12 December 2024
EMA/18711/2025 corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kostaive

International non-proprietary name: zapomeran

Procedure No. EMEA/H/C/006207/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 07 January 2025

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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List of abbreviations

Abbreviation	Definition
ACE2	Angiotensin-converting enzyme 2
ADME	Administration, distribution, metabolism, excretion
AE	Adverse event
B.1.1.7	Alpha variant
B.1.351	Beta variant
B.1.617.2	Delta variant
BAb	Binding antibody
BAL	Bronchoalveolar lavages
BMI	Body mass index
ChAdOx1	See Vaxzevria
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CoA	Certificate of analysis
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DNA	Deoxyribonucleic acid
D614G	Aspartic acid to glycine mutation in the SARS-CoV-2 spike protein.
EC	Ethic committee
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ETF	Emergency Task Force
FAS	Full analysis set
ERA	Environmental Risk Assessment
EU	European Union
FDA	US Food and Drug Administration
GCP	Good clinical practice
GD	Gestation days
GLP	Good laboratory practices
GMC	Geometric mean concentration of circulating antibodies
GMFR	Geometric mean fold rise in circulating antibodies
GMO	Genetically modified organism
GMP	Good manufacturing practices
GMT	Geometric mean titer of circulating antibodies
HED	Human equivalent dose
IAS	Immunogenicity analysis set
HIV	Human immunodeficiency virus
ICP	Immune correlate of protection
IM	Intramuscular
ITT	Intent-to-treat
IV	Intravenous
LNP	Lipid nanoparticle

Abbreviation	Definition
LUNAR	Lipid nanoparticle technology; encapsulation/delivery system for RNAs
MAA	Marketing authorisation application
MAAE	Medically attended adverse event
MERS	Middle East respiratory syndrome
mITT	Modified intent-to-treat
MNT	Microneutralisation assay
MOH	Ministry of Health
mRNA	Messenger ribonucleic acid
MSD	Meso scale discovery, serological assay format
NAb	Neutralising antibody
NAAT	Nucleic acid amplification-based test
NAS	New Active Substance
NHP	Non-human primate
NICD	National Institute of Communicable Diseases
NIHE	National Institute of Hygiene and Epidemiology, Vietnam
NOAEL	No observed adverse effect level
Omicron BA.4/BA.5	two related omicron lineages sharing identical spike protein sequence
P.1	Gamma variant
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PHEIC	Public Health Emergency of International Concern
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP	Per protocol
PPS	Per protocol set
PRAC	Pharmacovigilance Risk Assessment Committee
PRNT50	plaque reduction neutralisation test at 50% reduction
RAS	Reactogenicity analysis set
RBD	Receptor-binding domain of the spike protein
RNA	Ribonucleic acid
RT-PCR	Reverse transcription - Polymerase chain reaction
S	Spike protein of SASR-CoV-2
SAE	Serious adverse event
sa-mRNA	Self-amplifying mRNA
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SmPC	Summary of product characteristics
SOC	System organ class
SRR	Seroresponse rate
STARR	Self-transcribing and replicating RNA
sVNT	Surrogate virus neutralisation assay

Abbreviation	Definition
RAS	Reactogenicity analysis set
RBD	Receptor binding domain
TICD	Tissue culture infectious dose
TMPRSS2	Transmembrane serine protease 2
US	United States
UTR	Untranslated region
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy
VEEV	Venezuelan equine encephalitis virus
VOC	SARS-CoV-2 variant of concern
VOI	SARS-CoV-2 variant of interest
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Arcturus Therapeutics Europe B.V. submitted on 24 May 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Kostaive, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Kostaive is indicated 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0204/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0204/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's requests for consideration

1.5.1. New active substance status

The applicant requested the active substance zapomeran contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following two scientific advices for ARCT-021 and ARCT-154 respectively:

Date	**Reference**	**ETF co-ordinators**
02 February 2021	EMA/SA/0000051777	*Brigitte Schwarzer-Dau, Mair Powell*
03 March 2022	EMA/SA/0000081819	*Mair Powell, Ewa Balkowiec Iskra*

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Advice on ARCT-021:

- Comparability testing due to changes in formulation;
- Preclinical package to support phase 3 and approval, including vaccination of pregnant women;
- Requirement for ERA or GMO ERA;
- Immunogenicity assessment in clinical trials; safety database; design of the pivotal efficacy and safety trial; plan to evaluate an immune correlate of protection (ICP) within Ph3; alternative path to regulatory approval based on an established ICP; cross-over in the pivotal trial; paediatric development; Rolling review.

Advice on ARCT-154:

- Design of the pivotal safety and immunogenicity trial (ARCT-154-03) to support the licensure of ARCT-154 as a heterologous booster vaccine;
- Safety database to support MAA;
- Neutralising antibody assay for use in the proposed pivotal ARCT-154-03 trial;
- Guidance on procuring tozinameran for use as a comparator vaccine;
- Alternative approach of an open label, randomised trial comparing ARCT-154 and tozinameran;
- Adequacy of the clinical data package to support conditional marketing authorisation and full MA.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	24 May 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	20 November 2023
ETF discussion	28 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023

The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	11 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 May 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 September 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 September 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	05 December 2024
ETF discussion	06 December 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kostaive on	12 December 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 December 2024

The (Co-) Rapporteurs assessment reports have been discussed and supported by the Emergency Task Force (ETF) in the context of its public health preparedness activities.

During the assessment of the application for the marketing authorisation of Kostaive, the following non-EU authority was allowed to participate as part of the OPEN framework and contribute to the

scientific discussions of the ETF and CHMP: PMDA. This authority did not participate in the overall benefit/risk determination, which was decided by the CHMP.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the WHO informed about a cluster of cases of viral pneumonia of unknown cause in China, with the virus spreading rapidly to other countries across the world. This pathogen crossed the species barrier into humans, causing contagious, sometimes severe respiratory infection and other by now described clinical manifestations. In January 2020, the virus causing this pneumonia was identified as a novel zoonotic coronavirus (SARS-CoV-2) and the disease was named COVID-19. The disease was declared a PHEIC on 30 January 2020 and characterised as a pandemic on 11 March 2020. On 5 May 2023, more than three years into the pandemic, given that the disease was well established and ongoing, WHO considered that COVID-19 no longer met the definition of a PHEIC. COVID-19 is no longer a pandemic, but the virus is still present.

2.1.2. Epidemiology, risk factors and prevention

Globally, as of 22 September 2024, there have been over 776 million confirmed cases of COVID-19, including 7,067,260 deaths reported to the WHO. Since the COVID-19 pandemic started, over 2 million people in the European Region have died from the disease.

The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

As for other human/zoonotic coronaviruses such as SARS-CoV-1 and MERS, COVID-19 vaccines based on the spike protein of SARS-CoV-2 have shown high efficacy against symptomatic COVID-19. At present, a large percentage of the global population (70% approximately) is estimated to have been vaccinated against COVID-19, and there is a high seroprevalence globally from natural SARS-CoV-2 infection.

Nevertheless, COVID-19 remains a global health threat, it still places a burden on healthcare systems, and due to new birth cohorts, waning immunity and antigenic evolution of the virus, there is a recognised need for periodic COVID-19 vaccination. Also, there is a recognized need for development of next-generation COVID-19 vaccines providing protection also against transmission, providing greater breadth of protection against viral variants, and longer duration of immunity.

2.1.3. Aetiology and pathogenesis

COVID-19 is caused by SARS-CoV-2 (betacoronavirus genus, sarbecovirus sub-genus). SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2

has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The pathogenesis of SARS-CoV-2 involves binding of the spike protein (surface-exposed part of virions) to the human receptor (ACE2), followed by internalization to the cytosol (facilitated by cleavage of the spike protein by the membrane-bound TMPRRS2 protease), where intracellular viral replication takes place, leading to budding/release of progeny virions from the target cell, and typically ultimately death of target cells.

Disease manifestations reflect the typical route of infection (airborne transmission) and tissue distribution of the ACE2 receptor and TMPRRS2 protease (airways, endothelium, heart muscle, gastrointestinal epithelium). The virus has continually adapted to the new human host since the start of the pandemic, which is considered to have been associated with increased transmissibility but attenuated pathogenicity. However, the actual pathogenicity of currently circulating variants compared to the original index strain is difficult to estimate, due to the high level of population immunity, and even the current variants are considered to present a significant threat for at-risk populations. The aetiology and pathogenesis of the main acute COVID-19 disease manifestations (i.e., pneumonia, myocarditis) are well understood. COVID-19 is also associated with a heterogenous group of post-acute, persistent symptoms and sequelae (currently described as long COVID), for which aetiology and pathogenesis are less well understood.

2.1.4. Clinical presentation, diagnosis

The ECDC provides the following description of the clinical presentation of COVID-19 at the current post-pandemic stage:

- Symptoms may vary, both in frequency and severity, depending on the SARS-CoV-2 variant causing the disease episode.
- Most cases of COVID-19 are mild or moderate and do not require hospitalisation or advanced medical care.
- Severe disease usually manifests as pneumonia with shortness of breath and pulmonary infiltrates on chest imaging. Pneumonia can be complicated by respiratory failure requiring oxygen supplementation and mechanical ventilation. Other severe complications include thromboembolism (such as pulmonary embolism and stroke), circulatory shock, myocardial damage, arrhythmias, and encephalopathy. Severe illness usually develops approximately one week after the onset of symptoms.
- Children usually experience mild symptoms (mainly fever and cough), if any, and have a very low risk of hospitalisation or death. However, some children may develop severe disease after infection with COVID-19, defined as multi-system inflammatory syndrome in children (MIS-C).
- Some patients may experience long-term symptoms with unclear aetiology (collectively referred to as post-COVID-19 condition and long COVID). The presentation is heterogenous, often episodic, and affects multiple organ systems [respiratory, cardiovascular, neuropsychiatric/cognitive symptoms, such as chronic fatigue (most commonly), headaches and loss of smell, difficulty concentrating, sleep disturbances, and depression].

Diagnosis is by detection of viral nucleic acid and viral nucleocapsid antigen, typically in nasopharyngeal swab material (RT-PCR and rapid lateral-flow antigen tests).

2.1.5. Management

The most effective way to prevent COVID-19 is vaccination. There are currently 4 vaccines authorised in the EU (i.e., Comirnaty, Spikevax, Nuvaxovid, Bimervax). COVID-19 vaccines have been shown to be very effective in reducing the risk of infection and severe disease from SARS-CoV-2 infection.

The main treatment for most patients with severe disease is supportive care, which is often highly effective, and antiviral medication (monoclonal antibodies and/or available antiviral drugs) where appropriate.

See listing of approved COVID-19 vaccines and treatments at the EMA web page:

https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines

2.2. About the product

The applicant seeks approval of Kostaive for primary immunisation as well as heterologous boost indications against COVID-19 in adults.

Kostaive (ARCT-154, 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. One vial contains 16 doses of 0.5 mL after reconstitution with 10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection. One dose (0.5 mL) contains 5 micrograms of zapomeran.

The product is first-in-class as none of the currently approved mRNA vaccines are self-amplifying.

Mechanism of action

Following IM injection in the deltoid muscle, the LNP likely traffic to regional lymph nodes, where cellular uptake occurs. The Venezuelan equine encephalitis (VEE) capsid protein is not present in the vaccine in any form (i.e. cellular uptake is likely non-specific by endocytosis, and likely involves antigen-presenting cells). The low pH of endosomes is known to cause disintegration of the cationic LNP, releasing the mRNA payload.

In the cytoplasm, the replication and transcription of the mRNA occurs in two phases. First, the non-structural VEE proteins are produced, providing autonomous self-replication of the VEE mRNA, akin to what happens during natural VEE infection. As the non-structural VEE proteins are processed and accumulate to adequate levels, the replication process switches to preferential replication/transcription of the mRNA part downstream of the sub-genomic promoter, normally occupied by the gene for the VEE capsid proteins but replaced with the spike protein transgene in the vaccine mRNA.

Finally, the spike protein is presented on the cell surface, in naturally folded and glycosylated trimer form, as well as in degraded form in MHC-I and MHC-II context, triggering protective anti-spike antibody and T-cell responses.

The mechanism of action of Kostaive exhibits the following similarities to the currently approved non-replicating mRNA vaccines:

- The VEE replicon mRNA in Kostaive is encapsulated in LNP, and the VEE capsid protein is not present in the vaccine in any form (the replicon mRNA does not contain the VEE capsid protein gene, helper plasmids encoding VEE capsid are not used in the manufacturing process, etc). Thus, while the vaccine is self-replicating, it is propagation-incompetent (i.e., infectious particles cannot be made).

- Also, VEE replication does not involve DNA intermediate forms, i.e. the vaccine nucleic acid is expected to remain in the cytoplasm, as is also the case for currently approved non-replicating mRNA vaccines.
- Due to the LNP formulation, the biological mechanisms governing trafficking to regional lymph nodes, intracellular release of mRNA, and production and surface presentation of spike protein are also expected to be similar for Kostaive and non-replicating mRNA vaccines.
- Kostaive encodes the full-length membrane-anchored spike protein of index SARS-CoV-2 strain, with D614G mutation, prefusion-stabilized by two proline mutations, and with the furin cleavage site inactivated. In comparison, the currently approved mRNA vaccines also encode full-length spike proteins prefusion-stabilized by two proline mutations, albeit with functional furin cleavage sites.

Compared to non-replicating mRNA vaccines, Kostaive' s mechanism of action exhibits the following differences of relevance for clinical efficacy and posology:

- The large amounts of double-stranded RNA produced during replication/transcription of the vaccine mRNA triggers strong innate antiviral responses including interferon responses (this occurs to lesser extent for non-replicating mRNA vaccines, which are typically modified with methylpseudouridine to reduce activation of innate responses). The innate antiviral responses may be beneficial or detrimental for immunogenicity (may promote mRNA degradation and shut down translation of the spike protein but may also provide immune-stimulatory / adjuvant-like effects). The outcome of this balance is human-specific (not well predicted by preclinical models, as was also observed for Kostaive) and immunologically complex, which might add another layer of variability to individual vaccine responses, and another layer of complexity as regards extrapolation of immunogenicity/ efficacy between subgroups and populations.
- As VEE non-structural (replicase) proteins are produced in targeted cells, preexisting anti-replicase T-cell immunity from natural infection with other alphaviruses and/or immunisation with live alphavirus vaccines might theoretically impact Kostaive immunogenicity. By the same token, induction of such anti-vector T-cell responses might theoretically negatively impact immunogenicity on repeat vaccination.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a lyophilised powder for dispersion for injection in a multidose vial containing 5 micrograms per dose of zapomeran as active substance.

One vial contains 16 doses of 0.5 mL after reconstitution with 10 mL of sterile sodium chloride 9 mg/mL (0.9%) solution for injection. One dose (0.5 mL) contains 5 micrograms of zapomeran, a COVID-19 self-amplifying messenger RNA (sa-mRNA) (encapsulated in lipid nanoparticles).

Other ingredients are: Di(pentadecan-8-yl)-4,4'-((((3-(dimethylamino)propyl)thio)carbonyl)azanediyl)dibutyrate (ATX-126), Cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), Sucrose, Potassium sorbate, Sodium chloride, Trometamol, Poloxamer 188 (contains the antioxidant butylated hydroxytoluene).

The product is available in vial (type I glass) with a stopper (bromobutyl rubber) and a plastic flip-off cap with seal (aluminum crimp).

2.3.2. Active substance

2.3.2.1. General information

Kostaive contains the active substance zapomeran (also called mRNA-2105), which is a self-amplifying mRNA sequence coding for a replicase enzyme and the spike prefusion-stabilized furin-cleavage-site-inactivated glycoprotein of the G clade D614G variant of SARS-CoV-2.

Zapomeran is a single-stranded 11,848 base messenger ribonucleic acid (mRNA) consisting of a 5' cap; a 5' untranslated region (UTR); the reading frame of the replicase; the transgene UTR; the reading frame of the transgene encoding for the prefusion-stabilized, furin-cleavage-site-inactivated, spike glycoprotein of the G clade D614G variant of SARS-CoV-2; the 3' UTR; and the poly(A) tail. The physico-chemical characteristics, modifications leading to the prefusion stabilization and inactivation of furin – cleavage site, origin of the sequences and transcription/translation mechanisms were described as well as the mechanism of action.

2.3.2.2. Manufacture, process controls and characterisation

The active substance is manufactured by Catalent Pharma Solutions, LLC, 726 Heartland Trail, Madison, WI 53717 USA. During the procedure, a major objection (MO) was raised requesting a pre-approval inspection of the site be performed by the Supervisory Authority. The inspection was performed by the Health Products Regulatory Authority (HPRA), and a GMP certificate for the Catalent Madison WI, USA issued based on this inspection was provided confirming the GMP compliance of the site.

Description of manufacturing process and process controls

The zapomeran active substance manufacturing process has been adequately described and is considered acceptable.

The main steps are synthesis by in-vitro transcription, followed by purification steps, Tangential Flow Filtration (TFF) and Final Filtration. The commercial batch scale is defined. The batches used for developmental and clinical studies were manufactured at smaller scale. Detailed description of the manufacturing process steps, and steps objectives were provided, including tabled controlled process parameters. The ranges of critical process parameters and the routine in-process controls (IPCs) along with acceptance criteria are described for each step. The assessment of the criticality of the proposed process parameters and in-process controls to impact critical quality attributes is considered comprehensive. Appropriate controls of bioburden, endotoxin and other quality attributes are introduced. The number of chromatography cycle steps and maximum hold time for these cycles is defined and validated. The information on the analytical methods applied for in-process control testing is provided. Information on column preparation and performance is provided. The active substance is shipped using a qualified dry ice thermal shipper or equivalent shipper. Shipping qualification data from active substance manufacturing site to the active substance storage site and from the active substance storage site to the finished product manufacturing site were provided.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications for non-compendial raw materials are presented.

Acceptable specifications are set for the nucleotide triphosphate starting materials.

The cap used for manufacture of the RNA is a starting material. The description of synthesis is provided. The proposed specification of the cap is considered acceptable, the proposed limits for residual solvents and elemental impurities are in line with ICH Q3C and ICH Q3D. Qualification of the methods which are used for retesting of the starting material is still on-going. The Applicant committed to provide the cap method qualification reports as soon as they are available (2Q 2025) **(REC1).**

The information regarding the microbiological control of starting and raw materials is provided**.** The linearized pDNA template used for manufacture of the RNA is a starting material. The linearized pDNA is produced from circular pDNA. The linear pDNA template manufacturing is appropriately described, with associated process parameters and controls. Materials used during the manufacture are listed and the risk assessment evaluating the risk of residual impurities contamination in final linearized pDNA was provided.

Process validation

A lifecycle approach to process validation was followed so the process design stage, including process characterization (PC) studies, was completed contemporaneously with the initiation and completion of the PPQ studies as described in the PVMP (process validation master plan).

During the procedure, a MO was raised as the development and control of the manufacturing process was considered immature and inadequate. In response, the applicant provided further information on the development and validation of the manufacturing process. The manufacturing process CPP setpoints, NORs, PARs, and range justifications are provided. The justification of NORs and PARs is considered acceptable. The proposed commercial control limits are considered sufficiently narrow.

In conclusion, the active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program. Impact of the process steps on the critical quality attributes was assessed. Several important changes have been introduced during the development of the manufacturing process. For each change, the comparability was assessed by the analytical tests used for active substance release, which is considered sufficient. Quality data on the pre- and post-change product are generated and demonstrated that the changes did not have a significant influence on the quality of the active substance.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a self-amplifying mRNA sequence coding for a replicase enzyme and spike protein of SARS-CoV-2. The analytical results are consistent with the proposed structure.

2.3.2.3. Specification

The active substance specification includes tests for appearance, RNA concentration (UV), sequence identity (RT-PCR Sanger Sequencing), mRNA identification (AGE), mRNA purity (AGE), residual pDNA (qPCR), residual protein (NanoOrange), residual dsRNA (ELISA), pH (Ph. Eur.), endotoxin (Ph. Eur.),

microbial enumeration (Ph. Eur.), 5'-Capping Efficiency (IP-RP-HPLC), Poly(A) Tail Length (IP-RP-HPLC).

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Although it has been shown that Agarose Gel Electrophoresis is a suitable method to estimate purity, results for purity of clinical, PPQ and commercial active substance batches were found out of the linear range. The Applicant committed to validate the method for linearity and accuracy also in the range and optimize the method, if necessary, within two years **(REC2).** Acceptance limits are properly justified and acceptable. Active substance release limit for purity was tightened to account for the observed decrease in purity during finished product manufacture.

Batch analysis

Batch analysis data of the active substance (from batches covering development and commercial scale), were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Sufficient information has been provided regarding the reference standards. The uncertainties regarding the assignment of potency values to interim and primary reference standards, and the qualification of future reference standards are sufficiently addressed.

2.3.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container. mRNA-2105 was evaluated for stability at the indicated storage condition. Stability testing and storage were presented. The parameters tested are the same as for release. The shelf life at the designated storage temperature based on the stability data for commercial batch, is considered acceptable.

2.3.3. Finished Medicinal Product

2 . 3 . 3 . 1 . Description of the product and pharmaceutical development

Kostaive (ARCT-154) finished product is presented as a sterile, white to off-white solid with 100 µg of mRNA-2105 per vial. ARCT-154 must be reconstituted with 0.9% sodium chloride injection and is for IM injection.

ARCT-154 is provided in 8R elongated Type I glass vials (12 mL) sealed with bromobutyl rubber stoppers with an aluminium crimp seal and a polypropylene flip cap.

Each vial of lyophilized ARCT-154 is reconstituted with 10 mL of commercially available 0.9% sodium chloride for injection and is intended to deliver up to sixteen 5-µg doses for patients to be dosed at each vaccination session. Once reconstituted, a new sterile syringe and needle will be used to withdraw 0.5 mL from the vial for each patient administration. After preparation, the reconstituted vial or filled syringes must be stored in a secure location at refrigerated conditions or room temperature (2°C to 25°C) prior to administration and must be administered within 6 hours of initial puncture of the product stopper.

Pharmaceutical development

The ARCT-154 finished product is developed as part of the applicants LUNAR-COV19 vaccine platform, which also includes the frozen-liquid and lyophilized formulations both of which have been used in supportive clinical studies. The formulation studies performed when transitioning from the liquid-frozen to the lyophilized formulation were described. The comparability of the two formulations has been sufficiently demonstrated.

There is one novel excipient used in the finished product formulation, ATX-126, with the chemical name di(pentadecan-8-yl) 4,4'-((((3-(dimethylamino)propyl)thio)carbonyl)azanediyl)dibutyrate. Further information on this novel excipient is provided in Section 2.3.3.6.

All other excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, where applicable. The non-compendial excipients, DSPC and PEG2000-DMG, are controlled according to appropriately defined specifications.

A discussion of physico-chemical and biological properties of ARCT-154 was provided.

During the procedure, questions were raised due to numerous issues of comparability of liquid-frozen and lyophilized batches and the small-scale batch to the commercial process. In response to the D120 list of questions, the applicant has provided sufficient information regarding the comparison of the manufacturing processes, batch release results and extended characterisation to support the comparability claims. It is concluded that comparability of liquid-frozen and small-scale batches to the proposed commercial process is sufficiently demonstrated.

During the procedure, a MO was raised on manufacturing process control, as little or no information was provided regarding the process parameter classification, justification for proposed ranges and process characterisation. In response, the applicant has provided a number of reports and dossier updates which address the identified issues.

2.3.3.2. Manufacture of the product and process controls

The Kostaive (ARCT-154) finished product manufacturing process operations are performed at GMP compliant manufacturing sites.

The manufacturing process is subdivided into the steps leading to Intermediate Drug Product (bulk drug product) and the final Drug Product Fill/Finish (including lyophilization).

The Intermediate Drug Product Manufacturing steps include mRNA and lipid excipient dissolution, nanoparticle formation and dilution, concentration, buffer exchange and filtration, and concentration adjustment and filtration.

The Drug Product Fill/Finish steps include sterile filtration, aseptic fill and loading into freeze driers, freeze drying, unloading and crimping, visual inspection, labeling, packaging and intermediate storage.

Target values/ranges of process parameters are presented and acceptance limits for in process controls are provided.

Process validation/verification

Process validation was performed on four commercial-scale PPQ runs, using established critical process parameters and in-process controls. Validation data regarding the content uniformity at different stages of the filling process has been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

It is noted that PPQ batch numbers are presented in what appears to be a sub-batch format. It is clarified that "Lyophilized drug product batch separated into lots A and B if the number of vials filled exceeds the number that can be processed in one freeze-dryer unit". A report of the performed media fills has been provided.

2.3.3.3. Product specification

The finished product specifications include tests for appearance (visual), colour of reconstituted suspension (Ph. Eur.), Opalescence of Reconstituted Suspension (Ph. Eur.), particle contamination-visible particulate matter (Ph. Eur.), mRNA Identification (TR-PCR), mRNA Identification (AGE), total active ingredient content (IPRP-HPLC/ UV Detection), Purity Percent Full-length mRNA (AGE), % Encapsulated mRNA (RiboGreen Assay), identification of lipids (RP-HPLC/ CAD), Total lipids content (RP-HPLC/ CAD), Lipid:mRNA Ratio (calculated), Particle Size (z-average) (Ph. Eur.), pH of Reconstituted Solution (Ph. Eur.), osmolality of Reconstituted Solution (Ph. Eur.), moisture content (Ph. Eur.), residual ethanol (GC-HS), Particulate Contamination-Subvisible Particulate Matter (Ph. Eur.), Endotoxin (Ph. Eur.), Sterility (Ph. Eur.), Dose Uniformity (Ph. Eur.), Potency (ELISA), Reconstitution Time (visual) and Container Closure Integrity (USP, Headspace oxygen measurement)

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

During the procedure, a MO was raised on the applicant's approach to potency testing which was initially deemed inadequate due to issues relating to the principle, validation, and reporting of the results from the potency test method, and the absence of potency data of the small-scale clinical batch. In response the applicant provided a summary of the method validation and additional data. Discussion of the potency of the small-scale clinical batch has been provided. A previously requested product-specific validation for the potency assay was provided and the method was successfully transferred to an EU testing site.

Upon request the applicant has provided product-specific validation for all methods, including potency. The uncertainties regarding the validation of the method for mRNA purity (AGE), its suitability and stability indicating nature were adequately resolved.

During the procedure, a MO was raised as the initial acceptance criteria for a number of specification attributes were considered too wide and needed to be tightened. In response, the limits for a number of specification attributes were subsequently re-evaluated and tightened, where applicable. The finally approved release and stability specifications are sufficiently justified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

During the procedure, a MO was raised requesting that a risk evaluation concerning the presence of nitrosamine impurities in the finished product be performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on

the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis

Batch analysis data (from batches covering development and commercial scale) of the finished product were provided. The results are within specifications and consistent across the batches except for a single OOS in visible particles for which a satisfactory investigation report with CAPAs was provided.

Reference materials

Sufficient information has been provided regarding the reference standards. The uncertainties regarding the assignment of potency values to interim and primary reference standards, and the qualification of future reference standards are sufficiently addressed.

Container closure

Container closure system has been described, including the vial, stopper and seal schematics, in adequate detail. The lyophilized finished product is presented as a sterile, white to off-white solid with 100 µg of mRNA per vial, in 8R Type I glass vials sealed with bromobutyl rubber stoppers with an aluminum crimp seal and a polypropylene flip cap. The primary container materials coming into contact with the finished product are compliant with Ph. Eur. and USP. The vial and rubber stopper are claimed to be Ph. Eur (3.2.1 and 3.2.9) and USP (<660> and <381>) compliant.

2.3.3.4. *Stability of the product*

The approved shelf-life is 24 months when stored at -20 °C. Vials can be stored at room temperature (up to 25 °C) for up to 4 hours before reconstitution. After reconstitution, an in-use period of 6 hours under refrigerated conditions or at room temperature (2-25 °C) is defined, as per SmPC section 6.3.

The shelf-life is supported by 24 months of real-time/real-condition studies of 4 independent PPQ batches and 24 months of real-time/real-condition stability data for the small-scale clinical batch. Two commercial batches were also tested at accelerated conditions.

The stability testing included photostability and freeze-thaw testing. The in-use stability study results support the proposed in-use stability of 6 hours.

2.3.3.5. *Adventitious agents*

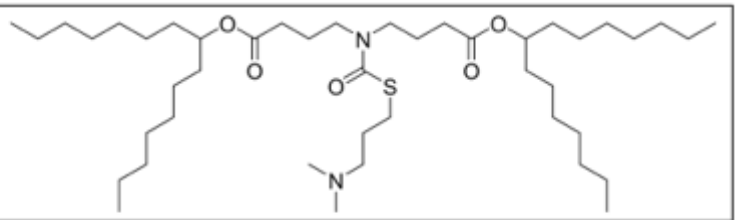
No raw materials of animal origin are used in the mRNA-2105 manufacturing process. However, the starting materials ATP, CTP, GTP, and UTP use animal-derived products in their manufacture (porcine shoulder; rabbit muscle; galactose from bovine milk). The country of origin for animal-sourced materials, a policy on animal sourcing, a statement on the production and purification process, and certificate of analysis was provided. Vendor declared that the animal-derived raw materials originate from healthy animals. The risk of BSE/TSE is considered negligible as only galactose from bovine milk (sourced from China) is used as the material of bovine origin and the bovine milk is unlikely to present a risk of TSE contamination according to EMA/410/01 rec.3. It was confirmed that the used bovine milk is collected from healthy animals which are in the same conditions as milk collected for human consumption.

