Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Kostaive powder for dispersion for injection
COVID-19 sa-mRNA Vaccine

zapomeran

PL 47991/0019

Seqirus UK Limited

LAY SUMMARY

Kostaive powder for dispersion for injection COVID-19 sa-mRNA Vaccine zapomeran

This is a summary of the Public Assessment Report (PAR) for Kostaive powder for dispersion for injection/ COVID-19 sa-mRNA Vaccine. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Kostaive in this lay summary for ease of reading.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number EMEA/H/C/006207/0000. The procedure followed route B.

This application were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

This application is full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

For practical information about using Kostaive, individuals should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Kostaive and what is it used for?
Kostaive is a vaccine that helps protect adults aged 18 years and older against COVID-19 caused by SARS-CoV-2.

How does Kostaive work?
Kostaive contains the active substance zapomeran. Kostaive helps the body get ready to fight the virus that causes COVID-19. It contains a special set of instructions (called sa-mRNA) that tells the cells in the body how to make copies of the SARS-CoV-2 virus protein called the “spike protein”.

Once the individual gets the vaccine, their body temporarily makes the spike protein. It does not cause COVID-19, but teaches the individual’s immune system to recognise it as something that does not belong in the body.

The individual’s immune system then builds defences like antibodies and white blood cells to fight off anything that looks like that spike protein in the future. So, if the individual is exposed to the real virus later on, their body will already know how to fight it off.

The use of this vaccine should be in accordance with official recommendations.

How is Kostaive used?
The pharmaceutical form of this medicine is a powder for dispersion for injection.

Kostaive is given as a single injection of 0.5 mL by a health professional, after reconstitution, into a muscle of the upper arm.

If the individual was previously vaccinated with a COVID-19 vaccine, they should receive a dose of Kostaive at least 5 months after the most recent dose.

For further information on how Kostaive is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The individual should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Kostaive have been shown in studies?
Studies showed that Kostaive is effective at triggering the production of antibodies against SARS-CoV-2 and protecting people against COVID-19.

A first study measured the efficacy of Kostaive in over 15,000 adults with no known history of COVID-19 who were given either the vaccine or placebo (a dummy injection); people received 2 doses given 4 weeks apart. In the study, between 36 and 92 days after the first dose, the risk of experiencing symptomatic COVID-19 was 56.7% lower in people who had received the vaccine (200 out of 7,762 people had COVID-19 symptoms) than in people who had received placebo (440 out of 7,696 had COVID-19 symptoms). This means that the vaccine showed a 56.7% efficacy in the study.

The study also looked at the reduction in the number of severe cases of COVID-19: 2 out of 7,762 vaccinated people had severe disease, compared with 41 out of 7,696 people who had received placebo. This means that vaccine's efficacy against severe COVID-19 was 95.3%.

The vaccine was also compared with an authorised mRNA COVID-19 vaccine (Comirnaty) when given as a booster to people who had previously been vaccinated with an mRNA vaccine (Spikevax or Comirnaty). The results showed that the level of antibodies against the spike protein in people who received a booster dose of Kostaive was at least as high as that seen in people who received a booster dose of Comirnaty.

What are the possible side effects of Kostaive?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If an individual gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Individuals can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, individuals can help provide more information on the safety of this medicine.

Why was Kostaive approved?
Kostaive has been shown to provide protection against COVID-19 when used as primary vaccination in people with no known history of COVID-19 and to trigger the production of antibodies against COVID-19 when used as a booster after vaccination with another mRNA

vaccine. Although Kostaive targets the original strain of SARS-CoV-2, it provided relevant protection against the strain circulating at the time of the main study. In terms of safety, most side effects with Kostaive are mild and in line with those seen with mRNA vaccines.

The MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

What measures are being taken to ensure the safe and effective use of Kostaive?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Kostaive. The RMP details the important risks of Kostaive, how these risks can be minimised, any uncertainties about Kostaive (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Kostaive:

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Myocarditis and pericarditis • Thromboembolic events
Missing information	• Use in pregnancy and while breastfeeding • Use in immunocompromised patients • Use in patients with autoimmune or inflammatory disorders • Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and individuals. Side effects of Kostaive are continuously monitored and reviewed including all reports of suspected side-effects from individuals, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Kostaive
A marketing authorisation was granted in the United Kingdom on 02 February 2026.

The full PAR for Kostaive follows this summary.

This summary was last updated in March 2026.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application Kostaive powder for dispersion for injection/COVID-19 sa-mRNA Vaccine (PL 47991/0019) could be approved. This product will be referred to as Kostaive in this scientific discussion for ease of reading.

The product is approved for the following indications:

- for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

  The use of this vaccine should be in accordance with official recommendations.

Kostaive is composed of a self-amplifying mRNA (sa-mRNA) encoding the spike protein of SARS-CoV-2 (zapomeran, the active substance), encapsulated in lipid nanoparticles. Zapomeran is a single-stranded, 5'-capped sa-mRNA replicon, produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding a replicase and the spike glycoprotein of the ancestral strain of SARS-CoV-2 with D614G mutation.

The sa-mRNA is designed to produce extra copies of mRNA within the host cells after intramuscular injection, to achieve enhanced expression of the spike protein antigen. This gives rise to neutralising antibody and cellular immune responses to the spike antigen, which contributes to protection against COVID-19. The mRNA self-amplification process is transient and does not generate infectious particles.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number EMEA/H/C/006207/0000. The procedure followed route B.

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the reference regulator, please refer to the public assessment report on the relevant competent authority’s website.

This application were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-102006-PIP01-25).

At the time of the submission of the application the PIP was completed.

The licensing authority issued an opinion on compliance of the PIP (MHRA-102006-PIP01-25-C).

Advice was sought from the Commission of Human Medicines (CHM) on 25 September 2025, following provision of additional data the marketing authorisation was considered approvable.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 02 January 2026.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for this application are satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

The MHRA has reviewed and largely endorses the EMA's assessment and main conclusions of the non-clinical data provided for Kostaive (zapomeran, encapsulated in lipid nanoparticles). However, in the MHRA's targeted assessment a few points were raised and addressed by the applicant. A summary of the EMA's and the MHRA's additional assessment and conclusions are provided below.

