

Kostaive: Periodic safety update report assessment

28 May 2025 to 27 November 2025

This document consists of:

1. The PRAC assessment report of the EMA/PSUR/0000327932 periodic safety update report (PSUR) covering the period 28 May 2025 to 27 November 2025, and;
2. The EMA/PSUR/0000327932 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.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMADOC-1700519818-2909954
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000327932

PRAC PSUR assessment report

EURD list no.: PSUSA/00011115/202511

Active substance: Zapomeraan

Period covered by the PSUR: 28 May 2025 to 27 November 2025

Centrally authorised Medicinal product:
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	5 February 2026	5 February 2026
☐	Start date	12 February 2026	12 February 2026
☐	PRAC Rapporteur AR	13 April 2026	7 April 2026
☐	PRAC/MAH comments	13 May 2026	13 May 2026
☐	Updated PRAC Rapporteur AR	28 May 2026	18 May 2026
☒	PRAC outcome	11 June 2026	11 June 2026



Procedure resources	
PRAC Rapporteur	Name: Dirk Mentzer
EMA Procedure Lead	Name: Tel: Email:
EMA Procedure Assistant	Name: Tel: Email:

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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 zapomeran.

2. Assessment conclusions and actions

This is the assessment of the fourth PSUR for zapomeran, for the reporting period 28 May 2025 up to 27 November 2025.

Zapomeran is a self-amplifying messenger ribonucleic acid (sa-mRNA) vaccine 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.

The sa-mRNA consists of a series of ribonucleotides encoding the replicase and a ribonucleic acid sequence encoding the SARS-CoV-2 S glycoprotein. After intramuscular delivery, 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 ribonucleic acid messenger.

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.

Cumulatively, 21,367 participants have been exposed in clinical trials (completed and ongoing) since the Development International Birth Date, on 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 120,434 standard doses sold.

At the time of the Data lock point of the report, Kostaive was authorised in 31 countries worldwide.

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

The missing information topics "Interaction with other vaccines" and "Long-term safety data" were removed from the EU Risk-Management Plan, version 2.0 dated 21 October 2025.

No signal evaluation was ongoing or completed during the reporting period. Review of the data received during the reporting period 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.

The current frequency of PSUR submission should be changed from six months to one year. In alignment with the international birth date (IBD), the next submitted PSUR will be an annual PSUR with data lock point (DLP) 27 November 2026 covering the period from 28 November 2025 to 27 November 2026.

The overall benefit-risk balance for zapomeran remains unchanged in the approved indication.

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

☒ Changes of PSUR frequency are proposed.

The current frequency of submission should be changed from 6 months to 1 year at the first possibility.
The list of Union reference dates (EURD) should be updated accordingly.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the assessment of the 4th PSUR for Zapomeran (Kostaive), covering the period 28 May 2025 to 27 November 2025. Reports and other data from the partner companies Meiji Seiki 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 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 sequence encoding the SARS-CoV-2 S glycoprotein. Unlike the mRNA in conventional 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 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.

LUNAR-COV19 formulations ARCT-021, ARCT-154, ARCT-165, ARCT-2303, ARCT2301 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 confirmation; 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 two replicons – one 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 CSL402 replicon DS Kostaive XEC (mRNA-2526) encodes the full-length spike glycoprotein of the Omicron XEC variant of SARS-CoV-2.

The IBD for Kostaive is 28 November 2023 in Japan. The approved indications 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.

The MAH did not propose changes to the product information as part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

Kostaive was first authorised on 28 November 2023 in Japan (where it is marketed by Meiji Seika Pharma) and in the EU on 12 February 2025. It is currently registered in 31 countries.

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 RSI in effect at the start of the reporting period was the Company Core Data Sheet (CCDS), version 2.0, dated 15 May 2025. During the reporting period, no changes were made to the RSI.

1.3.3. Estimated exposure and use patterns

• Cumulative subject exposure in clinical trials

Up to the DLP of the PBRER, 21,367 subjects have been treated with Kostaive in completed and ongoing clinical trials. 29 subjects have been treated with placebo (>18,000 participants received placebo either prior or after receiving Kostaive). 3,544 subjects have been treated with a 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

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

At the DLP, Kostaive was only commercially available in Japan. During the reporting period, [REDACTED] standard doses have been sold worldwide. Cumulatively, since October 2024 (first commercial launch), 120,434 standard doses have been sold worldwide. See also Table 1.

Table 1: Estimated worldwide patient exposure for Kostaive

	Previous period from commercial launch date (October 2024) to 27 May 2025	Current period 28 May 2028 to 27 November 2025	Cumulatively till 27 November 2025
Single-dose exposure	[REDACTED]	[REDACTED]	120,434

• Post-authorisation use in special populations

Use in paediatric patient population

During the reporting interval, there were two paediatric cases, both in adolescents (12 years to <18 years). Cumulatively, there were three paediatric cases, all in adolescents.

During the reporting period, a total of 2 non-serious spontaneous cases were retrieved from the global safety database. One case involved a 17-year-old patient (PT: Product administered to patient of

inappropriate age) who developed pyrexia after vaccination with Kostaive. Another case concerned a 14-year-old patient (PT: *Off-label use* / Lowest Level Term: *Off label use in unapproved age group*) who was vaccinated with Kostaive, and no adverse events were reported.

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

Use in elderly patient population

During the reporting period, a total of 105 cases (97 initial and 8 follow-up) were retrieved from the global safety database pertaining to use of Kostaive in elderly patients. See also Table 2.

Table 2: Number of post-authorisation cases in elderly

Age group	Interval number of cases	Cumulative number of cases
65 to 69 years	24	44
70 to 79 years	22	66
80 to 89 years	13	54
90 years and older	9	50
Unknown	37	88
Total	105	302

Of the 97 cases, 63 were spontaneous cases and 34 were originated from postmarketing safety study KO01 (Drug use-results survey, NIS_PVA159436).

Within these 97 initial cases, a total of 218 events were reported, of which 23 were serious (including 15 fatal events) and 195 were non-serious. The most frequently reported events were *vaccination site pain* (61), *pyrexia* (26), *malaise* (21), *vaccination site swelling* (17) and *myalgia* (13). The remaining adverse events were reported with frequency ≤ 10 and no trend was identified.

Of the 14 fatal cases (15 fatal events), 3 were reported in patients of advanced age with underlying comorbidities. The fatal events in these 3 cases were assessed as not related due to temporal and/or biological implausibility and confounders.

The remaining 11 fatal cases in elderly age group (exact ages unknown) were reported from Japan via the social networking site X. These cases reported event "Death" and were assessed as related for reporting purposes due to their spontaneous nature. However, insufficient information regarding time to onset (TTO), medical history, cause of death and autopsy results precluded meaningful case assessment.

During the reporting period, 8 follow-up cases were received for Kostaive, the follow-up information did not change the previous case assessments.

Cumulatively, 302 cases pertaining to use of Kostaive in elderly patients were received. Among these cases, 199 cases were spontaneous reports and 103 were originated from postmarketing safety study KO01. These cases encompassed 644 events, of which 67 were serious (including 36 fatal events) and 577 were non-serious. The most frequently reported events included *pyrexia* (146), *vaccination site pain* (112), *injection site pain* (47), *malaise* (42), *vaccination site swelling* (30), *headache* (24), *myalgia* (22), *chills* (17), *arthralgia* (14), *death* (12) and *vaccination site induration* (11). The remaining adverse events were reported with frequency ≤ 10 and no trend was identified. There was no specific pattern of reported non-serious events in the elderly population compared with the general population. The serious events were predominantly reflective of age-related comorbidities.

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

Pregnancy and lactation

- Use during pregnancy:

During the reporting period, 17 cases (10 initial, 7 follow-up) pertaining to pregnancy exposure with Kostaive were received from post-marketing reporting.

Cumulatively, 20 cases pertaining to pregnancy exposure were received from post-marketing reporting. In 4 of the 20 cases, no adverse events were reported. In the remaining 16 cases, the most frequently reported adverse events were *vaccination site pain* (20), *headache* (9), *malaise* (7), *chills*, *pyrexia* (6 each), *arthralgia* (5). The remaining adverse events were reported with frequency ≤ 5 and no trend was identified. There is no specific pattern of reported events in pregnant women compared with the general population.

Regarding the reported pregnancy outcomes, there were 6 interval cases (cumulatively 7 cases) reporting normal outcome (full term or live birth) and 9 interval cases (cumulatively 10 cases) reporting unknown outcome, lost to follow-up or outcome pending. Of note, 2 interval cases (cumulatively 3 cases) reporting foetal exposure during pregnancy were excluded as the cases with maternal outcome of live birth were considered.

Use of Kostaive during pregnancy is considered missing information.

- Use during lactation:

During the reporting period, 10 (6 initial, 4 follow-up) cases pertaining to exposure with Kostaive during breastfeeding were received from post-marketing reporting. Cumulatively, 20 cases pertaining to exposure with Kostaive during breastfeeding were received from post-marketing reporting. In 4 of the 20 cases, no adverse events were reported. In the remaining 16 cases, the most frequently reported adverse events were *vaccination site pain* (24), *headache* (11), *chills* and *malaise* (10 each), *vaccination site induration* (8), *pyrexia* and *arthralgia* (7 each), *myalgia* and *vaccination site swelling* (5 each). The remaining adverse events were reported with frequency < 5 and no trend was identified. There is no specific pattern of reported events in nursing women compared with the general population.

Use of Kostaive while breast-feeding is considered missing information.

Other post-authorisation use

- Off-label use:

A review of all post-authorisation experience pertaining to off-label use was performed by searching the global safety database for all cases (valid and invalid) pertaining to off-label use in the post-marketing setting regardless of causality.

During the reporting period, 2 non-serious spontaneous cases (both initial) pertaining to off-label use with Kostaive were received from post-marketing reporting. Both cases involved adolescents (< 18 years) where Kostaive was used in an unapproved age group.

Cumulatively, 3 spontaneous non-serious cases pertaining to off-label use with Kostaive were received from post-marketing reporting all involving use of the vaccine in adolescents (an unapproved population).

Review of the cases pertaining to off-label use did not change the current safety profile of the product. 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 1 PT included in the High Level Term 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 of Kostaive. The MAH will continue to monitor all cases pertaining to drug interaction per its routine pharmacovigilance procedures.

Rapporteur assessment comment: In this reporting period, there was a more than five times increase in exposure compared to the previous reporting period. There is no safety issue from the use in special populations.