The purification process of all nucleotides includes multiple steps that either remove or inactivate viral particles. Thus, the viral risk associated with nucleotides is considered minimal.

2.3.3.6. *Novel excipient*

ATX-126 is the novel excipient with the chemical name di(pentadecan-8-yl) 4,4'-((((3-(dimethylamino)propyl)thio)carbonyl)azanediyl)dibutyrate, and structure as shown in Figure 1.

Figure 1: Structure Information for ATX-126

Structure	
Molecular Formula	$C_{44}H_{88}N_2O_5S$
Molecular Weight	755.24
Exact Mass	754.63

The excipient is a colorless oil and has no chiral centra. Physical and chemical properties of ATX-126 were sufficiently described in the dossier. The ATX-126 is prepared by chemical manufacturing process.

During the procedure, a MO was raised on the initial proposed starting material. In response the applicant redefined the starting materials to an earlier stage in the process, which was considered acceptable. Reagents, solvents and auxiliary materials used in the synthesis of ATX-126 were listed in the dossier. Information on the quality and control of intermediate was provided. In-process controls were mentioned. The acceptance criteria for each IPC were mentioned. The provided information is considered acceptable. The manufacturing process has been demonstrated to be stable, robust, and reproducible.

The structure of ATX-126 was sufficiently discussed in detail. The combination of proposed specifications and spiking studies provides a sufficient control strategy for the present impurities. Residual solvents and elemental impurities are sufficiently controlled. The presence of mutagenic impurities in ATX-126 was adequately discussed. The levels were found under safety threshold of toxicological concern. The ATX-126 manufacturing process was assessed for the possibility of nitrosamine formation by evaluating all raw materials, intermediates, container closure systems, cleaning agents, solvents, reagents, equipment, and the manufacturing facility used in the process. Overall, the risk for presence of nitrosamines was evaluated as negligible and evaluated as no risk.

Specifications for ATX-126 were defined. The controlled attributes are considered sufficient. Justification of the proposed acceptance criteria was provided. The analytical procedures used to assess the attributes include compendial and non-compendial analytical procedures. A summary of the verification or validation results is provided.

Container closure system is defined. Stability study for novel excipient ATX-126 was conducted under long-term and accelerated storage conditions. A shelf-life is proposed for ATX-126 which is considered acceptable based on the provided stability results.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Kostaive (ARCT-154) is a novel self-replicating mRNA COVID-19 vaccine, containing 5 micrograms/dose, and presented as powder for dispersion for injection, in multidose vial to be reconstituted with 10 ml sodium chloride 9 mg/mL (0.9%) solution for injection.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure a number of major objections (MOs) were raised relating to the GMP status of the active substance manufacturing site, the development and control of the active substance manufacturing process, the development and control of the finished product manufacturing process, the approach to finished product potency testing, the acceptance criteria for a number of finished product specification attributes, the risk assessment on potential sources of nitrosamine impurities and the proposed starting materials for the synthesis of the novel excipient ATX-126.

The applicant provided detailed responses to each of these MOs and to the list of other concerns relating to the quality of the active substance and finished product. The applicant's responses were comprehensive and addressed all of the issues raised during assessment. The Applicant has agreed to address two recommendations post-authorisation as detailed below.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Applicant will provide the cap method qualification reports as soon as they are available (2Q 2025).
2. The Applicant commits to validate the purity (agarose gel electrophoresis (AGE)) method for the parameters linearity and accuracy by end of 2026 and optimize the method if necessary.

2.4. Non-clinical aspects

2.4.1. Introduction

ARCT-154 and ARCT-021 vaccine candidates represent a vaccine platform, in that they are chemically and physically similar in composition and cGMP manufacture. The immunogenicity and virus challenge studies in mouse for the human ACE2 receptor and NHPs for ARCT-021 are presented in support of the preclinical immunogenicity of ARCT-154.

ARCT-021 was fully evaluated in a non-clinical safety program composed of tissue distribution, repeat-dose toxicology, and reproductive toxicology. ARCT-154 (lyophilized formulation) was evaluated in a 4-week GLP toxicology study (020186-003) in rabbits.

This study used three dose levels, which all were higher than the clinical dose of 5 µg (approximately 17, 25 and 34 µg) administered three times 2 weeks apart. This design provided sufficient safety margin to clinical exposure in terms of both dose and repeated administrations, although the prime-boost posology in humans was with 4 weeks in between dosing.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Mouse ARCT-154

A non-clinical proof of concept study of ARCT-154 was performed in mice (ARC21-032). The first assay measured total mouse anti-spike glycoprotein IgG for each of four specific SARS-CoV-2 spike glycoproteins: the ancestral strain and Alpha, Beta, and Gamma variants. The second assay was a cell-free/virus-free sVNT and is based on antibody-mediated inhibition of the interaction between the ACE2 receptor and the specific spike glycoprotein RBD: ancestral strain or Alpha, Beta, or Gamma variant. The third assay was a cell-based SARS-CoV-2 MNT against ancestral strain.

Immunogenicity of ARCT-154 vaccine candidate was tested in mice at a single 2 µg IM dose in direct comparison with ARCT-021. Anti-spike glycoprotein IgG was assayed for inhibition of recombinant RBD to a derivative of human ACE2 receptor. There were 5 mice per treatment group and the groups were ARCT-154, ARCT-021 and PBS. Mice were bled on days 14, 28, 42 and day 56. Serum was diluted 1/2500 and assayed for % RBD binding inhibition for RBDs from Wuhan strain, and alpha, beta and gamma SARS-CoV-2 VOCs. ARCT-154 outperformed immunogenicity of ARCT-21 on all four tested strains.

Already after 14 days post vaccination, sera for ARCT-154 showed between 76% to 84% inhibition against the Wuhan strain and alpha variant, and 57% inhibition against the beta and gamma variants. By day 28 post vaccination, the % inhibition had increased to 84% to 94 % inhibition against the Wuhan strain, to 76% to 88% against the alpha variant, and to 57% to 80% inhibition against the beta and gamma variants. No further increase was detected on Day 42 or 56 after this single dose.

ARCT-154 also outperformed ARCT-021 on total spike IgG, which continued to rise through to Day 56 in the pseudovirus neutralisation assay.

NHP ARCT-154

Immunogenicity of ARCT-154 was further evaluated and compared to ARCT-021 in the NHP model with in-life phase. Male monkeys (N=4) were dosed twice 28 days apart at 7.5 µg/dose.

Sampling for immunogenicity assays was pre-vaccination, Day 15, 29 (prior to second dose), 43 and 57. Sampling for MNT and ELISpot was pre-vaccination, 29 and 57.

In NHPs vaccinated with 2 doses of ARCT-154 or ARCT-021 on Days 1 and 29, higher total anti-spike IgG protein and higher percent RBD binding inhibition, as measured by the sVNT assay, of ancestral strain and Alpha, Beta, and Gamma variants was observed at every postvaccination timepoint for ARCT-154 than for ARCT-021.

The second dose of both ARCT-154 and ARCT-021 elicited a boosting effect as measured by total anti-spike IgG and by ACE RBD inhibition.

Post vaccination with ARCT-154 or ARCT-021, RBD binding inhibition as measured by the sVNT assay was higher for the ancestral strain and Alpha variant than for the Beta and Gamma variants as these are closer to the mRNA coding in ARCT-154 and ARCT-021.

In the Saphire MN assay, ARCT-154 demonstrated both higher and broader neutralising antibody capacity than ARCT-021 already at Day 29 including the Delta and Omicron BA.1 variants. For ARCT-154, Day 57 neutralising activity was further increased above Day 29 activity, i.e., a boosting effect was observed.

PBMCs were harvested from whole blood in the monkeys treated with PBS (control group), ARCT-154 or ARCT-021. The PBMCs were analysed for cellular immune response via an ELISpot assay detecting interferon γ excreted from cells after activation with overlapping peptide pools of ancestral, alpha, beta, gamma SARS-CoV-2 variants. The mean interferon γ response from PBMCs of monkeys vaccinated with ARCT-154 was significant (~100 spots/10^6 PBMCs) but similar to monkeys vaccinated with ARCT-021. The variation in extent of interferon γ response was higher for ARCT-021 than for ARCT-154. Monkeys treated with PBS showed no or very little response.

2.4.2.2. Secondary pharmacodynamic studies

Immunogenicity in mouse

In mice, immunogenicity of a single doses of ARCT-021 versus conventional non-self-replicating mRNA (ARM3013) was compared (0.2, 2 or 10 µg/mouse, study ARC20-086, de Alwis, 2021).

When comparing spike specific IgG responses over time from Day 0 to Day 60, ARCT-21 peaked at Day 50 and at Day 60 a significant decrease was observed, whereas the conventional mRNA showed much lower response, i.e. at the highest dose (10 µg), the response was similar to the lowest dose for ARCT-021 (0.2 µg), indicating a 50 times higher potency of ARCT-021.

IgG responses were mapped to different regions of the spike protein at Day 30. Here all four regions (Spike, S1, S2 and RBD) was covered for both vaccines. However, ARCT-021 showed much higher titers than the conventional mRNA.

Neutralising antibodies were quantified on Day 30 and Day 60 using the PRNT. Dose related increase in PRINT50 was observed for ARCT-021, which were similar to convalescent sera for the doses 2 and 10 µg, while neutralising antibodies could not be detected for the conventional mRNA. The level of neutralising antibodies for the low dose of ARCT-021 (0.2 µg) was not significantly higher than the control group, although 3 out of five mice did show presence of neutralising antibodies. However, at 2 and 10 µg dose levels, neutralising antibodies continued to rise between Day 30 and Day 60.

Immunity profiling was performed to determine if the response was characterised as a Th1 or Th2 response. In mice dosed with ARCT-021, but not in mice dosed with the conventional mRNA, CD4+ T cells with IL-4 staining was decreased at the low and mid dose and CD8+ T cells with IFN-γ staining was increased at the mid and high dose leading to a positive Th1/Th2 ratio, predictive for a favourable and balanced immunogenic cellular response resembling what is observed in the clinic in COVID-19 patients. A similar picture was observed for IgGs as IgG2a was increased at all three dose levels for ARCT-021. For the conventional mRNA, an increase in IgG2a was only seen for the high dose reaching a level similar to the low dose for ARCT-021.

Moreover, when splenocytes harvested 7 days post vaccination in C57Bl/6J mice and was assayed for IFN-γ T cell activation when incubated with 4 different pools of peptides from the spike glycoprotein, especially the pool 2 showed a very high response even for the low dose of ARCT-021 as compared to the conventional mRNA. However, the number of T cells showing IFN-γ response was not dose-related.

Overall, non-clinical PD studies have shown a skewing towards Th1 responses (IFN-gamma producing $CD4^+$ and $CD8^+$ T cells) and this was also observed in humans. Although at early time point (24h) following vaccination, the cytokine response was lower for sa-mRNA compared to conventional mRNA, the reversed was the case at day 7. Clinical data further support the induction of early innate immune responses. These responses are comparable to vaccines known/developed to induce proper Th1-skewed and innate immune responses. An observed downregulation of inflammation genes is likely not related to potential inhibition of the innate immune system, as downregulated genes were involved in

e.g. inhibitory receptor signalling in T cells and associated with immune activation and migration. Based on this, an increased risk for VAERD with sa-mRNA is not expected.

Immunogenicity in NHP

Female rhesus macaques were treated in a dose range finding study of ARCT-021 (Study ARC20-123). Monkeys were dosed Day 0, 30 and 150 to inform on immunogenicity upon a booster dose of either 5 or 20 µg (N=5) versus control (Luciferase mRNA in LNP, N=3). Blood samples for testing micro neutralising antibody titer yielding 50% inhibition of SARS-CoV-2 infection were taken 15, 30, 45, 60, 75, 90, 120, 150 and 180 post first dose. As expected, the high dose of 20 µg yielded substantial higher titers of neutralising antibodies over time than the low dose of 5 µg at all time points. E.g. two weeks after the second dose (Day 45), the titers were 970 and 368, for 20 and 5 µg respectively. Similarly, 30 days after the booster dose (Day 180), the titers were 2560 and 844, for 20 and 5 µg respectively.

On day 30, 60 and 90, cell-mediated immune response after one and two doses was evaluated by the IFN-γ ELISpot assay.

The ELISpot assay results showed that the 5-µg RNA dose produced significant T-cell activation after the single injection and increased slightly after the second injection and peaked 60 days after the second injection. The 20-µg RNA dose showed lower T-cell activation after the single injection and the level of activation increased 30 days after the second injection and remained at that level of activation 60 days after the second injection.

Virus challenge in mouse

Study GSY03 evaluated the efficacy of ARCT-021 vaccination on viral burden and survival in the transgenic K18-hACE2 mouse model of lethal Sars-CoV-2 infection. I.e. mice that were transfected with the human ACE2 receptor were inoculated with a lethal dose of virus 30 days post a single dose vaccination of either 2 µg or 10 µg of ARCT-021.

This single dose vaccination provided 100% protection against lethality. By Day 7 after challenge, all mice in the PBS control group were dead and all mice in the two vaccinated groups continued to thrive and gain weight. Moreover, in a separate study, viral plaque titers were determined in lung and brain tissues. No infectious virus was detected in the lungs and brains of mice vaccinated with 2 or 10 µg ARCT-021, whereas unvaccinated mice had high titers of virus and copies of viral genomes that was higher in brain than in lung tissue.

In a subsequent study in the hACE2 transgenic mice, the impact of B-cell depletion 3 and 1 days prior to vaccination of a low dose of 1 µg ARCT-021 and T-cell depletion 3 and 1 days prior to viral challenge SARS CoV-2, 5×10^4 TCID50 would impact the infection in lungs and brain on Day 5 after viral challenge. It was clear that B-cell depletion even before vaccination did not impact the protection from viral infection in lung and brain tissues, whereas T-cell depletion just prior to challenge allowed significant infection of these tissues, indicating that the cellular immune response is the most important in protection against SARS-CoV-2 infection. The positive Th1/Th2 profile of ARCT-021 observed in the de Alwis studies supports the cellular immune response provided by activated T cells.

Virus challenge in NHP

The study included 5 groups of N=5 (3M/2F or vice versa) in the active groups and N=4 in the control group (PBS).

Rhesus macaques were treated with a single dose of 20 mcg or 40 mcg ARCT 021 (on Day 0), or with 2 doses of either 5 mcg or 20 mcg ARCT-021 or PBS on Days 0 and 28. Animals were challenged with SARS-CoV-2 viral strain/isolate USA-WA/2020, intratracheally and intranasally on Day 42 (i.e., 14 days

post second dose for the double-primed groups). The target dose was ~1 x 10^6 TCID50. Nasal and oropharyngeal swabs were performed on Days 42, 43, 44, 45, 46, 47, 48, 49, 52, and bronchoalveolar lavages performed on Days 43, 45, 47, 49, and 52. All samples were collected under anaesthesia.

A MNT was performed, and protection against infection was determined by reduction in infectious virus from BAL, nasal swabs, and oropharyngeal swabs.

While challenge with SARS-COV-2 was lethal after 7 days in the naïve non-vaccinated hACE-2 transgenic mouse, the naïve NHP were only developing very slight symptoms of SARS-COV-2 challenge if any and all animals were clear of virus in airways already after 2 weeks including the PBS vaccinated animals (e.g. BAL RT-qPCR) and no virus was detected in blood at any time point. Moreover, no significant differences were seen in median tissue culture infectious dose (TCID50, a cellular assay of viral load) values between any groups on any study days for nasal swabs, oropharyngeal swabs, or BAL fluid, indicating a very fast neutralisation of the challenge even in non-vaccinated animals and limited infection. Hence, these two models may represent the two extremes of outcomes of human infection with SARS-COV-2 and are not presented with optimal human disease relevance.

Nevertheless, the vaccine did raise an immune response in the monkeys as determined by IgG titers against recombinant spike protein. IgG increased from non-detectable prior to second dose of the 5 and 20 µg doses to much higher than for the two single doses of 20 and 40 µg two weeks after the second dose. After challenge, the vaccinated animals all reached an even higher level, while the control group rose to a similar levels two weeks after challenge as for the double vaccinated animals two weeks after the second dose.

The cell mediated immunogenic response to ARCT-021 was characterised approximately 24 hours post vaccinations in terms of selected serum cytokines and chemokines and intracellular cytokines from PBMCs.

More specifically, PBMCs from ARCT-021- and placebo-treated animals were isolated and the frequencies of interferon gamma- (IFN-y), interleukin-2- (IL-2), tumour necrosis factor alpha- (TNF-α), interleukin 4- (IL-4), and interleukin 13- (IL-13) expressing CD3+/CD4+ and CD3+/CD8+ T cells following in vitro stimulation with SARS-CoV-2 S peptide pools were measured to evaluate cellular immune responses.

Focusing on prime boost of 20 µg (Group 2) and 5 µg (group 4), the following data showed the largest shifts between baseline and post vaccinations (Day 14 and 39):

- There was a significant upward shift in IL-2+% CD4 responses against peptide pools for group 2 on Day 39 (range 2.3-2.7), but not for Group 4.

- There was a significant upward shift in IL-2+% CD8 responses against peptide pools for group 2 on Day 14 and 39 (range 2-7), but not for Group 4 where a decrease was observed.

- There was a significant upward shift in IL-13+% CD8 responses against peptide pools for group 2 on Day 39 (range 3-5), but only slightly (2.1) for Group 4 for peptide pool 2 on Day 14. - IFN-γ, TNF-α, and IL- 4 did not show strong shifts from baseline levels.

2.4.2.3. Safety pharmacology programme

No safety pharmacology endpoints were incorporated into the 2- and 4-week GLP toxicology studies in rabbits. This is acceptable, as the vaccine is not anticipated to affect physiological functions other than those of the immune system. In addition, no findings on vital organ functions were recorded in the repeat dose toxicology studies (WHO 2005).

2.4.2.4. Pharmacodynamic drug interactions

No studies of pharmacodynamic drug interactions were presented. This is acceptable.

2.4.3. Pharmacokinetics

Methods of analysis

According to WHO Guidance for the evaluation of the quality, safety, and efficacy of mRNA vaccines for the prevention of infectious diseases (WHO 2021), for mRNA vaccines delivered in LNPs, distribution studies are required for the mRNA and novel constituents of the LNP. A bioanalytical method for the mRNA in ARCT-154 was provided as a kit based on the QuantiGene Singleplex gene expression assay (branched DNA chemiluminescence). This assay was qualified with a dynamic range of at least 3 to 250 pg/g plasma or tissue in both mouse and rabbit, which is considered of sufficient sensitivity. The qualification included accuracy, precision, selectivity and dilutional linearity. mRNA is known for its inherent instability and therefore, stability was not included in the qualification. However, the bioanalytical method used proteinase K to inactivate nucleases in plasma and tissue homogenates during sample processing.

Nevertheless, meaningful data was obtained to evaluate the duration of exposure in plasma and tissues in mice and rabbits and to which organs the mRNA was distributed.

A bioanalytical method for the new component in the LNP ATX-126 in plasma and tissues of mice and rabbits was developed and qualified. The qualification included only accuracy and precision using plasma for calibration samples and tissue for quality controls. Stability of ATX-126 is not a concern as the apparent half-life is so long that it was difficult to calculate. However, evaluation of selectivity would have been of great value, since substantial interindividual variability was observed in study samples.

Moreover, the sensitivity of the method seems somewhat poor. However, considering the relatively high doses administered in the distribution studies in mice of ARCT-021 and general toxicity study in rabbits of ARCT-154, the method performance was sufficient for generating meaningful data for comparison of extent of exposure between organs of interest.

The assay for spike protein was not qualified and data are therefore only considered supportive.

Absorption

Absorption studies including classical pharmacokinetic studies are not required for vaccines.

Distribution

Luciferase mRNA

A distribution study of vaccines consisting of the same LNP as ARCT-021 and ARCT154 and mRNA or sa-mRNA for firefly luciferase was presented. The vaccines were dosed once IM to mice (N=5) at the level of 10 or 50 µg mRNA. Liver and muscle tissues were analysed for mRNA at the time points 2, 8, 24, 48, 72 hours and on Day 8, 15 and 30.

Focusing on the low dose of sa-mRNA, sa-mRNA concentrations were much higher at the injection site than in the liver. This can be exemplified at time for maximal concentration (2 hours), where the mean sa-mRNA concentration was 3804 pg/mg and 59.14 pg/mg in muscle and liver, respectively. As for duration of exposure, sa-mRNA could be quantified in all five animals up to Day 15 in muscle up to 24 hours in liver.

Comparing with conventional mRNA concentrations, which at time for maximal concentration (2 hours), the mean mRNA concentration was 3030 pg/mg and 28.99 pg/mg in muscle and liver, respectively. As for duration of exposure, mRNA could be quantified in all five animals up to Day 8 in muscle up to 24 hours in liver.

However, AUClast was 78409 pg/mL*hr for mRNA and 429445 pg/mL*hr for sa-mRNA substantiating the increase in exposure to RNA for the sa-mRNA compared to the conventional RNA. Moreover, the study shows that by Day 30, sa-mRNA is cleared in the mouse in 3 out of 5 animals, indicating that sa-mRNA is cleared after all. The mechanism by which the sa-mRNA is cleared is most likely due to the immune system of the host (patient) and/or eventual exhaustion of the cell machinery for protein production.

Tissue distribution in mouse

A dedicated distribution study of the sa-mRNA in ARCT-021 and ATX-126 was conducted in mice. Bioanalytical methods for mRNA-2002 and ATX-126 was sufficiently qualified, see section on Bioanalytical methods.

All animals received a single bolus IM unilateral injection of 50 µL on the left hind leg muscle (rectus femoris, N=5-6) of 0 (PBS), 25, or 50 µg of ARCT-021 (dose is expressed in terms of concentration of replicon RNA). The dose of ATX-126 was 525 and 1050 µg, respectively. Hence, the dose was 5 and 10 times higher than in patients, who weigh at least 50 kg compared to the 25 g body weight of a mouse. The applicant explained that the study was designed prior to any knowledge on the potency in the mouse model or clinical dose. Samples were taken at necropsy at 2 hr, 8 hr, 24 hr, 48 hr, 72 hr, Day 8, Day 15, and Day 31 post-dose.

Dose proportionality was evaluated by presenting the ratio of tissue concentrations of ATX-126 in terms of Cmax and AUC. For most tissues the ratio fell out in the vicinity of the expected two. However, for ovary, the concentration was much higher for 50 than for 25 µg, resulting in a ratio in the range of 5-7. Only one data point was presented for this tissue as the organs had to be pooled for analysis. Hence, for most tissues (except ovary), dose proportionality may be anticipated, and the relative tissue distribution and rate of clearance may then be representative for a clinically relevant dose. At least, at this point, respecting the principles of 3R, a new study using a lower dose will not be required.

Tissue pharmacokinetics of mRNA

Time for maximal concentration for mRNA-2002 was 2 hours in most tissues except inguinal lymph nodes (192 h), spleen (8 h) and poplithial lymph nodes (8 h). AUC was highest in muscle, then plasma, and then lymph nodes.

It was not possible to determine the half-life of mRNA-2002 for all tissues. The half-life of mRNA in the target tissue, the muscle ranged from 38 to 100 hours. While other tissues presented with half-lives of 17 to 91.5 hours, where ovary was observed with half-life of 91.5 hours at the 50µg dose. At the 25µg dose, half-life could not be calculated. However, at Day 15, no mRNA could be detected in the ovaries. Here it should be noted that the LLOQ for the mRNA is pg/mL.

Tissue pharmacokinetics of ATX-126

Time for maximal concentration for the cationic lipid ATX-126 varied greatly with a range from 2 h to 744 h (last time point) underpinning that ATX-126 has an extremely long half-life in plasma and tissues. AUC was highest in muscle>liver>lymph nodes>spleen. AUC was highest in muscle> plasma>lymph nodes.

It was not possible to determine the half-life of ATX-126 for the majority of tissues. The half-life of mRNA in the target tissue, the muscle ranged from 748-1544 hours (31-64 days). While lung and heart presented with half-lives of 502-815 hours. The half-life in plasma was 280-368 h in males, while this could not be determined in female mice. ATX-126 distributed to ovary with a time range for maximal exposure of 3-15 days.

ATX-126 was not detected in brain except in one female animal 2 hours after administration of the high dose. This is reassuring and probably mainly due to the ionisation at physiological pH, preventing diffusion/transport across the blood brain barrier.

It should be noted that the LLOQ for the ATX-126 is high (250-500 ng/g tissue). However, the concentrations of ATX-126 in all tissues were well above LLOQ except brain up to the end of study.

Tissue pharmacokinetics of the spike protein

At the low dose, the spike protein was detected in some samples of muscle from Day 1 to Day 8, in lung from Day 1 to Day 3. At the high dose, the spike protein was detected in some samples in plasma from Day 1 to Day 31, in muscle from Day 2 Day 8, lymph nodes from 2 hours through to Day 31 and in ovary from 2 hours to Day 8. However, many mean values for tissue concentration are reported as below lower limit of quantification (12 pg/mg).

Tissue distribution in rabbit

In a repeat dose toxicity study in rabbits (2505-037), ARCT-021 was dosed three times with 2 weeks in between at 20 or 40 µg (Day1, 15 and 29). Here, plasma and tissue samples were analysed for mRNA-2002 and ATX-126 at necropsy at Day 31 (main study animals administered the last dose on Day 29) and Day 57 (recovery groups).

All control animals showed no detectable levels of ATX-126 in any tissue at either timepoint. Within the ARCT-021 treated animals tissue samples from the liver and spleen had detectable levels of ATX-126 in every animal at both necropsy intervals. The other prominent tissues with detectable levels of ATX-126 were for plasma at termination and the injection sites and the gonads of the female animals at both terminal and recovery intervals. In addition, there were greater instances of ATX-126 detection at 40 µg compared to 20 µg for the injection sites and gonads.

Following ARCT-021 administration, there was no mRNA-2002 detected in the plasma, muscle, lymph node, ovary, liver, and lung of rabbit from each dose group including the PBS control at Day 31 and Day 57 (except one sample out of ten muscle samples which had very low mRNA levels at Day 31). However, mRNA-2002 was detected at low levels only in spleen at Day 31 from 20 and 40 µg doses, and it was below the lower limit of quantitation (<LLOQ or <0.24 pg/mg) at Day 57 from both dose groups.

ARCT-021 was evaluated in the Fertility, Embryofetal, and Postnatal Development Study of ARCT-021 in Rabbits. Rabbits were dosed either PBS, 10 µg or 20 µg mRNA-2002 in ARCT-021 28 days before mating (Day 1 of Study), 14 days prior to mating and gestation days 0, 14, and 28, all in all five doses two weeks apart. On gestation day 29, maternal and foetal plasma, placenta, foetal liver, foetal spleen and foetal kidney was samples and analysed for mRNA-2002 and ATX-126.

As observed in the repeat-dose toxicity in rabbits, the levels of mRNA-2002 were either very low or in the majority of samples not detected at all, despite sampling the day after the last dose.

ATX-126 was detected at low levels in maternal plasma (38-80 ng/mL) and somewhat higher levels in placenta (275-388 ng/g). No ATX-126 was detected in foetal tissues. However, it should be noted that the LLOQ is 250 ng/g in tissues, which is close to the concentration levels in found in placenta. Hence, transfer of low concentrations of ATX-126 to foetuses cannot be out-ruled.

Metabolism

ATX-126 was the only component in ARCT-154, for which the metabolism was evaluated. Other excipient components of the LNP are covered by already authorised/marketed products.

Metabolism of the mRNA component was not investigated as it is expected to catabolised and cleaved into small oligomers and eventually mononucleotides. This is acceptable.

Metabolism studies (in vitro in mouse, rat, rabbit, monkey and human and in vivo in mouse), were conducted. Resulting samples after incubation in liver microsomes, liver S9, plasma or hepatocytes were analysed using liquid chromatography and high-resolution mass spectrometry for tentative structural characterisation including high-resolution daughter spectra, but without comparison to synthesised standards. Moreover, suitable positive and negative controls were included in the studies.

In line with the distribution studies, ATX was quite stable in all in vitro systems with all metabolites formed in lower than 5% of parent compound. The biotransformation of metabolites in vitro was by oxidation, dehydrogenation or N-demethylation. M8 (+O) and M7 (-CH2) was formed in rabbit hepatocytes and M6 (+O-2H) and M8 was formed in human hepatocytes. Hence, as such, M6 is not covered by the rabbit, which is the species used for safety evaluation of ARCT-154.