The vaccine drug product, Kostaive, is also referred to as ARCT-154 in the EMA assessment report, and will be similarly referred to in this report

Pharmacology

The applicant characterised ARCT-154 in primary pharmacology studies but used the surrogate first generation vaccine candidate ARCT-021 in some studies which is considered acceptable. ARCT-021 encodes the SARS-CoV-2 spike protein in its native conformation (Wuhan strain) whereas ARCT-154 encodes a prefusion-stabilised spike protein, and the D614G (aspartic acid to glycine mutation in the SARS-CoV-2 spike protein) mutation which arose in the index spike very early on in the pandemic. Both vaccine candidates are formulated in the same lipid nanoparticle (LNP) and encompass the same mRNA components consisting of a 5' cap, a 5' untranslated region (UTR), the reading frame of replicase, the transgene UTR, the reading frame of the transgene encoding for the primary structure of the full-length SARS-CoV-2 spike glycoprotein, the 3′ UTR, and the poly A tail. The MHRA agrees with the EMA that the bridging study of liquid ARCT-021 to lyophilised ARCT-154 was acceptable.

Two immunogenicity studies were conducted with ARCT-154 in the mouse and non-human primate (NHP) and ARCT-021 was characterised in immunogenicity and challenge studies in the mouse and NHP models to evaluate potency and efficacy. In the ARC21-032 study, female mice were administered a single 2 µg IM dose of ARCT-154 or ARCT-021 and immunogenicity evaluated. Overall, ARCT-154 elicited anti-spike glycoprotein IgG titres and neutralising antibody (nAb) titres to the spike glycoprotein Receptor-binding domain of

the spike protein (RBD) against the ancestral virus strain and cross-neutralised Alpha, Beta, and Gamma variants for one month. At 28 days post-dose, mean RBD binding inhibition (nAb) of ARCT-154 showed between 84% and 76% binding against ancestral strain and Alpha variant, and 57% against Beta and Gamma variants. By Day 42 this increased to 95% against ancestral strain, 88% against Alpha, and to between 78% and 80%, respectively, against Gamma and Beta variants. Overall, ARCT-154 elicited higher anti-spike IgG titres and had higher overall RBD inhibition, with ARCT-21 achieving up to 53% inhibition against the ancestral strain. In study ARC21-036, NHPs were administered two 7.5 µg doses of ARC-154 or ARCT-021 28 days apart and immunogenicity measured by antibody and cell-mediated immune responses. Anti-spike IgG titres and RBD inhibition overall increased from the first dose to after the second dose, measured against the ancestral strain and Alpha, Delta, Gamma, Beta variants with highest average binding inhibition 28 days post second dose, measuring against the ancestral strain at 99% and Alpha variant at 98%. At the time of testing, Omicron was emerging as a variant therefore Day 43 sera were tested against BA.1 variant along with ancestral strain and Beta variants for nAb; overall a lower nAb titre was observed for Omicron BA.1 compared to ancestral strain and Beta variant. ARCT-154 cell-mediated immune responses in NHPs measured by IFN-γ secretion on Days 1 and 29 were regarded as equivalent to ARCT-021. Overall, immunogenicity (IgG titres, nAb and IFN-γ secretion) increased in NHPs after administration of two doses of ARCT-154 compared to one dose, the immunogenicity response was greater after ARCT-154 administration than ARCT-021 and highest ARCT-154 efficacy was observed against the ancestral strain and Alpha variant.

At the time of EMA (and MHRA) assessment, the prevailing variant landscape in the UK consisted of variants derived from the SARS-CoV-2 Omicron lineage, and lower neutralising antibody was measured against Omicron BA.1 compared to other variants tested; this was raised in the initial EMA assessment report but the point was not pursued. Also, at the time of the MHRA assessment, the most recent WHO COVID-19 dashboard, (dated 20 July to 17 August 2025) had published the most prevalent circulating variant as being XFG, accounting for 63% of all submitted sequences, followed by NB.1.8.1 accounting for 23%. Further, the UKHSA had COVID-19 surveillance data published between 4 August 2025 and 17 August 2025, of which the most prevalent variant was XFG at 38.33% followed by 32.78% classified as XFG.3, 12.22% NB.1.8.1, 5.56% LP.8.1, 5.0% XFG.3.1.

The Company has an established surveillance program to monitor the reactivity of ARCT-154 against circulating SARS-CoV-2 variants, including those relevant to the UK. The vaccine composition is reviewed regularly and will be updated in alignment with WHO and EMA strain selection recommendations. In the most recent season, sera from JN.1 sa-mRNA (Kostaive)-immunised animals and human clinical trial participants were evaluated for neutralisation activity against a representative panel of both historical and currently circulating variants. These included BA.2 Index (B.1), XBB.1.5, BA.4/5, JN.1, XEC, MC.1, LF.7.2.1, KP.3.1.1, LP.8.1, XEC.4, LP.8.1.1, LF.7, MC.10.1, XFG, KP.3, NB.1.8.1, NP.1, LB.1.3.1, and NY.7. Testing was performed using microneutralisation and ELISA assays; cell-mediated immunity was not included in the current program. The applicant has committed to continue seasonal surveillance with results reviewed internally, shared with WHO TAG-CO-VAC, and included in regulatory submissions; this ensuring ongoing monitoring of vaccine activity against both historical and newly emerging variants worldwide, including those circulating in the UK. As a post-authorisation measure, the applicant is committed to submit the data and study reports for the *in vivo* studies that are conducted to evaluate neutralisation activity against currently circulating variants in the UK.