1.3.4. Data in summary tabulations

The MAH provides cumulative summary tabulations of serious adverse events from clinical trials as well as cumulative and interval summary tabulations from post-marketing data sources. Table 3 gives an overview of interval and cumulative adverse drug reaction data.

Table 3: Overview of Adverse Drug Reaction Data

Source	Reporting period N / Reporting rate	Cumulative period N / Reporting rate
Non-serious ADRs – spontaneous	240 / 235.77	602 / 499.86
Serious ADRs – spontaneous	36 / 35.37	52 / 43.18
Serious ADRs – non-interventional studies and other solicited	3 / 2.95	11 / 9.13
Total ADRs	279 / 274.08	665 / 552.17

Rapporteur assessment comment:

Cumulatively, 1,538 SAEs have been reported in clinical trials, of these 701 in subjects receiving Kostaive. From post-marketing experience, 279 ADRs have been reported during the reporting period, of these 39 serious. Cumulatively, 665 ADRs have been reported, of these 63 serious.

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:**

No MAH-sponsored interventional clinical trials with Kostaive were completed during the reporting period.

- **Ongoing clinical trials:**

During the reporting period, 2 partner-sponsored clinical trials with Kostaive were ongoing in Japan: CSL402-J01 and CSL402-J02. No new clinically important efficacy and safety findings have arisen from these clinical trials.

- **Long-term follow-up:**

Participants completing clinical trials with Kostaive are not currently subject to long-term follow-up.

- **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, one ongoing non-interventional safety study (KO01 Drug use-results survey, NIS-PVA159436) was sponsored by Meiji Seika Pharma. Interim study results were published by Meiji Seika Pharma (Yuki et al, 2025). No new safety findings were identified upon review of these interim data. During the reporting period, no new important safety findings emerged from this study.

- **Other clinical trials:**

During the reporting period, 5 independent investigator research studies with Kostaive were ongoing, no clinically important safety information has arisen from these studies.

During the reporting period, one study that was co-sponsored by Meiji Seika Pharma and Hakata Clinic of Soseikai (a post-trial questionnaire survey following the completion of a phase 3 study evaluating the safety and immunogenicity of an additional immunisation with ARCT-154 in adult subjects) with Kostaive was completed on 18 September 2025. This safety survey was conducted among participants (27 Kostaive and 24 Comirnaty) enrolled by Hakata Clinic in the ARCT-154-J01 clinical trial in 2023. A survey was sent to investigate if any long-term safety events had occurred. No clinically important safety information has arisen from this source.

- **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 global safety database for all cases containing at least one PT pertaining to the Medication errors SMQ (narrow) and 2 additional PTs: *needle issue* and *syringe issue*.

During the reporting period, one initial non-serious spontaneous case was received for Kostaive (PT *Product administered to patient of inappropriate age*). The cumulative and interval reporting rates are provided in Table 4.

Table 4: Medication error interval and cumulative reporting rates (RR)

	Previous interval	Current interval	Cumulative
No. cases / RR (per 100,000 doses)	1 / 5.365	1 / 0.982	2 / 1.661

Conclusion: No patterns of medication errors have been identified relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. 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 (ARC24-052) titled "A single dose tissue distribution evaluation of ARCT-154 in female Balb/c mice: pharmacokinetics of genomic, subgenomic and negative RNA and spike and replicase proteins in the muscle and selected tissues" was finalized (14 July 2025).

This non-GLP tissue distribution study was designed to characterise the pharmacokinetics of genomic, subgenomic and negative-strand RNA species as well as the translated spike glycoprotein and non-structural protein 1 replicase protein, following a single intramuscular administration of ARCT-154 in female Balb/c mice. Two dose groups (5 µg and 25 µg) were evaluated. Tissues and plasma were collected at various timepoints up to day 60 to assess the biodistribution and clearance of RNA and protein biomarkers using strand-specific QuantiGene RNA assays and meso scale discovery-based ligand binding assays, respectively.

To summarise, as all 5 biomarkers (genomic RNA, subgenomic RNA, negative-strand RNA, S glycoprotein and nsP1 replicase protein) cleared from tissues, this study demonstrated the complete disappearance of replicase activity by the end of the study, thus supporting the safety and self-limited nature of this sa-mRNA vaccine platform.

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. The retrieved abstracts and/or full texts were reviewed for important safety findings.

During the reporting period, two articles relevant to Kostaive were retrieved. Review of these articles did not yield any significant safety findings which impacted benefit-risk profile.

Amarikwa L, 2025, Risk of developing thyroid eye disease in patients with thyroid dysfunction that received a COVID-19 vaccination. Can J Ophthalmol.

The study aimed to assess the risk of developing TED following mRNA COVID-19 vaccination in patients with pre-existing thyroid dysfunction, specifically hyperthyroidism. Using a large retrospective cohort from the TriNetX network and propensity score matching, the authors compared TED incidence among vaccinated and unvaccinated patients as well as those receiving influenza and Tdap vaccines. Results showed that COVID-19 vaccination were associated with a higher relative risk of TED (RR = 1.49; 95% CI: 1.39–1.58) compared with no vaccination and even higher when compared with influenza and Tdap cohorts.

MAH Assessment: The study indicates an increased relative risk of TED in hyperthyroid patients following mRNA COVID-19 vaccination; however, no causal relationship was established, only statistical disproportionality. Furthermore, TED is not an identified or potential risk for conventional mRNA COVID-19 vaccines. At present, no change to the benefit-risk balance of Kostaive is warranted but continued monitoring and literature review are recommended.

Bea S, 2025, Effect of COVID-19 vaccination on thyroid disease in 7 million adult and 0.2 million adolescent vaccine recipients. J Clin Endocrinol Metab.

A nationwide self-controlled case series study from South Korea evaluated the association between COVID-19 vaccination and thyroid diseases in 7.58 million adults and 241,063 adolescents. IRRs for

hyperthyroidism, hypothyroidism, subacute thyroiditis and TED were assessed during the 55-day postvaccination period compared with the baseline. Results showed no significant increase in the risk for most thyroid conditions, except a slight statistical signal for hypothyroidism exacerbation in adults. No increased risk was observed in adolescents, and subgroup analyses by age, sex and vaccine type revealed no significant differences. The authors concluded that COVID-19 vaccination is generally safe concerning thyroid health.

MAH Assessment: The study indicates no clinically relevant association between COVID-19 vaccination and new-onset thyroid disorders, except for a minor increase in hypothyroidism exacerbation. The risk of TED was not elevated. These findings are consistent with the current safety profile. At present, no change to the benefit-risk balance of Kostaive is warranted; continued monitoring will be maintained.

- **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.

Rapporteur assessment comment:

There is no new safety issue from the review of 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 the PSUR, no potentially 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 5: Summary of important safety concerns at the start 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 (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
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The missing information topics "Interaction with other vaccines" and "Long-term safety data" were removed from EU-RMP, version 2.0, dated 21 October 2025. The removal of these two missing information topics was endorsed by the CHMP.

2.2. Signal evaluation

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

2.3. Evaluation of risks and safety topics under monitoring

Adverse events of special interest (AESI) were agreed upon with EMA during the approval process of EU-RMP, version 1.0, with DLP of 27 March 2023, dated 02 December 2024. The MAH was requested to monitor the following AESIs and present in PSURs:

- **AESI: Acute disseminated encephalomyelitis**

A review of the new information received during the reporting period was performed by searching the global safety database for all cases containing at least one PT in the Customised MedDRA Query (CMQ) for Acute disseminated encephalomyelitis. No cases associated with Kostaive were identified during the reporting period. The MAH will continue to monitor all cases pertaining to Acute disseminated encephalomyelitis per its routine pharmacovigilance procedures.

- **AESI: Acute pancreatitis**

Search in the global safety database for cases containing at least one PT in the CMQ for Acute Pancreatitis identified no cases of acute pancreatitis associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to acute pancreatitis per its routine pharmacovigilance procedures.

- **AESI: Anaphylaxis**

Search in the global safety database for cases containing at least one PT in the CMQ for anaphylaxis identified no cases of anaphylaxis associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to anaphylaxis per its routine pharmacovigilance procedures.

- **AESI: Anosmia**

Search in the global safety database for cases containing at least one PT in the CMQ for anosmia identified no cases of anosmia associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to anosmia per its routine pharmacovigilance procedures.

- **AESI: Bell's palsy**

Search in the global safety database for cases containing at least one PT in the CMQ for Bell's palsy identified no cases of Bell's palsy associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to Bell's palsy per its routine pharmacovigilance procedures.

- **AESI: Delayed hypersensitivity**

A review of the new information received during the reporting period was performed by searching the global safety database for all cases containing at least one PT included in the CMQ for Delayed hypersensitivity. For further analysis, relevant potential cases 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 the "COVID arm") is an immune-mediated reaction characterised by the development of a well-demarcated, inflamed plaque, cellulitis-like reaction 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 191 cases (162 initial, 29 follow-up) concerning Kostaive were retrieved. Of the 162 initial cases, 154 originated from post-marketing safety study KO01 and 8 were spontaneous reports. Upon review of the initial cases, 6 cases reported a time to onset of more than 72 hours. Of these 6 cases, none were consistent with delayed hypersensitivity reaction. Twenty-nine follow-up cases (including 5 corrections of previously reported information) were received during the reporting period; none reported any new significant information.

In 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.

- **AESI: Erythema multiforme**

Search in the global safety database for cases containing at least one PT in the CMQ for Erythema multiforme identified no cases of Erythema multiforme associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to Erythema multiforme per its routine pharmacovigilance procedures.

- **AESI: Extensive limb swelling (ELS)**

A review of the new information received during the reporting period was performed by searching the 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 134 cases (114 initial, 20 follow-up) concerning Kostaive were retrieved. Of the 114 initial cases received, 107 were originated from post-marketing safety study KO01 and 7 were spontaneous reports. Of these 114 cases, none were consistent with ELS. Twenty follow-up cases (including 3 corrections of previously reported information) were received during the reporting period; none reported any new significant information.

In 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.

- **AESI: Facial swelling in persons with dermal fillers**

Search in the global safety database was performed for 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, a total of 2 cases (1 initial, 1 follow-up) concerning Kostaive were retrieved. One non-serious initial case was originated from post-marketing safety study KO01. The

event reported in this case was lip swelling; however, no medical history of facial dermal fillers injection was reported. One follow-up case received during the reporting period did not report any new significant information.

In 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.

- **AESI: Generalised convulsion**

Search in the global safety database for cases containing at least one PT in the CMQ for Convulsions identified no cases of convulsions associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to generalised convulsions per its routine pharmacovigilance procedures.