The in vivo metabolism of ATX-126 in mouse was investigated by analysing urine, bile, plasma, and liver tissue samples collected from CD-1 male mice 24 hours post IV bolus dosing of a LNP formulation containing ATX-126 and a siRNA.

In vivo metabolism was only evaluated in the mouse and not in the rabbit in which the repeat-dose toxicity and reproductive toxicity studies were conducted. Moreover, the route of administration was IV and metabolites in excreta was only evaluated 24 hours post dosing. Here, the major metabolites were ester hydrolysed (M2 and M4). Other metabolites were similar to those observed in vitro with or without ester hydrolysis.

Excretion

Excretion studies are normally not required for vaccines. An ADME study of ATX-126 in rabbit would have been of value. However, due to the very low dose and infrequent administration, this is acceptable.

Pharmacokinetic drug interactions

Studies of pharmacokinetic drug interactions are not required for vaccines.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single dose studies were not presented. Acute toxicity was assessed at several clinically relevant endpoints in the repeat-dose toxicity studies of both ARCT-021 and ARCT-154. This is acceptable for products intended for repeated administration.

2.4.4.2. Repeat dose toxicity

Overview of findings in repeat-dose toxicity studies:

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
2505-036 (GLP)	ARCT-021 Rabbit/M/F/7 2/7 in recovery group	20 or 40 µg IM	2 weeks/2 doses two weeks apart 2 weeks recovery	40 µg	**Clinical signs** (≥ 20 µg): Transient fever **Clinical chemistry** (≥ 20 µg): ↑: monocytes, CRP, IL-6, IP-10, MCP-1, platelets, fibrinogen, triglyceride (40 µg, F), ↓: albumin, red cell mass parameters, 40 µg: ↓ reticulocyte counts. **Histopathology:** (≥ 20 µg): Injection site reactions showing partial recovery. ♀: mononuclear infiltration kidney (1/5 at 20 µg), bile duct hyperplasia (1/5 at 40 µg)
2505-037 (GLP)	ARCT-021 Rabbit/M/F/7 2/7 in recovery group	20 or 40 µg IM	4 weeks/3 doses two weeks apart 4 weeks recovery	40 µg	**Clinical signs** (≥ 20 µg): Transient fever **Clinical chemistry** (≥ 20 µg): ↑: monocytes, CRP, IL-6, IP-10, MCP-1, platelets, fibrinogen, triglyceride (40 µg, F), ↓: albumin (F ≥ 20 µg), red cell mass parameters, reticulocyte counts. **Histopathology:** (≥ 20 µg): Injection site reactions showing partial recovery. Males showed sporadic histopathological findings in the high dose group; ♂ 40 µg: Mineralisation in aorta (2/5 minimal to mild), mononuclear infiltration in heart (1/5 minimal), mineralization in kidney basophilic tubule (2/5 mild). Females showed sporadic histopathological findings in the low dose group with none in the high dose group; ♀ 20 µg: Mineralisation in aorta (1/5 minimal, 1/2 in recovery), mononuclear infiltration in heart (1/5 minimal), liver fibrosis (1/5 minimal)

020186.003 (GLP)	ARCT-154 Rabbit/M/F/7 2/7 in recovery group	16.75, 25.1 or 33.55 µg IM	4 weeks/3 doses two weeks apart 4 weeks recovery	33.55 µg	**Clinical signs** ≥16.75 µg: Transient fever **Clinical chemistry** ≥16.75 µg: ↑: neutrophils and monocytes, IL-6, IP-10, MCP-1, platelets, fibrinogen ↓: albumin, red cell mass parameters, reticulocyte counts. **No increase in CRP** **Histopathology:** Injection site reactions appear lower in incidence and severity compared to the two ARCT-021 studies. However, increased cellularity (lymphocytes) were observed in spleen and lymph nodes

2-week repeat-dose study of ARCT-021 in rabbits (study 2505 036)

Rabbits (N=7, 2/7 in recovery group), were dosed either vehicle, 20 or 40 µg mRNA in ARCT-021 on Day 1 and 15. Main study animals were necropsied on Day 17 and recovery animals two weeks after the last dose on Day 29.

Classical core endpoint was included in the study supported by analysis of selected cytokines and anti-spike antibodies.

The repeated biweekly IM vaccination was well tolerated without any AEs on ophthalmology, body weight parameters, food consumption, organ weight. Transient elevations in body temperature (up to 4%) were observed post-dose.

Clinical chemistry (≥ 20 µg) showed significant increases in monocytes, CRP, cytokines (IL-6, IP-10, MCP-1), coagulation parameters (platelets, fibrinogen), triglyceride (although only at 40 µg in females, F) and decreases in albumin and red cell mass parameters (erythrocytes, haematocrit, haemoglobin). At dose 40 µg, reticulocyte counts were decreased. All these findings were not considered adverse but rather expected inflammatory reactions to the vaccines. This is supported.

Slight erythema and oedema were observed at some injection sites after the first dose, but no Draize scores were higher than 2. Hence, from the outside, injection site reactions appeared benign.

Histopathology examinations revealed injection site reactions of dose related incidence of fibrosis, degeneration/necrosis, inflammation in hair follicles/epidermis, infiltration of mononuclear cells, heterophilic cells and leucocytes showing partial recovery (≥ 20 µg).

Both SARS-CoV-2 spike-specific IgG and neutralising antibodies to SARS-CoV-2 were detected, indicating an immunogenic response to the vaccine.

Sporadic findings of bile duct hyperplasia (40 µg) in 1/5 female rabbits and mononuclear cell infiltration in kidneys in 1/5 female rabbits (20 µg) was observed.

NOAEL was determined to be 40 µg. Since all findings can be ascribed to reactogenicity to the vaccine and that the histopathology findings in bile duct and kidneys are only in one single animal and may be considered incidental. This is supported.

4-week repeat-dose study of ARCT-021 in rabbits (study 2505-037)

With a similar design, this 3-dose study used the same biweekly doses (20 or 40 µg mRNA), but included a third dose on Day 29 and extended the recovery time to 4 weeks. Moreover, sampling for evaluating distribution of mRNA and ATX-126 was included up to Day 57.

Findings of transient fever, oedema and erythema at injection sites and clinical pathology were similar to the 2-dose study. However, the cytokines IL-6 (both sexes) and MCP-1 (females) were still slightly increased on Day 57, 28 days after the last dose.

Males showed sporadic histopathological findings in the high dose group; Mineralisation in aorta (2/5 minimal to mild), mononuclear infiltration in heart (1/5 minimal), mineralization in kidney basophilic tubule (2/5 mild). Females showed sporadic histopathological findings in the low dose group with none in the high dose group; Mineralisation in aorta (1/5 minimal, 1/2 in recovery), mononuclear infiltration in heart (1/5 minimal), liver fibrosis (1/5 minimal). More histopathological findings were observed in this study as compared to the two-dose study.

NOAEL was again determined to be 40 µg. This is supported since no direct link was observed between the presence of ATX-126 in tissues and histopathological findings.

4-week repeat-dose study of ARCT-154 in rabbits (Study 020186.003)

Quality assurance audits took place all through the study and included e.g. protocol, protocol amendments, necropsy, clinical pathology, draft and final report.

The study design was similar to study 2505-037. However, it did not include analysis for distribution of ATX-126, mRNA and Spike protein. Analysis of dosing solutions revealed lower than acceptable concentration of Group 4 males on Dosing Phase Days 1 (80%) and 29 (84%) and Group 4 females on Dosing Phase Day 1 (82%). All samples were within the range of 80-89% of nominal concentration. Moreover, the target dose levels were 40, 60, 80 µg, however it was chosen to use the corrected dose according to an updated certificate of analysis, i.e. 16.75, 25.1 and 33.55 µg. This is acceptable.

Findings were similar to findings in the 4 week repeat-dose toxicity study on ARCT-021 at all three dose levels with transient fever, increased neutrophils and monocytes, IL-6, IP-10, MCP-1, platelets, fibrinogen and decreased albumin, red cell mass parameters and reticulocyte counts. Reticulocyte counts was only partially resolved at the end of recovery in high dose males and females ≥ 16.75 µg.

However, in this study there was no increase in CRP and the injection site reactions appeared lower in incidence and severity, although increased cellularity (lymphocytes) was observed in spleen and lymph nodes. Transient decrease in food consumption was noted for 1-3 days post dosing, but did not impact body weight.

Female animals showed higher levels of anti-Spike protein total IgG for the mid and high dose on Day 31 than at the end of the recovery phase, but the other way around for the low dose. All male animals increased levels from Day 31 to the end of recovery phase. This difference could be driven by interindividual variability and low number of animals at the end of recovery (N=2). All recovery animals showed robust neutralisation titers at the end of the study (Day 57).

All findings can be ascribed to inflammatory reaction to the vaccine and were not considered adverse. This is supported. NOAEL is the highest dose of 33.55 µg. This dose provides sufficient safety margin to the human dose of 5 µg.

2.4.4.3. Genotoxicity

Neither in vitro nor in vivo genotoxicity testing was performed on ARCT-154. Instead, a read-across strategy was applied combined with in silico evaluation for genotoxic potential of the new cationic lipid

constituent ATX-126. mRNA is not considered genotoxic, however a LNP with and without another mRNA than the one in ARCT-154 was evaluated for genotoxicity (mutagenicity and clastogenicity) in bacteria (*salmonella and E. coli*), mammalian cells (TK6) and mice with negative outcome (i.e. no genotoxic potential).

All in vitro studies and in vivo micronucleus study in mice were performed in compliance with GLP using proper study design and positive controls with and without metabolic activation.

PEG2000, DSPC and cholesterol is used in an already approved product (Onpattro) and is therefore considered qualified.

The in-silico assessment was performed using Expert Alert and Quantitative Structure Activity Relationship predictions performed using the Leadscope Model Applier. The outcome was unequivocally negative.

2.4.4.4. Carcinogenicity

No carcinogenicity testing was carried out, as it is not a general requirement for vaccines. This is acceptable.

2.4.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity was evaluated for ARCT-021 in one single study in rabbits. Rabbits (N=44) were dosed 28 days before mating (Day 1 of study, 14 days prior to mating (DS15) and GDs 0, 14, and 28. Hence, 5 doses in all were administered biweekly. The dose levels were half the levels in the 4-week repeat dose toxicity study, namely 10 or 20 µg compared to control (vehicle PBS). Half the does were C-sectioned GD 29 for maternal and foetal examinations of core end points of fertility and macroscopic pathology. In addition, at C-section on GD 29, maternal and foetal plasma, placenta, and foetal tissues (liver, kidney, and spleen) were analysed for mRNA-2002 and ATX-126 lipid. The remaining does were allowed to proceed to natural delivery. The F1 generation was monitored for viability, clinical observations, body weights, preweaning development (auditory startle, pupil constriction), visceral and skeletal abnormalities and neutralising antibodies up to postpartum Day 28.

Maternal findings

The major finding in maternal rabbits was body weight loss compared to the control group during the GD 0-29, which in high dose group was considered adverse. The loss was less severe in the low dose group where the body weight did not influence the overall body weight gain during the gestation period. During the lactation period, the does increased more in body weight than the control group by more than 50% indicating sufficient compensation. Moreover, the foetuses and pups were not impacted by the low body weight of the does. The body weight loss was correlated to decreased food consumption, again for the high dose this was considered adverse.

However, no differences on fertility parameters were noted for the three study groups (number of females pregnant/number of females with evidence of mating, number of pregnant females/number of females paired, number of females pregnant/number of females with evidence of mating and classical litter parameters).

Nevertheless, as the body weight losses indicate, a general inflammatory reaction to the 5 doses of vaccine was observed through the increased levels of cytokines (IL-6 and MCP-1 and IP-10), but no increase in IFN-γ, TNF-α or CRP. Increase in CRP was observed in the 4-week study of ARCT-021, but not in the 4-week study of ARCT-154.

NOAEL for maternal toxicity was set to 10 µg. This is supported.

Foetal findings

Foetal evaluations were based on 152, 140 and 155 live GD 29, Caesarean-delivered foetuses in 19, 20 and 20 litters in the vehicle and 10 µg and 20 µg dose groups, respectively. Each of these foetuses was examined for foetal external and visceral abnormalities. Of these foetuses, 152, 140 and 146 were examined for skeletal and foetal ossification site averages in 19, 20 and 19 litters in the vehicle and 10 µg and 20 µg dose groups, respectively. This is considered a sufficient basis for evaluating teratogenicity or other end points suggesting foetal toxicity.

External and visceral abnormalities were observed in all three groups, although in very low numbers and the incidence was without any dose relation. Hence, all findings were considered unrelated to the treatment with ARCT-021 and therefore NOAEL for the F1 generation was set to 20 µg. This conclusion is supported.

Litter observations up to lactation Day 28 included mortality, maternal care of the offspring, clinical signs, body weights, preweaning developmental effects including testing for acoustic startle and pupil constriction. No differences were noted in kits between the dosing groups on these end points.

At scheduled euthanasia on postpartum Day 28, several internal findings in the kits were noted across the dosing groups (dilation of the third ventricle of the brain, discoloured bladder, cyst on the left kidney, discoloured liver or discoloured lung). However, these were rare and the incidence not dose-related or occurred only in the control group. Hence, the conclusion was that no necropsy observations, which were noted in any of the F1 generation kits, could be attributed to the exposure to ARCT-021. This conclusion is supported.

Transfer of immunity (IgG) from does to foetuses through placenta was demonstrated by the analysis of Spike specific IgG in serum of does, foetuses and kits. Levels of spike specific IgG was dose dependent in does but not in foetuses and kits. IgG levels in foetuses were similar to does at GD29, but had waned of considerably at DP27 (in kits) as would be expected as at that time, kits start to develop their own immune system.

Hence, no AEs were observed in kits on any classical end point of postnatal development and transfer of maternal immunity was demonstrated, although IgG levels were low in kits on DP27.

NOAEL effect level for postnatal development (kits) was set to the highest dose 20 µg. This conclusion is supported.

Studies in juvenile animals

The indication for Kostaive is not including adolescents or children.

2.4.4.6. Toxicokinetic data

Toxicokinetics was not provided for ARCT-154. However, non-GLP bioanalysis of mRNA and ATX-126 was performed in the 4-week repeat-dose toxicity study of ARCT-021.

The applicant did not provide data to be able to perform classical interspecies comparison of toxicokinetics as this is not required for vaccines, although such data for ATX-126 in serum or plasma would have been of value for its safety evaluation. Determination of safety margin will therefore be based on dose.

The NOAEL was the high dose in all three repeat-dose toxicity studies and these doses were sufficiently higher than the human dose without correction for mg/kg or allometric scaling.

NOAEL in the 4-week study of ARCT-154 was 33.55 µg to rabbits and the human dose is 5 µg.

2.4.4.7. Local tolerance

Local tolerance is discussed in repeat-dose toxicity sections.

2.4.4.8. Other toxicity studies

Antigenicity and immunotoxicity

Due to character of the product, i.e. antigenicity is the pharmacological effect. Antigenicity is covered in other sections. Moreover, potential immunotoxicity is monitored in non-clinical proof of concept studies and repeat-dose toxicity studies. This is considered sufficient.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature, vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, ERA studies are not provided in this application for Marketing Authorisation.

2.4.6. Discussion on non-clinical aspects

GLP

The 4-week IM study of ARCT-154 in rabbit was claimed to be conducted according to GLP. Exceptions were described in the main report (e.g. for biomarkers of CRP, cytokine and immunogenicity), which were not conducted in compliance with GLP regulations. Activities pertaining to CoA, concentration and purity of test article were performed in accordance with GMP.

Otherwise, this study underwent a comprehensive audit program covering all protocol amendments, necropsy, clinical pathology data and the ophthalmology report.

Regarding the 2-week and the 4-week studies in rabbits of ARCT-021, it is described in the main reports that Nab, ATX-126 and mRNA analysis were not conducted in compliance with GLP regulations. Even though these are important endpoints for risk assessment, this is not required for vaccines. Moreover, the bioanalytical methods are considered sufficiently qualified.

There is no reason for triggering a GLP inspection.

Pharmacology

The primary pharmacology studies of ARCT-154 were limited to immunogenicity studies in mouse and NHP at only one dose level. Dose response immunogenicity studies and challenge studies were presented as secondary pharmacology studies on ARCT-021.

In NPH ARCT-154 study, non-clinical proof of concept is confirmed in the monkey using both cell free, cellular and ex vivo assay immunogenicity end points. However, it is accepted that challenge studies are omitted for ARCT-154 referring to the platform strategy as such studies are available for ARCT-021 (mice and monkeys).

The potency and efficacy of ARCT-021 was thoroughly characterised by de Alwis et al (2021) in C57Bl/6J mice using traditional IgG, and cellular immunogenicity assays supplemented with gene array analysis.

This was supported by data from the transcriptomic analysis of whole blood cells 1 day post vaccination (Study GSY02), which suggests an increase in antiviral responses and a downregulation of inflammation genes. The dose-range finding immunogenicity study performed in NHP showed as expected that the high dose of 20 µg yielded substantial higher titers of neutralising antibodies over time than the low dose of 5 µg at all time points. However, it was observed, that the IFN-γ response from activated T-cells was consistently much higher for the low dose than for high dose. In a study of another vaccine, similar response of IFN-γ was observed for the low and the high dose and this was similar to the observations in the Phase 1/2 clinical studies with ARCT-021, where spike-specific CD4 T-cell responses were dominated by Th1, IFN-γ-producing cells and not Th2, IL-4-producing cells. This is reassuring. Hence, the observations in the monkeys could be a result of interindividual variability and not necessarily an inverse dose-related activation of T-cells.

The study GSY03 is considered highly clinically relevant due to the transfection with the human target of the SARS COV-2 virus (ACE2). Both dose levels provided full protection from the virus, whereas the non-vaccinated animals all died within 7 days of challenge. While this challenge study in hACE2 transfected mice is accepted as a non-clinical proof of concept study, the doses of 2 and 10 µg per mouse are far from the selected dose in humans (i.e. 5 µg).

The applicant mentioned that other mRNA vaccines (conventional type) used much higher RNA doses in animals and stated that it could be difficult to translate immunogenicity (and efficacy) data from animals to humans. Therefore, the human starting dose was based on rabbit safety data and doses used in NHP immunogenicity studies, but not on a mg/kg basis. This approach is used more often for vaccines. This is considered acceptable.

Moreover, protein expression could provide some insight in the comparison between ARCT-based vaccination and conventional mRNA vaccination, as the latter is anticipated to have initial higher spike protein expression. The discussion based on the induction of S protein expression was not provided as these data are not available in NHP. Data in mice are available, but in the study from de Alwis et al. (2021) the same dose for sa-mRNA and conventional mRNA was used. This was not considered relevant for the current clinical practice, in which humans have been vaccinated with conventional mRNA vaccines containing a higher mRNA starting concentration than the currently proposed vaccine.

The NHP is genetically closer to human than rodents, however, may not be the optimal challenge model as even without protection by vaccination, NHP recover quickly from challenge with SARS COV-2 virus. Nevertheless, meaningful data was obtained on several traditional immunogenicity endpoints as well as viral load and reduction in virus in respiratory system over time. The upward shift of IL-13 was only observed in the high dose (20 µg) in the monkeys, which is not considered clinically relevant (5 µg). Moreover, as this dose was able to reduce viral titers, it did induce vaccine associated AEs and did not induce Th2 cytokines similar to clinical studies. This finding is not considered of concern.

Pharmacokinetics

Firstly, the distribution study of luciferase sa-mRNA compared with conventional luciferase mRNA showed that the exposure of the sa-RNA was higher and longer lasting than the conventional mRNA and importantly, the sa-mRNA was cleared from muscle tissue at 15 days post a single dose of up to 50 µg mRNA.

Secondly, a study of distribution of the mRNA, synthesised spike protein and ATX-126 in ARCT-021 was performed in mouse and showed that mRNA in ARCT-021 is present in plasma and tissues in mice

for only two weeks, despite the self-amplifying nature of the construct. Hence, there should be no concern for long term exposure to the active drug substance in the vaccine.

It was not possible to determine the half-life of ATX-126 for the majority of tissues. As ATX-126 was also found in ovaries in rabbits at the end of recovery in the repeat-dose toxicity study, further information on potential clinical implications of the long half-life in the ovary in both mice and rabbits was requested.

The findings in the pivotal repeat-dose toxicity studies do not indicate a concern for ATX-126 in ovaries despite its very long half-life. However, as this is not a GLP-compliant safety study with systematic histopathology, safety margins cannot be based on it.

Instead, the rabbit study (2505-037) is accepted for this exercise. It should be noted that the rabbits received 3 biweekly vaccinations, whereas the vaccine will be administered as an annual boost in the clinical setting. For the 20-mcg rabbit dose, each rabbit received 420 mcg of ATX-126 (equivalent to 127 mcg/kg, assuming an average rabbit weight of 3.3 kg). Using the 0.32 conversion factor for rabbit dose to HED outlined in the US FDA guidance on maximum safe starting doses, the HED would be 41 mcg/kg. For the 5-mcg annual vaccine dose, each person will receive 105 mcg of ATX-126 in each dose, which is equivalent to 1.5 mcg/kg (assuming a 70-kg human body weight). Thus, the study provides a safety margin of 27 (41 mcg/kg/1.5 mcg/kg). This safety margin is considered sufficient provided the below summarised arguments:

- While it was agreed that accumulation of ATX-126 could potentially adversely affect sperm, oocytes and follicles, there was no effect on fertility in the female rabbits in the EFD study of ARCT-021. While impact on male fertility in vivo has not been investigated, the repeat-dose toxicity studies did not show any changes in tissues of male reproductive organs.
- As discussed in Jörgensen et al., LNPs have the potential to perturb cellular and nuclear membranes (target) that can result in the release of degrading enzymes from liposomes, cause mitochondrial permeabilisation and dysfunction, generate reactive oxygen species, alter cytoplasmic enzyme functions, and damage DNA. A lipid similar to ATX-126 was evaluated in in vitro and in vivo assays of genotoxicity and was found negative both as empty nanoparticle and as carrier for another mRNA.
- With regard to the potential for cellular toxicity, characteristics of the lipids discussed by Jörgensen et al., which could lead to toxicity was compared with SM-102, the major lipid component of Spikevax, which is also a cationic ionisable lipid.
- Although the degradation of ATX-126 is very slow, ATX-126 is indeed cleaved by esterase/lipase into a hydrophobic tail and a polar head group. It is believed that the esterase/lipase-mediated cleavage is slow because of the steric bulk around the ester bonds. Mechanisms of degradation are suggested and metabolites of ATX-126 are not considered more toxic than metabolites of SM-102.
- Micellar formation may lead to micelles to extract cell membrane lipids to form mixed micelles. This toxic effect increases with the length of the hydrophobic chain of lipids in the head group. The head group hydrophobicity of ATX-126 is lower than for SM-102.
- Micellar formation is believed to be less than for SM-102, due to the limited positive charge outside the endosomal compartment.
- The tail of ATX-126 and SM-102 are made of similar medium length branched fatty alcohols.
- Each dose of Kostaive has less ATX-126 lipid than the amount of SM-102 an individual would receive when vaccinated by Spikevax.

- The polar head of ATX-126 is a tertiary amine, whereas for SM-102 it is and alcohol group. According to Jörgensen et al., amines are less toxic and MC-3, another ionisable lipid already used in a marketed LNP also has a tertiary amine as polar head similar to ATX-126.

The high variability in quantification of spike protein was explained by variability in sampling of tissues as the distribution of spike protein may not be uniform in the organs of the animals and naturally more variability was then observed at time points and tissues at or near the lower limit of quantification. Moreover, it was observed that, whereas the full spike protein (S1+S2) was detected in muscle, subunits of the spike protein were found in other organs such as the lung. This could be due to inflammatory cells transporting subunits from the muscle tissue to other organs adding to the variability of the assay for spike protein. This explanation is accepted and at 72 hours only 3 animals out of 20 were below LLOQ at 72 h for spike protein, hence confirming the reliability of this assay.

Distribution of mRNA and ATX-126 was evaluated in the 4 week repeat-dose toxicity study of ARCT-021 in rabbit in selected tissues on Day 31 (two days after the last dose) and 57 (end of recovery). Also, in this study ATX-126 show very slow clearance from some of the analysed tissues (spleen, liver and ovary). As expected from the mouse study, mRNA-2002 was not detectable in rabbit tissues at the end of recovery. However, that no mRNA in a panel of tissues, except low levels in spleen, could be detected 2 days after the last (third) dose, is unexpected. Moreover, the seroconversion between Day 29/31 and 57 is rather poor.

The low concentrations of sa-mRNA in tissues in rabbit as compared to the mouse 2 days after dosing was explained by the much lower dose in mg/kg in the rabbit in combination with the inherent short half-life of mRNA in tissues. The low seroconversion was explained by the exaggerated vaccination regime used in order to confirm safety and not efficacy. A more clinically relevant vaccination regime was used in a monkey study (ARC21-036), in which sufficient seroconversion was observed.

The assay used to detect the sa-mRNA does not distinguish between intact sa-mRNA or smaller fragments. Measurement of mRNA will therefore likely be an overestimation of functional mRNA. The mRNA detected in the plasma could have resulted from systemic exposure following the IM administration and may be representative of intact LNP-mRNA or individual analytes (mRNA) derived from extracellular vesicles. Free mRNA, released from the LNP in the plasma, will be degraded rapidly. mRNA in plasma was undetectable after 48h. Spike protein in mouse plasma is still detectable after 744h (31 days), but only at a very low amount (10 ng/ml). In addition, in terms of safe breastfeeding, when compared on a mg/kg bw basis, the doses that the mice received in this study are much higher than the dose used in humans (14,000-fold). Therefore, the systemic exposure to mRNA and spike protein in humans will be negligible and Kostaive can be used during breastfeeding.

Detection/distribution of ATX-126 is not similar to detection/distribution of intact LNPs (and thus, tissues where translation into spike protein will take place). It is difficult to quantify intact LNPs directly in biological matrices and that instead, the LC-MS/MS method is used to detect ATX-126 in tissues. This method does not detect intact LNP. In addition, it is anticipated, that LNPs are characterised by their ability to remain stable in the bloodstream but to undergo rapid processing after cellular uptake. Comparative analyses between QWBA (as an indication for intact LNP distribution) and LC-MS/MS data show comparable results. Detection of ATX-126 in tissues may therefore reflect uptake and degradation of LNPs.

Since, ATX126 is a new lipid component, the very long half-life observed in mouse and rabbit tissues and that no human AME data was presented, the lack of an ADME study in rabbit is considered a deficiency.

However, since i) metabolic pathways is demonstrated in vitro for both rabbit, human and ii) the in vivo study in mouse shows ester hydrolysis, which was not detectable in vitro, iii) the dose of ATX-126

is very low (105 µg/dose) and infrequent administration, no further studies of metabolism of ATX-126 will be required.

Toxicology

The platform strategy was also employed in evaluating repeat-dose toxicity and reproductive and developmental toxicity of ARCT-154 in rabbits.

In study 2505-037, the findings are presented as minimal and were not dose-related, they are accepted as incidental or reflecting inflammatory reactions to the vaccine.

The increase of inflammatory markers as observed by higher levels of IL-6 and MCP-1 in the repeat-dose toxicity study of ARCT-021 was not observed in the study of ARCT-154 of similar design. The applicant clarified that this finding could be caused by a higher concentration of double stranded RNA in the formulation of ARCT-021 compared to ARCT-154, which is associated with increased reactogenicity. Hence, as also explained in the distribution section, ATX-126 cannot be directly linked to long term inflammation or any other observed toxicities.

Studies of the genotoxic potential of ARCT-154 were presented, again in a platform context. The only study presented for ATX-126, which is a new cationic LNP constituent, which has not been included in any marketed products, was an in-silico mutagenicity prediction. All in vitro studies fell out unequivocally negative. In the in vivo study, all animals survived to the scheduled euthanasia in both the range-finding and definitive phases. A very low increase in micronucleated cells were observed in males dosed with both the LNP with and without mRNA, when compared to the control group. But the numbers were still within 95% CI for the vehicle in male and females and no dose-response was observed. Hence, the response was deemed negative. This is supported.

While the theoretical risk of nitrosamine formation of ATX-126 is noted, as the compound contains a tertiary amine that could be desmethylated and nitrosated, it is specifically stated in the quality assessment that the risk of nitrosamine formation is negligible as no nitrosating agents are present during the drug product manufacturing process. A specific toxicological risk assessment of the nitrosamine of ATX-126 is therefore not considered warranted.

The read across/platform strategy for evaluating the genotoxic potential for ARCT-154 is considered sufficient.

In terms of evaluating the risk of reproductive and developmental toxicity, ARCT-154 have not been included in such studies. Instead, a comprehensive study of ARCT-021 in rabbits dosed with 5 doses covering pre-mating and through to delivery at 10 and 20 µg. While the maternal animals lost weight in the high dose group, no findings on fertility or foetal development could be attributed to ARCT-021. Hence, NOAEL was 10 µg for does and 20 µg for foetal development. Using ARCT-021 as surrogate for evaluating the potential for reproductive and developmental toxicity of ARCT-154 is accepted.