Further characterisation studies were conducted with ARCT-021 and ARM3013 (conventional non-self-amplifying mRNA), both drug products (DPs) were formulated with the same LNP lipid excipients. Immunogenicity of ARCT-021 was compared to ARM3013 in C5BL/6 and BALB/c mice after administering either one or two (30 days apart) doses of either 0.2, 2 or 10 µg IM. Overall, the applicant noted that ARCT-021 generated a higher quality of immune responses compared to the conventional mRNA ARM3013. After 1 dose, a higher proportion of B cells were measured in both ARCT-021 and ARM3013 groups in the spleen. After ARCT-021 administration, a higher $CD8^+$ T cell effector memory population was present, higher T helper 1 (Th1) cell response rather than T helper 2 (Th2) cell response, and increased prevalence of TNF-α and IFN-γ. On Day 7, T cells responses measured by interferon gamma (IFN-γ) ELISpot incubating with four different spike glycoprotein peptide libraries that span the entire spike glycoprotein sequence and were increased in ARCT-021 compared to ARM3013. After two doses, these parameters increased for ARCT-021. Humoral responses were also measured after two doses and saw a 50-fold higher potency of anti-spike IgG from ARCT-021 compared to 3013, and considerably higher presence of SARS-CoV-2 nAbs. The EMA noted that the skewing towards Th1 responses was also observed clinically and responses seen were comparable to vaccines known/developed to induce Th1-skewed and innate responses. The EMA discussed that downregulation of inflammation genes seen in study GSY02 are likely not related to potential inhibition of the innate immune system and based on this an increased risk for vaccine associated enhanced respiratory disease (VAERD) with sa-mRNA is not expected, and the MHRA agrees.

In NHPs administered 0, 5 or 20 µg ARCT-021 on Days 0, 30, and 150 the highest titres of nAb were seen in the 20 µg group. However, elevated levels of IFN-γ from activated T cells were consistently greater in the low dose group. The EMA discussed that this finding was present in a study of another vaccine and comparable to what was seen in ARCT-021 Phase 1/2 clinical studies that T cell responses were dominated by Th1 response; therefore, the observations in monkeys could be a result of interindividual variability and not necessarily dose-related. The MHRA endorses the EMA conclusion on this.

Viral challenge studies were conducted in transgenic K18-hACE2 mice and NHPs. After mice were administered a single dose of 2 or 10 µg ARCT-021 and subsequently challenged 30 days after, mice in both groups survived and were protected with minimal pathology and 70% nAb titres. A subset of mice were included that had B and/or T cells depleted and saw depletion of T cells or both B and T cells resulted in infection, whereas mice depleted of just B cells were completely protected from lung and brain infection and T cell depleted mice did not have lung and brain protection. NHPs were administered a single 20 or 40 µg ARCT-021 dose or two 5 or 20 µg ARCT-021 doses on 28 days apart and challenged with SARS-CoV-2 viral strain/isolate USA-WA/2020, intratracheally and intranasally on Day 42 with a target dose of ~1 x 10^6 $TCID_{50}$. Increased levels of IL-2+% CD4 and CD8 responses and IL-13+% CD8 responses were noted from serum and reduced viral load noted in nasal swabs, bronchoalveolar lavages and oropharyngeal swabs within 3 days. Anti-spike IgG titres increased after the second dose in the two-dose regimen and to a much higher degree than the single dose 20 and 40 µg groups and increased further post-challenge. The EMA noted that naïve NHPs develop slight symptoms of SARS-CoV-2 but provided meaningful immunogenicity data. It was also noted that although IL-13 is a mediator of allergic inflammation in airways, the increase in IL-13 was present in the 20 µg group of the two dose regimen which is not clinically relevant (5 µg) and at this dose viral titres were reduced and vaccine associated allergic responses were absent therefore this finding was not of concern and the MHRA agrees.

Pharmacokinetics

Pharmacokinetic studies were conducted with ARCT-021 and a self-amplifying mRNA encoding firefly-luciferase protein formulated in the same LNP as ARCT-021 and ARCT-154. Both vaccines contain the self-replicating RNA component encapsulated within the same LNP containing the novel ionisable lipid, ATX-126, and DPSC, cholesterol, and PEG2000-DMG,

Following the MHRA assessment and request, the applicant has presented a comparison of the properties of the luciferase sa-mRNA drug product compared to the test articles used in studies ARC20-121 and in other pharmacokinetic (PK) studies; these attributes are considered comparable.

The applicant submitted a further non-GLP single-dose ARCT-154 biodistribution study (ARC24-052) conducted in mice on a limited panel of tissues to further characterise the duration of the self-amplification process after IM administration. Mice were administered 50 µL PBS or 5 or 25 µg of ARCT-154 and tissues were collected on Day 1 (15 minutes, 2 hours, 8 hours, 24 hours) and Day 3, 5, 8, 15, 30 and 60. RNA species were quantified using a QuantiGene single plex gene expression assay using three probes specific for genomic mRNA, negative strand RNA and a probe that binds the spike sequence in both genomic and subgenomic mRNAs. Meso Scale Discovery immunoassays were used to quantify spike glycoprotein and nsP1 replicase protein concentrations.

Genomic mRNA was measured in plasma and all tissues and was predominantly at the site of injection, spleen and popliteal lymph node. Genomic mRNA was measured at the earliest timepoint (15 minutes) and declined steadily and cleared in the plasma by Day 8, lung by Day 15 and the contralateral muscle by Day 30. Genomic mRNA was measured at Day 60 at the site of injection however this was only measured in 1 out of 10 mice at 1.29 pg/mL that received a 25 µg dose.

Negative-strand RNA was measured at low concentrations in the site of administration only at Day 5 (1.52 pg/mL), in the spleen at 8 and 24 hours, and in the popliteal lymph node at 72 hours. The applicant has stated/claimed that the negative strand RNA plays a role in the self-amplification process therefore the low concentrations are reflective of the transient role it plays in this process; this is accepted . The PK study in the initial submission conducted with firefly luciferase sa-mRNA encapsulated in LNP in muscle saw the peak concentration of negative strand RNA at Day 8 with an approximate 160-fold decrease measured by Day 30 that supports the self-limiting nature of the self-amplification process.

Subgenomic mRNA was measured in plasma and all tissues at the earliest timepoint and followed a similar tissue distribution and clearance pattern to genomic mRNA except in the injected muscle. Subgenomic mRNA cleared from plasma, lung and liver by Day 8, contralateral muscle, spleen and inguinal lymph nodes by Day 30 and the injected muscle and popliteal lymph nodes by Day 60.

Non-structural protein 1 (nsP1) was measured in the injected muscle (24 hours to Day 5), inguinal lymph node (8 hours) and spleen (2, 8 hours and in one animal on Day 15). The applicant note the transient nature of the enzyme with shorter duration of expression and limited distribution that correlates to the negative strand and subgenomic concentrations in the tissues.