- **AESI: Guillain-Barre syndrome (GBS)**

Search in the global safety database for cases containing at least one PT in the CMQ for Guillain-Barre syndrome identified no cases of GBS associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to GBS per its routine pharmacovigilance procedures.

- **AESI: Multisystem inflammatory syndrome in adults**

Search in the global safety database for cases containing at least one PT in the CMQ for Multisystem inflammatory syndrome in adults identified no cases of multisystem inflammatory syndrome associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to multisystem inflammatory syndrome in adults per its routine pharmacovigilance procedures.

- **Important potential risk: Myocarditis, myopericarditis, pericarditis**

A review of the new information received during the reporting period was performed by searching the global safety database for all cases containing at least one PT in the CMQ for Myocarditis / pericarditis. During the reporting period, one clinical trial follow-up case concerning Kostaive was retrieved, which did not report any new significant information.

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 myocarditis / pericarditis per its routine pharmacovigilance procedures. Moreover, study V206_06 is planned as an additional pharmacovigilance activity to further assess the potential risk of myocarditis / pericarditis.

- **AESI: Rhabdomyolysis**

Search in the global safety database for cases containing at least one PT in the CMQ for Rhabdomyolysis identified no cases of rhabdomyolysis associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to rhabdomyolysis per its routine pharmacovigilance procedures.

- **AESI: Subacute thyroiditis**

Search in the global safety database for cases containing at least one PT in the CMQ for subacute thyroiditis identified no cases of subacute thyroiditis associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to subacute thyroiditis per its routine pharmacovigilance procedures.

- **AESI: Thrombocytopenia**

Review of the new information received during the reporting period was performed by searching the global safety database for all cases containing at least one PT in the CMQ for Thrombocytopenia. During the reporting period, a total of 3 cases (1 initial, 2 follow-up) concerning Kostaive were retrieved. One non-serious initial case was reported from the post-marketing safety study KO01, involving mild intermenstrual bleeding. The event was assessed as related due to plausible temporal relationship (time to onset seven days after vaccination). No thrombocytopenia was reported in this case. None of the two follow-up cases reported new clinically significant information during the reporting period.

Review of the data pertaining to thrombocytopenia 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.

- **Important potential risk: Thrombosis / thromboembolism**

A review of the new information received during the reporting period was performed by searching the global safety database for all cases containing at least one PT in the CMQ for Thromboembolic events. During the reporting period, one clinical trial follow-up case was retrieved concerning Kostaive. This follow-up case did not report any new significant information. The cumulative and interval Reporting Rates are provided in Table 6:

Table 6: Thromboembolic events interval and cumulative reporting rates

	Previous interval	Current interval	Cumulative
No cases / RR (per 100,000 doses)	1 / 5.365	0 / not applicable	1 / 0.830

Conclusion: review of the cases pertaining to thromboembolic events did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to thromboembolic events per its routine pharmacovigilance procedures. Moreover, study V206_06 is planned as an additional pharmacovigilance activity to further assess the potential risk of thromboembolic events.

- **AESI: Transverse myelitis**

Search in the global safety database for cases containing at least one PT in the CMQ for Transverse myelitis identified no cases of transverse myelitis associated with Kostaive during the reporting period. The MAH will continue to monitor all cases pertaining to transverse myelitis per its routine pharmacovigilance procedures.

- **Missing information: Use in pregnancy and while breastfeeding**

According to the 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.

Pregnancy:

During the reporting period, a total of 19 cases (10 initial and 9 follow-up) pertaining to pregnancy exposure with Kostaive were retrieved. Of the 10 initial cases received, 7 were originated from post-marketing safety study KO01 and 3 were spontaneous.

Of the 10 initial cases, 2 cases which reported foetal exposure during pregnancy were assessed by the MAH as not related. In another case, a comprehensive medical assessment cannot be performed due to insufficient data; a neonate was exposed in utero to Kostaive at 7 weeks of gestation and was subsequently diagnosed with patent ductus arteriosus, simple coarctation of aorta and pulmonary hypertension. The neonate was delivered via caesarean section (multiple birth). No information regarding the mother's medical, obstetrical or family history was available.

Of the remaining 7 maternal cases, 3 cases did not report adverse events. The remaining 4 cases reported 23 non-serious adverse events: *vaccination site pain* (7), *malaise* (3), *arthralgia*, *chills*, *headache* and *myalgia* (2 each) and *diarrhoea*, *pyrexia*, *somnolence*, *vaccination site induration* and *vaccination site swelling* (1 each). No specific pattern of reported adverse events was observed. The pregnancy outcome of these 7 cases was reported as outcome pending (5), live birth (1) and unknown (1).

No new clinically significant information was reported in the nine follow-up cases.

Breast-feeding:

During the reporting period, a total of 10 cases (6 initial, 4 follow-up) in breast-feeding women who were vaccinated with Kostaive were identified. Of the 6 initial cases received, 5 were originated from post-marketing safety study KO01 and one was a spontaneous report.

Within these 6 initial cases, a total of 18 non-serious events were reported: *vaccination site pain* (7), *malaise* (3), *chills* (2) and *arthralgia*, *myalgia*, *headache*, *vaccination site erythema*, *vaccination site induration* and *vaccination site swelling* (1 each). No specific pattern of reported AEs was observed. No baby cases were reported.

The four follow-up cases did not report any new significant information.

MAH's note: conservative case coding convention currently in use includes proactive coding of two 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.

MAH's conclusion: There is no specific pattern of reported events in nursing women compared with the general population. 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 use in pregnancy and while breastfeeding per its routine pharmacovigilance procedures. Moreover, study V206_03 is planned as an additional pharmacovigilance activity to further evaluate "use in pregnancy and while breastfeeding".

- **Missing information: Use in immunocompromised patients**

Review of all post-authorisation cases pertaining to "use in immunocompromised patients" was performed by searching the global safety database for all cases in which the medical history contained at least one PT in the CMQ for *Use in immunocompromised patients*. During the reporting period, a total of 6 cases (4 initial, 2 follow-up) concerning Kostaive were identified. These 4 non-serious initial cases were received from the post-authorisation safety study KO01. The reported relevant medical history conditions were lung adenocarcinoma, papillary thyroid cancer, breast cancer and colon cancer (1 each).

Within these four initial cases, a total of 25 non-serious events were reported. No specific pattern of reported AEs was observed. The most frequently reported non-serious events were *vaccination site pain* (7) and *malaise* (4). The remaining adverse events were reported with frequency <4 and no trend was identified.

Of the 2 follow-up cases received, one case reported significant new information regarding the cause of death (pneumonia with *E. coli* detected); however, this did not change the previous assessment. In the other case, a correction of previously reported information was made during the reporting period.

MAH's 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. Moreover, study V206_05 is planned as an additional pharmacovigilance activity to further evaluate "use in immunocompromised patients".

- **Missing information: Interaction with other vaccines**

Review of all post-authorisation cases pertaining to interaction with other vaccines revealed 2 initial, non-serious, spontaneous cases received during the reporting period. Both cases involved simultaneous administration of Kostaive and influenza vaccines. The first case reported malaise and headache, while the second case reported pyrexia and vaccination site pain. No specific pattern of reported adverse events was observed.

MAH's conclusion: review of the data pertaining to interaction with other vaccines did not raise any safety concerns related to Kostaive. The missing information "Interaction with other vaccines" has been removed from the EU-RMP, version 1.2, dated 21 October 2025 and approved by EMA on 27 November 2025. As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025, after the DLP of the PSUR.

- **Missing information: use in patients with autoimmune or inflammatory disorders**

During the reporting period, a total of 17 cases (13 initial, 4 follow-up) concerning Kostaive were identified. Of these 13 initial cases received, 12 were from post-marketing safety study KO01, and one was a spontaneous report.

Of the 13 initial cases, the relevant medical history, included colitis ulcerative (4), systemic lupus erythematosus (2) and autoimmune thyroiditis, chronic gastritis, gangrene, IgA nephropathy, immune thrombocytopenia, Kawasaki's disease, multiple sclerosis, primary biliary cholangitis and rheumatoid arthritis (1 each). Within these 13 initial cases, a total of 59 events were reported, of which 5 were serious (no fatal events) and 54 were non-serious.

One case reported 5 serious events (depressed level of consciousness, hallucination visual, pyrexia, somnolence and vomiting), all of which were assessed by the MAH as related due to close temporal relationship (immediately after vaccination). However, there is insufficient information (suspect product indication, clinical course, lab investigations, treatment details and concomitant medications) to perform in-depth analysis.

The most frequently reported non-serious events were vaccination site pain (18) and malaise (6). The remaining adverse events were reported with frequency ≤ 5 and no trend was identified. No specific pattern of reported adverse events was observed.

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

Four follow-up cases (including 2 corrections of previously reported information) received during the reporting period did not report any new significant information.

MAH's 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. Moreover, study V206_05 is

planned as an additional pharmacovigilance activity to further evaluate “Use in patients with autoimmune inflammatory disorders”.

- **Missing information: Long-term safety data**

Based on the completion of studies ARCT-165-01, ARCT-154-01 and ARCT-154-J01, which 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, missing information “Long-term safety data” has been removed from the EU-RMP version 1.2, dated 21 October 2025 and approved by EMA on 27 November 2025. As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025 after the DLP of the PSUR.

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

During the reporting period, a total of 50 cases (37 initial, 13 follow-up) concerning Kostaive were identified. Of these 37 initial cases, 28 were originated from postmarketing safety study KO01 and 9 were spontaneous reports.

The most frequently reported potentially unstable chronic medical conditions in the 37 initial cases were hypertension (24), diabetes mellitus (13), chronic kidney disease (6), dementia and liver disorder (2 each). The remaining potentially unstable chronic medical conditions were reported with singular frequency.

Within these 37 initial cases, a total of 140 adverse events were reported, of which 11 were serious (including four fatal events) and 129 were non-serious events. The four fatal events COVID-19, cardiac failure acute, drowning and pneumonia aspiration were reported in 3 cases involving patients of advanced age (88, 89 and 91 years). The remaining seven serious events included COVID-19 (2), depressed level of consciousness, pyrexia, somnolence, vomiting and hallucination, visual (1 each). The event COVID-19 was assessed as not-related by the MAH due to insufficient information for a meaningful assessment (event onset date, temporality, relevant medical history etc.). The other serious events were reported from the same case, all of which were assessed by the MAH as related due to close temporal relationship (immediately after vaccination).