ERA

There is a potential risk for recombination of the vaccine with a wild type VEEV-like virus when a patient becomes infected prior to or following ARCT-154 vaccination. This vaccine is considered a non-GMO and the absence of an environmental risk assessment can therefore be endorsed. The anticipated risk and consequences of recombination of the vaccine with a wild type VEEV-like virus is low, due to several reasons. First, simultaneous infection by two different alphaviruses in the same cell is extremely unlikely because of superinfection exclusion. Second, sequestration of sa-mRNA to the cytoplasm prevents recombination with a wild-type virus. Third, codon optimisation performed on sequences encoded by zapomeran have sufficiently changed the coding as to make recombination with wild-type sequences highly unlikely. In addition, if recombination should occur, the mutations in the replicase coding region would likely lead to a substantial decrease in pathogenicity of VEEV.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical documentation is considered sufficient for the sought indication in individuals 18 years of age or above.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study number, sites, dates	**Study status**	**Study design**	**Test products, dosage regimen**	**Study objectives**	**Study duration**	**Study population**	**Efficacy/ immunogenicity endpoints**
Pivotal Studies							
ARCT-154-01 (total of 17 sites in Vietnam; 1 site conducted Phase 3c only). Aug-2021 – 23-Jan-2023.	Completed	Phase 1/2/3, randomised, observer-blind, placebo-controlled; crossover.	Phase 1/2/3a/3b ARCT-154 5 µg or placebo. Primary immunisation, 2 doses spaced by 4 weeks. After crossover, some participants received a 3rd dose. Phase 3c: ARCT-154 5 µg, or comparator (Vaxzevria). Primary immunisation, 2 doses spaced by 4 weeks.	Safety, efficacy, immunogenicity.	12 months after completion of initial 2-dose vaccination series.	Phase 1 Healthy volunteers 18 to <60 years of age. Phase 2/3 Volunteers ≥18 years of ages, healthy as well as at-risk of severe COVID-19.	Phase 1/2/3a NAb seroconversion rate by sVNT (ACE2 blocking assay) at day 57. Phase 3b Efficacy of ARCT-154 for prevention of protocol-defined COVID-19 between days 36 and 92. Phase 3c Non-inferiority of neutralising antibody responses versus comparator (index strain). Efficacy included as exploratory endpoint.
ARCT-154-J01 (11 sites in Japan). Nov-2022 – 27-March-2023.	Enrolment completed, follow-up ongoing.	Phase 3, randomised, observer-blind, active-controlled.	Second booster (4th immunisation). One dose of ARCT-154 5 µg or Comirnaty original 30 µg.	Safety, immunogenicity.	12 months after vaccination.	Healthy adults ≥18 years of age who have received three doses of approved mRNA COVID-19 vaccine at least 3 months prior.	GMT and SRR of NAb against SARS-CoV-2 (index and omicron BA.4/5 strain) by sVNT (ACE2 blocking assay) at day 29.

Study number, sites, dates	Study status	Study design	Test products, dosage regimen	Study objectives	Study duration	Study population	Efficacy/ immunogenicity endpoints
Supportive Studies							
ARCT-021-01 (1 site, Singapore) Aug-2020 – Jan-2021	Completed	Phase 1/2, randomised, double-blind, placebo-controlled.	ARCT-021: 1 to 10 u (1 and 2 doses).	Safety, immunogenicity, dose-escalation	Phase 1: 57 days Phase 2: 85 days	Healthy volunteers 21 to 80 years of age	Antibody responses day 29 (phase 1, single-injection cohorts) and day 57 (phase 2, 2 injection cohorts). T-cell responses and immune gene expression evaluated as exploratory objectives.
ARCT-021-02 (1 site, Singapore) Jan 2021 – Dec 2021	Completed (terminated early).	Phase 2a, open-label extension of parent study ARCT-021-01. Cohort 1a: Placebo recipients from ARCT-021-01. Cohort 1b: Received 1 immunisation in ARCT-021-01; seronegative on screening for ARCT-002. Cohort 2: Received 1 or 2 immunisations in ARCT-021-01; seropositive on screening for ARCT-002.	Cohorts 1a and 1b: Single dose of ARCT-021, 7.5 µg. Cohort 2: None (monitoring of safety and immunogenicity responses only).	Safety and long-term immunogenicity.	Terminated early, as 63 of the 65 participants received non-study authorized COID-19 vaccine after enrolling in ARCT-021-02. 7-month safety follow-up after last vaccination available.	Participants from ARCT-021-01.	Long-term NAb and anti-spike protein antibody responses following vaccination with ARCT-021.
ARCT-021-04 (15 sites, 12 in the US, and 3 in Singapore) Jan-2021 – Mar-2022	Completed (terminated early).	Phase 2, randomised, observer-blind, placebo-controlled.	Primary immunisation: ARCT-021. 5 µg, 7.5 µg, or placebo (1 and 2 doses, days 0 and 28). Booster (day 208): 5 µg of ARCT-021, ARCT-154, or ARCT-165, or placebo/no booster.	Immunogenicity, safety, reactogenicity, dose-ranging.	Terminated early. 56 days safety follow-up after last vaccination available.	Healthy volunteers ≥18 years of age.	NAb responses of ARCT-021 versus placebo for priming vaccinations.

Study number, sites, dates	Study status	Study design	Test products, dosage regimen	Study objectives	Study duration	Study population	Efficacy/ immunogenicity endpoints
ARCT-165-01 (cohort A, 1 site in South Africa; cohort B, 1 site in Singapore and 2 sites in US) Aug 2021-ongoing	Enrollment completed.	Phase 1/2, randomised, observer blind.	Primary series (cohort A): ARCT-154, ARCT-165, or ARCT-021 5 µg, 2 doses, spaced by 28 days. Booster vaccination approx. 5 months after two primary doses of Comirnaty (cohort B): ARCT-154, ARCT-165, or ARCT-021 5 µg.	Safety, reactogenicity, immunogenicity.	12 months after last vaccination.	Healthy volunteers 21 to 65 years of age.	NAb and BAb responses (descriptive)

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pharmacokinetic studies are generally not considered relevant for vaccines. Kostaive is replication-competent (the vaccine mRNA self-replicates after entry into patient's cells) but it is propagation-defective (infectious VEE particles cannot be generated and therefore, the vaccine mRNA cannot spread between cells). Thus, there is not considered to be a need for special pharmacokinetic studies.

2.5.2.2. Pharmacodynamics

Mechanism of action

See section 2.2 (About the product).

Secondary pharmacology (immunogenicity assays)

For vaccines, pharmacodynamic effects are considered to equate with immunogenicity (antibody and T-cell responses induced by the vaccine).

2.5.3. Discussion on clinical pharmacology

PK/PD studies are not relevant for vaccines.

All currently authorised COVID-19 vaccines employ the spike protein as immunogen, albeit in different engineered formats. Hence, the protective immunity induced by the immunogen employed in Kostaive is mechanistically well understood, and it is generally accepted that virus-neutralising antibodies induced by the spike protein are important for protection against disease, and correlate with protection. While other immune mechanisms such as Fc effector functions of spike-specific, non-neutralising antibodies and spike-specific T-cell responses are also considered to contribute to protection, neutralising antibody responses are considered the PD parameter of prime importance for evaluation of spike protein-based COVID-19 vaccines such as Kostaive. Accordingly, and appropriately,

neutralising antibody responses were employed as primary immunogenicity endpoints in the performed clinical studies.

As regards validation of immunogenicity assays, the data from the index +D614G and omicron BA.4/BA.5 neutralisation assays are the most critical for the current MAA, as immunogenicity naturally comprised the primary as well as secondary endpoints in the pivotal ARCT-154-J01 immunobridging study for the heterologous booster indication.

2.5.4. Conclusions on clinical pharmacology

The pseudovirus neutralisation assays employed in the pivotal immunobridging study for the heterologous boost indication are considered adequately validated and fit-for-purpose for use in the pivotal ARCT-154-J01 immunobridging study. In addition, a number of immunogenicity assays were used in the supportive clinical studies and in phases 1/2/3a of the pivotal ARCT-154-01 study.

2.5.5. Clinical efficacy

Kostaive (ARCT-154) shares many similarities with the currently approved non-replicating mRNA COVID-19 vaccines (i.e. LNP encapsulation of mRNA, use of full-length, prefusion-stabilized spike protein immunogen). However, the product is first-in-class because none of the currently approved mRNA vaccines are self-replicating.

The primary series indication is supported by a large, placebo-controlled efficacy study in Vietnam (ARCT-154-01) and the heterologous boost indication is supported by an ongoing smaller immunobridging study in Japan, for which 29-day and 6-month interim reports were provided (ARTC-154-J01).

2.5.5.1. Dose response studies

There is dose-response immunogenicity data available from 4 supportive studies with the Applicant's self-replicating, lipid encapsulated mRNA vaccine platform (STARR/LUNAR platform), comprising the ARCT-021, ARCT-154 and ARCT-165 COVID-19 vaccines.

Two studies were performed exclusively with the ARCT-021 vaccine in Singapore (ARCT-021-01 and ARCT-021-02 studies), and two studies provided comparison of the ARCT-021, ARCT-154 and ARCT-165 vaccines (ARCT-021-04 and ARCT-165-01 studies, performed in Singapore/US and South Africa/Singapore/US, respectively):

- ARCT-021-01 was the first-in-human study for the ARCT STARR/LUNAR platform.
    - In this study, different doses and administration schedules were employed for the primary immunisation series.
- ARCT-021-02 was an open-label extension of ARCT-021, where participants were offered the opportunity to receive a 3rd immunisation (homologous boost) with 7.5 µg of ARCT-021, approximately 3 months after the primary series.
    - The study was terminated early and enrolled very few participants, as it coincided with the rollout of national COVID-19 vaccination campaigns in the initial phase of the pandemic (approximately spring-autumn 2021), and also, the study population was very heterogenous as regards the primary immunisation series.

- In ARCT-021-04, participants were primary-immunised with ARCT-021 by three different posologies (single immunisation at 7.5 µg, two immunisations at 5 µg or 7.5 µg), and received a booster with 5 µg of different ARCT vaccines approximately 6 months later (ARCT-021, ARCT-154 and ARCT-165).
    - The study was terminated early as ARCT-021-02 but it is of interest as the majority of participants were from the US (approximately 514 or 88% in the primary immunisation part, and approximately 186 or 81% in booster part).
- ARCT-165-01 study (cohort B): a total of 36 participants were randomised 1:1:1 to receive a booster with 5 µg of either ARCT-021, ARCT-154 or ARCT-165 vaccines at ≥ 5 months after primary-immunisation with Comirnaty original, and were followed for a year post-boost).
    - While group sizes were very small (n=12 in each of the 3 booster groups at the start), dropping to 1, 5 and 6, respectively, in ARCT-021, ARCT-154 or ARCT-165 booster groups by day 271, due to censoring for natural SARS-CoV-2 infection, the data is of interest as the majority of participants were enrolled at US sites (27, i.e. 75.0% of participants).

In ARCT-021-01, ARCT-021-02 and the primary-series part of ARCT-021-04, the frozen liquid vaccine formulation was used (storage at -70Cº), which was switched to the commercial lyophilized formulation (storage at -20Cº) for the booster part of ARCT-021-04 and all successive supportive and pivotal studies.

The 4-week interval between the two immunisation in the ACT-154 primary series was selected based on the posology for approved, non-replicating mRNA vaccines.

Data from the supportive studies does not provide positive support for the 4-week interval between the 2 immunisations comprising the Kostaive primary series (for example, for the ARCT-021 vaccine, the second dose of the primary vaccination series provided only minimal increase in the response seen after the first dose, 4 weeks earlier).

Taken together, data from the ARCT-021-04 and ARCT-165-01 studies provide early indication that the ARCT-154 vaccine may be a stronger immunogen in a heterologous booster than in a homologous booster setting. Also, ARCT-165-01 provides evidence of T-cell responses after heterologous boost with ARCT-154. ARCT-021-04 and ARCT-165-01 studies provide some immunogenicity data form ARCT-154 in Caucasian populations.

2.5.5.2. Main studies

Data from two pivotal efficacy studies were submitted:

- ARCT 154-01, a phase 1/2/3, randomised, placebo- and active-controlled, observer blind study designed to assess the safety, immunogenicity, and efficacy of Kostaive (ARCT-154) in Vietnamese vaccine-naïve healthy adult participants ≥18 years old.
    - ARCT 154-01 is the pivotal study supporting the development of ARCT-154 for the prevention of COVID-19 in adults 18 years of age or older.
- ARCT-154-J01, a phase 3, non-inferiority immunobridging study comparing a second boost (4th immunisation) with Kostaive (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.

- ARCT-154-J01 is the pivotal study supporting the use of ARCT-154 vaccine as a booster dose given at least three months after the previous COVID-19 vaccine in adults 18 years of age and older.

2.5.5.2.1 ARCT-154-01

Methods

The study was divided into five parts:

- Phase 1: Initial assessment of immunogenicity of primary series of Kostaive.
- Phase 2 and 3a: Assessment of immunogenicity of primary series as well as a homologous booster of Kostaive.
- Phase 3b: Assessment of Kostaive efficacy (pivotal efficacy data).
- Phase 3c: Immunobridging of primary series of ARCT-154 versus Vaxzevria (non-inferiority of neutralising antibody levels; efficacy included as exploratory endpoint).

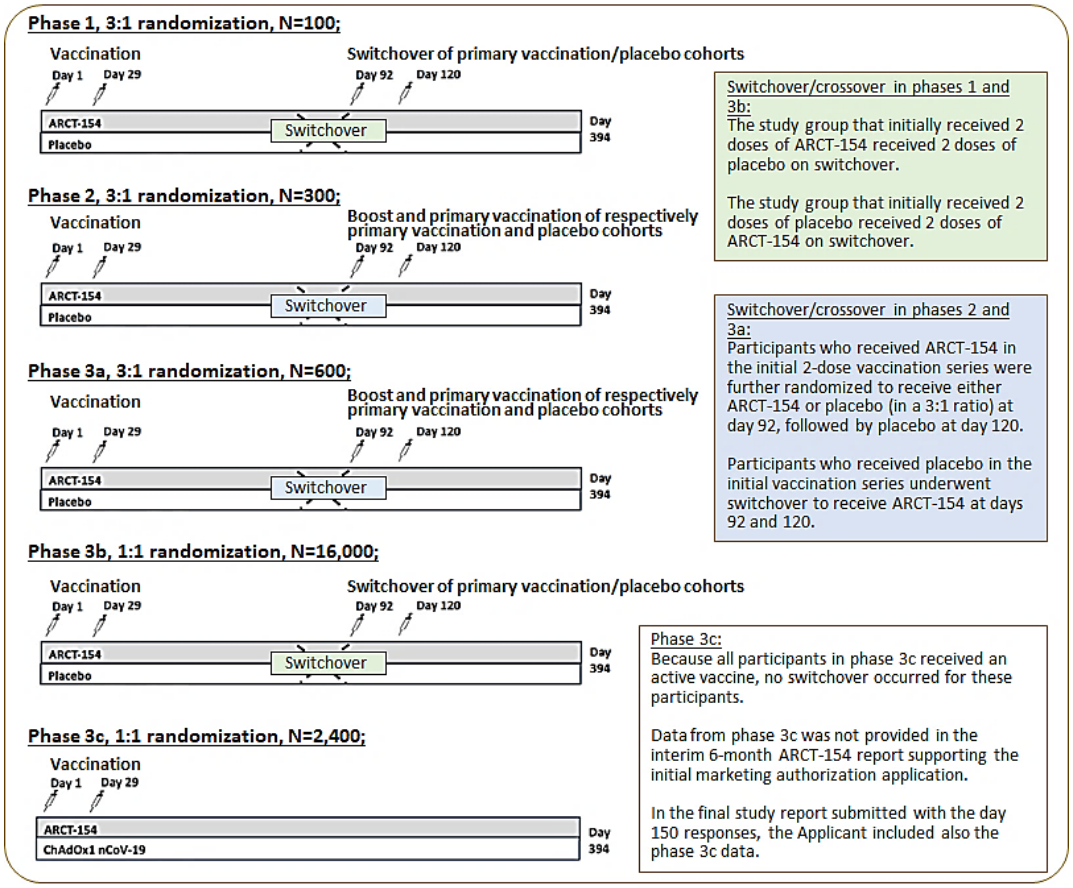
Phase 3b was enriched for participants at higher risk for COVID-19 by deliberate enrollment of individuals considered at high risk of exposure to SARS-CoV-2 due to their workplace environment or living conditions.

As the study was conducted during the SARS-CoV-2 pandemic, when authorised COVID-19 vaccines became available and a mass vaccination campaign was initiated in Vietnam, a switchover vaccination was offered to all placebo recipients at days 92 and 120 for ethical reasons.

The epidemiological context differed between phases 3b and 3c of ARCT-154-01. While phase 3b coincided with the delta variant wave, phase 3c coincided with the tail end of the delta variant period and the peaks of the subsequent omicron BA.2 and BA.5 waves.

A 6-month interim report with an addendum was provided for the initial MAA, comprising phase 1, 2 and 3b data (report v1 of 25 April 2023, and addendum v1 of 16 May 2023).

The Applicant further provided the final ARTC-154-01 report including also phase 3c data (report dated 29 January 2024), as part of the Day 150 responses of this procedure.



- **Study Participants**

ARCT-154-01 was conducted in Vietnam in a total of 17 sites (i.e., 16 sites for phases 1, 2 and 3b; 1 site for phase 3c).

The study enrolled participants ≥ 18 years of age, considered at risk for COVID-19 due to work or living environment in the opinion of the investigator.

Participants had to adhere to contraceptive requirements.

In phases 1 and 2, it was a requirement that participants had access to and could use an eDiary.

Participants were excluded for the following reasons:

- Significant infection or other acute illness, including body temperature >100.4°F (>38.0°C) on the day prior to or day 1.
- Pregnant or breastfeeding.
- Known history of COVID-19 (nucleocapsid positive test is not exclusionary) or positive nasal swab SARS-CoV-2 by RT-PCR test.
- Close contact with a person known to be SARS-CoV-2 positive or with a clinical diagnosis of COVID-19 within 7 days prior to enrolment.
- Receipt of MERS, SARS-CoV or off-study SARS-CoV-2 vaccines.
- Medical conditions considered to interfere with vaccine responses or being contraindications to vaccination or IM injection: Immunosuppressed or -deficient; recurrent severe infections; HIV positive; bleeding disorders; known history of anaphylaxis or urticaria.

- Treatments considered to interfere with vaccination responses: Immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, within 6 months prior to screening, or planned receipt throughout the study; systemic immunoglobulins or blood products within 3 months prior to first study vaccine administration or plans to receive such products during the study; short-term (<14 days) systemic corticosteroid treatment was allowed if discontinued least 28 days prior to 1st study vaccination, and inhaled/nebulized, intraarticular, intrabursal, or topical (skin or eyes) corticosteroids were also permitted.
- Contraindications as specified in the prescribing information to receiving the ChAdOx1 vaccine.

In phase 1, participants ≥ 60 years of age and participants with significant abnormalities were excluded [respiratory disease warranting hospitalization or an emergency room visit or supplemental oxygen in the last 5 year, significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease), history of myocarditis or pericarditis, significant hematologic abnormalities (e.g., sickle cell disease, beta thalassemia, coagulation disorders), chronic liver disease], as well as participants with major surgery within 6 months prior to 1st study vaccination.

Phases 2, 3a, 3b and 3c included patients ≥ 60 years of age and patients with comorbidities increasing the risk of severe COVID-19 (advanced malignancy, chronic kidney disease, chronic liver disease, asthma, COPD, emphysema, cystic fibrosis, pulmonary fibrosis, down syndrome, significant cardiovascular disease, obesity, smoker, type 1 and 2 diabetes, cerebrovascular disease).

Phase 3b was enriched for participants at higher risk for COVID-19 by deliberate enrolment of individuals considered at high risk of exposure to SARS-CoV-2 due to their workplace environment or living conditions.

- **Treatments**

During the course of the clinical development, the formulation of the ARCT-021 vaccine was switched from a frozen liquid to a lyophilized formulation intended for marketing, and the process was upscaled.

The lyophilized formulation was used in ARCT-154-01, and only one vaccine batch was used (drug product batch 159568A, from the small-scale manufacturing process). The same batch of ARCT-154 was also used for the ARCT-021-04, and ARCT-165-01 studies.

In the ARCT-154-J01 study a process performance qualification batch of ARCT-154 from the large-scale manufacturing process was used.

ARCT-154 was used at a 5 µg dose (dissolved in 0.5 mL sterile isotonic saline). Administration was by IM injection into the lateral aspect of the deltoid muscle of the non-dominant arm, where possible. The comparator (placebo) for phases 1, 2, 3a, and 3b was sterile 0.9% sodium chloride.

The selected 5 µg dose level of ARCT-154 was based on results with the ARCT-02 vaccine, where this dose level had acceptable immunogenicity and safety. The 4-week interval between the two immunisations in the ACT-154 primary series was selected based on the posology for approved, non-replicating mRNA vaccines.

A subgroup in the phase 2/3a study received one additional dose of ARCT-154 to assess the immune response to 3 doses of ARCT-154.

In phase 3c, participants were immunised with Vaxzevria according to the product information (two separate doses of 0.5 ml each, spaced by 4 weeks). There was no placebo arm in phase 3c.

- **Objectives**

Immunogenicity and efficacy objectives are detailed in this section.

Phases 1, 2, and 3a; primary objective for immunogenicity

To assess the NAb responses to ARCT-154 by sVNT at day 57.

Phase 3b; primary objective for efficacy

To evaluate the efficacy of ARCT-154 and placebo for the prevention of virologically confirmed, protocol-defined COVID-19.

- The objective was evaluated in all participants in the phase 3b mITT set, based on the first occurrence of confirmed, protocol-defined COVID-19 with onset between days 36 and 92, included.

Phase 3c; primary objective for immunobridging to ChAdOx1

To evaluate non-inferiority of ARCT-154 versus ChAdOx1 at day 57. However, as a significant number of protocol-defined COVID-19 cases were reported during phase 3b, the Applicant instead decided to perform post-hoc exploratory comparison of immunogenicity between ARCT-154-01 and ChAdOx1.

- **Outcomes/endpoints**

Immunogenicity and efficacy endpoints are detailed in this section.

Phases 1, 2, and 3a; primary endpoint for immunogenicity (IAS set)

- NAb responses by sVNT evaluated at day 1 (baseline) and day 57 for assessment of seroconversion.
- The endpoint is defined as the proportion of participants in each study vaccine group that demonstrate seroconversion (defined as 4-fold increase in antibody concentration from baseline).

Phase 3b primary endpoint for efficacy (mITT set)

- The first occurrence of confirmed, protocol-defined COVID-19 with onset between day 36 and day 92, inclusive (mITT set).

Phase 3c; primary endpoint for immunobridging to ChAdOx1 (IAS set)

- GMC for circulating virus-neutralising antibodies, index strain.

Evaluation of participants with suspected COVID-19

Primary case definition and grading of case severity were based on US FDA and WHO recommendations (2020), as pre-specified in the study protocol.

Confirmed COVID-19 must meet the protocol-defined COVID-19 case definition and either the US FDA or the WHO criteria for severe COVID-19 to be considered an event of severe COVID-19 for the evaluation of this endpoint.

To be considered as a protocol-defined COVID-19 case, virological confirmation (by RT-PCR) of SARS-CoV-2 and demonstration of at least one of the pre-specified symptoms or clinical findings were required. This criterion could be met by any of the following tests:

- RT-PCR test or other equivalent NAAT. Results from a laboratory test were only considered acceptable if it was obtained using:
    - An assay accredited by the Vietnam MOH;
    - Additional accreditation of the assay by US FDA was also preferred;

- OR an assay performed in a laboratory that is currently Clinical Laboratory Improvement Amendment-certified.
- OR an assay performed by a laboratory accredited according to the ISO 15189 standard.

Asymptomatic SARS-CoV-2 infection was defined as a participant with a positive NAAT test for SARS-CoV-2 without the presence of protocol-specified COVID-19 or atypical COVID-19 symptoms. These cases were collected as disease events but not analysed toward COVID-19 endpoint cases.

Atypical COVID-19 was defined as a participant with a positive NAAT test for SARS-CoV-2 virus and contemporaneous symptoms that are not those listed in US FDA and WHO recommendations, but nevertheless clinically suspected to represent a manifestation of COVID-19. These cases are to be used for exploratory analyses of COVID-19 cases only, as necessary.

All suspected COVID-19 cases were to undergo tiered review by the EAC according to a written charter. The EAC was composed of clinical experts with experience in the diagnosis, care, and treatment of COVID-19 participants. EAC experts reviewed blinded COVID-19 data and provided conclusions on whether the case met the protocol-defined COVID-19 case criteria.

Any participant who died during the study participation was evaluated for suspected/confirmed causes of death. Autopsy results and histopathology results, as available, were requested. Any death attributed to confirmed COVID-19 was evaluated for the death endpoint.

All deaths were subject to review by the blinded EAC for confirmation of whether these met the "Death Attributed to COVID-19" endpoint.

Primary Case Definition, COVID-19 (based on FDA recommendation, DHHS 2020)

Case Definition	Laboratory Finding*	Clinical Status	
		Symptoms	Other Clinical Parameters
Uninfected	No positive SARS-CoV-2 test	None	None relevant
Asymptomatic SARS-CoV-2 Infection	Positive SARS-CoV-2 test	None	None relevant
Protocol-defined COVID-19	Positive SARS-CoV-2 test	At least one of the following that is a NEW or WORSENING finding: • Fever or chills • Cough • Shortness of breath or difficulty breathing • Fatigue • Muscle or body aches • Headache • New loss of taste or smell • Sore throat • Congestion or runny nose • Nausea or vomiting • Diarrhea	None relevant
Atypical COVID-19	Positive SARS-CoV-2 test	Clinical findings suggestive of COVID-19 but not included in the row above	None relevant
Severe COVID-19	Positive SARS-CoV-2 test	As above for protocol-defined COVID-19	Any of the following: • Clinical signs at rest indicative of severe systemic illness: - Respiratory rate ≥30 per minute, - Heart rate ≥125 per minute, - SpO_2 ≤93% on room air at sea level or PO_2/FiO_2 <300 mm Hg • Respiratory failure (defined as needing high flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO) • Evidence of shock: - SBP <90 mm Hg, or - DBP <60 mm Hg, - or requiring vasopressors • Significant acute renal, hepatic, or neurologic dysfunction • Admission to an ICU • Death

Abbreviations: COVID-19=coronavirus disease 2019; DBP=diastolic blood pressure; ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; ICU=intensive care unit; pO_2=partial pressure of oxygen; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SBP=systolic blood pressure; SpO_2=oxygen saturation

Alternate case definition for grading of severity of SARS-CoV-2 infection/COVID-19 (based on WHO 2020)

Case Definition	Lab Finding*	Clinical Status	Other Clinical Parameters	Score
Uninfected	No positive SARS-CoV-2 test	N/A	N/A	0
Mild Disease	Positive SARS-CoV-2 test	Ambulatory	Asymptomatic	1
			Symptomatic; independent	2
			Symptomatic; assistance needed	3
Moderate Disease	Positive SARS-CoV-2 test	Hospitalized	No oxygen therapy NOTE: If hospitalized for isolation only, record status as for ambulatory patient	4
			Oxygen by mask or nasal prongs	5
Severe Disease	Positive SARS-CoV-2 test	Hospitalized	Oxygen by NIV or high flow	6
			Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
			Mechanical ventilation, $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ or vasopressors	8
			Mechanical ventilation, $pO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Positive SARS-CoV-2 test	Dead	N/A	10

Abbreviations: ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; N/A=not applicable; NIV=noninvasive ventilation; pO_2=partial pressure of oxygen; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=oxygen saturation

- **Sample size**

Phases 1/2/3

Phases 1/2/3a was not specifically powered for assessment of vaccine efficacy, a descriptive efficacy analysis was performed to supplement the primary efficacy analysis.

Phase 3b

Sample size for Phase 3b was driven by the total number of events required to demonstrate VE.

Under the following assumptions, a sample size of approximately 20,000 participants was anticipated to accrue sufficient events for the final analysis of VE within a 6-month time frame:

- The target VE against COVID-19 is 60% (with 95% CI lower bound ruling out 30%, rejecting the null hypothesis H0: VE ≤ 30%).
- A 1-month COVID-19 incidence rate of 0.3% in the placebo arm or 6-month incidence rate of 1.8%.
- A dropout rate and participants to be excluded from the mITT population of 10%.
- One IA at 50% of total target cases across the 2 study groups with O'Brien-Fleming boundaries for efficacy monitoring.

- **Randomisation and blinding**

Participants in phases 1, 2, and 3a were randomly assigned 3:1 to treatment (ARCT-154: placebo), while participants in phase 3b were randomly assigned 1:1 to treatment (ARCT-154: placebo).