Spike protein expression was also measured and was first detected in the injected muscle at 2 hours post dose reaching its C_{max} at Day 5 that corresponded to the peak concentration of negative and subgenomic RNAs and nsP1. Spike protein was also measured in the spleen and lymph nodes but cleared from the muscle, spleen, popliteal lymph node and inguinal lymph node by Day 15, 5, 30, and 60, respectively.

Overall, study ARC24-052 further supported the self-limitation nature of the self-amplification process of ARCT-154 and provided more information regarding the biodistribution and persistence of ARCT-154.

In mice, replicon sa-mRNA and conventional mRNA encoding firefly luciferase encapsulated in the same LNPs to ARCT-154 and ARCT-021 were detected in the muscle with higher concentrations of sa-mRNA measured compared to conventional mRNA. Peak concentrations were measured at 2 hours post-dose for both mRNAs and overall sa-mRNA had 5.47-fold and 2.85-fold higher exposure in the muscle for the 10 and 50 µg groups compared to conventional mRNA measured by AUC. Concentrations decreased on Day 8; negligible amounts of mRNA were measured on Day 15 for conventional mRNA or on day 30 for sa-mRNA. Lower concentrations of mRNA were exhibited in the liver: sa-mRNA had 3.12- and 1.74-fold higher exposure than conventional mRNA for the 10 and 50 µg groups, respectively. In the 10 µg group, sa-mRNA and conventional mRNA concentrations peaked at 2 hours with none detected at 72 hours or Day 8 and beyond.

The distribution of the mRNA, synthesised spike protein and ATX-126 lipid in ARCT-021 were measured in mice. mRNA and ATX-126 were measured in plasma at 2 hours post-dose and cleared by Day 8. mRNA was detected in all tissues at 2 hours but cleared by Day 31 apart from in the muscle and lymph nodes, a dose-related increase was noted. Spike protein was measured in muscle, lymph nodes and at low concentrations in the lung and ovaries; no correlation between mRNA concentration and spike protein concentration was noted. ATX-126 was present in all tissues except brain and a dose-related increase was noted with the muscle and liver, and by Day 31 3% and 4% of the administered dose was present in these tissues, respectively. ATX-126 was also found in ovaries of rabbits in the repeat-dose toxicity studies at the end of the reversibility phase, this was raised by the RR as a potential concern. As the mouse study was conducted with very high doses (25 and 50 µg) and not according to GLP, the repeat-dose toxicity rabbit study was used to assess correlative safety findings and establish the safety margin for the 20 µg mRNA dose of 27-fold. The applicant noted that once in systemic circulation, LNP/mRNAs are taken up via Apo-E low density lipoprotein receptor (LDLR)-mediated endocytosis, LDLR are also expressed in ovaries and testes that is involved in lipoprotein metabolism and steroid hormones, therefore some localisation to these organs might be expected. No fertility parameters were affected due to ARCT-021 administration in the EFD study which is encouraging. The EMA accepted that establishing the safety margin of 27-fold from administration of 420 µg ATX-126 to rabbits is accepted based on further conclusions relating to potential toxicities as compared to SM-102 (major lipid component of Spikevax).

Measurement of mRNA in plasma and different tissues in the studies did not distinguish whether measured mRNA was intact, functional or were smaller fragments. Firefly luciferase sa-mRNA encapsulated in LNP was administered to mice and the mRNA species were measured in muscle to address this. The pharmacokinetics of genomic and subgenomic mRNA in the muscle were similar until 72 hours post-dose where maximum concentrations occurred, however after this genomic mRNA concentration decreased 30-fold whilst subgenomic mRNA did not decrease until Day 8. Maximum concentration was achieved by

Day 8 for negative strand mRNA, however dropped substantially ~160-fold by Day 30 that indicate the self-amplification process is self-limiting and reassuring given that the negative strand is responsible for this process.

From the 4-week repeat-dose toxicity rabbit study, mRNA was measured in the spleen on Day 31 and ATX-126 was detected in plasma and mesenteric lymph node on Day 31 but in liver, spleen, injection sites, and ovaries on both Day 31 and 57. In the reproductive and developmental study, mRNA was detected in low concentrations on gestation day (GD) 29 in maternal plasma and in 1/20 fetal plasma samples and ATX-126 was present in maternal plasma and placenta samples. No mRNA or ATX-126 was measured in fetal tissues indicating a lack of fetal transfer, however the EMA noted that the LLOQ for ATX-126 was 250 ng/g in tissues that was close to levels found in the placenta; therefore, transfer of ATX-126 to fetuses cannot be ruled out.

ATX-126 metabolism was explored *in vitro* in human, mouse, rat, rabbit, and monkey and in vivo in mice: metabolism *in vitro* was by oxidation, dehydrogenation or N-demethylation whereas for *in vivo* metabolites were ester hydrolysed.

Mice and rabbits were not dosed on a mg/kg basis and the applicant notes that due to calculation of translation of systemic exposure of RNA therapeutics from animal to man is typically performed on a mg/kg basis, the tissue distribution and clearance of mRNA and ATX-126 may not be representative of human organ exposure. For ATX-126, the applicant estimated a 14,000-fold margin of ATX-126 compared with the mouse and for rabbits an approximate 85-fold margin by correcting on a mg/kg basis. Based on these calculations, the annual dosing regimen, lack of correlative adverse histopathology and effects on fertility, ARCT-154 is not expected to persist and cause adverse effects clinically and the EMA assessment on PK is endorsed.

Toxicology

Toxicology findings from the EMA report and findings from the MHRA are summarised below.

The toxicology programme used ARCT-154 in a repeat-dose toxicity study in rabbits (Good Laboratory Practice (GLP) compliant study) and cross referred to ARCT-021 used in two repeat-dose toxicity studies in rabbits (GLP compliant studies) and a reproductive and developmental study also conducted in rabbits. ARCT-154 and ARCT-021 were not characterised in genotoxicity studies, however the ionisable lipid component of the LNP, ATX-126, was characterised for bacterial mutagenic potential in an *in silico* study. The applicant cross-referred to studies conducted with ARCT-810, a product that shares lipid components with ARCT-154 (and is in clinical development) that encodes the human ornithine transcarbamylase enzyme.