Of the 129 non-serious events, the most frequently reported were vaccination site pain (38), vaccination site swelling (13), malaise and myalgia (11 each). All other non-serious events were reported with frequency ≤ 10 . No specific pattern of reported adverse events was observed.

Of the 13 follow-up cases received, 12 cases (including 4 case correction of previously reported information) did not report any new significant information. The remaining one case reported addition of cardiac failure chronic as medical history.

MAH’s 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 of “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.

Special vaccine-related topics:

- **Issues related to batches**

The monthly batch trend analysis is performed at the formulated batch level and on a cumulative basis for each batch distributed. This analysis is included in the Monthly Signal Detection Review activity for Kostaive. The RR, serious RR (SRR), alert, serious alert and new/updated alert are calculated during this analysis for all batches distributed. Only cases with valid batch numbers are analysed, and analysis is performed by seriousness, product and initial or follow-up case status.

The ICSR RR thresholds considered as alert limits indicating the presence of a potential batch-related safety signal are as follows:

- A RR of at least 5 ICSRs regardless of seriousness, per 100,000 doses distributed
- An SRR of at least 1 serious ICSR per 100,000 doses distributed and at least 3 serious cases within the same formulated batch

Any batch meeting the prespecified alert limits for either RR or SRR thresholds is further reviewed. The review is performed in the context of medical concept, clustering and plausibility of batch-related quality issue. A review of ICSRs associated with RR and SRR alerts conducted during the reporting period of this report did not reveal any issues related to specific batches that would impact the benefit-risk profile of Kostaive. No batch-related safety signals were identified.

- **Age-related adverse reactions**

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

- **Reports of vaccination failure / lack of efficacy**

A search in the global safety database for all cases containing at least one PT in the CMQ for vaccination failure / lack of efficacy was performed. For further analysis, cases of potential vaccination failure were evaluated, where the patient was diagnosed with COVID-19 infection no earlier than two weeks and no later than 6 months after vaccination. The cases with unknown time between vaccination and COVID-19 diagnosis were not further evaluated.

During the reporting period, a total of 5 cases (3 initial and 2 follow-up) concerning Kostaive were identified. These 3 initial cases were spontaneous reports. These cases reported 5 serious events: COVID-19 (3), SARS-CoV-2 test positive and vaccination failure (1 each). Further, these cases were not evaluated as the time to onset was more than 6 months in 2 cases. Time to onset was not reported / unknown in one case.

The cumulative and interval RRs are provided in Table 7.

Table 7: Vaccination failure interval and cumulative reporting rates

	Previous interval	Current interval	Cumulative*
No. cases / RR (per 100,000 doses)	4 / 21.459	0 / not applicable	4 / 3.321

*one case is not considered as vaccination failure and therefore not included in RR calculations.

During the reporting period, 2 follow-up cases were received; however, no significant information pertaining to vaccination failure was reported.

MAH's conclusion: a review of reports of vaccination failure 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.

- **Immunisation stress-related response reactions**

A search of the global safety database was performed using at least one PT in the CMQ for Immunisation stress-related response reactions.

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 >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 four cases (3 initial, 1 follow-up) concerning Kostaive were identified. The 3 initial cases were spontaneous reports. The reported events were *altered state of consciousness, depressed level of consciousness, fall* and *hyperhidrosis* (1 each). Of these, two cases were not further evaluated as the time to onset was >30 minutes after vaccination.

The remaining case concerned a 90-year-old female patient with a history of atrial fibrillation, hypertension, dementia and [REDACTED] who developed depressed level of consciousness (being only half conscious) immediately after receiving Kostaive. The MAH assessed this serious event as related considering plausible temporal relationship (immediately after vaccination). The event was reported as resolved.

The cumulative and interval RRs are provided in Table 8.

Table 8: Vaccination failure interval and cumulative reporting rates

	Previous interval	Current interval	Cumulative
No. cases / RR (per 100,000 doses)	0 / not applicable	1 / 0.982	1 / 0.830

Note: cases reported time to onset >30 minutes (1 day) post-vaccination are not considered in RR calculations.

RR = reporting rate

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

MAH's conclusion: A review of reports of immunisation stress-related response reactions 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 immunisation stress-related response reactions per its routine pharmacovigilance procedures.

Rapporteur assessment comment:

There is no new safety issue from the evaluation of risks and safety topics under monitoring. No further action is considered warranted at this stage.

2.4. Characterisation of risks

- **Important identified risks:**

There are no important identified risks for Kostaive.

- **Important potential risk: myocarditis and pericarditis**

The mode of action of myocarditis and pericarditis has not been fully characterised. Hypotheses include an immune-stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response.

Myocarditis and pericarditis have been reported in post-marketing surveillance of other mRNA COVID-19 vaccines. Cumulatively, up to the DLP, no cases that were related to Kostaive were received from clinical studies nor from post-marketing use.

Risk factors and risk groups: post-authorisation reports from other mRNA vaccine manufacturers have been received for more males than females, over a wide age range and following dose 1 and dose 2 of the vaccine. Evaluation by 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.

Preventability: according to the CCDS, version 2.0, 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.

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. Considering the low rates of myocarditis and pericarditis reported following vaccination, balances with the risk of death and illness (including myocarditis) caused by SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

- **Important potential risk: thromboembolic events**

The mechanism by which Kostaive may cause thromboembolic events has not yet been elucidated.

Several observational studies indicate an increased rate of coagulation disorders following COVID-19 vaccines.

With respect to Kostaive, the following cases have been received:

Clinical trials: up to the DLP, two cases (Cerebral infarction, deep vein thrombosis, n=1 each) related to Kostaive were received from clinical studies. Post-marketing: cumulatively to the DLP, one spontaneous case (cerebral infarction) was received for Kostaive.

Risk factors: 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 risk-benefit balance: 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.

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

- **Missing information: Use in pregnancy and while breastfeeding**

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 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.

The lack of data is communicated in CCDS, version 2.0. 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).

- **Missing information: use in immunocompromised patients**

Kostaive has not been studied in individuals with overt immunocompromised conditions. Therefore, this population will be further studied in the post-marketing setting. A post-authorisation safety study to collect additional safety data in immunocompromised individuals, individuals with autoimmune disease and patients who are on immunosuppressive therapies is planned.

- **Missing information: interaction with other vaccines**

Limited information is available on the interaction with other vaccines. 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, which supports the removal of this missing information. There was no evidence of an impact on the safety and reactogenicity profiles for each vaccine when co-administered versus standalone. The CCDS 2.0 states that Kostaive may be administered concomitantly with influenza vaccine.

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.

- **Missing information: use in patients with autoimmune or inflammatory disorders**

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

- **Missing information: long-term safety data**

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. No new clinically important safety findings have arisen from these clinical trials up to 12 months.

- **Missing information: use in patients with significant, unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)**

The vaccine has been studied in individuals with stable chronic diseases (e.g., hypertension, obesity); however, it has not been studied in individuals with significant, unstable chronic medical conditions (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) that may compromise the immune function due to the condition or treatment of the condition. Therefore, further safety data will be sought in this population. Safety data will be collected through routine pharmacovigilance activities.

Rapporteur assessment comment:

The safety concerns remain unchanged.

3. Benefit evaluation

Kostaive has undergone an extensive clinical development program, in which it demonstrated efficacy and effectiveness in individuals 18 years of age and older in the prevention of COVID-19, caused by SARS-CoV-2.

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:

A test-negative case-control study evaluating absolute effectiveness of Kostaive is currently being conducted at ten medical institutions across Japan; this is an investigator-initiated study conducted by Nagasaki University. Eligible participants were adults aged ≥ 60 years with ≥ 1 acute respiratory symptom who were tested for SARS-CoV-2. Cases were test-positive patients and controls were test-negative. Influenza-positive individuals were excluded to reduce confounding by vaccination behaviour. Absolute vaccine effectiveness of mRNA vaccines encoding for the JN.1 variant, including conventional mRNA vaccines (Comirnaty and Spikevax) as well as Kostaive, was estimated relative to individuals who had not been vaccinated (either never vaccinated or vaccinated only with pre-JN.1 vaccines). Multivariable logistic regression was used, adjusting for age group, sex, underlying medical conditions, calendar month of testing, prior SARS-CoV-2 infection and nursing-home residence. Separate estimates were generated for pooled JN.1-adapted mRNA vaccines and for Kostaive alone.

The median age of participants was 75 years; 58.2% were female; 39.1% had ≥ 1 underlying medical condition and 17.7% were nursing-home residents. The pooled effectiveness of conventional mRNA vaccines was 46.1% (95% CI: 7.3-68.7) at ≥ 7 days, 55.1% (95% CI: 0.9-79.6) at 7 to 60 days and 37.0% (95% CI: -22.7-67.7) at > 60 days after vaccination. Absolute vaccine effectiveness of Kostaive was 69.9% (95% CI: 20.0-88.6) at ≥ 7 days after vaccination, with wide CIs due to the small sample size.

In conclusion, JN.1-adapted mRNA COVID-19 vaccines, including Kostaive, showed evidence of protection against symptomatic infection among adults aged ≥ 60 years in Japan. While acknowledging the limitations of this interim analysis with a small sample size, these results are supportive of real-world effectiveness of Kostaive.

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 an investigator-initiated study conducted by Nagasaki University that supports 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 ratio for Kostaive remains unchanged.

5. Comments from Member States

MS1 - We fully endorse the PRAC rapporteur assessment and have no further comments.

	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 International 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 May 2025 to 27 November 2025 Date of this Report: 28 January 2026 Report Number: 4
--

Marketing Authorisation Holder's Name and Address:

Seqirus Netherlands B.V.
Paasheuvelweg 28,
1105 BJ Amsterdam,
Netherlands

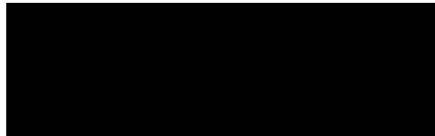
Name and Contact Details of the QPPV:

Dr. med. Juergen Zorn
CSL Innovation GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Mobile:

Telefax:

E-Mail:



Approved by (QPPV OR Delegate):

e-signature (see last page)



Global Safety Lead

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Executive Summary

Introduction:

This is the fourth 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 May 2025 up to and including the Data Lock Point (DLP) of 27 November 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 (EMA) 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 ribonucleic acid (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 sequence encoding the SARS-CoV-2 S glycoprotein. Unlike the mRNA in conventional 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 ribonucleic acid 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 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) 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 CSL402 replicon DS Kostaive XEC (mRNA-2526) encodes the full-length spike glycoprotein of the Omicron XEC variant of SARS-CoV-2.