- Participants in phase 1 and 3b received two doses of one type of study vaccine on day 1 and 29 (ARCT 154 or placebo) and then two doses of the opposite vaccine (placebo or ARCT-154) on day 92 and 120 (referred to as 'switchover').
- Participants in phase 2/3a who received ARCT-154 in the initial two-dose vaccination series were further randomised to receive either ARCT-154 or placebo (in a 3:1 ratio) at day 92 followed by placebo at day 120. Participants that received placebo in the initial vaccination series switched over to receive ARCT-154 at day 92 and 120.

For Phases 2, 3a, prior to randomisation, participants were stratified by the following 2 stratification factors:

- Study Site: There are 3 study sites in the phase 2/3a.
- Risk Group:
    - Age < 60 at high risk of severe COVID-19.
    - Age < 60 not at high risk of severe COVID-19.
    - Age ≥ 60 years of age (considered at risk of severe COVID-19 by default).

Phase 3b participants were randomly assigned 1:1 (ARCT-154: placebo). The block randomisation was performed stratified by the following 2 stratification factors:

- Study site: total of 16 sites for phase 1/2/3a/3b.
- Risk group:
    - Age< 60 at high risk of severe COVID-19.
    - Age < 60 not at high risk of severe COVID-19.
    - Age ≥ 60 years.

Phase 3c participants were randomised 1:1 to receive ARCT-154 or ChAdOx1. No switchover occurred for Phase 3c participants as all participants in this cohort receive active vaccine.

As the eligibility criteria for Phase 1 excluded participants ≥60 years old or otherwise at risk for severe COVID-19, stratification did not occur for phase 1.

For several of the immunogenicity analyses including the key analyses, participants were selected in a non-random manner (see Table 7 below).

Table 1: Summary of Sample Selection for Immunogenicity Analyses

Non-random selection

Summary of Sample Selection for Immunogenicity Analyses

Laboratory/Assay	Phase	No. of Participants[a]	Selection Method	Timepoints
NIHE/ sVNT [2 dose]	1/2/3a	1001	All Phase 1/2/3a participants	Days 1, 29 and 57
NIHE Anti-S [2 dose]				
NIHE PRNT50 ancestral strain [2 dose]	1/2	150	First 150 participants[b]	Days 1, 29, and 57
NIHE PRNT50 Delta strain [2 dose]				
PPD MNT D614G [2 dose]	1/2/3a	539	First 250 participants[c] + 289 randomly selected[d]	Days 1 and 57
		298	289 randomly selected[d] + 9 older adults from sequential selected cohort[e]	Day 92
PPD MNT D614G [3 dose]	2/3a	439	First 150 participants[f] + 289 randomly selected[d]	Days 1 and 57
		298	Older adults (9)[e] + 289 randomly selected[d]	Days 92 and 120
PPD MNT Delta [2 and 3 dose]	2/3a	298	Older adults (9)[e] + 289 randomly selected[d]	Days 1, 57, 92, 120
PPD MNT Omicron BA.1 [2 and 3 dose]	2/3a, 1/2/3a	298	Older adults (9)[e] + 289 randomly selected[d]	Days 1, 57, 92, 120
PPD ACE2i sVNT	1/2	250	First 250 participants[c]	Days 1 and 57
PPD MaSD BAb	1/2	250	First 250 participants[c]	Days 1 and 57

Abbreviations: ACE2i, angiotensin-converting enzyme 2 i; Anti-S, Antigen Sandwich Immunoassay; BAb, binding antibody; MNT, microneutralization test; NIHE, National Institute of Hygiene and Epidemiology; PRNT50, plaque reduction neutralization test at 50% reduction; sVNT, surrogate virus neutralization test.

[a] The total number of participants, including individuals with missing data, before the exclusions assignment.

[b] Participants were selected according to the enrollment sequence: all Phase 1 (100) and the first 50 of Phase 2 participants.

[c] Participants were selected according to the enrollment sequence: all Phase 1 (100) and the first 150 of Phase 2 participants.

[d] A random set of participants of Phases 2 and 3a with samples available through Day 120 was generated by risk group (<60 years and healthy, <60 years and at risk, >60 years) and treatment group (ARCT-154 and placebo). Phase 2 participants who were included in the analysis in a sequential manner were not included in the random set. The first 75 participants in each ARCT-154 risk strata and the first 25 in each placebo risk strata were selected. For participants >60 years of age, there were insufficient participants available in Phase 2/3, so all participants >60 years of age were selected (68 who received ARCT-154 and 21 who received placebo).

[e] All (9) Phase 2 participants > 60 years of age who was included in the sequentially selected set of participants.

[f] Participants were selected according to the enrollment sequence: the first 150 Phase 2 participants.

The study treatments (ARCT-154, Vaxzevria and placebo) were administered in an observer-blind fashion.

All ARCT-154 study treatments (ARCT-154, placebo, and ChAdOx1) were administered as 0.5 mL IM injections, using same type of 1 mL syringes, which were blinded by wrapping syringe cylinders in an adhesive syringe label, in a manner that obscured the fluid components of the syringe, while allowing a small space to make the syringe plunger and meniscus visible.

- **Analysis sets**

Randomised set

Included all participants who were randomly assigned in the study regardless of the participants' vaccination status in the study.

Intent-to-Treat (ITT) analysis set

Included all participants who received any dose of study vaccine (ARCT-154 or placebo).

Modified Intent-to-treat (mITT) analysis sets

Included all participants who received all protocol-required doses of study vaccine (ARCT-154 or placebo) up to the evaluation timepoint concerned, and who had no evidence of SARS-CoV-2 infection on day 1 up to 7 days after the second study vaccination:

- Phase 3b mITT.
- Phase 3c mITT.
- Pooled mITT: Pooled data from all phases 1/2/3a/3b of the study, evaluations up to day 92 only.

Per-protocol (PP) analysis set

Included all eligible randomised participants who received all protocol-required doses of study treatment (ARCT-154, placebo or ChAdOx1) up to the evaluation timepoint concerned and within the protocol predefined window, and who had no major protocol deviations expected to affect efficacy and immunogenicity.

- Phase 3b PP set: Excluded any participant with evidence of SARS-CoV-infection on day 1 up to 7 days after the second study vaccination (IcEv3) or that received an off-study COVID-19 vaccine prior to day 92 (IcEv2).
- Phase 3c-1 PP set: Included just the participants enrolled in the Phase 3c-1 subset of phase 3c but excluded any participant that had evidence of SARS-CoV-2 infection at baseline or prior to the analysis time point concerned (IcEv3) or that receives an off-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2).
- Phase 3c PP set: Included all of Phase 3c but excluded any participant that has evidence of SARS-CoV-2 infection at baseline or prior to the analysis time point concerned (IcEv3) or that received an off-study COVID-19 vaccine prior to the analysis time point concerned (IcEv2).

The immunogenicity analysis set (IAS)

IAS included all participants who received all the protocol required doses of study treatment (ARCT-154, placebo or ChAdOx1) up to the evaluation time point concerned, who had no evidence of prior SARS-CoV-2 infection (no positive RT-PCR or other COVID-19 test or seropositivity for anti-N antibody) at day 1 (IcEv3), and who had at least 1 valid post-vaccination immunogenicity assay result.

Data at timepoints following evidence of a SARS-CoV-2 infection (IcEv3), use of immune-modifying drugs, blood products or immunoglobulins (IcEv5) or non-study COVID-19 vaccines (IcEv2), or protocol deviations (e.g., time windows for doses and blood draws for the time period summarized) that may impact immunogenicity as determined by the sponsor medical monitor or designee in a blinded manner were excluded.

- Statistical methods

Missing data and outliers

In ARCT-154-01, missing data were not imputed and were analysed under the assumption that they were missing completely at random. Approximately 400 participants (2.6%) had not received the second full dose of the assigned study vaccine by day 29, and this remained until the analysis was conducted on day 92.

Multiple Comparisons/Multiplicity

Pooled analyses of efficacy and safety are nominally declared as primary, secondary, and exploratory to align with the equivalent endpoints in the phase 3b population, but any statistical analysis performed will be nominal. The pooled analysis endpoints will be evaluated in the same fashion as the equivalent analyses in the Phase 3b population.

Key secondary endpoints are analysed in a hierarchical fashion and are only evaluated as hypothesis testing if the primary endpoint in the Phase 3b mITT population rejects the null hypothesis.

The pivotal ARCT-154-01 study has one primary endpoint and several secondary endpoints. Multiplicity correction due to several secondary endpoints was not planned. This approach is considered acceptable.

Statistical methods

The primary efficacy endpoint is the VE of ARCT-154 in preventing the occurrence of virologically confirmed COVID-19 from 7 days (inclusive) after second dose of study vaccine.

For the primary efficacy objective of phase 3b, the null hypothesis is that the VE of ARCT-154 to prevent first occurrence of virologically confirmed COVID-19 is ≤30% (or H0efficacy: VE ≤0.3).

The Phase 3b study will be considered to meet the primary efficacy objective if the corresponding 95% CI of VE rules out 30% at the final analysis.

A Cox proportional hazard model adjusting for randomisation stratification factors was used to assess the magnitude of the VE between ARCT-154 and placebo at a 1-sided 0.025 significance level. The implementation of the Cox proportional hazards model stratified by the randomisation factors to analyse VE is acceptable. For the primary endpoint, the lower limit of the 95% CI around the VE exceeded 30%. The secondary efficacy objective was met as the limit of the 95% CI for VE exceeded 0%.

Regarding the use of pooled data of phases 1/2/3a and 3b, Phase 1 primarily served as a sentinel cohort, focusing primarily on safety assessment. Phase 2 expanded the evaluation of safety and immunogenicity, involving a larger group of participants. Phase 3a and 3b further extended enrolment to participants with higher exposure risk. The target populations did not significantly differ across these phases despite the risk of exposure due to live and working condition and take the consideration that Phase 3b included a substantial cohort of 16,120 participants. Additionally, pooled analyses were employed as sensitivity analyses and exploratory, and as the results consistently align, the use pooled data is acceptable, providing representative results for the target population.

Results

- **Participant flow**

In phases 1/2/3a, 749 participants in the ARCT-154 group and 252 participants in the placebo group received at least 1 dose of the study treatment and were included in the ITT.

In phase 3b, 8056 participants in the ARCT-154 group and 8044 participants in the placebo group received at least 1 dose of the study treatment and were included in the ITT.

- 1099/8059 participants in the ARCT-154 group and 1251/8048 participants in the placebo group discontinued from the vaccination schedule for the initial (dose 1/2) or switchover (dose 3/4) series.
    - The most frequent reasons for discontinuation were participant request (1061 ARCT-154; 1203 placebo) and pregnancy (13 ARCT-154; 16 placebo).

- 953 (11.8%) participants in the ARCT-154 group and 1067 (13.3%) participants in the placebo group discontinued the study.
    - The most frequent reasons for discontinuation were the participant request (918 ARCT-154; 1029 placebo), death (17 ARCT-154; 24 placebo), and lost to follow-up (16 ARCT-154; 10 placebo).

In phase 3c, 1184 participants in ARCT-154 group and 1182 participants in the ChAdOx1 group received at least 1 dose of the study vaccine.

- 45 participants were excluded from mITT, 28 participants (17 ARCT 154; 7 ChAdOx1) did not receive the second vaccination dose and 17 participants (6 ARCT-154; 11 ChAdOx1) had evidence of COVID-19 between day 1 and day 35.

Study discontinuation rates were overall comparable in ARCT-154 and placebo groups for all phases of the study. The disposition and flow of participants is shown in the two figures below.

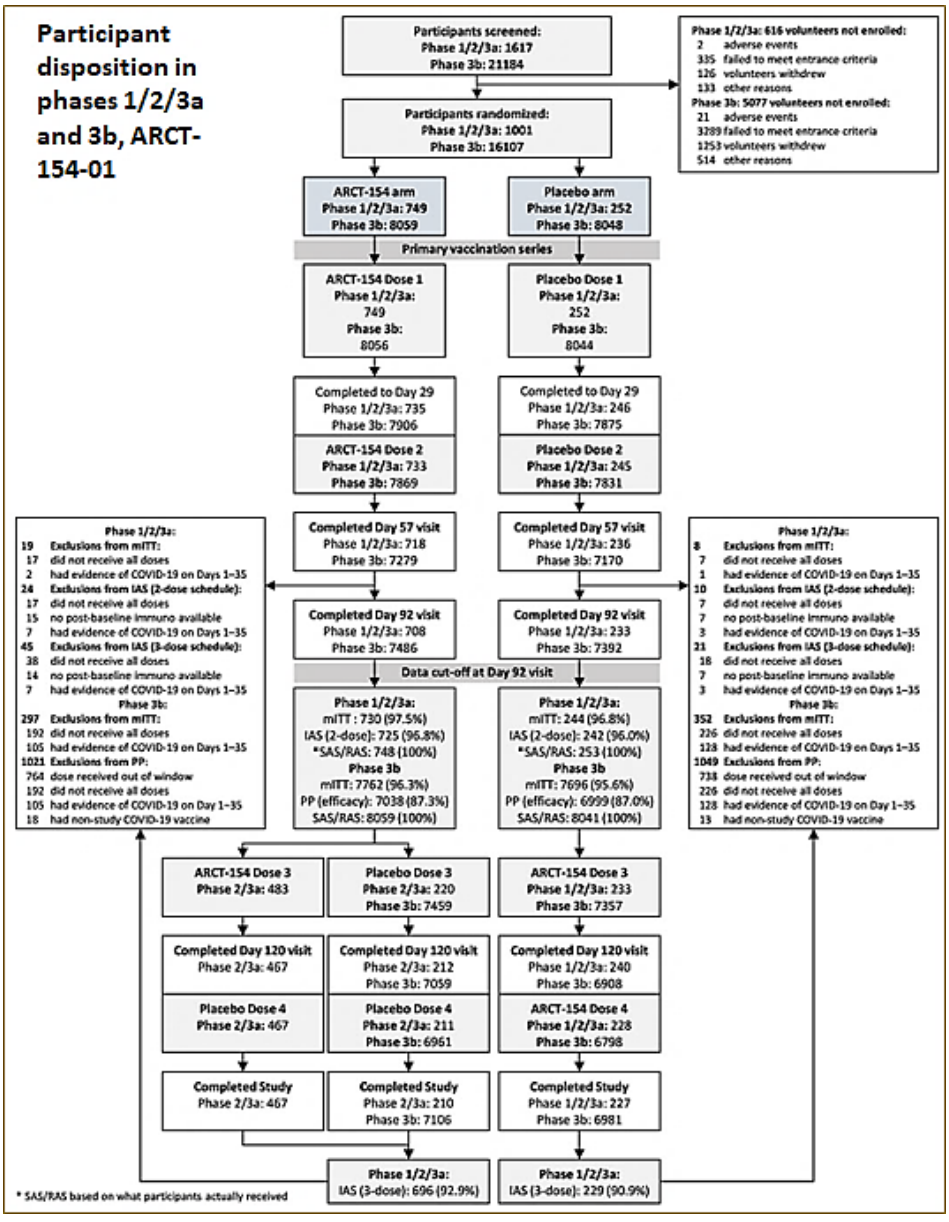


Figure 2: Participant disposition in phases 1/2/3a and 3b, ARTC-154-01

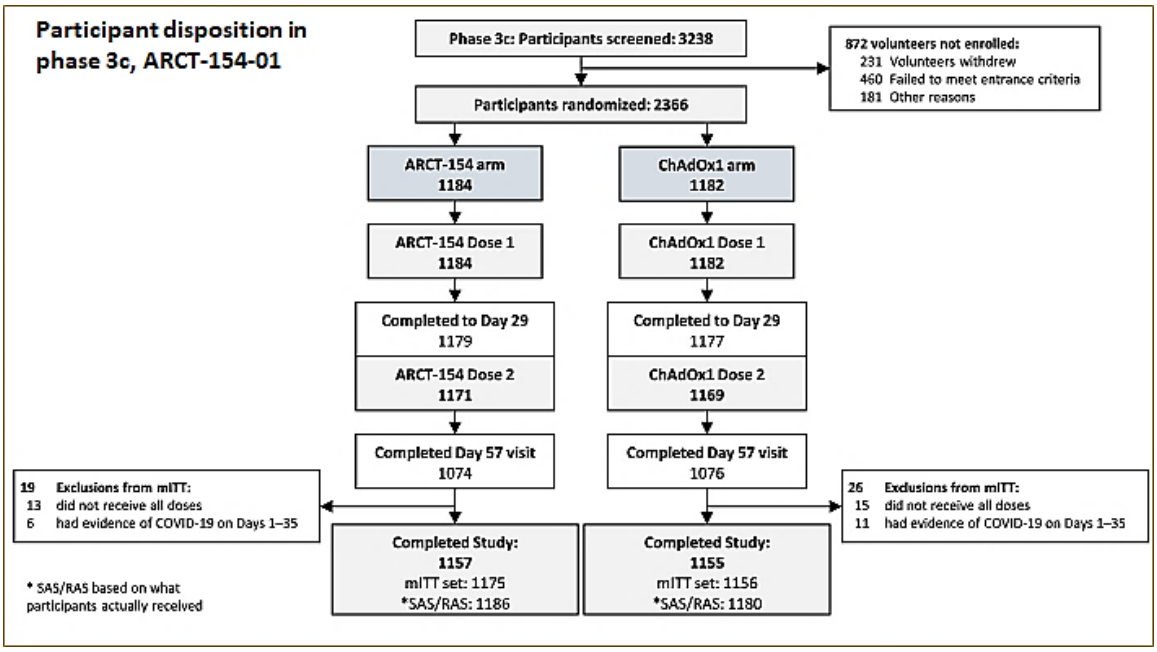


Figure 3: Participant disposition in phase 3c, ARTC-154-01

- **Recruitment**

Recruitment dates across phases 1-3c are shown in the Table 8 below.

Table 2: Key Recruitment Dates

Key Recruitment Dates

	Phase 1	Phase 2	Phase 3a	Phase 3b	Phase 3c
First participant randomized	15 Aug 2021	21 Sep 2021	25 Sep 2021	12 Oct 2021	02 Nov 2021
Last participant randomized	16 Aug 2021	28 Sep 2021	29 Sep 2021	29 Oct 2021	09 Nov 2021

Enrollment in the study began on 11 August 2021 and ended on 09 November 2021.

The efficacy surveillance period for phase 3b started on 16 November 2021, and the cut-off date for the final efficacy analysis was 12 January 2022. The efficacy surveillance period for phase 3c spanned from 02 November 2021 (first participant randomised) to November 2022.

The pivotal efficacy data for the primary series with ARCT-154 reflects a reasonably long follow-up time (days 92-243, with the primary-series immunisations given at days 1 and 29).

- **Conduct of the study**

The first approved study protocol was version 3.0 (amendment 2), approved on 02 August 2021.

There were 8 amendments to the study protocol. Versions 4 and 6 of the protocol were never approved.

Amendment 4 (version 5), 24 August 2021: The primary purpose was to allow phase 3a to be initiated at the same time as phase 2 and to change the randomisation ratio for phases 2 and 3a to 3:1 ARCT-154 to placebo.

Amendment 6 (version 7), 28 October 2021: The primary purpose was to correct errors in the size of cohorts in phase 3b and phase 3c. The other major change was returning the phase 3b efficacy endpoint from protocol Version 6.0's exploratory to secondary, which was requested by the EC.

Amendment 7 (Version 8), 14 December 2021: The primary purpose was to add to the design that participants in phases 2 and 3a who received ARCT-154 in the initial vaccination series will be further randomised to receive a third vaccination of either ARCT-154 or placebo at day 92 followed by placebo at day 120 in order to compare immunogenicity after 3 injections of ARCT-154 with that after 2 injections. In addition, the primary analysis of efficacy was changed to be performed as a secondary analysis in the pooled participant populations from phases 1, 2, 3a, and 3b to increase the statistical power of this analysis.

Amendment 8 (Version 9), 07 February 2022: The primary purpose was to declare the phase 3b efficacy and safety analyses to be the overall primary endpoints for this study.

The protocol version referred to in the 6-month interim report is version 9.

Protocol versions 5, 7, 8 and 9 were all generated after the study enrollment had started on 11 August 2021, but before the unblinding of data for the first interim analysis which was conducted for submission of an emergency use authorisation in Vietnam on 10 April 2022. These changes are not considered to affect the interpretation of the results.

- **Baseline data**

Essentially all study participants are identified as Asian/the Kinh (≥ 98%).

The participant demographics were overall balanced on treatment and placebo groups (see the Table 9 below).

Phase 3b and 3c participants were on average older than those in phase 1/2/3a (participants ≥60 years old were not recruited for phase 1).

Table 3: Demographics (Phase 1/2/3a SAS)

Demographics (Phase 1/2/3a SAS)	ARCT-154 (Initial) (N=748)		Placebo (Initial) (N=253)	
	n	(%)	n	(%)
Age, years, median (range)	41.0	(18-76)	42.0	(18-72)
• Age category, years, n (%)				
≥18 to <60	668	(89.3)	224	(88.5)
≥60	80	(10.7)	29	(11.5)
• Risk group, n (%)				
≥18 to <60, healthy	457	(61.1)	151	(59.7)
≥18 to <60, at risk of severe COVID-19	211	(28.2)	73	(28.9)
≥60	80	(10.7)	29	(11.5)
Female, n (%)	337	(45.1)	118	(46.6)
Height, cm, median (range)	159.0	(139-189)	159.0	(141-184)
Weight, kg, median (range)	59.0	(33.5-105.2)	58.0	(36.2-90.5)
BMI, kg/m^2, median (range)	23.37	(15.1-37.0)	22.97	(15.7-35.8)

Demographics (Phase 3b SAS)	ARCT-154 (Initial) (N=8059)		Placebo (Initial) (N=8041)	
	n	(%)	n	(%)
Age, median (range)	48.0	(18-89)	48.0	(18-86)
• Age category, n (%)				
≥18 to <60	6656	(82.6)	6643	(82.6)
≥60	1403	(17.4)	1398	(17.4)
• Risk group, n (%)				
≥18 to <60, healthy	4040	(50.1)	4054	(50.4)
≥18 to <60, at risk of severe # COVID-19	2616	(32.5)	2589	(32.2)
≥60	1403	(17.4)	1398	(17.4)
Female, n (%)	4104	(50.9)	4088	(50.8)
Height, cm, median (range)	158.0	(134-185)	158.0	(128-190)
Weight, kg, median (range)	56.0	(30.0-110.0)	56.0	(29.0-136.0)
BMI, kg/m2, median (range)	22.58	(13.8-42.4)	22.51	(13.3-47.6)

Demographics (Phase 3c SAS)	ARCT-154 (Initial) (N=1186)		ChAdOx1 (Initial) (N=1180)	
	n	(%)	n	(%)
Age, median (range)	52.0	(18-85)	52.0	(18-81)
• Age category, n (%)				
≥18 to <60	859	(72.4)	855	(72.5)
≥60	327	(27.6)	325	(27.5)
• Risk group, n (%)				
≥18 to <60, healthy	442	(37.3)	435	(36.9)
≥18 to <60, at risk of severe COVID-19 #	417	(35.2)	420	(35.6)
≥60	327	(27.6)	325	(27.5)
Female, n (%)	603	(50.8)	613	(51.9)
Height, cm, median (range)	156.0	(126-180)	156.0	(126-181)
Weight, kg, median (range)	54.5	(31.0-95.0)	55.0	(31.0-89.0)
BMI, kg/m², median (range)	22.26	(15.1-35.9)	22.37	(14.0-38.5)

In ARCT-154-01 phases 1/2/3a/3b, 5.5% of participants had at least one of the following conditions: significant cardiovascular conditions, diabetes and obesity, liver diseases, COPD, and asthma.
In ARTC-154-01 phase 3c, 10.9% of participants had at least one of the abovementioned conditions.

- **Numbers analysed**

The number pf participants in ARCT-154-01 is considered sufficient to ascertain the efficacy as well as immunogenicity of the vaccine, according to the study objectives.

The analysis sets are shown in the Table 4 below.

Table 4: Analysis sets (Phase 1/2/3a)

Phase 1/2/3a			
	ARCT-154 (Initial) (N=749)	Placebo (Initial) (N=252)	Total (N=1001)
ITT	749	252	1001
mITT	730	244	974
Phase 3b			
	ARCT-154 (Initial) (N=8059)	Placebo (Initial) (N=8048)	Total (N=16107)
ITT	8056	8044	16100
mITT	7762	7696	15458
PP Efficacy	7038	6999	14037
Pooled set (Phase 1/2/3a/3b)			
	ARCT-154 (Initial) (N=8808)	Placebo (Initial) (N=8300)	Total (N=17108)
ITT	8805	8296	17101
mITT	8492	7940	16432
PP Efficacy	7743	7235	14978

Phase 3c:
1184 participants in ARCT-154 group and 1182 participants in the ChAdOx1 group received at least 1 dose of the study vaccine.

45 participants were excluded from mITT, 28 participants (17 ARCT 154; 7 ChAdOx1) did not receive the second vaccination dose and 17 participants (6 ARCT-154 ; 11 ChAdOx1) had evidence of COVID-19 between day 1 and day 35.

- **Outcomes and estimation, efficacy (phase 3b)**

Epidemiological context and case ascertainment for the ARC-154 study

Individuals with suspected COVID-19 symptoms and/or exposures were evaluated, preferably within 72 hours, to determine if there was a potential COVID-19 case. Nasal swabs were collected with subsequent measurement of the SARS-CoV-2 virus using RT-PCR assay.

A total of 916 cases of virologically confirmed COVID-19 were detected and adjudicated across all phases of the study. In total, 734 cases of confirmed, protocol-defined COVID-19 were adjudicated for phase 3b participants, including 48 severe cases and 10 deaths attributed to COVID-19.

The primary definition of severe COVID-19 was based on the FDA recommendations.

In addition, 102 asymptomatic cases of SARS-CoV-2 infection were reported among phase 3b study participants.

Based on genetic characterisation of SARS-CoV-2 in patient's nasal swabs, the delta variant was dominant during the study period (> approx. 85% of cases). Only 2 cases of the Omicron variant were detected in the study.

Virologically confirmed, protocol-defined COVID-19 with first occurrence of onset between days 36 and 92 (primary efficacy endpoint, phase 3b)

Vaccine efficacy against COVID-19 of any severity in the mITT population of phase 3b participants was 56.7% (95% CI: 48.8% to 63.4%).

The lower limit of the 95% CI was above the prespecified success threshold of 30%, and therefore the study met its primary endpoint (see Figure 8 below).

Results for the PP analysis set were consistent with the primary analysis in the mITT (VE 55.5%, 95% CI 46.4% to 63.1%).

Only 1.5% (233/16107) were excluded from mITT because of evidence of COVID-19 between days 1 and 35 (positive RT-PCR or seropositivity for anti-nucleocapsid antibody at baseline). Altogether, most of the study population was COVID-19 naïve and unvaccinated.

Number of Participants	Number of Participants Censored	Cumulative Follow-up Period (Person-Years)	Number of Participants With Cases Reported	% VE[a] (95% CI)
ARCT-154 (N= 7762)	7562	1146.2	200	56.7 (48.8-63.4)
Placebo (N= 7696)	7256	1120.2	440	

Abbreviations: CI, confidence interval; HR, hazard ratio; COVID-19, coronavirus disease 2019; mITT, modified Intent-to-Treat; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine efficacy.
[a]VE was calculated by 1-HR from cox regression adjusting for risk group and region of study site.

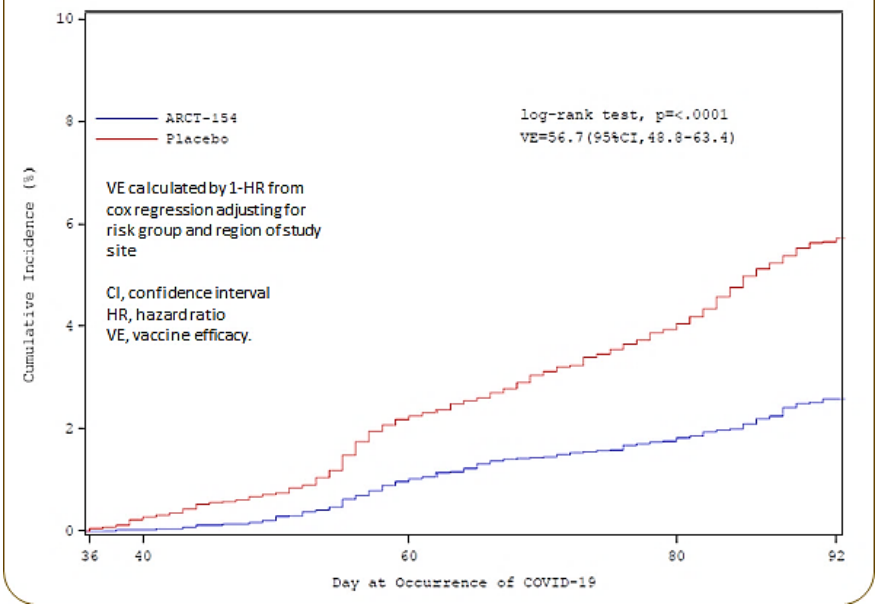


Figure 4: VE Against Confirmed Protocol-Defined COVID-19 Between Day 36 and Day 92 (Phase 3b mITT)

Severe COVID-19 with onset between day 36 and day 92 (secondary efficacy endpoint, phase 3b)

As the primary endpoint was met, hierarchical testing of the first secondary endpoint was conducted.