For repeat-dose toxicity analyses, two studies were submitted that were conducted with ARCT-021 whereby the 0 (PBS), 20 or 40 µg ARCT-021 was administered IM to rabbits bi-weekly for two weeks with two-week recovery (2 doses) or four weeks with four-week recovery (3 doses). Findings included transient fever and similar injection site erythema and oedema that were comparable in the two studies. Cytokine levels were elevated for Interleukin-6 (IL-6), Interferon-gamma-induced protein 10 kDa (IP-10) and Monocyte Chemoattractant Protein-1 (MCP-1) that fully resolved in the 2-week study but IL-6 and MCP-1 were sustained in the 4-week study on Day 57, that was 28 days after the last dose. C-reactive protein (CRP) was found to be elevated in the 2-week study up to 407 times but

resolved. Haematology parameters were increased including monocytes, fibrinogen, platelets, red cell parameters and decreased albumin and reticulocyte counts; these had partially or fully reversed. ATX-126 was measured for biodistribution in the 4-week study and was present in liver and spleen in high concentrations (2-6 µg/g) on Day 57; the EMA considered, that due to the long half-life of ATX-126 seen in mice, the presence of ATX-126 in rabbits is to be expected; the MHRA agrees. SARS-CoV-2 spike-specific IgG were detected in animals administered ARCT-021 across both studies and neutralising antibodies developed in all rabbits in the 4-week study but not the 2-week study.

In the repeat-dose toxicity study conducted with ARCT-154, rabbits were administered 16.75, 25.1 or 33.55 µg ARCT-154 IM bi-weekly for four weeks (3 doses). Findings were noted similar to that of ARCT-021 however levels of IL-6 were minimal and there were no effects on CRP; injection site histopathology were reduced. Spleen weights were increased with correlative increased cellularity (lymphocytes) that were present upon assessment of reversibility. The company noted that ARCT-154 appeared less reactogenic than ARCT-021 and deemed that this was due to the ARCT-021 lots used in the repeat-dose toxicity studies to be from a research production run for the mRNA and an early engineering campaign therefore there was higher levels of double-stranded mRNA (dsRNA) present; dsRNA is known to activate the innate immune response therefore the company factored this being the cause of increased reactogenicity. The no observed adverse effect level (NOAEL) was set to the highest dose for all three repeat-dose toxicity studies; this was accepted by the EMA and is endorsed by the MHRA.

For genotoxicity, an *in silico* mutagenicity assessment was conducted on the novel lipid cationic component, ATX-126, that returned a negative result. A genotoxicity package conducted with ARCT-810 was included in the dossier as ARCT-810 contains a cationic lipid component, ATX-95, that is similar to ATX-126. *In vitro* assays were negative however a very low increase in micronucleated cells were noted in males dosed with ATX-95 with and without mRNA. The overall response was deemed negative due to lack of dose-response and numbers within 95% confidence interval for the vehicle. ATX-126 is a novel lipid, and although similar in structure to ATX-95 and not expected to interact with the nucleus, a battery of genotoxicity tests would be expected to characterise the genotoxicity of the actual lipid. In response to the MHRA request, the applicant provided physicochemical and composition information for the drug product, ARCT-810, used in genotoxicity studies compared to ARCT-021 and ARCT-154.

The biodistribution study conducted in mice with ARCT-021 revealed that ATX-126 cleared by Day 8 in plasma and was present at 3% and 4%, in the muscle and liver, respectively, by Day 31. Further, in the four-week rabbit repeat-dose toxicity study ATX-126 was detected in plasma on Day 31 and in the liver, spleen, injection sites, and ovaries on both Day 31 and 57. It was noted that the doses used in the mouse study were very high (exposure margin of approximately 14,000-fold) and the exposure margin in the rabbit study was 85-fold therefore persistence in these tissues to this extent would not be clinically relevant. Exposure to ATX-126 is not expected to this extent and so where there is short term exposure, genotoxic risk is reduced and the nature of use with the vaccine is expected to result in short term exposure to the lipids. Together with the proposed single administration of ARCT-154, similarity in chemical structures and LNP physicochemical properties, the use of the battery of genotoxicity studies with ARCT-810 lots it is accepted to conclude that the risk of ARCT-154 genotoxicity is low and that a battery of genotoxicity tests with ARCT-154 would not result in any meaningful clarification of a risk with use of the product.

ARCT-021 was used to evaluate reproductive and developmental toxicity that encompassed pre-mating through to delivery. Five doses of 10 or 20 µg ARCT-021 was administered IM to rabbits biweekly and there were no apparent effect on fertility or mating parameters. However, there was body weight loss and reduced body weight gain across both groups of does that was considered adverse in the 20 µg group due to overall weight loss over the gestation period, this was also attributed to reduced food consumption on gestation Days 28 and 29 and overall inflammatory reaction to the vaccine owed to increased levels of IL-6, MCP-1 and IP-10 (also observed in repeat-dose toxicity studies). The NOAEL for maternal toxicity was set to 10 µg; the MHRA agrees with the EMA that this is supported. There were no findings in fetuses or kits that were attributed to ARCT-021 administration due to either being sporadic, comparable to control and/or historical data or not being dose-dependent. The NOAEL for the fetuses at caesarean and kits for postnatal development were set to 20 µg and the MHRA agrees with the EMA conclusion that this is acceptable.

It is accepted that an environmental risk assessment (ERA) is not required for a vaccine and the ERA statement to support this is acceptable.-However, there is concern of risk of recombination or complementation of deleted genes for recombination with wild-type VEEV(Venezuelan equine encephalitis virus -like) viruses due to presence of replicase proteins from VEEV in the mRNA construct. This point was raised by the EMA and the applicant concluded this theoretical risk as being low due to the mechanism superinfection exclusion (simultaneous infection by two different alphaviruses in the same cell is said to be extremely unlikely), sequestration of sa-mRNA to the cytoplasm prevents recombination with a wild-type virus and low risk due to codon optimisation. The applicant also noted that if recombination should occur, the mutations in the replicase coding region would decrease the pathogenicity of VEEV. The response from the applicant to the EMA is deemed as acceptable, and although theoretical concerns may remain, there is no clinical evidence of concern and no evidence in the current dataset thus far, therefore this is considered resolved to an acceptable degree. Sections 4.6 and 5.3 proposed in the SmPC are acceptable.