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, 21,367 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 120,434 standard doses sold.

Worldwide Marketing Authorisation Status:

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

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 missing information topics 'Interaction with other vaccines' and 'Long-term safety data' were removed from the European Union-Risk Management Plan, version 1.2, dated 21 October 2025. The EMA endorsed the removal of these 2 missing information topics, and the Committee for Medicinal Products for Human Use issued a Positive Opinion on 27 November 2025. As indicated by EMA, the approved European Union-Risk Management Plan was updated from version 1.2 to version 2.0 on 05 December 2025, after the DLP of this report. No other changes were made.

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
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMQ	Customised Medical Dictionary for Regulatory Activities Query
COVID-19	Coronavirus Disease 2019
DLP	Data Lock Point
ELS	Extensive Limb Swelling
EMA	European Medicines Agency
EU	European Union
GMT	Geometric Mean Titre
HLT	High Level Term
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
PBRER	Periodic Benefit-Risk Evaluation Report
PT	Preferred Term
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
S glycoprotein	Spike Glycoprotein
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
SRR	Serious Reporting Rate
TTO	Time to Onset

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1 Introduction

This is the fourth 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 May 2025 up to and including the Data Lock Point (DLP) of 27 November 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 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 mRNA in conventional 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 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

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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 CSL402 replicon DS Kostaive XEC (mRNA-2526) encodes the full-length spike glycoprotein of the Omicron XEC variant of SARS-CoV-2.

The approved indications 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 recommended doses can be found in the RSI presented in [Appendix 1](#).

This PBRER is prepared on behalf of all MAH partner companies.

The composition of Kostaive is 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	
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	

PEG = polyethylene glycol; 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) and is currently registered in 31 countries. 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.

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 the Reference Safety Information

The RSI in effect at the start of the reporting period was the Company Core Data Sheet (CCDS), version 2.0, dated 15 May 2025.

During the reporting period, no changes were made to the RSI. A copy of the RSI 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, 21,367 subjects have been treated with Kostaive in completed and ongoing clinical trials, 29 subjects have been treated with placebo (> 18,000 participants received placebo either prior or after receiving Kostaive), 3544 subjects have been treated with a 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
Completed Trials	
Drug	20,749
Comparator	3544
Placebo	29
Ongoing Trials^a	
Drug	711
Comparator	0
Placebo	0
Completed and Ongoing Trials^b	
Drug	21,367
Comparator	3544
Placebo	29

^a Estimates of ongoing trials based upon the scheduled enrolment / randomisation schemes as of 27 November 2025.

^b Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials (see [Table 5-2](#)) and the enrolment / randomisation schemes for ongoing trials (CSL402-J01 and CSL402-J02) as of 27 November 2025.

Table 5-2: Estimated Cumulative Subject Exposure to Kostaive from Completed and Ongoing Clinical Studies by Age 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
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
CSL402-J01	
< 18 years	148
≥ 18 - < 65 years	363
≥ 65 years	68
CSL402-J02	
< 18 years	65
≥ 18 - < 65 years	56
≥ 65 years	11
Total	21,367

^a Data from completed and ongoing studies as of 27 November 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: Estimated Cumulative Subject Exposure to Kostaive from Completed and Ongoing 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
CSL402-J01	331	248
CSL402-J02	60	72
Total	10,458	11,012

^a Data from completed and ongoing studies as of 27 November 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 and Ongoing 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

Ethnic Origin	Number of Subjects
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
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

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Ethnic Origin	Number of Subjects
CSL402-J01	
Asian	579
Black	0
Caucasian	0
American Indian or Alaska Native	0
Other	0
Study total	579
CSL402-J02	
Asian	132
Black	0
Caucasian	0
American Indian or Alaska Native	0
Other	0
Study total	132
Total	21,367

^a Data from completed and ongoing studies as of 27 November 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.

At the DLP, Kostaive was only commercially available in Japan. Estimated interval and cumulative worldwide patient exposure is presented in [Table 5-5](#).

During the reporting period, [REDACTED] standard doses have been sold worldwide.

Cumulatively, since October 2024 (the first commercial launch), 120,434 standard doses have been sold worldwide.

Table 5-5: Estimated Worldwide Patient Exposure for Kostaive

	Previous Period from Commercial Launch Date (October 2024) to 27 May 2025	Current Period 28 May 2025 to 27 November 2025	Cumulatively till 27 November 2025
Single-dose Exposure			120,434

Note: On 28 August 2025, Meiji Seika Pharma Co., Ltd, received approval for a New Drug Application to introduce the 2-dose lyophilised presentation. Therefore, calculations are not presented in vials instead presented only in doses.

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 global 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 5-6](#).

Table 5-6: 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)	2	3
Total	2	3

During the reporting period, a total of 2 nonserious spontaneous cases were retrieved from the global safety database. One case involved a 17-year-old patient (Preferred Term [PT]: Product administered to patient of inappropriate age) who developed pyrexia after vaccination with Kostaive. Another case concerned a 14-year-old patient (PT: Off label use / Lowest Level Term: Off label use in unapproved age group) who was vaccinated with

Kostaive, and no adverse events (AEs) were reported. These cases are also discussed in [Section 5.2.3.1](#).

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 5-7](#).

Table 5-7: Number of Postauthorisation Cases

Age Group	Interval Number of Cases	Cumulative Number of Cases
65 to 69 years	24	44
70 to 79 years	22	66
80 to 89 years	13	54
90 years and older	9	50
Unknown	37	88
Total	105	302

During the reporting period, a total of 105 (97 initial and 8 follow-up) cases were retrieved from the global safety database pertaining to use of Kostaive in elderly patients. Of the 97 initial cases received, 63 were spontaneous cases and 34 were originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436).

Within these 97 initial cases, a total of 218 events were reported, of which 23 were serious (including 15 fatal events) and 195 were nonserious. The most frequently reported events were vaccination site pain (61), pyrexia (26), malaise (21), vaccination site swelling (17) and myalgia (13). The remaining AEs were reported with frequency ≤ 10 and no trend was identified.

Of the 14 fatal cases (15 fatal events), 3 were reported in patients of advanced age with underlying comorbidities. The fatal events in these 3 cases were assessed as not related due to temporal and / or biological implausibility and confounders.

The remaining 11 fatal cases in elderly age group (exact ages unknown) were reported from Japan via the social networking site X. These cases reported event 'Death' and were assessed as related for reporting purposes due to their spontaneous nature. However, insufficient

information regarding time to onset (TTO), medical history, cause of death and autopsy results precluded meaningful case assessment.

During the reporting period, 8 follow-up cases were received for Kostaive, the follow-up information did not change the previous case assessments.

Cumulatively, 302 cases pertaining to use of Kostaive in elderly patients were received. Among these cases, 199 cases were spontaneous reports and 103 were originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436). These cases encompassed 644 events, of which 67 were serious (including 36 fatal events) and 577 were nonserious. The most frequently reported events included pyrexia (146), vaccination site pain (112), injection site pain (47), malaise (42), vaccination site swelling (30), headache (24), myalgia (22), chills (17), arthralgia (14), death (12) and vaccination site induration (11). The remaining AEs were reported with frequency ≤ 10 and no trend was identified. There was no specific pattern of reported nonserious events in the elderly population compared with the general population. The serious events were predominantly reflective of age-related comorbidities.

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

5.2.2.3 Pregnancy and Lactation

5.2.2.3.1 Use during Pregnancy

During the reporting period, 17 cases (10 initial; 7 follow-up) pertaining to pregnancy exposure with Kostaive were received from postmarketing reporting. These 17 cases are summarised in [Section 16.3.5.1](#).

Cumulatively, 20 cases pertaining to pregnancy exposure with Kostaive were received from postmarketing reporting. In 4 of the 20 cases, no AEs were reported. In the remaining 16 cases, the most frequently reported AEs were vaccination site pain (20); headache (9); malaise (7); chills, pyrexia (6 each); arthralgia (5). The remaining AEs were reported with frequency ≤ 5 and no trend was identified. There is no specific pattern of reported events in pregnant women compared with the general population.

An overview of the reported pregnancy outcomes cumulatively and during interval period is provided in [Table 5-8](#).

Table 5-8: Reported Pregnancy Outcomes during Interval and Cumulative Period

Outcome	Interval Period	Cumulative Period
Normal (full term or live birth)	6	7
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	9	10

Note: Cumulatively, 3 cases (including 2 interval cases) reporting foetal exposure during pregnancy were excluded as the cases with maternal outcome of live birth were 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 risk of pregnancy exposure is presented in [Section 16.4.3](#).

5.2.2.3.2 Use during Lactation

During the reporting period, 10 (6 initial, 4 follow-up) cases pertaining to exposure with Kostaive during breastfeeding were received from postmarketing reporting. These 10 cases are summarised in [Section 16.3.5.1](#).

Cumulatively, 20 cases pertaining to exposure with Kostaive during breastfeeding were received from postmarketing reporting. In 4 of the 20 cases, no AEs were reported. In the remaining 16 cases, the most frequently reported AEs were vaccination site pain (24), headache (11), chills and malaise (10 each), vaccination site induration (8), pyrexia and arthralgia (7 each), myalgia and vaccination site swelling (5 each). The remaining AEs were reported with frequency < 5 and no trend was identified. There is no specific pattern of reported events in nursing women compared with the general population.

Use of Kostaive while breast-feeding 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 risk in woman while breast-feeding is presented in [Section 16.4.3](#).

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 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, 2 nonserious spontaneous cases (both initial) pertaining to off-label use with Kostaive were received from postmarketing reporting. Both cases involved adolescents (< 18 years) where Kostaive was used in an unapproved age group and are discussed in [Section 5.2.2.1](#).

Cumulatively, 3 spontaneous nonserious cases pertaining to off-label use with Kostaive were received from postmarketing reporting all involving use of the vaccine in adolescents (an unapproved population).

Review of the cases pertaining to off-label use did not change the current safety profile of the product. 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 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 postmarketing reporting; hence, there was no new safety information relevant to the benefit-risk assessment of 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) / AE terms in the summary tabulations are arranged alphabetically by primary System Organ Class 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 28.1, 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.

In ongoing, blinded clinical trials, treatment is unblinded only for cases with suspected unexpected serious adverse reactions in all line listings and summary tabulations. For all other cases reported from ongoing, blinded studies, treatment is kept blinded.