In the ARCT-154 group, 2 cases of severe COVID-19 were reported among the 7762 participants who were at risk for developing severe COVID-19, whereas 41 cases were reported in the placebo group among the 7696 participants who were at risk.

Vaccine efficacy against severe COVID-19 was 95.3% (95% CI: 80.5% to 98.9%), and the lower limit of the CI was above the prespecified success threshold of 0%; i.e. the study met this secondary endpoint (see Figure 4 below).

Results for the PP analysis set were consistent with the analysis conducted in the mITT (VE 93.7%, 95% CI 73.6% to 98.5%).

Number of Participants	Number of Participants Censored	Cumulative Follow-up Period (Person-Years)	Number of Participants With Cases Reported	% VE[a] (95% CI)
ARCT-154 (N=7762)	7760	1162.9	2	95.3 (80.5-98.9)
Placebo (N=7696)	7655	1154.7	41	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; mITT, modified Intent-to-Treat; VE, vaccine efficacy.
[a]VE was calculated by 1-HR from cox regression adjusting for risk group and region of study site.
Source: Table 14.2.1.2.1.

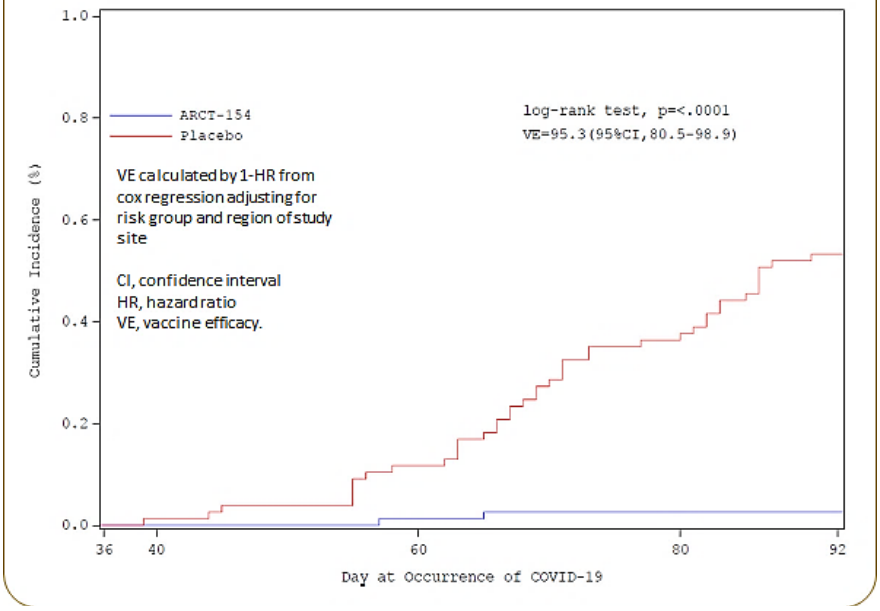


Figure 5: VE Against Confirmed Protocol-Defined Severe COVID-19 Between Day 36 and Day 92 (Phase 3b mITT)

Any COVID-19 with onset any time after the first vaccination up to day 92 (secondary efficacy endpoint, phase 3b)

As the previous secondary endpoint was met, hierarchical testing of the next secondary endpoint was conducted.

In phase 3b ITT participants with no evidence of infection prior to vaccination, in the ARCT-154 group, 223 cases were reported among the 8056 participants, whereas 496 cases were reported in the placebo group among 8043 participants who were at risk.

Vaccine efficacy against any protocol-defined COVID-19 disease reported between day 1 and day 92 was 56.7% (95% CI: 49.3% to 63.1%) (see Figure 6 below).

The lower limit of the CI was above the prespecified success threshold of 0%, and the study therefore met this second secondary endpoint.

The incidence rate of COVID-19 among the ARCT-154 recipients appeared to become lower than that among placebo recipients already from day 20, i.e. before completion of the primary immunisation series (see Figure 6 below).

Number of Participants	Number of Participants Censored	Cumulative Follow-up Period (Person-Years)	Number of Participants With Case Reported	% VE[a] (95% CI)
ARCT-154 (N=8056)	7833	1961.5	223	56.7 (49.3-63.1)
Placebo (N=8043)	7547	1935.8	496	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; ITT, Intent-to-Treat; VE, vaccine efficacy.

[a]VE was calculated by 1-HR from cox regression adjusting for risk group and region of study site.

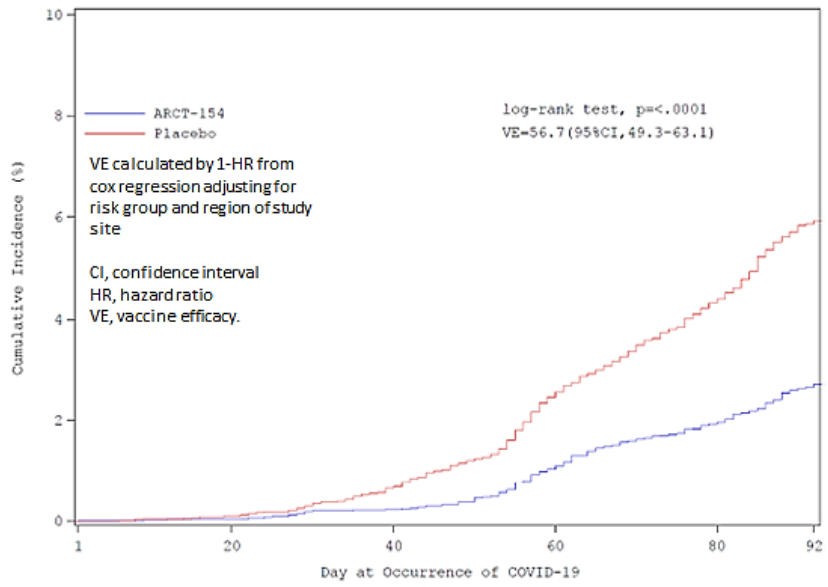


Figure 6: VE Against Confirmed Protocol-Defined COVID-19 Between Day 1 and Day 92 (Phase 3b ITT with no Evidence of COVID-19 to Vaccination)

Death attributed to COVID-19 between day 36 and day 92 (secondary efficacy endpoint, phase 3b)

As the previous secondary endpoint was met, hierarchical testing of the next secondary endpoint was conducted.

In the phase 3b mITT population, in the ARCT-154 group, 1 death attributed to protocol-confirmed COVID-19 was reported among 7762 participants, whereas in the placebo group, 9 such deaths were reported among the 7696 participants.

Vaccine efficacy against any death attributed to protocol-confirmed COVID-19 was 86.3% (95% CI: -8.9% to 98.3%).

The lower limit of the CI was below the prespecified success threshold of 0%, and this endpoint was thus not met.

The wide 95% CI is likely due to the small number of deaths attributed to COVID-19 overall, and though the endpoint was not met, the results show a favourable trend for ARCT-154 vaccine versus placebo.

Protocol-confirmed COVID-19 regardless of baseline evidence of prior SARS-CoV-2 infection reported between day 36 and 92 (secondary efficacy endpoint, phase 3b)

As the previous secondary endpoint was met, hierarchical testing of the next secondary endpoint was conducted.

Only one additional participant in the placebo group had evidence of prior SARS-CoV-2 infection, and therefore the estimate of vaccine efficacy was essentially identical to the primary analysis: VE against COVID-19 of any severity was 56.7% (95% CI: 48.8% to 63.4%), and the lower limit of the CI was above 30%.

Exploratory efficacy endpoints (phase 3b) and supplementary efficacy data from phase 1/2/3a

A number of exploratory efficacy endpoints were reported in the interim report:

- Severe COVID-19 reported between day 1 and day 92 (exploratory efficacy endpoint, phase 3b);
- Death attributed to COVID-19 reported between day 1 and day 92;
- COVID-19 reported between day 1 and day 92 regardless of baseline evidence of prior SARS-CoV-2 infection;
- COVID-19 with onset between day 36 and day 92 by strain, and severe COVID-19 with onset between day 36 and day 92 by strain.

The results from the exploratory analyses were consistent with the primary and secondary analyses. Also, supplementary efficacy data from phase 1/2/3a was reported.

The phase 1/2/3a stages were not powered for efficacy analysis but was evaluated as an exploratory endpoint (descriptive efficacy analysis), to supplement the primary efficacy analysis.

The phase 1/2/3a estimates for VE against COVID-19 through days 36-92 and 1-92 were consistent with the pivotal phase 3b efficacy data.

- **Outcomes and estimation, immunogenicity (phase 1/2/3a)**

Functional antibody responses by ACE2-blocking ELISA at day 57 (sVNT assay, Vietnam NIHE; formal primary immunogenicity endpoint, phase 1/2/3a)

At day 57, the seroconversion rate for the ancestral strain by sVNT was 94.1% (95% CI: 92.1%, 95.8%) in the ARCT-154 group, whereas the seroconversion rate was 0.4% (95% CI: 0.0%, 2.4%) in the placebo group (see Table 5 below).

The lower bound of the 95% CI of the seroconversion rate in the ARCT-154 group (92.1%) was significantly higher than the point estimate of the seroconversion rate observed in the placebo group (0.4%).

The study met the primary immunogenicity objective which was employed for the emergency use authorisation application to the Vietnam Ministry of Health.

Results for the seroconversion rate were consistent for analyses based on the PP analysis set.

Table 5: ACE2-blocking assay (index strain spike, cPass kit, Genscript)

ACE2-blocking assay (index strain spike, cPass kit, Genscript) performed at the Vietnam NIHE

Seroconversion Based on NAb by sVNT (ancestral strain) - IAS – Phase 1/2/3a (2-dose Schedule)

Seroconversion With NAb ≥4-fold Rise Compared to the Baseline (Day 1)		Study Treatment	
		ARCT-154 (N=724)	Placebo (N=242)
Day 29	nm	717	240
	n (%)	386 (53.8%)	4 (1.7%)
	(95% CI)	(50.1% - 57.5%)	(0.5% - 4.2%)
Day 57	nm	699	231
	n (%)	658 (94.1%)	1 (0.4%)
	(95% CI)	(92.1% - 95.8%)	(0.0% - 2.4%)

Abbreviations: CI, confidence interval; IAS, Immunogenicity Analysis Set; NAb, neutralizing antibody; sVNT, surrogate virus neutralization test.
Percentages were based on nm, the number of participants with available data.

Day 29: 28 days after 1st immunization in primary series.
Day 57: 28 days after 2nd immunization in primary series.

Seroconversion was defined as a 4-fold increase in the assay readout from baseline.
Assay results below the lower limit of quantification were imputed as LLOQ/2.

Neutralising antibody responses at day 57 and 92 (post hoc revised primary immunogenicity endpoint, phase 1/2/3a)

By the validated pseudovirus neutralisation assay (VAC62, index strain spike with D614G mutation), seroconversion at day 57 was achieved in 95.9% (95% CI: 93.4% to 97.6%) of participants in the ARCT-154 group compared with 2.3% (95% CI: 0.5% to 6.5%) in the placebo group (see figure below).

Similar results were observed at day 57 based on the PP analysis set.

I.e., the results from the validated pseudovirus neutralisation assay supported the data from the ACE2 blocking ELISA, and the conclusion that the study met the primary immunogenicity objective.

At day 57, anti-index neutralising antibody levels of 145.7 IU/mL were reached (GMFR 20.9), waning to 107.4 IU/mL by day 92 (see figure below).

The data from the pseudovirus neutralisation assay were largely in agreement with data from a live virus assay (see figure below).

For the vaccine mismatched delta strain, the day 57 seroconversion rate was only 43.2% in the authentic virus assay (see figure below).

By the VAC62 assay, at day 92, the seroconversion rate was 86.6% in the ARCT-154 group and 11.0% in the placebo group (see figure below). The increase in seroconversion rates in the placebo group between days 57 and 92 is consistent with the incidence of symptomatic COVID-19 disease (7.1%) reported between days 1 and 92 among phase 1/2/3a placebo recipients, and is also consistent with epidemiological data from the national surveillance system which indicates a significant increase in the incidence of COVID-19 cases starting from October 2021 (recruitment of phase 1/2/3a participants was performed between 15 august and 29 September 2021, prior to the delta variant surge in Vietnam, which occurred October 2021 to march 2022). The incidence of symptomatic COVID-19 disease among ARCT-154 recipients from phase 1/2/3a part of the study was 3.1% for the period from day 1 to day 92. Assuming a certain rate of asymptomatic infection, it might be expected that in up to 5% of the vaccinated population, antibody titres might further increase due to a natural infection. As such, the

impact of natural infection on antibody titres of the recently vaccinated population is expected to be minimal.

Figure 7: Pseudovirus neutralization assay; spike protein of index strain with D614G mutation (VAC62)

Pseudovirus neutralization assay performed at PPD Laboratories; spike protein of index strain with D614G mutation (VAC62)

Summary of Immunogenicity by S (D614G) MNT Assay (Phase 1/2/3a IAS subset [2-dose Schedule])

Endpoint		ARCT-154 (N=725)[a]	Placebo (N=242)[a]	GMC Ratio
Day 1	nm	404	134	
	GMC (IU/mL)	7.0	6.5	
	95% CI of GMC	6.6-7.5	5.8-7.3	
Day 57	nm	393	131	
	GMC (IU/mL)	145.7	7.7	18.9
	95% CI of GMC	135.1-157.1	6.9-8.7	16.3-21.9
	nm	392	131	
	SCR, n (%)	376 (95.9)	3 (2.3)	
	95% CI of SCR	93.5 – 97.6	0.5 – 6.5	
	nm	392	131	
	GMFR	20.9	1.2	
	95% CI of GMFR	19.2-22.9	1.1-1.3	
Day 92	nm	217	73	
	GMC (IU/mL)	107.4	11.4	9.4
	95% CI of GMC	91.1-126.5	8.9-14.6	6.9-12.9
	nm	216	73	
	SCR, n (%)	187 (86.6)	8 (11.0)	
	95% CI of SCR	81.3 – 90.8	4.9 – 20.5	
	nm	216	73	
	GMFR	13.2	1.5	
	95% CI of GMFR	11.0-15.8	1.2-1.8	

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; GMC ratio, GMC ratio of ARCT 154 versus placebo; GMFR, geometric mean fold rise; IAS, Immunogenicity Analysis Set; LLOQ, lower limit of quantification; MNT, microneutralization test; nm, number of participants with available data.
[a]N represents the total number of participants in IAS for Phase 1/2/3a. MNT D614G was performed in a subset of the full IAS for Phase 1/2/3a.
The baseline reference for SCR and GMFR was Day 1.
Percentages were based on number of participants with available data (nm) who seroconverted, where seroconversion was defined as a 4-fold increase in the assay readout from baseline. Readout values below the lower limit of quantification were (LLOQ) were imputed as LLOQ/2.

Authentic virus neutralisation assay performed at the Vietnam NIHE; index strain (PRNT50 assay, index strain)

Seroconversion Rate (SCR, %) by PRNT50 of Ancestral Strain and Delta Variant (IAS – Phase 1/2 [2-dose Schedule])

			ARCT-154 (N=296)[a]	Placebo (N=99)[a]
Ancestral Clinical Isolate	Day 29	nm	111	37
		n (%)	17 (15.3%)	0 (0.0%)
		(95% CI)	(9.2% - 23.4%)	(0.0% - 9.5%)
	Day 57	nm	111	37
		n (%)	86 (77.5%)	0 (0.0%)
		(95% CI)	(68.6% - 84.9%)	(0.0% - 9.5%)
Delta (B.1.617.2) Clinical Isolate	Day 29	nm	111	37
		n (%)	3 (2.7%)	0 (0.0%)
		(95% CI)	(0.6% - 7.7%)	(0.0% - 9.5%)
	Day 57	nm	111	37
		n (%)	48 (43.2%)	0 (0.0%)
		(95% CI)	(33.9% - 53.0%)	(0.0% - 9.5%)

Abbreviations: CI, confidence interval; IAS, Immunogenicity Analysis Set; nm, number of participants with available data; PRNT50, plaque reduction neutralization test at 50% reduction.
[a]N represents the total number of participants in the immunogenicity analysis set for Phase 1/2 overall. PRNT50 was performed in a subset of the full IAS for Phase 1/2, including all 100 participants from Phase 1 and the first 50 participants enrolled in Phase 2. Overall, 148 participants in this subset were evaluable; 111 in the ARCT-154 group and 37 in the Placebo group.
Percentages were based on number of participants with available data (nm) who seroconverted, where seroconversion was defined as a 4-fold increase in the assay readout from baseline. Readout values below the lower limit of quantification were (LLOQ) were imputed as LLOQ/2.

Immunizations with 5 ug ARCT-154 were performed days 1 and 29 (primary immunization).
Days 57 and 92 correspond to one and three months after completed primary immunization.
AU: Arbitrary units.
IU: International WHO units.
For the D614G assay (VAC62), 1 IU/mL = 1.275 AU/mL.

Figure 8: Authentic virus neutralisation assay performed at the Vietnam NIHE; index strain (PRNT50 assay, index strain)

Functional and spike-binding binding antibody responses over time (Vietnam NIHE ACE2-blocking ELISA and anti-S IgG ELISA assays; formal secondary immunogenicity endpoints, phase 1/2/3a)

The kinetics of functional (ACE2-blocking) and binding antibodies were essentially identical. Titers were low at baseline (day 1), increased day 29 (28 days after first immunisation in primary series), increased further day 57 (28 days after second immunisation), and exhibited waning by day 92 (three months after second immunisation) (see Figure 9 below).

GMT, GMFR, and SCR Based on NAb by NIHE sVNT (Ancestral strain) - IAS - Phase 1/2/3a (2-dose Schedule)

Endpoint		ARCT-154 (N=725)		Placebo (N=242)	
		nm	Value (95% CI)	nm	Value (95% CI)
Day 1	GMT, IU/mL	724	15.3 (15.2-15.4)	242	15.2 (15.0-15.3)
Day 29	GMT, IU/mL	719	60.7 (56.6-65.1)	240	15.7 (15.2-16.1)
	GMFR	718	4.0 (3.7-4.3)	240	1.0 (1.0-1.1)
	SCR, %	718	54.0 (50.3-57.7)	240	1.7 (0.5-4.2)
Day 57	GMT, IU/mL	700	221.2 (207.3-235.9)	231	15.2 (15.2-15.2)
	GMFR	699	14.5 (13.6-15.5)	231	1.0 (1.0-1.0)
	SCR, %	699	94.1 (92.1-95.8)	231	0.4 (0.0-2.4)
Day 92	GMT, IU/mL	668	209.6 (188.2-233.3)	221	20.3 (18.0-22.9)
	GMFR	667	13.7 (12.3-15.3)	221	1.3 (1.2-1.5)
	SCR, %	667	85.6 (82.7-88.2)	221	9.5 (6.0-14.2)

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titers; IAS, immunogenicity analysis set; NAb, neutralizing antibody; nm, number of participants with available data; SCR, seroconversion rate; sVNT, surrogate virus neutralization test.

Percentages were based on number of participants with available data (nm) who seroconverted, where seroconversion was defined as a 4-fold increase in the assay readout from baseline. Readout values below the lower limit of quantification were (LLOQ) were imputed as LLOQ/2.

IU, international WHO units (conversion to IU done according to the manual for the sVNT i.e. Genscript cPass kit).

Anti-spike IgG ELISA (index strain spike, Advia Centaur system) performed at the Vietnam NIHE

GMC, GMFR, and SCR Based on IgG Binding to Spike Protein (Ancestral strain) - IAS - Phase 1/2/3a (2-dose Schedule)

Endpoint		ARCT-154 (N=725)		Placebo (N=242)	
		nm	Value (95% CI)	nm	Value (95% CI)
Day 1	GMC, U/mL	725	0.3 (0.3-0.3)	242	0.3 (0.3-0.3)
Day 29	GMC, U/mL	719	2.1 (2.0-2.3)	240	0.3 (0.3-0.3)
	GMFR	719	7.5 (6.9-8.1)	240	1.0 (0.9-1.0)
	SCR, %	719	73.3 (69.9-76.5)	240	1.3 (0.3-3.6)
Day 57	GMC, U/mL	701	20.3 (19.0-21.7)	231	0.3 (0.3-0.3)
	GMFR	701	71.4 (66.6-76.5)	231	1.0 (0.9-1.0)
	SCR, %	701	99.6 (98.8-99.9)	231	1.3 (0.3-3.7)
Day 92	GMC, U/mL	668	11.9 (10.6-13.3)	221	0.4 (0.3-0.5)
	GMFR	668	42.0 (37.5-47.1)	221	1.5 (1.2-1.8)
	SCR, %	668	97.6 (96.1-98.6)	221	13.1 (9.0-18.3)

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titers; IAS, immunogenicity analysis set; NAb, neutralizing antibody; nm, number of participants with available data; SCR, seroconversion rate.

Percentages were based on number of participants with available data (nm) who seroconverted, where seroconversion was defined as a 4-fold increase in the assay readout from baseline. Readout values below the lower limit of quantification were (LLOQ) were imputed as LLOQ/2.

Day 1: Baseline.
Day 29: 28 days after 1st immunization in primary series.
Day 57: 28 days after 2nd immunization in primary series.
Day 92: Approx. 3 months after completed primary series.

Figure 9: ACE-blocking assay (index strain spike, cPass kit, Genescript)

Functional and spike-binding antibody responses at day 57 (post hoc revised secondary immunogenicity endpoint, phase 1/2/3a)

By a validated multiplex ELISA assay (VAC72), at day 57, the following seroconversion rates and GMFR for binding antibodies against the index spike protein were observed:

- The seroconversion rate against full-length spike protein was 100% (95% CI: 98.0% to 100%) in the ARCT-154 group.
- The seroconversion rate for the receptor-binding domain was 99.5% (95% CI: 97.0% to 100%) in the ARCT-154 group.
- For each of the above, there was no seroconversion observed in the placebo group.
- GMFR for the full-length S protein was 690.0 (95% CI: 575.7 to 827.1) in the ARCT-154 group and 0.8 (95% CI: 0.8 to 0.9) in the placebo group.

- GMFR (95% CI) for RBD was 864.6 (95% CI: 744.5 to 1004.1) in the ARCT-154 group and 0.9 (95% CI: 0.8, 1.0) in the placebo group.
- The level of binding antibodies to the full-length index spike protein was 29646.3 AU/mL (95% CI: 26976.0 to 32580.8) in the ARCT-154 group, versus 37.2 AU/mL (95% CI: 28.3 to 49.0) in the placebo group.

The results for spike-binding antibody responses were supported by data from assays measuring functional anti-spike responses (validated ACE2 blocking ELISA, VAC114). At day 57, the level of antibodies able to block the interaction between ACE 2 and the index spike protein was 7.9 U/mL (95% CI: 7.0-8.8) in the ARCT-154 group, versus 0.4 AU/mL (95% CI: 0.4-0.4) in the placebo group.

Anti-nucleocapsid antibody levels

By a validated multiplex ELISA assay (VAC72), at day 57, the level of participants who seroconverted for anti-nucleocapsid antibodies was 3/186 (1.6%) and 1/99 (1.7%) in ARCT-154 and placebo groups, respectively.

Neutralising antibody responses after third immunisation (boost) with ARCT-154 against variants (exploratory immunogenicity endpoint; phase 2/3a)

Immunisations with 5 µg ARCT-154 were performed at days 1 and 29 (primary immunisation) and after switchover, at day 92 (third dose/first booster).

By day 120 (approximately 1 month after homologous ARCT-154 boost), the following results were obtained by the validated pseudovirus neutralisation assays:

- For participants who received a 2-dose primary series of ARCT-154 but were administered placebo as a third dose, seroconversion against the index, delta and omicron BA.1 strains was 92%, 21% and 23% respectively (see table below).
- For participants who received a third dose of ARCT-154, seroconversion rose to 100%, 86% and 72%, respectively.
- For participants who received a third dose of ARCT-154, the GMFR against the index, delta and omicron BA.1 strains was 86-fold, 10-fold and 6-fold, respectively (see Table 6 below).
- For participants who received a third dose of ARCT-154, antibody levels against the index strain were 718 IU/mL, i.e. approximately 4-fold higher than the maximal levels obtained after the primary series (146 IU/mL).

Table 6: Pseudovirus neutralisation assay performed; spike protein of index strain with D614G mutation, delta strain and omicron BA.1 strain (VAC62, VAC120 and VAC122)

Summary of SCRs, GMC and GMFRs at Day 120 of NAbs against the Ancestral Strain (D614G), Delta/B.1.617.2, and Omicron BA.1 by MNT (Phase 2/3a IAS Subset [3-dose Schedule])

Timepoint	ARCT-154 (Initial; Dose 1 and 2)			
	ARCT-154 (Dose 3)/Placebo (Dose 4) (N=477)		Placebo (Dose 3 and 4) (N=152)	
	Ancestral Strain (D614G)			
	nm	GMC (95% CI)	nm	GMC (95% CI)
Day 1	243	7.9 (7.2–8.7)	82	7.1 (6.3–8.0)
Day 57	238	155.2 (140.9–171.0)	76	155.0 (133.6–179.8)
Day 92	165	111.1 (90.3–136.7)	52	96.3 (78.7–117.7)
Day 120	165	718.1 (624.0–826.3)	52	134.9 (84.7–214.9)
	nm	GMFR (95% CI)	nm	GMFR (95% CI)
Day 57	237	19.8 (17.5–22.3)	76	22.2 (18.5–26.6)
Day 92	164	13.4 (10.7–16.9)	52	12.4 (9.9–15.6)
Day 120	164	86.8 (73.8–102.0)	52	17.4 (10.9–27.9)
	n/nm	SCR (95% CI)	n/nm	SCR (95% CI)
Day 57	223/237	94.1 (90.3–96.7)	75/76	98.7 (92.9–100.0)
Day 120	164/164	100 (97.8–100.0)	48/52	92.3 (81.5–97.9)
	Delta/B.1.617.2 Variant			
	nm	GMC (95% CI)	nm	GMC (95% CI)
Day 1	167	11.0 (11.0–11.0)	56	11.0 (11.0–11.0)
Day 57	165	19.7 (17.8–21.8)	51	21.8 (17.6–27.0)
Day 92	164	18.4 (15.2–22.2)	51	14.9 (12.6–17.6)
Day 120	165	116.9 (101.2–135.0)	52	23.6 (15.5–35.8)
	nm	GMFR (95% CI)	nm	GMFR (95% CI)
Day 57	164	1.8 (1.6–2.0)	51	2.0 (1.6–2.5)
Day 92	163	1.7 (1.4–2.0)	51	1.4 (1.1–1.6)
Day 120	164	10.7 (9.2–12.3)	52	2.1 (1.4–3.3)
	n/nm	SCR (95% CI)	n/nm	SCR (95% CI)
Day 57	22/164	13.4 (8.6–19.6)	9/51	17.6 (8.4–30.9)
Day 120	142/164	86.6 (80.4–91.4)	11/52	21.2 (11.1–34.7)
	Omicron BA.1 Variant			
	nm	GMC (95% CI)	nm	GMC (95% CI)
Day 1	167	6.8 (6.4–7.3)	56	6.6 (5.9–7.5)
Day 57	165	7.6 (7.1–8.2)	51	8.2 (7.1–9.4)
Day 92	165	10.6 (8.9–12.5)	52	7.7 (6.6–9.1)
Day 120	165	45.7 (39.5–52.7)	52	15.0 (10.0–22.6)
	nm	GMFR (95% CI)	nm	GMFR (95% CI)
Day 57	164	1.1 (1.0–1.2)	51	1.3 (1.0–1.5)
Day 92	164	1.5 (1.3–1.9)	52	1.2 (1.0–1.4)
Day 120	164	6.7 (5.8–7.8)	52	2.3 (1.5–3.5)
	n/nm	SCR (95% CI)	n/nm	SCR (95% CI)
Day 57	4/164	2.4 (0.7–6.1)	1/51	2 (0.0–10.4)
Day 120	118/164	72 (64.4–78.7)	12/52	23.1 (12.5–36.8)

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold rise; IAS, Immunogenicity Analysis Set; LLOQ, lower limit of quantification; MNT, microneutralization test; NAb, neutralization antibody; nm, number of participants with available data. Pb, placebo; Vx, ARCT-154 (vaccine).
The baseline reference for SCR and GMFR was Day 1.
Percentages were based on number of participants with available data (nm) who seroconverted, where seroconversion was defined as a 4-fold increase in the assay readout from baseline. Readout values below the lower limit of quantification were (LLOQ) were imputed as LLOQ/2.
GMC is presented in AU/mL for Delta and Omicron BA.1 variants and IU/mL for the ancestral (D614G) strain.

