodies (nAbs) against this variant to ARCT-154 that encodes the ancestral / Wuhan strain.
- The coadministration of ARCT-2303 with QIV in adults aged 18 to 64 years was immunologically noninferior to standalone administration for each vaccine in terms of the induction of nAbs against the Omicron XBB.1.5 variant and haemagglutination inhibition antibodies specific for the 4 QIV strains.

The study also showed the following:

- The coadministration of ARCT-2303 with aQIV appeared not to affect the immunogenicities of the respective standalone vaccines.
- A single booster dose of ARCT-2303 appeared to induce durable nAb titres against Omicron XBB.1.5 for up to 6 months in both younger (18 to 64 years) and older (above 64 years) adults.

17.3 Characterisation of Benefits

No new relevant benefit data for Kostaive have become available during the reporting period. Refer to Section 17.1 for information on efficacy and effectiveness of Kostaive.

18 Integrated Benefit-Risk Analysis for Authorised Indications

18.1 Benefit-Risk Context – Medical Need and Important Alternatives

The SARS-CoV-2 pandemic that was declared in 2020 is continuing to cause global COVID-19 in 2024 despite success in the development and use of vaccines directed against SARS-CoV-2. Control of the disease is complicated by waning vaccine immunogenicity in the face of ongoing outbreaks and the emergence of variant strains that may partially or totally evade vaccine-induced immunity. Additional vaccines that can possibly provide protection against emerging variants are needed. Given the global spread of SARS-CoV-2, the emergence of variants and logistical issues that have hindered the implementation of vaccination, there remains an unmet need for more vaccines to prevent transmission of SARS-CoV-2 and the need to develop vaccines with broad protection against a range of SARS-CoV-2 variants. The Centers for Disease Control and Prevention estimates that in the United States, there were 78,000 to 130,000 Covid-related hospitalisations from October to December 2024 and 8900 to 15,000 deaths in the same time frame (CDC, 2025).

Currently or previously approved COVID-19 vaccine availability varies based on local authorisations, including, but not limited to Cominarty (BioNTech), Spikevax (Moderna), Nuvaxovid (Novavax) and Bimervax (HIPRA, Human Health S.L.U). Nonvaccine treatments for COVID-19 include monoclonal antibodies targeting the spike protein of SARS-CoV-2 (Evusheld [tixagevimab / cilgavimab], Regkirona [regdanvimab], Ronapreve [casirivimab / imdevimab], RoActemra [tocilizumab] and Xevudy [sotrovimab]) as well as antivirals (Paxlovid [nirmatrelvir] and Veklury [remdesivir]) and others (Kineret [anakinra], an interleukin-1 receptor antagonist) (EMA, 2025). No primary series and / or booster vaccination or treatment remains an option. Given that the LUNAR-COV19 vaccines share the same lipid nanoparticle, the same replicase mRNA and primarily differ only in the composition of the transgene that expresses the SARS-CoV-2 S protein, the safety and tolerability profile for these vaccines is anticipated to be similar across the LUNAR-COV19 platform.

An unmet medical need still exists for COVID-19 vaccines to address the emergence of new variants.

18.2 Benefit-Risk Analysis Evaluation

18.2.1 Benefit-Risk Assessment Methodology

The MAH employs a predominantly qualitative approach based on the pre-determined quantitative benefit outcomes for the benefit-risk assessment of Kostaive.

Assessment of Condition / Medical Need

COVID-19 is an infectious acute respiratory disease of global importance, with unmet medical needs for at risk populations and for a durable protection from SARS-CoV-2 variants.

Assessment of Efficacy

As specified in the 2023 Center for Biologics Evaluation and Research Guideline 'Development-and-Licensure-of-Vaccines-to-Prevent-COVID-19' (https://www.fda.gov/media/139638/download) either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial.

The Food and Drug Administration also recommends that severe COVID-19 should be evaluated as a secondary endpoint if not evaluated as a primary endpoint.

Additionally, the immune responses to SARS-CoV-2 pandemic COVID-19 vaccines are generally assessed using serological surrogates that are likely to predict protection against COVID-19. The use of a serological surrogate as a measure of COVID-19 vaccine efficacy is an important component of COVID-19 vaccine development, recognised by regulatory bodies, as specified in the 2023 CBER Guideline 'Development-and-Licensure-of-Vaccines-to-Prevent-COVID-19'.

Assessment of Risks

For evaluation of risks, all solicited local and systemic AEs collected for 7 days after each vaccination, are considered related to vaccination (vaccine reactogenicity). For unsolicited AEs, SAEs and AEs of special interest, related events are considered for potential adverse reactions or risks. In addition, known class risks or important medical events usually listed in COVID-19 vaccines RMP are included and assessed for safety signal monitoring.

Integrated Benefit-Risk Assessment

The determination of the final benefit-risk assessment is taken in the framework of analysis of condition and unmet medical needs for at risk populations, summary of key benefits (efficacy / effectiveness and surrogate immunogenicity) which are weighed against identified / potential adverse reactions, important identified or potential risks summarised in the RMP and associated risk mitigation measures to reach the overall conclusion.