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	240/235.77	602/499.86
Serious ADRs – spontaneous	36/35.37	52/43.18
Serious ADRs – noninterventional studies and other solicited	3/2.95	11/9.13
Total ADRs	279/274.08	665/552.17

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 MAH- and partner-sponsored interventional trials are presented in this section.

An overview of all MAH- and partner-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

No MAH-sponsored interventional clinical trials with Kostaive were completed during the reporting period.

7.2 Ongoing Clinical Trials

During the reporting period, 2 partner-sponsored clinical trials with Kostaive (CSL402-J01 and CSL402-J02) were ongoing in Japan. No new clinically important efficacy and safety findings have arisen from these clinical trials.

7.3 Long-term Follow-up

Participants completing clinical trials with Kostaive are not currently subject to long-term follow-up.

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, 1 ongoing noninterventional safety study (KO01 Drug Use-results Survey, NIS_PVA159436) was sponsored by Meiji Seika Pharma. Interim study results were published by Meiji Seika Pharma ([Yuki et al, 2025](#)). No new safety findings were identified upon review of these interim data. During the reporting period, no new important safety findings emerged from this study.

An overview of all MAH- and partner-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

During the reporting period, 5 independent investigator research studies with Kostaive were ongoing, no clinically important safety information has arisen from these studies.

During the reporting period, 1 study that was cosponsored study by Meiji Seika Pharma and Hakata Clinic of Soseikai (a post-trial questionnaire survey following the completion of a phase 3 study evaluating the safety and immunogenicity of an additional immunisation with ARCT-154 in adult subjects) with Kostaive was completed on 18 September 2025. This safety survey was conducted among participants (27 Kostaive and 24 Comirnaty) enrolled by Hakata Clinic in the ARCT-154-J01 clinical trial in 2023. A survey was sent to investigate if any long-term safety events had occurred. No clinically important safety information has arisen from this source.

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 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 initial nonserious spontaneous case was received for Kostaive (PT Product administered to patient of inappropriate age). This case is discussed in detail in [Section 5.2.3.1](#).

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
No cases/RR (per 100,000 doses)	1/5.365	1/0.982	2/1.661

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 the medicinal product. 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.

10 Nonclinical Data

During the reporting period, 1 nonclinical study (Study ARC24-052) titled 'A Single Dose Tissue Distribution Evaluation of ARCT-154 in Female Balb/c Mice: Pharmacokinetics of genomic, subgenomic, and negative RNA and spike and replicase proteins in the muscle and selected tissues' was finalised (14 July 2025).

This non-Good Laboratory Practicetissue distribution study was designed to characterise the pharmacokinetics of genomic, subgenomic and negative-strand RNA species as well as the translated Spike glycoprotein and nonstructural protein 1 replicase protein, following a single intramuscular administration of ARCT-154 in female Balb/c mice. Two dose groups (5 µg and 25 µg) were evaluated. Tissues and plasma were collected at various timepoints up to Day 60 to assess the biodistribution and clearance of RNA and protein biomarkers using strand-specific QuantiGene RNA assays and meso scale discovery-based ligand binding assays, respectively.

To summarise, as all 5 biomarkers (genomic RNA, subgenomic RNA, negative-strand RNA, S glycoprotein and nsP1 replicase protein) cleared from tissues, this study demonstrated the complete disappearance of replicase activity by the end of the study, thus supporting the safety and self-limited nature of this sa-mRNA vaccine platform.

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 published and unpublished literature retrieved during the reporting period identified 2 articles relevant to Kostaive. Review of these articles did not yield any significant safety findings which impacted benefit-risk profile. These articles are presented in below [Table 11-1](#).

Table 11-1: Summary of Literature Received

Reference	Summary
Amarikwa L, 2025, Risk of developing thyroid eye disease in patients with thyroid dysfunction that received a COVID-19 vaccination, Can J Ophthalmol	The study aimed to assess the risk of developing TED following mRNA COVID-19 vaccination in patients with pre-existing thyroid dysfunction, specifically hyperthyroidism. Using a large retrospective cohort from the TriNetX network and propensity score matching, the authors compared TED incidence among vaccinated and unvaccinated patients as well as those receiving influenza and Tdap vaccines. Results showed that COVID-19 vaccination were associated with a higher relative risk of TED (RR = 1.49; 95% CI: 1.39–1.58) compared with no vaccination and even higher when compared with influenza and Tdap cohorts. MAH Assessment: The study indicates an increased relative risk of TED in hyperthyroid patients following mRNA COVID-19 vaccination; however, no causal relationship was established, only statistical disproportionality. Furthermore, TED is not an identified or potential risk for conventional mRNA COVID-19 vaccines. At present, no change to the benefit-risk balance of Kostaive is warranted but continued monitoring and literature review are recommended.

Reference	Summary
Bea S, 2025, Effect of COVID-19 vaccination on thyroid disease in 7 million adult and 0.2 million adolescent vaccine recipients, J Clin Endocrinol Metab	A nationwide self-controlled case series study from South Korea evaluated the association between COVID-19 vaccination and thyroid diseases in 7.58 million adults and 241,063 adolescents. IRRs for hyperthyroidism, hypothyroidism, subacute thyroiditis and TED were assessed during the 55-day postvaccination period compared with the baseline. Results showed no significant increase in the risk for most thyroid conditions, except a slight statistical signal for hypothyroidism exacerbation in adults. No increased risk was observed in adolescents, and subgroup analyses by age, sex and vaccine type revealed no significant differences. The authors concluded that COVID-19 vaccination is generally safe concerning thyroid health. MAH Assessment: The study indicates no clinically relevant association between COVID-19 vaccination and new-onset thyroid disorders, except for a minor increase in hypothyroidism exacerbation. The risk of TED was not elevated. These findings are consistent with the current safety profile. At present, no change to the benefit-risk balance of Kostaive is warranted; continued monitoring will be maintained.

CI = confidence interval; COVID-19 = coronavirus disease 2019; IRR = incidence rate ratio; MAH = marketing Authorisation author; mRNA = messenger ribonucleic acid; RR = relative risk; Tdap = tetanus, diphtheria, and acellular pertussis; TED = thyroid eye disease

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 potentially 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.

15.2 Monitored Topics

The AEs of special interest were agreed upon with EMA during the approval process of European Union (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 (GBS)
- 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 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:

During the reporting period, no cases of acute disseminated encephalomyelitis associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Acute pancreatitis (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of acute pancreatitis associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Anaphylaxis (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of anaphylaxis concerning Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Anosmia (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of anosmia associated with Kostaive were identified.

Conclusion:

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 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:

During the reporting period, no cases of Bell's palsy associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT included 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 TTO more than 72 hours (≥ 3 days) following Kostaive vaccination. A delayed local reaction secondary to COVID-19 vaccination (also known as the 'COVID arm') is an immune-mediated reaction characterised 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.

Results and Discussion:

During the reporting period, a total of 191 cases (162 initial; 29 follow-up) concerning Kostaive were retrieved. Of the 162 initial cases received, 154 originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 8 were spontaneous reports.

Upon review of the initial cases, 6 cases reported a TTO of more than 72 hours (≥ 3 days). Of these 6 cases, none were consistent with delayed hypersensitivity reaction.

Twenty-nine follow-up cases (including 5 corrections of previously reported information) were received during the reporting period; none reported any new significant information.

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 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:

During the reporting period, no cases of erythema multiforme associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Extensive limb swelling (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.

Results and Discussion:

During the reporting period, a total of 134 cases (114 initial; 20 follow-up) concerning Kostaive were retrieved. Of the 114 initial cases received, 107 were originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 7 were spontaneous reports. Of these 114 cases, none were consistent with ELS.

Twenty follow-up cases (including 3 corrections of previously reported information) were received during the reporting period; none reported any new significant information.

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 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.

Results and Discussion:

During the reporting period, a total of 2 cases (1 initial; 1 follow-up) concerning Kostaive were retrieved. One nonserious initial case was originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436). The event reported in this case was lip swelling; however, no medical history of facial dermal fillers injection was reported.

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

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 global safety database for all cases containing at least 1 PT in the CMQ for Convulsions (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of convulsions associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Guillain-Barre syndrome (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of GBS associated with Kostaive were identified.

Conclusion:

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 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:

During the reporting period, no cases of multisystem inflammatory syndrome associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Rhabdomyolysis (see [Appendix 5.2](#) for more details).

Results:

During the reporting period, no cases of rhabdomyolysis associated with Kostaive were identified.

Conclusion:

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 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:

During the reporting period, no cases of subacute thyroiditis associated with Kostaive were identified.

Conclusion:

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 global safety database for all cases containing at least 1 PT in the CMQ for Thrombocytopenia (see [Appendix 5.2](#) for more details).

Results and Discussion:

During the reporting period, a total of 3 cases (1 initial; 2 follow-up) concerning Kostaive were retrieved.

One nonserious initial case was reported from a postmarketing safety study (KO01 Drug Use-Results Survey, NIS_PVA159436) involving mild intermenstrual bleeding. The event was assessed as related due to plausible temporal relationship (TTO 7 days after vaccination). No thrombocytopenia was reported in this case.

None of the 2 follow-up cases reported new clinically significant information during the reporting period.

Conclusion:

Review of the data pertaining to thrombocytopenia 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 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:

During the reporting period, no cases of transverse myelitis associated with Kostaive were identified.

Conclusion:

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

The missing information topics 'Interaction with other vaccines' and 'Long-term safety data' were removed from EU-RMP, version 1.2, dated 21 October 2025. The EMA endorsed the removal of these 2 missing information topics, and the Committee for Medicinal Products for Human Use (CHMP) issued a Positive Opinion on 27 November 2025. As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025, after the DLP of this report. No other changes were made.

The summary of important safety concerns at the end of the reporting period is presented in [Table 16-2](#).

Table 16-2: Summary of Important Safety Concerns at the End 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 • 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 2.0, dated 05 December 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 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, 1 clinical trial follow-up case concerning Kostaive was retrieved. This follow-up case did not report any new significant information.

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 myocarditis / pericarditis per its routine pharmacovigilance procedures. Moreover, study V206_06 is planned as an additional pharmacovigilance activity to further assess the potential risk of myocarditis / pericarditis.

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 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 and Discussion

During the reporting period, 1 clinical trial follow-up case was retrieved concerning Kostaive. This follow-up case did not report any new significant information.

The cumulative and interval RRs are provided in [Table 16-3](#).