Immunizations with 5 ug ARCT-154 were performed days 1 and 29 (primary immunization) and 92 (3rd dose/1st booster). Day 120 corresponds to approx one month after the 3rd immunization.
AU: Arbitrary units.
IU: International WHO units.
For the D614G assay (VAC62), 1 IU/mL = 1.275 AU/mL

- **Outcomes and estimation, comparison of immunogenicity and efficacy to ChAdOx1 (phase 3c)**

The protocol-defined primary objective in phase 3c was to demonstrate non-inferiority of a primary series of ARCT-154 to ChAdOx1, based on circulating virus-neutralising antibody levels.

However, as a significant number of protocol-defined COVID-19 cases were reported during phase 3b, the applicant decided to perform post-hoc exploratory comparison of immunogenicity between ARCT-154-01 and ChAdOx1, as opposed to formal non-inferiority testing.

Comparison of efficacy for the ARCT-154 and ChAdOx1 primary series was an exploratory objective in phase 3c.

Compared to the ChAdOx1 primary series, levels of circulating neutralising antibodies were higher in ARCT-154 vaccinees throughout the 394 day phase 3c study period, most pronounced in vaccinees who remained COVID-19 naïve through the 394 day study period (approximately 2 to 3-fold higher in naïve, approximately 2-fold higher in participants who seroconverted for anti-nucleocapsid antibodies during the 394 day study period (see first two figures below).

In phase 3c, compared a ChAdOx1 primary series, the relative efficacy of the primary series of ARCT-154 against COVID-19 was 30.7% through 36 days post-dose 2 to day 92 (95% CI: -23.0 to 61.0), 19.3% through 36 days post-dose 2 to day 211 (95% CI: 2.8% to 32.9), and 19.8% through 36 days post-dose 2 to the end of the study (95% CI: 4.0% to 33.0%).

The higher efficacy of the ARTC-154 primary series compared to the ChAdOx1 primary series was seen for all age groups (see third figure below).

Immunogenicity of ARTC-154 primary series, relative to ChAdOx1 primary series

Authentic virus neutralization assay performed at VisMederi laboratories; index strain

Participants who remained negative for anti-nucleocapsid antibody through the 394 day study period.

			ARCT-154 (N=100)		ChAdOx1 (N=76)	
Timepoint	Endpoint	Unit	n	Value	n	Value
Day 1	GMT (95% CI)	1/dilution	100	10.03 (9.97, 10.10)	76	10.09 (9.91, 10.28)
	GMT (95% CI)	IU/mL	100	3.20 (3.18, 3.22)	76	3.22 (3.16, 3.28)
Day 29	GMT (95% CI)	1/dilution	100	75.16 (59.97, 94.20)	76	32.14 (26.03, 39.68)
	GMT (95% CI)	IU/mL	100	23.98 (19.13, 30.05)	76	10.25 (8.30, 12.66)
Day 57	GMT (95% CI)	1/dilution	100	299.61 (247.09, 363.28)	76	111.09 (87.84, 140.51)
	GMT (95% CI)	IU/mL	100	95.57 (78.82, 115.89)	76	35.44 (28.02, 44.82)
Day 211	GMT (95% CI)	1/dilution	100	125.53 (86.24, 182.73)	76	77.49 (48.32, 124.25)
	GMT (95% CI)	IU/mL	100	40.05 (27.51, 58.29)	76	24.72 (15.41, 39.64)
Day 394	GMT (95% CI)	1/dilution	69	252.71 (153.40, 416.33)	53	68.38 (40.82, 114.56)
	GMT (95% CI)	IU/mL	69	80.62 (48.93, 132.81)	53	21.81 (13.02, 36.54)

Participants who seroconverted to nucleocapsid antigen through the 393 day study period.

			ARCT-154 (N=105)		ChAdOx1 (N=105)	
Timepoint	Endpoint	Unit	n	Value	n	Value
Day 1	GMT (95% CI)	1/dilution	105	10.03 (9.97, 10.10)	105	10.03 (9.97, 10.10)
	GMT (95% CI)	IU/mL	105	3.20 (3.18, 3.22)	105	3.20 (3.18, 3.22)
Day 29	GMT (95% CI)	1/dilution	105	79.21 (62.42, 100.53)	105	50.73 (40.40, 63.70)
	GMT (95% CI)	IU/mL	105	25.27 (19.91, 32.07)	105	16.18 (12.89, 20.32)
Day 57	GMT (95% CI)	1/dilution	104	343.20 (282.63, 416.74)	105	154.29 (118.92, 200.19)
	GMT (95% CI)	IU/mL	104	109.48 (90.16, 132.94)	105	49.22 (37.94, 63.86)
Day 211	GMT (95% CI)	1/dilution	105	838.93 (579.17, 1215.18)	103	642.16 (460.35, 895.76)
	GMT (95% CI)	IU/mL	105	267.62 (184.76, 387.64)	103	204.85 (146.85, 285.75)
Day 394	GMT (95% CI)	1/dilution	95	2049.24 (1632.69, 2572.07)	88	1093.44 (812.93, 1470.74)
	GMT (95% CI)	IU/mL	95	653.71 (520.83, 820.49)	88	348.81 (259.32, 469.17)

Primary-series immunizations with 5 ug ARCT-154 or ChAdOx1 were performed days 1 and 29.

GMT: Geometric mean titer.
IU: International WHO units.

Figure 10: Immunogenicity of ARTC-154 primary series, relative to ChAdOx1 primary series

Authentic virus neutralisation assay; index strain

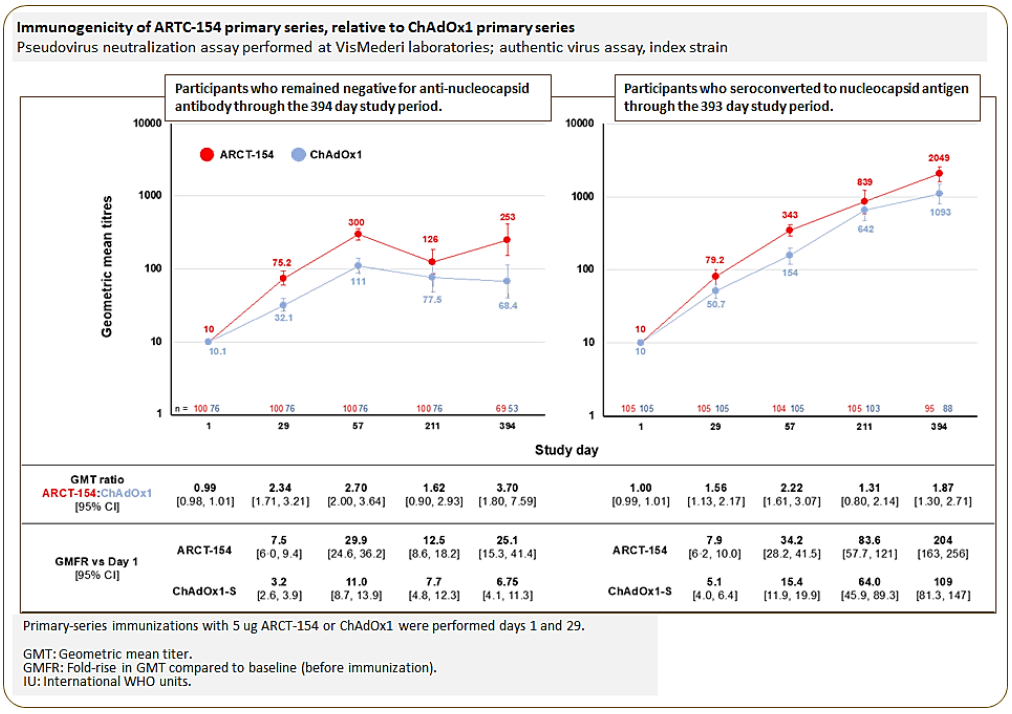
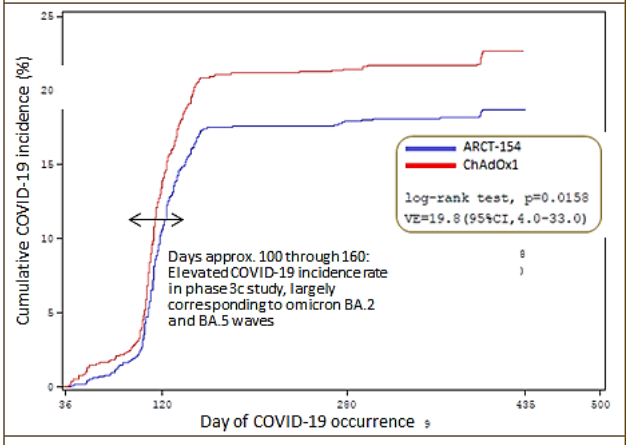


Figure 11: Immunogenicity of ARTC-154 primary series, relative to ChAdOx1 primary series

Pseudovirus neutralisation assay, authentic virus assay, index strain

rVE Against Virologically Confirmed, Protocol-Defined COVID-19 Between Day 36 and End of the Study – Subgroup Analyses (Phase 3c mITT)

Subgroup	Treatment Group	Number of Participants	Cumulative Follow-up Period (Person-Years)	Number of Participants with Case Reported n (%)	% rVE* (95% CI)
COVID-19 of any severity					
≥18 years (all age groups)	ARCT-154	1165	965.7	218 (18.7)	19.8 (4.0 - 33.0)
	ChAdOx1	1156	922.4	262 (22.7)	
≥18 to <50 years	ARCT-154	503	424.9	88 (17.5)	21.6 (-4.2 - 41.0)
	ChAdOx1	486	393.1	104 (21.4)	
≥50 years	ARCT-154	662	540.7	130 (19.6)	18.3 (-3.0 - 35.3)
	ChAdOx1	670	529.4	158 (23,6)	
≥60 years	ARCT-154	319	267.1	51 (16.0)	29.8 (-0.7 - 51.0)
	ChAdOx1	321	260.3	71 (22.1)	
≥ 65 years	ARCT-154	166	137.0	28 (16.9)	33.5 (-7.8 - 59.0)
	ChAdOx1	160	127.8	40 (25.0)	
≥ 70 years	ARCT-154	71	60.5	11 (15.5)	43.5 (-20.0 - 73.4)
	ChAdOx1	68	53.7	18 (26.5)	



Primary-series immunizations with 5 ug ARCT-154 or ChAdOx1 were performed days 1 and 29.

In total, 45 participants were excluded from mITT, 28 participants (17 ARCT 154; 7 ChAdOx1) did not receive the second vaccination dose and 17 participants (6 ARCT-154 group; 11 ChAdOx1) had evidence of COVID-19 between day 1 and day 35.

VE: Relative Vaccine Efficacy calculated by 1-HR from Cox regression adjusting for risk group and region of study site.

Figure 12: Efficacy of ARTC-154 primary series, relative to ChAdOx1 primary series

- **Ancillary analyses, phase 3b**

For the primary efficacy endpoint (efficacy against virologically confirmed, protocol-defined COVID-19 with first occurrence of onset between days 36 and 92, mITT set) as well as the first secondary endpoint (efficacy against severe COVID-19 with onset between day 36 and day 92, mITT set), subgroup analyses were performed for the categories age, comorbidities predisposing for severe COVID-19, gender and geographical region (the incidence of COVID-19 differed significantly between the regions of Vietnam during the study period, being highest in Ho Chi Minh City).

For the primary efficacy endpoint (efficacy against COVID-19, days 36-92, mITT), for all subgroups analysed, the 95% CI for VE excluded 30% except for participants who were ≥ 60 years old. This finding may be due to a wider CIs for this subgroup due to the smaller sample size and the relatively low number of COVID-19 cases in this subgroup (see table below).

The VE observed in North HMU and North VMMU appeared to be higher compared with the VE in South Pasteur region, although the 95% CIs for the estimates overlapped (see Table 7 below).

For the first secondary endpoint (efficacy against severe COVID-19, days 36-92, mITT), for all subgroups analysed, the 95% CI for VE excluded 30%.

Table 7: VE of Confirmed Protocol-Defined COVID-19 Between Day 36 and Day 92 – Subgroup Analyses (Phase 3b mITT)

	Group	Number of Participants	Cumulative Follow-up Period (Person-Years)	Number of Participants With Cases Reported	% VE* (95% CI)
Age/Risk Group					
≥18 to ≤60 years 'healthy'	ARCT-154	3882	572.1	126	49.8 (37.8-59.5)
	Placebo	3896	566.1	246	
≥18 to <60 years 'at risk'	ARCT-154	2519	372.9	46	69.7 (57.6-78.3)
	Placebo	2471	359.5	138	
≥18 to <50 years	ARCT-154	4213	623.2	123	57.9 (47.9-65.9)
	Placebo	4164	604.7	276	
≥50 years	ARCT-154	3549	523	77	54.7 (40.6-65.4)
	Placebo	3532	515.5	164	
≥18 to <60 years	ARCT-154	6401	945.1	172	57.2 (48.7-64.2)
	Placebo	6367	925.6	384	
≥60 years	ARCT-154	1361	201.2	28	53.5 (26.8-70.5)
	Placebo	1329	194.5	56	
≥18 to <65 years	ARCT-154	7251	1070.1	190	56.4 (48.3-63.3)
	Placebo	7205	1047.5	416	
≥65 years	ARCT-154	511	76.1	10	60.6 (17.6-81.1)
	Placebo	491	72.7	24	
≥18 to <75 years	ARCT-154	7714	1139	200	56.6 (48.7-63.3)
	Placebo	7645	1112.5	439	
≥75 years	ARCT-154	48	7.2	0	NE (NE - NE)
	Placebo	51	7.7	1	
Sex					
Female	ARCT-154	3965	584.3	115	53.0 (41.3-62.5)
	Placebo	3918	569.6	231	
Male	ARCT-154	3797	561.9	85	61.4 (50.3-70.0)
	Placebo	3778	550.6	209	
Region					
North HMU	ARCT-154	1888	265.4	10	76.6 (53.3-88.3)
	Placebo	1883	262.9	42	
North VMMU	ARCT-154	2797	420.0	4	73.5 (20.1-91.2)
	Placebo	2784	416.1	15	
South Pasteur	ARCT-154	3077	460.8	186	53.9 (45.1-61.3)
	Placebo	3029	441.1	383	

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HCM, Ho Chi Minh; HMU, Hanoi Medical University; HR, hazard ratio; mITT, modified Intent-to-Treat; NE, non estimatable; VE, vaccine efficacy; VMMU, Vietnam Military Medical University.
*VE was calculated by 1-HR from cox regression adjusting for risk group and region of study site.

- **Ancillary analyses, phase 3c**

The higher efficacy of the ARTC-154 primary series compared to the ChAdOx1 primary series was seen for all age groups (see figure above).

- **Summary of main efficacy results**

This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 8: Summary of efficacy for trial ARCT-154-01 trial (pivotal efficacy, Vietnam)

Title: A Randomised, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self Amplifying RNA Vaccine ARCT-154 in Adults		
Study identifier: NCT05012943		
Design	Phase 1/2/3, randomised, placebo- and active-controlled, observer-blind study designed to evaluate the safety, immunogenicity, and efficacy of a 2-dose priming regimen of ARCT-154 (each dose 5 mcg) in adult participants in Vietnam.	
Duration	Duration of main phase:	Primary-series immunisations given day 1 and 29; efficacy evaluated up to 92 days, immunogenicity up to 52-120 days (depending on assay).
	Run-in and extension phases:	Not relevant.
Hypothesis	Efficacy (phase 3b): Vaccine efficacy against virologically confirmed COVID-19. The primary efficacy objective will be met if the lower limit of the 95% CI for VE exceeds 30%. Immunogenicity (phases 1/2/3a): Seroconversion compared to placebo. The phase 1/2/3a part of the study will be considered to meet the primary immunogenicity objective if the lower bound of the 95% CI for seroconversion in ARCT-154-immunised participants is > placebo.	
Treatments groups	ARCT-154 vaccine, phases 1, 2, 3a	Five µg ARCT-154 dissolved in 0.5 mL sterile isotonic saline, by IM injection days 1 and 29 (primary series) and days 92 and 120 (crossover immunisation). 749 participants randomised; 749 and 733 received first and second immunisation (primary series); 483 and 467 received third and fourth immunisation, respectively.
	Placebo (saline), phases 1, 2, 3a	0.5 mL saline by IM injection, days 1 and 29, and days 92 and 120. 252 participants randomised; 252 and 245 received first and second injections, respectively.
	ARCT-154 vaccine, phase 3b (enriched for participants at higher risk for COVID-19 by deliberate enrollment of individuals considered at high risk of exposure to SARS-CoV-2 due to their workplace environment or living conditions).	Five µg ARCT-154 dissolved in 0.5 mL sterile isotonic saline, by IM injection days 1 and 29 (primary series) and days 92 and 120 (crossover immunisation). 8059 participants randomised, 8056 and 7869 received first and second immunisation (primary series).

Title: A Randomised, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self Amplifying RNA Vaccine ARCT-154 in Adults			
Study identifier: NCT05012943			
	Placebo, phase 3b (enriched for participants at higher risk for COVID-19 by deliberate enrollment of individuals considered at high risk of exposure to SARS-CoV-2 due to their workplace environment or living conditions).		0.5 mL saline by IM injection, days 1 and 29, and days 92 and 120. 8048 participants randomised; 8044 and 7831 received first and second injections, respectively.
	ARCT-154 and ChAdOx1 vaccines, phase 3c		1184 and 1182 randomised to ARCT-154 and ChAdOx1 arms, respectively. For ARCT-154, 1184 and 1171 received first and second immunisations, respectively. For ChAdOx1, 1182 and 1169 received first and second immunisations, respectively.
Endpoints and definitions	Primary endpoint, efficacy (phase 3b)	Vaccine efficacy against virologically confirmed, protocol-defined COVID 19 with first occurrence of onset between days 36 and 92, inclusive.	The objective was evaluated in all participants in the phase 3b mITT set, based on the first occurrence of confirmed, protocol-defined COVID-19 with onset between days 36 and day 92, inclusive.
	Secondary endpoint, efficacy (phase 3b)	Vaccine efficacy against virologically confirmed, protocol-defined severe COVID-19 with first occurrence of onset between days 36 and 92, inclusive.	The objective was evaluated in all participants in the phase 3b mITT set, based on the first occurrence of confirmed, protocol defined severe COVID-19 with onset between days 36 and 92, inclusive.
	Secondary endpoint, efficacy (phase 3b)	Vaccine efficacy against virologically confirmed, protocol-defined COVID-19 with first occurrence of onset at any time after the first vaccination.	The objective was evaluated in all participants in the phase 3b ITT set who had received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (RT-PCR testing of nasal swabs and nucleocapsid ELISA), based on first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to day 92, inclusive.
	Secondary endpoint, efficacy (phase 3b)	Vaccine efficacy against death due to virologically confirmed, protocol-defined COVID-19 between days 36 and 92, inclusive.	The objective was evaluated in all participants in the phase 3b mITT set, based on the occurrence of death attributed to COVID-19 occurring between day 36 and 92, inclusive.
	Secondary endpoint, efficacy (phase 3b)	Vaccine efficacy against virologically confirmed, protocol-defined COVID-19 regardless of baseline status for evidence of prior SARS-CoV-2 infection.	The objective was evaluated in all participants in the phase 3b ITT set who had received both vaccinations in the first vaccination series and who had no evidence of onset of SARS-CoV-2 infection between day 1 and 35 included, based on the first occurrence of confirmed, protocol-defined COVID-19 with onset between day 36 and 92, inclusive.

Title: A Randomised, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self Amplifying RNA Vaccine ARCT-154 in Adults			
Study identifier: NCT05012943			
	Exploratory endpoints for efficacy (phase 3b)	Not listed here, as they are not considered to be of main relevance for the conclusions on vaccine efficacy.	
	Vaccine efficacy compared to ChAdOx1 (phase 3c)	Non-inferiority of ARCT-154 versus ChAdOx1 at day 57.	As a significant number of protocol-defined COVID-19 cases were reported during phase 3b, the applicant instead decided to perform post-hoc exploratory comparison of ARCT-154-01 efficacy versus ChAdOx1.
	Immunogenicity endpoints (phases 1/2/3a	The immunogenicity endpoints are considered relevant and supplementary for interpretation of the efficacy data but are not of main relevance in this placebo-controlled efficacy study; they are therefore not listed here.	
Database lock	The study started 11 August 2021 (first participant enrolled, phase 1). As predefined in the protocol, the primary efficacy analysis was performed when all participants in phase 3b had reached day 92 and all potential COVID-19 events in these participants up to day 92 had been adjudicated by the blinded independent adjudication committee. For the initial MAA, a 6-month interim report was provided (25 April 2023, data extraction date 12 January 2023), with an addendum (version1, 16 May 2023, data extraction date 12 January 2023). With the day 150 responses, the final report was provided (29 January 2024, date extraction date 30 March 2022).		

Results and Analysis

Analysis description	**Primary Analysis: Vaccine efficacy against virologically confirmed, protocol-defined COVID 19 with first occurrence of onset between days 36 and 92, included.**		
Analysis population and time point description	The objective was evaluated in all participants in the phase 3b mITT set, based on the first occurrence of confirmed, protocol-defined COVID-19 with onset between days 36 and 92, included.		
Descriptive statistics and estimate variability	Treatment group	ARCT-154	Placebo
	Number of subjects	7562	7256
	Confirmed, protocol-defined COVID-19	200	440
Effect estimates per comparison	Endpoint	Comparison groups	ARCT-154 vs. placebo
		Vaccine efficacy (%)	56.7
		95% CI (%)	48.8, 63.4
Notes	The lower limit of the 95% CI was above the prespecified success threshold of 30%, and therefore the study met its primary endpoint. Results for the PP analysis set were consistent with the primary analysis in the mITT. VE estimates for examined subgroups (elderly, comorbidities predisposing for severe COVID-19, sex, geographical region) were overall consistent with the main analysis.		
Analysis description	**Secondary analysis: Vaccine efficacy against virologically confirmed, protocol-defined severe COVID-19 with first occurrence of onset between days 36 and 92, inclusive.**		
Analysis population and time point description	The objective was evaluated in all participants in the phase 3b mITT set, based on the first occurrence of confirmed, protocol-defined severe COVID-19 with onset between days 36 and 92, inclusive.		
Descriptive statistics and estimate variability	Treatment group	ARCT-154	Placebo
	Number of subjects	7760	7655

Title: A Randomised, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self Amplifying RNA Vaccine ARCT-154 in Adults			
Study identifier: NCT05012943			
	Confirmed, protocol-defined severe COVID-19	2	41
Effect estimates per comparison	Endpoint	Comparison groups	ARCT-154 vs. placebo
		Vaccine efficacy (%)	95.3
		96.95% CI (%)	80.5, 98.9
Notes	The lower limit of the CI was above the prespecified success threshold of 0%; i.e. the study met this secondary endpoint. Results for the PP analysis set were consistent with the analysis conducted in the mITT. VE estimates for examined subgroups (elderly, comorbidities predisposing for severe COVID-19, sex, geographical region) were overall consistent with the main analysis.		
Analysis description	**Secondary analysis: Vaccine efficacy against virologically confirmed, protocol-defined COVID-19 with first occurrence of onset at any time after the first vaccination.**		
Analysis population and time point description	The objective was evaluated in all participants in the phase 3b ITT set who had received any dose of study vaccine in the first vaccination series, with no evidence of infection prior to vaccination (RT-PCR testing of nasal swabs and nucleocapsid ELISA), based on first occurrence of confirmed, protocol-defined COVID-19 with onset at any time after the first study vaccination and up to day 92, inclusive.		
Descriptive statistics and estimate variability	Treatment group	ARCT-154	Placebo
	Number of subjects	7833	7547
	Confirmed, protocol-defined COVID-19	223	496
Effect estimates per comparison	Endpoint	Comparison groups	ARCT-154 vs. placebo
		Vaccine efficacy (%)	56.7
		96.95% CI (%)	49.3, 63.1
Notes	The lower limit of the CI was above the prespecified success threshold of 0%, and the study therefore met this second secondary endpoint.		
Analysis description	**Secondary analysis: Vaccine efficacy against death due to virologically confirmed, protocol-defined COVID-19 between days 36 and 92, inclusive**		
Analysis population and time point description	The objective was evaluated in all participants in the phase 3b mITT set, based on the occurrence of death attributed to COVID-19 occurring between day 36 and 92, inclusive.		
Descriptive statistics and estimate variability	Treatment group	ARCT-154	Placebo
	Number of subjects	7762	7696
	Death attributed to COVID-19	1	9
Effect estimates per comparison	Endpoint	Comparison groups	ARCT-154 vs. placebo
		Vaccine efficacy (%)	86.3
		96.95% CI (%)	-8.9, 98.3

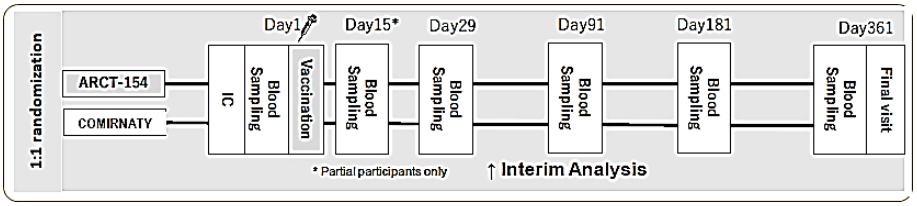
Title: A Randomised, Observer-Blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self Amplifying RNA Vaccine ARCT-154 in Adults			
Study identifier: NCT05012943			
Notes	This endpoint was not met. The wide 95% CI is likely due to the small number of deaths attributed to COVID-19 overall, and though the endpoint was not met, the results show a favourable trend for ARCT-154 vaccine versus placebo.		
Analysis description	**Post-hoc exploratory analysis: Vaccine efficacy compared to ChAdOx1 (phase 3c).**		
Analysis population and time point description	The objective was evaluated in all participants in the phase 3c mITT set, based on the first occurrence of confirmed, protocol-defined COVID-19 with onset between days 36-92, 36-211 and 36-study end (day approximately 394).		
Descriptive statistics and estimate variability	Treatment group	ARCT-154	ChAdOx1
	Number of subjects	1145, 960 and 947 for the three-time windows, respectively	1128, 911 and 894 for the three-time windows, respectively
	Confirmed, protocol-defined COVID-19	20, 205 and 218 for the three-time windows, respectively	28, 245 and 262 for the three-time windows, respectively
Effect estimates per comparison	Endpoints	Comparison groups	ARCT-154 vs. ChAdOx1
		Relative vaccine efficacy (%)	30.7%, 19.3% and 19.8% for the three-time windows, respectively.
		96.95% CI (%)	(-23.0, 61.0), (2.8, 32.9) and (4.0, 33.0) for the three-time windows, respectively.
Notes	The initial primary objective was to evaluate non-inferiority of ARCT-154 versus ChAdOx1 at day 57. However, as a significant number of protocol-defined COVID-19 cases were reported during phase 3b, the applicant instead decided to perform post-hoc exploratory comparison of efficacy between ARCT-154-01 and ChAdOx1.		

2.5.5.2.2 ARCT-154-J01

Methods

First subject visit was on 13 December 2022 and the enrolment was completed on 27 February 2023.

An interim report (dated 21 June 2023) providing immunogenicity analyses up to day 29 was provided for the initial MAA. With the day 150 responses, the applicant further provided a 6-month interim report (dated 18 January 2024).



ARCT-154 and the comparator are both LNP-formulated mRNA vaccines (albeit the comparator mRNA vaccine is non-replicating), both based on the prefusion-stabilized, full-length (membrane-anchored) form of the spike protein of the index SARS-CoV-2 strain. Furthermore, for the comparator, correlates of protection have been established, and a large amount of efficacy data exists, and mRNA vaccines have been used for primary-immunisation and boosting for a large proportion of the EU population.

Therefore, the comparator product and overall study design was appropriate to allow inferring the efficacy of heterologous boost with ARCT-154 in a real-world setting.

As approximately 80% of the participants received primary immunisation with Comirnaty original (see section on participant disposition). The Comirnaty boost is also referred to as homologous hereinafter.

- **Study Participants**

ARCT-154-J01 was conducted in 11 sites in Japan.

The study enrolled healthy participants ≥ 18 years of age, who had been previously vaccinated with mRNA COVID-19 vaccine, and satisfied the following criteria:

- Received 3 complete doses of mRNA COVID-19 vaccine and the last dose received with Comirnaty occurred ≥ 3 months prior to screening.
- Receipt of these vaccines is supported by any documents and application software.

Participants had to adhere to contraceptive requirements.