18.2.2 Key Benefits

SARS-CoV-2 has continued to be a burden of disease worldwide. Control of the disease is complicated by waning vaccine immunogenicity in the face of ongoing outbreaks and by the emergence of variant strains that may partially or totally evade vaccine induced immunity. Unmet need for additional vaccines that can provide protection against a range of SARS-CoV-2 variants are needed.

The clinical development of Kostaive as a 2-dose primary vaccination series relies on a pivotal phases 1 / 2 / 3 ARCT-154-01 study including more than 17,000 participants, with the majority of participants being exposed to 2 doses of ARCT-154 vaccine given at least 28 days apart. Data from this study demonstrate that 2 doses of the ARCT-154 vaccine given at least 28 days apart offer substantial protection against COVID-19 of any severity caused by SARS-CoV-2. In addition, the ARCT-154 vaccine also demonstrated its protective effect against the globally dominant Delta variant during the study period. ARCT-154 vaccine offered protection against the more severe forms of COVID-19. ARCT-154 vaccine provided similar protection in participants with high and low risk of severe COVID-19 disease, young adults (18 to 59 years of age) and older individuals (≥60 years of age), as well as across sex. Two doses of ARCT-154 induced humoral immunity against SARS-CoV-2.

Kostaive also demonstrated benefits when used as a booster. This is supported by the evaluation of the ARCT-154 vaccine given as a booster dose in an adult population primed at least 3 months earlier with different mRNA COVID-19 vaccines. The ARCT-154 booster elicited a higher and more durable immune responses across multiple variants as compared to an approved conventional mRNA vaccine. A subsequent booster study with the bivalent vaccine ARCT-2301 confirmed these findings. This further supports that Kostaive elicits a broader and more durable immune response compared to conventional mRNA vaccines and demonstrates the robustness of the platform.

A study conducted with Kostaive as an XBB.1.5 targeting booster, demonstrated that Kostaive can be concomitantly administered with influenza vaccines without impact on the immune response induced.

18.2.3 Key Risks

Kostaive has been administered to over 20,000 participants in clinical studies; ARCT-021 has been administered to over 700 adults, ARCT-154 has been administered to over 19,000 adults, ARCT-2301 has been administered to 465 adults, ARCT-2303 to 1499 adults and CSL402 to 431 adults and 148 adolescents.

The pivotal and supportive studies included in this overview have included healthy adults and adolescents and individuals with medically stable chronic disorders, who were unvaccinated (adults only), or who received previous vaccination with authorized COVID-19 vaccines (adults and adolescents). Individuals who were pregnant or breastfeeding, individuals with a history of autoimmune disease and individuals with a known allergy to vaccine components were excluded from the study enrolment.

Kostaive was shown to have an acceptable safety profile following primary vaccination in a population 18 years of age and older and following booster vaccination, with the most common risks of vaccination being solicited local and systemic reactions. Those events were generally mild to moderate in severity and resolved within the 7-day follow-up period.

No new safety issues arose from the evaluation of the more than 20,000 exposed participants when reviewing the data on SAEs with an outcome of death, SAEs and Medically Attended Adverse Events (MAAEs). Severe AEs and SAEs occurred with low frequency. The safety profile of Kostaive was similar across all age groups, with no new safety signals of concern in young adults or in older adults.

Development of Kostaive in a paediatric population has been initiated with a study in adolescents. Interim results showed a good immune response in this age group which is noninferior to the immune response in adults. No safety concerns were identified with the 5 mcg dose formulation, but a more optimal benefit-risk profile could exist for a different dose level in adolescents.

18.2.4 Integrated Benefit-Risk Evaluation

The totality of efficacy, immunogenicity and safety data from the clinical development program demonstrates that Kostaive is safe and effective when used both as a primary vaccination series and booster dose in the adult population. This supports a favourable benefit-risk balance at both the individual and public health levels.

Based on the review of the safety data presented in this report, the benefit-risk evaluation of Kostaive remains favourable for its approved indication.

Overall, the information presented in the current RSI is considered to sufficiently minimise the risk related to the use of Kostaive; therefore, no additional measures are warranted as of the DLP of this report.

19 Conclusions and Actions

No new information has arisen during the reporting period that would change the overall evaluation of benefit-risk for Kostaive when used for active immunisation to prevent COVID-19 caused by SARS-CoV-2.

Based on the evaluation of information collected during this reporting period and the cumulative data review, no changes in the benefit-risk profile for Kostaive have been observed. The overall benefit-risk analysis for Kostaive remains favourable.

The MAH proposes to remove the missing information topics Interaction with other vaccines and Long-term safety data in the updated RMP, version 1.1, with DLP 27 May 2025 which was submitted to EMA on 03 July 2025.

The safety profile of Kostaive is considered adequately reflected in the current RSI, and no safety amendments are warranted at present.