Table 16-3: Thromboembolic Events Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative
No cases/RR (per 100,000 doses)	1/5.365	0/Not applicable	1/0.830

RR = reporting rate

Conclusion

Review of the cases pertaining to thromboembolic events did not change the current safety profile of Kostaive. The MAH will continue to monitor all cases pertaining to thromboembolic events per its routine pharmacovigilance procedures. Moreover, study

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V206_06 is planned as an additional pharmacovigilance activity to further assess the potential risk of thromboembolic events.

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 the 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 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 global safety database for all cases concerning pregnant and / or lactating patients.

Results and Discussion

During the reporting period, a total of 19 cases (10 initial; 9 follow-up) pertaining to pregnancy exposure with Kostaive were retrieved. Of the 10 initial cases received, 7 were originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 3 were spontaneous reports.

Of the 10 initial cases, 2 cases which reported foetal exposure during pregnancy were assessed by the MAH as not related. In another case, a comprehensive medical assessment cannot be performed due to insufficient data; a neonate was exposed in utero to Kostaive at 7 weeks of gestation and was subsequently diagnosed with patent ductus arteriosus, simple coarctation of aorta and pulmonary hypertension. The neonate was delivered via caesarean section (multiple birth). No information regarding the mother's medical, obstetrical or family history was available.

Of the remaining 7 maternal cases, 3 cases did not report AEs. The remaining 4 cases reported 23 nonserious AEs: vaccination site pain (7); malaise (3); arthralgia, chills, headache and myalgia (2 each) and diarrhoea, pyrexia, somnolence, vaccination site induration and vaccination site swelling (1 each). No specific pattern of reported AEs was observed. The pregnancy outcome of these 7 cases was reported as outcome pending (5), live birth (1) and unknown (1).

No new clinically significant information was reported in the 9 follow-up cases.

During the reporting period, a total of 10 cases (6 initial; 4 follow-up) in breast-feeding woman who were vaccinated with Kostaive were identified. Of the 6 initial cases received, 5 were originated from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 1 was a spontaneous report.

Within these 6 initial cases, a total of 18 nonserious events were reported: vaccination site pain (7); malaise (3); chills (2) and arthralgia, myalgia, headache, vaccination site erythema,

vaccination site induration and vaccination site swelling (1 each). No specific pattern of reported AEs was observed. No baby cases were reported.

The 4 follow-up cases did not report any new significant information.

Note: 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.

Conclusion

There is no specific pattern of reported events in nursing women compared with the general population. 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 use in pregnancy and while breastfeeding per its routine pharmacovigilance procedures. Moreover, study V206_03 is planned as an additional pharmacovigilance activity to further evaluate 'use in pregnancy and while breastfeeding'.

16.3.5.2 New Information on Missing Information: Use in Immunocompromised Patients

Introduction

According to the 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 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 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 6 cases (4 initial; 2 follow-up) concerning Kostaive were identified. These 4 nonserious initial cases were received from the postauthorisation safety study (KO01 Drug Use-results Survey, NIS_PVA159436). The reported relevant medical history conditions were lung adenocarcinoma, papillary thyroid cancer, breast cancer and colon cancer (1 each).

Within these 4 initial cases, a total of 25 nonserious events were reported. No specific pattern of reported AEs was observed. The most frequently reported nonserious events were vaccination site pain (7) and malaise (4). The remaining AEs were reported with frequency, < 4 and no trend was identified.

Of the 2 follow-up cases received, 1 case reported significant new information regarding the cause of death (pneumonia with *E. coli* detected); however, this did not change the previous assessment. In the other case, a correction of previously reported information was made 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. Moreover, study V206_05 is planned as an additional pharmacovigilance activity to further evaluate ‘use in immunocompromised patients’.

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 EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in [Section 16.4.3](#).

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

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Methodology

A review of all postauthorisation cases pertaining to interaction with other vaccines was performed by searching the global safety database for all cases with Kostaive where another vaccine is reported as a cosuspect (eg, influenza vaccine).

Results and Discussion

During reporting period, 2 initial nonserious spontaneous cases pertaining to the interaction of Kostaive with other vaccines were received. Both cases involved simultaneous administration of Kostaive and influenza vaccines. The first case reported malaise and headache, while the second case reported pyrexia and vaccination site pain. No specific pattern of reported AEs was observed.

Conclusion

Review of the data pertaining to interaction with other vaccines did not raise any safety concerns related to Kostaive. The missing information 'Interaction with other vaccines' has been removed from the EU-RMP, version 1.2, dated 21 October 2025 and approved by the EMA on 27 November 2025 (CHMP Positive Opinion). As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025, after the DLP of this report.

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 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 17 cases (13 initial; 4 follow-up) concerning Kostaive were identified. Of these 13 initial cases received, 12 were from postmarketing safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 1 was a spontaneous report.

Of the 13 initial cases, the relevant medical history included colitis ulcerative (4); systemic lupus erythematosus (2) and autoimmune thyroiditis, chronic gastritis, gangrene, IgA nephropathy, immune thrombocytopenia, Kawasaki's disease, multiple sclerosis, primary biliary cholangitis and rheumatoid arthritis (1 each).

Within these 13 initial cases, a total of 59 events were reported, of which 5 were serious (no fatal events) and 54 were nonserious.

One case reported 5 serious events (depressed level of consciousness, hallucination, visual, pyrexia, somnolence and vomiting), all of which were assessed by the MAH as related due to close temporal relationship (immediately after vaccination). However, there is insufficient information (suspect product indication, clinical course, lab investigations, treatment details and concomitant medications) to perform in-depth analysis.

The most frequently reported nonserious events were vaccination site pain (18) and malaise (6). The remaining AEs were reported with frequency ≤ 5 and no trend was identified. No specific pattern of reported AEs was observed.

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

Four follow-up cases (including 2 corrections of previously reported information) received during the reporting period did not report any new significant information.

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. Moreover, study V206_05 is planned as an additional pharmacovigilance activity to further evaluate 'use in patients with autoimmune or inflammatory disorders'.

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 EU-RMP, version 1.0, dated 02 December 2024. Characterisation of this safety concern is provided in [Section 16.4.3](#).

Based on the completion of studies ARCT-165-01, ARCT-154-01 and ARCT-154-J01 which 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,

missing information 'Long-term safety data' has been removed from the EU-RMP version 1.2, dated 21 October 2025, and approved by the EMA on 27 November 2025 (CHMP Positive Opinion). As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025 after the DLP of this report.

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 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 received during the reporting period was performed by searching the global safety database for all cases in which the medical history containing at least 1 PT in the CMQ for 'Use in Patients with Significant, Unstable Chronic Medical Conditions' (see [Appendix 5.2](#) for more details).

Result and Discussion

During the reporting period, a total of 50 cases (37 initial; 13 follow-up) concerning Kostaive were identified. Of these 37 initial cases received, 28 were originated from postmarketing

safety study (KO01 Drug Use-results Survey, NIS_PVA159436) and 9 were spontaneous reports.

The most frequently reported potentially unstable chronic medical conditions in these 37 initial cases were hypertension (24), diabetes mellitus (13), chronic kidney disease (6), dementia and liver disorder (2, each). The remaining potentially unstable chronic medical conditions reported with singular frequency.

Within these 37 initial cases, a total of 140 AEs were reported, of which 11 were serious (including 4 fatal events) and 129 were nonserious events.

The 4 fatal events COVID-19, Cardiac failure acute, drowning and pneumonia aspiration were reported in 3 cases involving patients of advanced age (88, 89 and 91 years). These cases are discussed in [Section 5.2.2.2](#).

The remaining 7 serious events included COVID-19 (2), depressed level of consciousness, pyrexia, somnolence, vomiting and hallucination, visual (1 each). The event COVID-19 was assessed as nonrelated by MAH due to insufficient information for a meaningful assessment (event onset date, temporality, relevant medical history, etc). The other serious events were reported from the same case, all of which were assessed by the MAH as related due to close temporal relationship (immediately after vaccination). This case is discussed in detail in [Section 16.3.5.4](#).

Of the 129 nonserious events, the most frequently reported were vaccination site pain (38), vaccination site swelling (13), malaise and myalgia (11 each). All other nonserious events were reported with frequency ≤ 10 . No specific pattern of reported AEs was observed.

Of the 13 follow-up cases received, 12 cases (including 4 case correction of previously reported information) did not report any new significant information. The remaining 1 case reported addition of cardiac failure chronic as medical history.

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 of '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)

The monthly batch trend analysis is performed at the formulated batch level and on a cumulative basis for each batch distributed. This analysis is included in the Monthly Signal Detection Review activity for Kostaive. The RR, serious RR (SRR), alert, serious alert and new / updated alert are calculated during this analysis for all batches distributed. Only cases with valid batch numbers are analysed, and analysis is performed by seriousness, product and initial or follow-up case status.

The ICSR RR thresholds considered as alert limits indicating the presence of a potential batch-related safety signal are as follows:

- A RR of at least 5 ICSRs regardless of seriousness, per 100,000 doses distributed.
- An SRR of at least 1 serious ICSR per 100,000 doses distributed and at least 3 serious cases within the same formulated batch.

Any batch meeting the prespecified alert limits for either RR or SRR thresholds (described above) is further reviewed. The review is performed in the context of medical concept, clustering and plausibility of batch-related quality issue. A review of ICSRs associated with RR and SRR alerts conducted during the reporting period of this report did not reveal any issues related to specific batches that would impact the benefit-risk profile of Kostaive. No batch-related safety signals were identified.

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 pertaining to the elderly age group are discussed 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 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).

For further analysis, cases of potential vaccination failure were evaluated, where the patient was diagnosed with COVID-19 infection no earlier than 2 weeks and no later than 6 months after vaccination. The cases with unknown time between vaccination and COVID-19 diagnosis were not further evaluated.

Result and Discussion

During the reporting period, a total of 5 cases (3 initial, 2 follow-up) concerning Kostaive were identified. These 3 initial cases were spontaneous reports. These cases reported 5 serious events: COVID-19 (3), SARS-CoV-2 test positive and vaccination failure (1 each). Further, these cases were not evaluated as the TTO was more than 6 months in 2 cases and the TTO was not reported / unknown in 1 case.

The cumulative and interval RRs are provided in [Table 16-4](#).

Table 16-4: Vaccination Failure Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative ^a
No. cases/RR (per 100,000 doses)	4/21.459	0/Not applicable	4/3.321

RR = reporting rate

^a One case is not considered as vaccination failure therefore not included in RR calculations.

During reporting period, 2 follow-up cases were received; however, no significant information pertaining to vaccination failure was reported.

Conclusion

A review of reports of vaccination failure 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.