Further to the MHRA's assessment and request, the applicant has further discussed the plausibility of the replicase component of Kostaive to induce recombination events with other viruses and alphaviruses. The mechanism of superinfection exclusion and supporting literature present compounding evidence of the unlikelihood of the emergence of recombinant viruses. The applicant has noted that codon optimisation has been considered to mitigate the risk of recombination and that the specificity of replicase for cis-acting sequence elements present only in the Kostaive construct further reduces this risk. It was accepted that a theoretical risk for recombination events to occur cannot be completely ruled out, however this risk was considered low, and the applicant has discussed the reasons for this satisfactorily. The applicant's viewpoint on the unlikelihood of replication of concomitantly administered mRNA vaccines due to the specificity of the Kostaive replicase to the Kostaive RNA construct is also accepted.

Regarding replicase immunogenicity, the applicant has claimed that the replicase is likely to remain in the cytoplasm therefore prior alphavirus infection or exposure to other sa-mRNA products are not expected to have an impact on efficacy due to not being a target of the humoral or cell-mediated response. From the data presented in the dossier, there does not appear to be an impact on Kostaive efficacy, therefore the applicant's viewpoint on potential impact of replicase immunogenicity is accepted.

MHRA considered that the non-clinical data submitted for this application are satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

The MHRA has reviewed and endorses the EMA's assessment and main conclusions of the clinical data provided for Kostaive (zapomeran, encapsulated in lipid nanoparticles). However, during the MHRA's assessment in response to a point raised, the applicant provided available data concerning post-marketing experience as it related to the RMP and use in the elderly over 65 years old. A summary of the data provided and the MHRA's conclusions are included in this section of this report. A summary of the EMA's and MHRA's assessment/conclusions are provided below.

Clinical immunogenicity and efficacy
Data were submitted from two pivotal clinical studies of Kostaive (ARCT-154) along with data from other supportive studies. The dose of 5 micrograms used in the pivotal studies was justified based on dose-finding data from ARCT-021, another developmental COVID-19 sa-mRNA vaccine using the same platform.

Study ARCT 154-01
This was a Phase 1/2/3 randomised controlled observer-blind immunogenicity, efficacy and safety study, and the Phase 3b part was the pivotal study to demonstrate efficacy in prevention of COVID-19. The study was conducted in Vietnam during 2021-2022, when delta and omicron BA.2/BA.5 variants were circulating. Recruitment was of a primarily SARS-CoV-2 naïve population, preceding the main delta peak. Participants received primary immunisation with 2 doses 4 weeks apart and were followed up for 12 months.

Seroconversion (more than 4-fold rise) for neutralising antibody (index strain) was measured for 966 participants during phases 1/2/3a. By Day 57 (28 days after second dose), seroconversion (95% confidence intervals (CI)) was achieved for 94.1% (92.1, 95.8) in the vaccine arm compared to 0.4% (0.0, 2.4) in the placebo arm. By Day 92, waning of neutralising and binding antibody levels was observed.

The Phase 3b part of the study was placebo-controlled and powered for efficacy, the cohorts switching between vaccine and placebo at Day 92 for ethical reasons. The primary endpoint for part 3b was first occurrence of confirmed COVID-19 between Days 36 and 92 inclusive.

Part 3c used Vaxzevria as an active comparator and was powered primarily for comparative immunogenicity: geometric mean concentration (GMC) of neutralising antibody. There was no switchover.

The study excluded individuals with a known history of COVID-19 or positive polymerase chain reaction (PCR). Immunosuppressed, immunodeficient or HIV positive individuals, or those on immunosuppressive therapy, were excluded.

Approximately, 100 participants in Phase 3b were positive for anti-nucleocapsid antibodies at baseline (54 participants [0.7%] in ARCT-154 and 49 participants [0.6%] in placebo). In the modified intention-to-treat population of 15,458 participants in part 3b, the vaccine efficacy (VE) (95% CI) was 56.7% (48.8, 63.4). In the 2690 participants ≥ 60 years of age, the VE was 53.5% (26.8, 70.5).

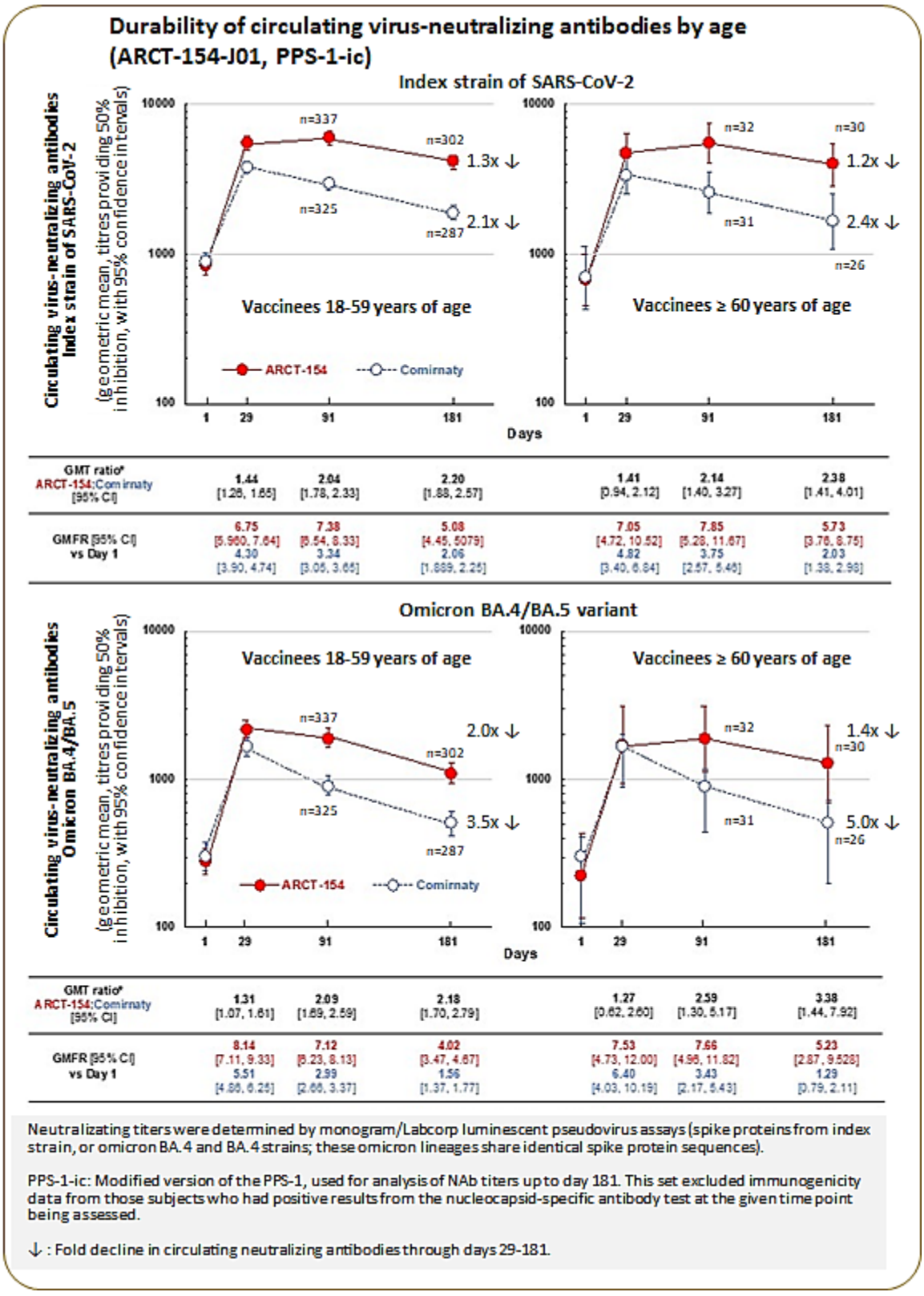
VE against severe COVID-19 was 95.3% (80.5, 98.9) in the overall population and 94.4% (58.2, 99.3) in those ≥ 60 years of age.