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16.3.6.4 Immunisation Stress-related Response Reactions

Introduction

As per the 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 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 TTO within 30 minutes following Kostaive vaccination. Cases that did not specify an exact TTO 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 minutes), 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 4 cases (3 initial; 1 follow-up) concerning Kostaive were identified. The 3 initial cases were spontaneous reports. The reported events were altered state of consciousness, depressed level of consciousness, fall and hyperhidrosis (1 each). Of these, 2 cases were not further evaluated as the TTO was > 30 minutes after vaccination. The remaining case is discussed below:

This case concerned a 90-year-old female patient with a history of atrial fibrillation, hypertension, dementia and [REDACTED] who developed depressed level of consciousness (being only half conscious) immediately after receiving Kostaive. The MAH assessed this serious event as related considering plausible temporal relationship (immediately after vaccination). The event was reported as resolved.

The cumulative and interval RRs are provided in [Table 16-5](#).

Table 16-5: Immunisation Stress-related Response Reactions Interval and Cumulative Reporting Rates

	Previous Interval	Current Interval	Cumulative
No. cases/RR (per 100,000 doses)	0/Not applicable	1/0.982	1/0.830

Note: Cases reported time to onset > 30 minutes (1 day) postvaccination are not considered in RR calculations.

RR = reporting rate

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

Conclusion

A review of reports of immunisation stress-related response reactions 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 immunisation stress-related response reactions 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

Table 16-6: 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.

Important Potential Risk	Myocarditis and Pericarditis
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 2.0, 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) (see Appendix 5.2 for further details).

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

Table 16-7: 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, 2 cases for thromboembolic events (Cerebral infarction, Deep vein thrombosis [n=1 each]) related to Kostaive were received from clinical studies.

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Important Potential Risk	Thromboembolic Events
	Postmarketing: Cumulatively up to the DLP, 1 spontaneous case (Cerebral infarction) was received for Kostaive from postmarketing use.
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) (see Appendix 5.2 for further details).

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

Table 16-8: 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	

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Missing Information:	Use in Pregnancy and While Breastfeeding
vaccines suggests a favourable risk-benefit balance when weighing the increased risks of COVID-19 in pregnant women.	
<u>Population in Need of Further Characterisation:</u> The lack of data is communicated in CCDS, version 2.0. 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).	

CCDS = company core data sheet; COVID-19 = coronavirus disease 2019; mRNA = messenger ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Table 16-9: Missing Information: Use in Immunocompromised Patients

Missing Information:	Use in Immunocompromised Patients
<u>Evidence Source:</u> Kostaive has not been studied in individuals with overt immunocompromised conditions. Therefore, this population will be further studied in the postmarketing setting.	
<u>Population in Need of Further Characterisation:</u> A postauthorisation safety study to collect additional safety data in immunocompromised individuals, individuals with autoimmune disease and patients who are on immunosuppressive therapies is planned.	

Table 16-10: Missing Information: Interaction with Other Vaccines

Missing Information:	Interaction with Other Vaccines
<u>Evidence Source:</u> Limited information is available on the interaction with other vaccines. 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 which supports the removal of this missing information. There was no evidence of an impact on the safety and reactogenicity profiles for each vaccine when coadministered versus standalone. Please refer to Section 17.2 . The CCDS 2.0 states that Kostaive may be administered concomitantly with influenza vaccine.	
<u>Population in Need of Further Characterisation:</u> 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.	

CCDS = company core data sheet; COVID-19 = coronavirus disease 2019

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

Missing Information:	Use in Patients with Autoimmune or Inflammatory Disorders
<u>Evidence Source:</u> Limited information is available on the safety of the vaccine in patients with autoimmune or inflammatory disorders.	

Missing Information:	Use in Patients with Autoimmune or Inflammatory Disorders
<u>Population in Need of Further Characterisation:</u> Adverse events in individuals with a medical history significant for autoimmune or inflammatory disorders will be monitored on an aggregate level. A postauthorisation safety study to collect additional safety data in immunocompromised individuals, individuals with autoimmune disease and patients who are on immunosuppressive therapies is planned.	

Table 16-12: Missing Information: Long-term Safety Data

Missing Information:	Long-term Safety Data
<u>Evidence Source:</u> 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.	
<u>Population in Need of Further Characterisation:</u> Not applicable	

Table 16-13: 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)
<u>Evidence Source:</u> 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.	
<u>Population in Need of Further Characterisation:</u> 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

Kostaive is composed of a sa-mRNA encoding for the spike protein of SARS-CoV-2 and encapsulated in lipid nanoparticles. It has undergone an extensive clinical development programme, and the data have demonstrated efficacy and effectiveness in the individuals 18 years of age and older. On that basis, Kostaive has been internationally approved for the indication of preventing COVID-19 caused by SARS-CoV-2 as the benefit has been demonstrated in this population.

As of 16 November 2025, over 778,941,000 cases of COVID-19 have been confirmed worldwide and over 7 million people have died ([WHO, 2025a](#)). 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 Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) advises manufacturers that monovalent JN.1 or KP.2 vaccines remain appropriate vaccine antigens; monovalent LP.8.1 is a suitable alternative vaccine antigen (15 May 2025) ([WHO, 2025b](#)).

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 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 that against severe COVID-19 was 94.3% (95% CI: 57.4%, 99.2%). For approximately 8.6% of isolated SARS-CoV-2 variants, sequencing could not 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 the 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 SRR difference.

17.2 Newly Identified Information on Efficacy and Effectiveness

The following information on the efficacy and effectiveness of Kostaive has become available during the reporting period:

A test-negative case-control study evaluating absolute effectiveness of Kostaive is currently being conducted at 10 medical institutions across Japan; this is an investigator-initiated study conducted by Nagasaki University.

Eligible participants were adults aged ≥ 60 years with ≥ 1 acute respiratory symptom who were tested for SARS-CoV-2. Cases were test-positive patients and controls were test-negative. Influenza-positive individuals were excluded to reduce confounding by vaccination behaviour. Absolute vaccine effectiveness of mRNA vaccines encoding for the JN.1 variant, including conventional mRNA vaccines (Comirnaty and Spikevax) as well as Kostaive, was estimated relative to individuals who had not been vaccinated (either never vaccinated or vaccinated only with pre-JN.1 vaccines). Multivariable logistic regression was used, adjusting for age group, sex, underlying medical conditions, calendar month of testing, prior SARS-CoV-2 infection and nursing-home residence. Separate estimates were generated for pooled JN.1-adapted mRNA vaccines and for Kostaive alone.

The median age of participants was 75 years; 58.2% were female; 39.1% had ≥ 1 underlying medical condition and 17.7% were nursing-home residents. The pooled effectiveness of conventional mRNA vaccines was 46.1% (95% CI: 7.3–68.7) at ≥ 7 days, 55.1%

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(95% CI: 0.9-79.6) at 7 to 60 days and 37.0% (95% CI: -22.7-67.7) at > 60 days after vaccination. Absolute vaccine effectiveness of Kostaive was 69.9% (95% CI: 20.0-88.6) at ≥ 7 days after vaccination, with wide CIs due to the small sample size.

In conclusion, JN.1-adapted mRNA COVID-19 vaccines, including Kostaive, showed evidence of protection against symptomatic infection among adults aged ≥ 60 years in Japan. While acknowledging the limitations of this interim analysis with a small sample size, these results are supportive of real-world effectiveness of Kostaive.

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

18.1.1 Medical Need

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 380,000 to 540,000 COVID-related hospitalisations from 01 October 2024 to 20 September 2025 and 44,000 to 63,000 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.

18.1.2 Important Alternative Therapies

As of 25 November 2025, 5 COVID-19 vaccines are authorised for COVID-19 prevention in the EU, including Comirnaty (BioNTech), Nuvaxovid (Novavax), Spikevax (Moderna), Bimervax (HIPRA Human Health S.L.U) and Kostaive (Seqirus Netherlands B.V.) (EMA, 2025). Updated versions of these vaccines are - manufactured and authorised to provide protection against current virus variants, following guidance from the World Health Organization and Regulatory Agencies including EMA.

The treatment of COVID-19 depends upon the stage and severity of disease as well as upon the individual risks of developing severe COVID-19, such as age and comorbidities. Patients with mild illness usually recover on an outpatient basis with supportive care and isolation to prevent disease transmission. Symptomatic treatment with antipyretics and analgesics (ie, paracetamol and nonsteroidal anti-inflammatory drugs) are also recommended. Moderate illness requires monitoring for progression of symptoms and may require hospitalisation. Patients with severe COVID-19 symptoms may require supportive care and oxygen supplementation via noninvasive or mechanical ventilation. Treatment of COVID-19 in individuals with a moderate-to-high risk of hospitalisation may require other treatments including, eg, antivirals and corticosteroids (WHO, 2023a; WHO, 2023b).

As of November 2025, nonvaccine medicines authorised for COVID-19 treatment in the EU include monoclonal antibodies targeting the spike protein of the SARS-CoV-2 (Kavigale [sipavibart], Regkirona [regdanvimab], Ronapreve [casirivimab / imdevimab], RoActemra [tocilizumab] and Xevudy [sotrovimab]) as well as antivirals (Paxlovid [nirmatrelvir] and Veklury [remdesivir]) and others (Gohibic [vilobelimab], a monoclonal antibody targeting the C5a protein) (EMA, 2025).

18.2 Benefit-Risk Analysis Evaluation

18.2.1 Benefit-Risk Assessment Methodology

The MAH employs a predominantly qualitative approach based on the predetermined 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' ([CBER, 2023](#)), 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 'Developmentand-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 vaccine 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. The 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 higher and more durable immune responses across multiple variants than 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 than 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 authorised 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. 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

Kostaive has been marketed since October 2024 and is approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

When used for the prevention of COVID 19, Kostaive has demonstrated important benefits to vaccinees. The important risk(s) associated with the use of the product are judged to be outweighed by its benefits when used in accordance with the product labelling.

The totality of efficacy, immunogenicity and safety data from the clinical development programme 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 missing information topics 'Interaction with other vaccines' and 'Long-term safety data' were removed from the EU-RMP, version 1.2, dated 21 October 2025. The EMA endorsed the removal of these 2 missing information topics, and the CHMP issued a Positive Opinion on 27 November 2025. As indicated by the EMA, the approved EU-RMP was updated from version 1.2 to version 2.0 on 05 December 2025 after the DLP of this report. No other changes were made.

No changes to the RMP are recommended. The safety profile of Kostaive is considered adequately reflected in the current RSI and no safety amendments are warranted at present.