In part 3c, neutralising antibody geometric mean concentration of circulating antibodies (GMC) levels were consistently higher for ARCT-154 compared to Vaxzevria throughout the 394-day study period.

Study ARCT 154-J01

This second pivotal study, to support use in heterologous boosting, was a non-inferiority immunobridging study comparing a second boost with ARCT-154 or Comirnaty original in Japanese participants ≥18 years who had previously been primary-immunised with two doses of mRNA COVID-19 vaccine (Comirnaty original or Spikevax original) and boosted with Comirnaty original at least 3 months prior to enrollment. The number of study participants 65 years of age and older in that study was 20, 12 of whom were exposed to ARCT-154.The study ran during 2022 to 2023. Participants were randomised 1:1 (observer blind) to 5 micrograms of ARCT-154 or 30 micrograms of Comirnaty original. The study excluded participants with a history of COVID-19 or confirmed SARS-CoV-2 infection in the last 4 months.

The primary endpoint was GMT and sero-response rate (SRR) for neutralising antibody (nAb) against the index strain (D614G mutation) at Day 29, with non-inferiority margins of 0.67 and 10%, respectively. nAb against BA.4/5 was also measured. Non-inferiority was confirmed for the index strain and superiority of ARCT-154 for the BA.4/5 strain. The following figure summarises durability of nAb by age:



The pattern was similar for more recent variants (delta, BA.2, BA.2.86, XBB.1.5.6) although in smaller datasets. There was a lack of T cell data; however, the applicant plans to generate these data during clinical studies to support variant updated versions.

Clinical safety

In total 16869 participants received at least one dose of ARCT-154, and 15139 participants received two doses. Reactogenicity data were collected in a subset for seven days. One year of safety data is available from Study 154-01.

Solicited adverse events

In Study 154-01, the frequencies of local solicited adverse events (AEs) after the first dose were: injection site pain (38%), injection site tenderness (38%), swelling (3%), and erythema (1%).

The frequencies of systemic solicited AEs were fatigue (30%), headache (24%), myalgia (20%), chills (19%), arthralgia (18%), dizziness (13%), fever (5%), diarrhoea (4%), nausea (3%) and vomiting (1%).

In general, the frequencies of solicited AEs were lower after the second dose. Grade 3 solicited AEs were reported by 3% after the first or second dose. Most solicited AEs occurred within 2 days after vaccination and resolved within 2-4 days. Frequencies were similar to Vaxzevria in phase 3c. As expected, frequencies were lower in the over 65s.

Study 154-J01 allowed a randomised comparison of solicited AEs in the ARCT-154 (n=420) and Comirnaty (n=408) arms. In general, frequencies in both arms were increased compared to Study 154-01, which could be explained partly by the different study settings. Frequencies overall and for Grade 3 were similar for ARCT-154 and Comirnaty, although injection site erythema, injection site swelling, and injection site induration occurred less frequently in the ARCT-154 group compared to in the Comirnaty group.

Study ARCT-021 of an earlier version of the COVID-19 vaccine, but using the same platform, provides evidence of safety in White participants. The frequencies of local and systemic solicited AEs were marginally higher than Phase 3b of Study 154-01.

Unsolicited adverse events

In Study 154-01, there were fewer serious AEs in the ARCT-154 arm compared to placebo: 1.5% versus 2.5% up to Day 92 and 1.2% versus 1.2% from Day 92 to Day 210. In Phase 3b there were 5 versus 16 deaths up to Day 92. These differences were explained by fewer COVID-19 cases. Serious AEs of hypersensitivity occurred in seven participants in the ARCT-154 arm including one case of anaphylaxis. This is reflected in the SmPC. In study 154-J01, the frequencies of serious AEs were 1.2% and 1.0% for ARCT-154 and Comirnaty, respectively. There were no deaths.

Overall, data for the elderly population was limited to approximately 500 participants > 65 years exposed to ARCT-154, of whom 51 participants were > 75 years. From the available data at the time of the EMA assessment, there were no important differences in the safety profile compared to the 18 to 64 years population.

Among the 12 thromboembolic events reported within 28 days of administration, six events were reported after ARCT-154, and six events were reported after controls. However, there was one death 20 days after ARCT-154 with little information, and two further events were deemed related by the sponsor. Thromboembolism is included as an important potential risk in the RMP.

No cases of myocarditis or pericarditis were reported across the clinical development programme; however, a warning is included in the SmPC based on experience with other COVID-19 vaccines.

There were 76 pregnancies in Study 154-01 with 13 cases of spontaneous abortion, anembryonic pregnancy and premature births. In three cases exposure during pregnancy could not be ruled out. The limited data is reflected in the SmPC and RMP.

Supportive study- ARCT-2303-01 study
During the MHRA assessment, the applicant presented the results of a randomised, controlled Phase 3 study (ARCT-2303-01) which assessed the immunogenicity, reactogenicity and safety of a single booster dose of ARCT-2303 (monovalent Omicron XBB.1.5), administered as a standalone vaccine, or concomitantly with a seasonal quadrivalent influenza vaccine (QIV), in participants aged 18 - <65 years and participants 65 years and older. A total of 295 participants aged ≥ 65 years were exposed to Kostaive in this study. Adult participants were included in the study only if they had previously received at least 3 doses of a US-authorised mRNA COVID-19 vaccine.

The frequency and severity of adverse reactions were lower in older adults compared to younger adults. Although more adults aged over 65 years reported solicited adverse reactions after co-administration of Kostaive (ARCT-2303) and the quadrivalent influenza vaccine (QIV), compared to either of these vaccines being given alone, there was no associated increase in the severity of solicited reactions in the context of co-administration. Related unsolicited adverse events were more frequently observed in the younger age group compared to older adults (18-65 years: ≤6.2% cf. >65 years: ≤2.0%) and related medically attended adverse events were infrequent

Post marketing experience
During the time of the MHRA assessment, the applicant provided an analysis of new post-marketing data for Kostaive. This was primarily based on spontaneous reports from Japan, where a total of 18,640 single doses had been sold as of 27 May 2025. Cumulatively, a total of 205 post-marketing cases have been reported concerning the use in elderly individuals. Of these cases, 136 cases were received through spontaneous reporting and 69 originated from a post-authorisation safety study being conducted in Japan. A cumulative total of 15 post-marketing cases concerning Kostaive in immunocompromised individuals were retrieved. Of these, one case originated from spontaneous reporting, while the remaining 14 were derived from a post-authorisation safety study

For both elderly and immuno-compromised individuals, the most frequently reported events were expected local or systemic reactogenic adverse reactions such as pain at the injection site, malaise, headache, myalgia, arthralgia and fever. A review of the cases in these populations did not result in any changes to the current safety profile of Kostaive. In individuals with underlying co-morbidities exposed to Kostaive, fever was reported most frequently. The reported serious adverse events (SAEs) were mostly reflective of age-related comorbidities. Further, a review of cases reported in individuals with underlying co-morbidities did not result in any changes to the current safety profile of Kostaive.

Post-authorisation use in the elderly patient population will continue to be monitored through routine pharmacovigilance activities and addressed in the Periodic Benefit-Risk Evaluation Reports (PBRERs).

Overall, analysis of post-marketing data did not raise any new safety concerns.

Conclusion on clinical aspects

The vaccine efficacy outcome of Study 154-01 reflected that Study ARCT-154 was mis-matched to the delta variant, which was predominant during the study. Despite this, the lower bound 95% CI was 48.8%. The comparison with Vaxzevria provides evidence of similar efficacy to a vaccine which was authorised in the UK to prevent the index strain. Although there are less data in the over 65 year old subgroup, the VE point estimate was similar. Importantly, efficacy for the prevention of severe COVID-19 was demonstrated in the overall population and the over 65 year old subgroup.

Study 154-J01 supported efficacy in the proposed use as a single booster dose in the UK population, with demonstrated non-inferiority to Comirnaty original for neutralising antibody response. In addition, waning appeared less pronounced for ARCT-154. There were few participants over the age of 65 years. However, it is considered that non-inferiority can be extrapolated.

Clinical safety was based on exposure in more than 16,000 participants, with adequate follow-up. The reactogenicity profile observed in the Vietnamese population was consistent with that observed after primary series of Comirnaty in a US population, based on a crude comparison. In the Japanese population the reactogenicity profile was less favourable, but similar to Comirnaty on direct comparison. Despite the novel self-replicating mechanism of action, the reactogenicity profile is expected to be similar to currently authorised mRNA vaccines, including the time course.

Assessment of unsolicited adverse events raised no specific concerns.

Overall, analysis of post-marketing data available at the time of MHRA assessment raised no new safety concerns.

The MHRA considered that the clinical data submitted for this application are satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional pharmacovigilance activities have been proposed (see table below for the additional pharmacovigilance activities for all safety concerns):

Table 1: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed
Category 1 (N/A)	N/A	N/A
Category 2 (N/A)	N/A	N/A
Category 3		
V206_06: A retrospective post-authorisation safety study to assess the risk of cardiac inflammatory and thromboembolic events following vaccination with sa-mRNA COVID-19 vaccine in adult individuals Planned	To assess the real-world risk of myocarditis, myopericarditis, pericarditis, and thromboembolic events following Kostaive vaccination using a self-controlled risk interval design among individuals aged 18 years and older. To evaluate the rates of myocarditis, myopericarditis, pericarditis, and thromboembolic events during the risk period following Kostaive vaccination compared to a control period in the same individuals, overall and among the following subgroups: age (<30, 30-59 and ≥60 years), sex (male, female), and other characteristics, as applicable.	Myocarditis and pericarditis Thromboembolic events
V206_05: A phase IIb, single-arm, open label study to evaluate the safety, tolerability and immunogenicity of Kostaive when administered to adults and elderly subjects with immunosuppressive disorders, or receiving immunosuppressive therapies, who are indicated for a booster dose of COVID-19 vaccine.	To assess the safety and tolerability profile of Kostaive in adults and elderly subjects with immunosuppressive disorders (including autoimmune conditions) or receiving immunosuppressive therapies. To evaluate immunogenicity of Kostaive, as determined by virus neutralisation assay for the SARS-CoV-2 variant recommended by WHO in adults and elderly subjects with immunosuppressive disorders (including autoimmune	Missing information: Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the PIL was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

As a booster, ARCT-154 is non-inferior to Comirnaty for neutralising antibody response, with some cross-protection against more recent variants. The vaccine will be updated to reflect the relevant circulating variants in due course.

The following post-authorisation measures are recorded which should be fulfilled by the MAH by the dates shown.

Description	Due date
1. The MAH is requested to submit the data and study reports for the *in vivo* studies that were conducted to evaluate neutralisation activity against currently circulating variants.	30/06/2026

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N