Participants were excluded for the following reasons:

- Acute medical illness or febrile illness, including oral temperature >37.5ºC within 1 day prior to screening.
- Pregnant or breastfeeding.
- Positive SARS-CoV-2 rapid antigen test at screening (RT-PCR test could be performed according to institutional policy in addition to rapid antigen testing but was not considered a screening requirement and should not delay vaccine administration).
- History of COVID-19 or virologically confirmed SARS-CoV-2 infection within the past 4 months or history of COVID-19 with ongoing sequelae.
- Receipt of MERS, SARS-CoV or off-study SARS-CoV-2 vaccines (non-adjuvant inactivated influenza vaccines and non-replicating influenza vaccines were allowed to be given 14 days before or after receipt of a study vaccine).
- Medical conditions considered to interfere with vaccine responses or being contraindications to vaccination or IM injection: Known history of hypersensitivity or other significant adverse reactions to ARCT-154, Comirnaty, or their excipients; myocarditis, pericarditis, or cardiomyopathy; uncontrolled hypertension; history of Guillain-Barre syndrome, encephalomyelitis, or transverse myelitis; significant hematologic abnormalities, thrombosis with thrombocytopenia syndrome; congenital or acquired immunodeficiency; chronic infection including HIV, HBV, HCV, and active tuberculosis.
- Treatments considered to interfere with vaccination responses: Immunomodulatory, immunostimulatory, or immunosuppressant drugs including interferon and cytotoxic drugs within 3 months of 3 months of screening/day 1; immunoglobulins and/or any blood or blood products within the 4 months before the first vaccine administration; another investigational drug, biological agent, or device within 28 days of screening, or 5 half-lives of the investigational drug, whichever is longer; systemic corticosteroids exceeding 10 mg/day of prednisone equivalent for ≥ 10 days within 30 days of screening; topical, ophthalmic, inhaled, and intranasal steroid preparations was be permitted.

As the study population was young and healthy, it is not representative for the populations considered highest priority for COVID-19 boosters (i.e. elderly and individuals with comorbidities predisposing for severe COVID-19).

- **Treatments**

ARCT-154 vaccine: The contents of a vial was diluted with 10 mL of saline, and participants were vaccinated with a single intramuscular dose of 0.5 mL (5 µg).

Comirnaty original vaccine: The content of a vial was diluted with 1.8 mL of saline, and participants were vaccinated with a single IM dose of 0.3 mL (30 µg).

Summary of ARCT-154

Name	ARCT-154
Name of Active Ingredient	mRNA-2105 (RNA coding for the SARS CoV-2 full-length spike (S) glycoprotein)
Dosage Form	Vial containing lyophilized mRNA-2105
Storage	Store at below -20°C
Manufacturer	Arcturus Therapeutics, Inc.

Each vial contained 100 µg lyophilized active ingredient.

The following bulk batch numbers were used in the study:

Drug Substance Batch Number	Drug Product Batch Number	Description	Use in Study
21-AU04G003	159800A	Lyophilized ARCT-154	Booster

Summary of COMIRNATY

Name	COMIRNATY
Name of Active Ingredient	Tozinameran (a nucleoside-modified messenger RNA encoding the viral S glycoprotein of SARS-CoV-2)
Dosage Form	Vial containing solution for injection
Storage	Store at -60°C to -90°C
Manufacturer	Pfizer Co., Ltd.

Each vial contained 225 µg active ingredient in 0.45 mL solution.

Figure 13: Treatment summary - ARCT-154 and Comirnaty

In this study, the dose and vaccine formulation were the same as in the pivotal efficacy study for the primary series. The Comirnaty dose was according to the label.

- **Objectives**

The primary objective was to demonstrate the non-inferiority of the immune response against SARS-CoV-2 (Wuhan strain) four weeks after an ARCT-154 booster dose compared with that elicited by a Comirnaty booster, in mRNA-immunised adults.

The immunogenicity objectives are overall appropriate for a pivotal immunobridging study intended to support a MAA for a COVID-19 vaccine.

- **Outcomes/endpoints**

Primary endpoints

- Non-inferiority of ARCT-154 in the GMT of neutralising antibody against SARS-CoV-2 (index strain) on day 29, compared to Comirnaty.
- Non-inferiority of ARCT-154 in the SRR of neutralising antibodies against SARS-CoV-2 (index strain) on day 29, compared to Comirnaty.
    - SRR: Percentage of participants whose neutralising antibody titer against SARS-CoV-2 after study vaccine administration increased 4-fold or more from day 1 value. If day 1 is antibody-negative, the increase should be 4-fold or more relative to the 1/2 value

of the lower limit of quantitation.

Secondary endpoints

- To evaluate non-inferiority of ARCT-154 in GMT and SRR of neutralising antibody against SARS-CoV-2 (omicron BA.4/5 strain) on day 29, compared to Comirnaty.
- If a non-inferiority is confirmed, superiority of ARCT-154 in the GMT and SRR of the neutralising antibody over Comirnaty will be evaluated. For GMT, significant superiority over Comirnaty will also be evaluated.
- Time profile of GMT of neutralising antibody against SARS-CoV-2 (Wuhan and omicron BA.4/5 strains) on day 1, day 29, day 91, day 181 and day 361.
- SRR of neutralising antibody against SARS-CoV-2 (index and omicron BA.4/5 strains) at day 29, day 91, day 181 and day 361.
- GMFR in neutralising antibody titer against SARS-CoV-2 (index and omicron BA.4/5 strains) on day 29, day 91, day 181 and day 361 relative to day 1.
    - GMFR: Geometric mean of the ratio of the neutralising antibody titer on day 1 to the neutralising antibody titer at each time point in the same participant.

Interim analyses were conducted after all subjects completed day 61 assessments. The interim analysis consisted of two stages: analysis of neutralising antibody measurement data and safety data up to day 29 of all subjects, and analysis of COVID-19 case data collected up to day 61.

The provided report summarizes immunogenicity and safety results collected up to day 29. Summaries of efficacy data up to day 61 and some immunogenicity data including cell-mediated immunity are separately reported.

As Kostaive as well as the comparator are based on the index spike, basing the primary endpoint on neutralising responses to the index strain is appropriate.

The secondary endpoint is based on neutralising responses to omicron BA.4/BA.5. While this strain is no longer circulating, it is known to be antigenically very different from the index strain and is thus considered appropriate to gauge the breadth of neutralising antibody responses in the trial.

The interim report provides only humoral immunogenicity data, and this only for a single timepoint, corresponding to the time of expected maximal neutralising responses post-boost (i.e. day 29).

- **Sample size**

The GMT ratio of the neutralising antibody titer to the conventional strain in the booster vaccination was assumed to be 1.0, the standard deviation of the neutralising antibody titer was assumed to be 0.400, and the SRR of each inoculation group was assumed to be 85%.

To obtain 90% of statistical power to detect non-inferiority of ARCT-154 to Comirnaty in GMT and SRR (GMT non-inferiority margin = 0.67, SRR non-inferiority margin = -10%, significance level = 1-sided 2.5%), 270 subjects/group were required for analysis.

Assuming 10% of randomised subjects dropping out from immunogenicity analyses, 600 subjects/group were needed.

In addition to this, assuming 20% of randomised subjects being excluded from PPS-1 population due to the positive antibody result to the nucleocapsid of SARS-CoV-2 before study vaccine administration, 780 subjects/group were needed.

In the provided interim report, a total 828 participants were analysed, 420 and 408 in the ARCT-154 and Comirnaty groups, respectively.

The choices of non-inferiority margin are in general accordance with the scientific advice provided to the applicant, and general expectations for pivotal immunobridging trials for COVID-19 vaccines. The sample size estimations are acceptable.

- **Randomisation and blinding**

Participants were randomised 1:1 to ARCT-154 and Comirnaty groups.

Both study treatments (ARCT-154 and Comirnaty; 0.5 mL and 0.3 mL injection volumes, respectively) were administered using same type of 1 mL syringes, with procedures in place to prevent participants from deducing the received treatment (e.g. wearing eye mask or shielding vaccination arm with curtain).

The delineation of responsibilities for the randomisation process is clear and assigns tasks to specific individuals or roles. The provided code breaking procedures are comprehensive and well-structured. The randomisation scheme is appropriate.

The employed blinding procedures are standard, and appropriate to ensure the intended observer-blind study design.

- **Analysis sets**

Three analysis sets were used for analysis; FAS, PPS-1 and PPS-2:

- FAS: A set of participants who received a dose of study vaccine, excluding those with no data of neutralising antibody titer against SARS-CoV-2 (Wuhan strain) pseudovirus after a dose of study vaccine, or those with GCP deviations. Analyses were performed by group to which the subjects are assigned.
- PPS-1 (non-infection): A set of participants in the FAS, excluding those with positive for antibody to the nucleocapsid of SARS-CoV-2 before study vaccine administration, and those with deviations related to eligibility criteria, dosage and administration, concomitant drugs/therapies, immunogenicity data, and confirmation items on the day of study vaccine administration.
- PPS-2 (included participants positive for antibody to the nucleocapsid of SARS-CoV-2): A set of participants in the FAS, excluding those with deviations related to eligibility criteria, dosage and administration, concomitant drugs/therapies, immunogenicity data, and confirmation items on the day of study vaccine administration.
- PPS-1-ic: Modified version of the PPS-1, used for analysis of NAb titers up to day 181. This set excluded immunogenicity data from those subjects who had positive results from the nucleocapsid-specific antibody test at the given time point being assessed.

The analyses in the PPS-1 were considered the primary immunogenicity results.

The FAS in this study is a modified version of full analysis set, it was not a complete representation of all vaccine recipients, PPS-1 excluded those with specific deviations, and PPS-2 included participants with pre-existing antibodies. The primary immunogenicity results came from PPS-1.

The definition of analysis sets is agreed. The non-inferiority test needs also to be conducted in additional analysis set which contains all participants who received at least one dose (full dose), since there were only 3 participants excluded from the analysis due to no data, this issue is no further sought.

- Handling of Missing Data

Missing data were not imputed in ARCT-154-J01.

- Multiplicity Adjustment

No multiplicity adjustments were made, and only the primary hypothesis was formally tested using a sequential approach to control type 1 error for primary endpoints to non-inferiority and superiority. This approach is acceptable.

- **Statistical methods**

For primary Immunogenicity endpoints: The analysis of GMT involved ANCOVA, including treatment group and covariates like time since the last vaccination, gender, and age, with a 95% CI for the GMR to assess non-inferiority.

For SRR, the Miettinen-Nurminen method was used, with randomisation factors as adjustment, and non-inferiority assessed based on the lower limit of the 95% CI not exceeding -10%.

For secondary endpoints: For FAS and PPS (PPS-1, PPS-2), evaluation of non-inferiority of ARCT-154 to Comirnaty for neutralising antibody titers against Omicron BA4/5 variant on Day 29 was conducted in the same manner as the primary endpoint analysis, together with the application of box plot. If non-inferiority was confirmed, the superiority of ARCT-154 over Comirnaty was evaluated. If the anti-log-transformed lower bound of the 95% CI was greater than 1, then the superiority of ARCT-154 to Comirnaty was confirmed.

For efficacy endpoints: COVID-19 incidence, including severe cases, and cumulative incidence rates were addressed by the efficacy endpoints analyses. Furthermore, the assessment of neutralising antibody titers against various SARS-CoV-2 strains based on COVID-19 onset and days to recovery from onset was included in the plan. Subgroup analyses were also performed for different age and duration categories. Of note, the efficacy analyses were not conducted for the interim CSR and according to the applicant, the results obtained from the efficacy analyses would be reported separately.

The statistical methods used for multiple endpoints are considered adequate.

Results

- **Participant flow**

A total of 986 healthy volunteers were screened, and 828 subjects were randomised 1:1 to the ARCT-154 and Comirnaty arms. All 828 randomised subjects received the study vaccine.

- **Recruitment**

First subject visit was on 13 December 2022 and the enrolment was completed on 27 February 2023.

- **Conduct of the study**

The provided study protocol is version 5.0 (dated 01 March 2023).

A series of changes were made to the protocol:

- Changes of 16 November 2022, based on comments from the Japan Pharmaceuticals and Medical Devices Agency.
- Changes of 25 November 2022, based on applicant's discussion with the study drug supplier.
- Changes of 01 January 2023, based on applicant's discussion with the study drug supplier.

- Changes of 01 March 2023, based on applicant's discussion with the study drug supplier.

The protocol changes of 01 January 2023 and 01 March 2023 were made after the enrollment started. Reasoning have been provided for the changes, and they are evaluated as being minor.

- **Baseline data**

Of the 828 randomised participants, all 828 received the study vaccine. Overall, 825 participants completed the day 29 assessments after administration of the study vaccines.

Of the 828 participants who were randomised and received the study vaccine, 825, 759, and 813 participants were included in the FAS, PPS-1 and PPS-2, respectively.

Of 825 participants in the FAS, 805 (97.6%) participants were ≥18 to <65 years and 20 (2.4%) participants were ≥65 years of age. 340 (41.2%) participants were male, and 485 (58.8%) participants were female.

Time since the last vaccination was 3-5 months in 15 (1.8%) participants and ≥ 5 months in 810 (98.2%) participants.

Most of the participants were negative for anti-nucleocapsid antibodies (>95% negative).

In general, the demographics and other baseline characteristics were well balanced between ARCT-154 and Comirnaty groups.

Details for the demographics are provided in the Table 9 below.

Table 9: Summary of Demographic and Other Baseline Characteristics (FAS) (ARCT-154-J01)

Item	Level/ Statistic	ARCT-154	Comirnaty	Total
Participants in the analysis set		417	408	825
Age [Years]	N	417	408	825
	Mean	45.2	46.2	45.7
	SD	12.0	11.6	11.8
	Min	18	18	18
	Median	48.0	49.0	48.0
	Max	77	76	77
	< 65 years old	405(97.1)	400(98.0)	805(97.6)
	≥ 65 years old	12(2.9)	8(2.0)	20(2.4)
	18 – 29 years old	59(14.1)	49(12.0)	108(13.1)
	30 – 45 years old	125(30.0)	113(27.7)	238(28.8)
	46 – 64 years old	221(53.0)	238(58.3)	459(55.6)
	65 – 80 years old	12(2.9)	8(2.0)	20(2.4)
	≥ 81 years old	0(0.0)	0(0.0)	0(0.0)
Gender	Male	171(41.0)	169(41.4)	340(41.2)
	Female	246(59.0)	239(58.6)	485(58.8)
Period from last (3rd) vaccination	< 5 months	11(2.6)	4(1.0)	15(1.8)
	≥ 5 months	406(97.4)	404(99.0)	810(98.2)
Participants Requiring Caution in Vaccination (rows 1-5 immediately below)	No	265(63.5)	269(65.9)	534(64.7)
	Yes	152(36.5)	139(34.1)	291(35.3)
(1) underlying diseases	No	345(82.7)	346(84.8)	691(83.8)
	Yes	72(17.3)	62(15.2)	134(16.2)
(2) pyrexia within 2 days after vaccination in the past or symptoms	No	327(78.4)	320(78.4)	647(78.4)
	Yes	90(21.6)	88(21.6)	178(21.6)

Table 9: Summary of Demographic and Other Baseline Characteristics (FAS) (ARCT-154-J01)

Item	Level/ Statistic	ARCT-154	Comirnaty	Total
suspected of being allergic in the past				
(3) histories of convulsion in the past	No	411(98.6)	407(99.8)	818(99.2)
	Yes	6(1.4)	1(0.2)	7(0.8)
(4) a close relative with congenital immunodeficiency	No	417(100.0)	408(100.0)	825(100.0)
	Yes	0(0.0)	0(0.0)	0(0.0)
(5) may be allergic to any of the ingredients of the study vaccines	No	417(100.0)	408(100.0)	825(100.0)
	Yes	0(0.0)	0(0.0)	0(0.0)
Neutralising antibody titer against SARS-CoV-2 (Ancestral strain) before administration of study vaccine	N	417	408	825
	Geometric Mean	922.2	951.3	936.5
	Geometric SD	3.8	3.9	3.8
	Min	20	20	20
	Median	910.0	941.5	914.0
	Max	22987	32074	32074
	Negative	5(1.2)	3(0.7)	8(1.0)
	Positive	412(98.8)	405(99.3)	817(99.0)
Neutralising antibody titer against SARS-CoV-2 (Omicron BA.4/5) before administration of study vaccine	N	417	408	825
	Geometric Mean	337.0	343.3	340.1
	Geometric SD	7.6	8.2	7.9
	Min	20	20	20
	Median	322.0	301.5	314.0
	Max	43004	35866	43004
	Negative	84(20.1)	87(21.3)	171(20.7)
	Positive	333(79.9)	321(78.7)	654(79.3)
Brand of the vaccine administrated in the past	C+C+C	329(78.9)	329(80.6)	658(79.8)
	S+S+C	87(20.9)	79(19.4)	166(20.1)
	S+C+C	1(0.2)	0(0.0)	1(0.1)
	C+S+C	0(0.0)	0(0.0)	0(0.0)
Nucleocapsid antibody before administration of study vaccine	Negative	388(93.0)	381(93.4)	769(93.2)
	Positive	29(7.0)	27(6.6)	56(6.8)

Abbreviations: C, Comirnaty; FAS, full analysis set; S, Spikevax; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.
Positivity: Based on the criteria in the assessment vendor
Age: Age at randomisation

The overview of the study demographics provided by the applicant is sufficient for understanding and interpreting the immunogenicity results in young Japanese adults (median age approx. 45 years).

Most of the participants received a primary series with Comirnaty original (approx. 78%), with a minority having received a primary series with Spikevax original (approx. 20%), and >90% of participants were negative for anti-nucleocapsid antibodies.

The study provides very limited information on immunogenicity for the ≥ 65 years of age group.

- **Numbers analysed**

For the pivotal day 29 data, analyses were performed on 3 analysis sets i.e., FAS, PPS-1, and PPS-2.

The number of subjects who were excluded from each analysis set and the reasons for the exclusion are summarized in the Figure 14 below.

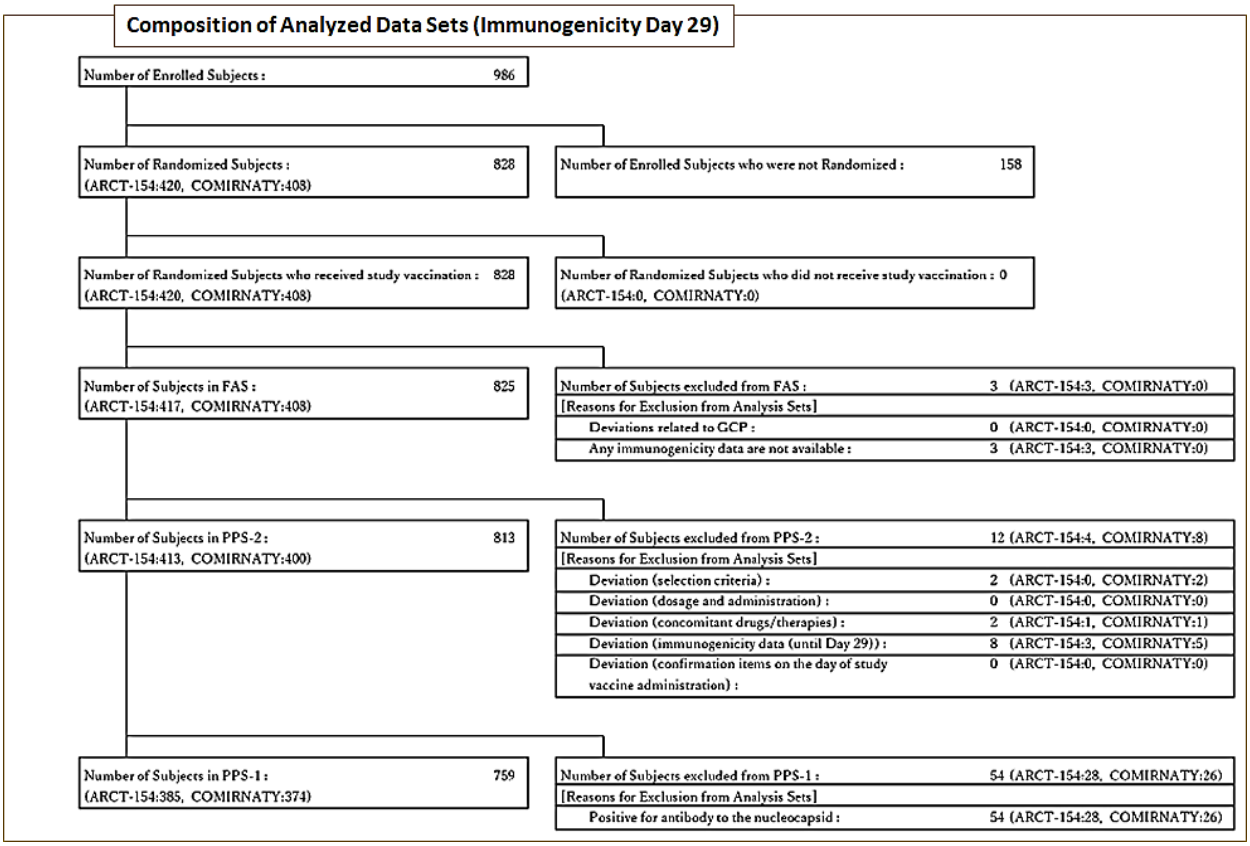


Figure 14: Composition of Analysed Data Sets (immunogenicity Day 29)

According to the statistical justification for the required sample size, 270 participants/group were required to detect non-inferiority of ARCT-154 to Comirnaty with the prespecified non-inferiority margins and significance level (see subsection above).

The numbers analysed exceeded those considered required to detect non-inferiority of ARCT-154 to Comirnaty.

- **Outcomes and estimation, pivotal day 29 immunobridging data**

<u>GMTs and seroresponse rates of circulating neutralising antibodies against SARS-CoV-2 index strain +D614G on day 29 post boost (primary endpoints, ARCT-154-J01)</u>

The GMT (95% CI) of neutralising antibodies against SARS-CoV-2 (ancestral strain with D614G mutation) on day 29 was 5640.7 (4321.2, 7363.2) in the ARCT-154 group and 3933.6 (2993.4, 5169.1) in the Comirnaty group and the GMT ratio (95% CI) of ARCT-154 compared with Comirnaty was 1.434 (1.265, 1.626). Because the lower limit of the 95% CI exceeded the predefined non-inferiority margin of 0.67, non-inferiority of ARCT-154 to Comirnaty was confirmed (see Table 10 below).

The SRR (95% CI) against SARS-CoV-2 (Ancestral strain) on Day 29 was 65.2% (60.2, 69.9) in the ARCT-154 group and 51.6% (46.4, 56.8) in the Comirnaty group and its difference (95% CI) was 13.6% (6.8, 20.5). Because the lower limit of the 95% CI exceeded the predefined non-inferiority margin of -10%, non-inferiority of ARCT-154 to Comirnaty was confirmed (see Table 11 below).

Consistent results were obtained from the analyses using FAS and PPS-2. Thus, the primary study objective was met.

Table 10: Geometric Mean Titer of Neutralising Antibodies Against SARS-CoV-2 (Ancestral Strain + D614G) on Day 29 (PPS-1) (Study ARCT-154-J01)

Endpoint	Treatment	N	GMT[a]			GMT Ratio[b]		
			GMT	95%CI		GMT Ratio	95%CI	
				Lower	Upper		Lower	Upper
GMT (NT50)	ARCT-154	385	5640.7	4321.2	7363.2	1.43	1.26	1.63
	Comirnaty	374	3933.6	2993.4	5169.1	—	—	—

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from index strain with D614G mutation). NT50, reciprocal of vaccinee serum dilution providing 50% virus inhibition, geometric mean.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; LS, least squares; N, number of participants; PPS-1, per protocol set 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Log-transformed neutralising antibody titer value was analysed using ANCOVA model.
Log-transformed neutralising antibody titer value was used as dependent variable.
Age was used as covariate.
Gender and period from last (3rd) vaccination (< 5 months, ≥ 5 months) were used as factors.
If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a Exponentiated LS-means.
b Exponentiated LS-means difference.

Table 11: **Seroresponse Rate of Neutralising Antibodies Against SARS-CoV-2 (Ancestral Strain +D614G) on Day 29 (ARCT-154-J01 PPS-1)**

Endpoint	Treatment	N	n	SRR (%)[a]			SRR Difference[b]		
				SRR	95%CI		SRR Difference	95%CI	
					Lower	Upper		Lower	Upper
Seroresponse rate	ARCT-154	385	251	65.2	60.2	69.9	13.6	6.8	20.5
	Comirnaty	374	193	51.6	46.4	56.8	—	—	—

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from index strain with D614G mutation).

Abbreviations: CI, confidence interval; N, number of participants; n, number of participants achieving seroresponse; PPS-1, per protocol set 1; SRR, seroresponse rate.
Seroresponse: neutralising antibody titer against SARS-CoV-2 after administration with the study vaccine increased 4-fold or more compared to the Day 1 value. If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a Crude SRR.
b SRR difference and its 95% confidence interval was calculated using Miettinen-Numerinen method.

GMT and SRR of circulating neutralising antibodies against SARS-CoV-2 omicron BA.4/BA.5 strain on day 29 post boost (secondary endpoints, ARCT-154-J01)

The GMT against SARS-CoV-2 (Omicron BA.4/5 strain) on day 29 was 2551.1 (95% CI: 1686.5, 3858.9) in the ARCT-154 group and 1958.3 (1281.3, 2993.0) in the Comirnaty group, and the GMT ratio of ARCT-154 compared with Comirnaty was 1.303 (95% CI: 1.072, 1.583). Since the lower limit of the 95% CI exceeded the predefined non-inferiority margin of 0.67, non-inferiority of ARCT-154 to Comirnaty was confirmed. In addition, since the lower limit of 95% CI of the GMT ratio was greater than the predefined superiority margin of 1, the superiority of ARCT-154 over Comirnaty was confirmed (see Table 12 below).

The SRR against SARS-CoV-2 (Omicron BA.4/5 strain) on Day 29 was 69.9% (95% CI: 65.0, 74.4) in the ARCT-154 group and 58.0% (95% CI: 52.8, 63.1) in the Comirnaty group and its difference (95% CI) of ARCT-154 and Comirnaty was 11.6% (4.9, 18.3). Since the lower limit of the 95% CI exceeded the predefined non-inferiority margin of -10%, non-inferiority of ARCT-154 to Comirnaty was confirmed. In addition, since the lower limit of 95% CI of the SRR difference was greater than the predefined superiority margin of 0, the superiority of ARCT-154 over Comirnaty was confirmed (see Table 12 below).

Thus, the secondary study objective was met.

Table 12: Geometric Mean Titer of Neutralising Antibodies Against SARS-CoV-2 (Omicron BA.4/5 Strain) on Day 29 (ARCT-154-J01 PPS-1)

Endpoint	Treatment	N	GMT[a]			GMT Ratio[b]		
			GMT	95%CI		GMT Ratio	95%CI	
				Lower	Upper		Lower	Upper
GMT (NT50)	ARCT-154	385	2551.1	1686.5	3858.9	1.30	1.07	1.58
	Comirnaty	374	1958.3	1281.3	2993.0	—	—	—

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from omicron BA.4 and BA.4 strains; these omicron lineages share identical spike protein sequences). NT50, reciprocal of vaccinee serum dilution providing 50% virus inhibition, geometric mean.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GMT, geometric mean titer; LS, least squares; N, number of participants; PPS-1, per protocol set 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Log-transformed neutralising antibody titer value was analysed using ANCOVA model.
Log-transformed neutralising antibody titer value was used as dependent variable.
Age was used as covariate.
Gender and period from last (3rd) vaccination (< 5 months, ≥ 5 months) were used as factors.
If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a Exponentiated LS-means.
b Exponentiated LS-means difference.

Table 13: Seroresponse Rate of Neutralising Antibodies Against SARS-CoV-2 (Omicron BA.4/5 Strain) on Day 29 (ARCT-154-J01 PPS-1)

Endpoint	Treatment	N	n	SRR (%)[a]			SRR Difference[b]		
				SRR	95%CI		SRR Difference	95%CI	
					Lower	Upper		Lower	Upper
Seroresponse rate	ARCT-154	385	269	69.9	65.0	74.4	11.6	4.9	18.3
	Comirnaty	374	217	58.0	52.8	63.1	—	—	—

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from omicron BA.4 and BA.4 strains; these omicron lineages share identical spike protein sequences).

Abbreviations: CI, confidence interval; N, number of participants; n, number of participants achieving seroresponse; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRR, seroresponse rate.
Seroresponse: neutralising antibody titer against SARS-CoV-2 after administration with the study vaccine increased 4-fold or more compared to the Day 1 value. If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a Crude SRR.
b SRR difference and its 95% confidence interval was calculated using Miettinen-Numerinen method.

GMFR in circulating neutralising antibodies at day 29 after boost (secondary endpoint, ARCT-154-J01)

The GMFR against SARS-CoV-2 (index strain) on day 29 was 6.7-fold (95% CI: 6.0, 7.5) in the ARCT-154 group and 4.4 (95% CI: 4.0, 4.8) in the Comirnaty group.

The GMFR against SARS-CoV-2 (Omicron BA.4/5 strain) on day 29 was higher in the ARCT-154 group (8.0; 95% CI: 7.0, 9.1) than in the Comirnaty group (5.7; 95% CI: 5.0, 6.4).

In both cases, the higher fold-rises in circulating neutralising antibodies in the ARCT-154 group compared to the Comirnaty group were statistically significant (95% CIs did not overlap). See details in the below Table 14 and Table 15.

Table 14: Summary Statistics of Geometric Mean Fold Rise in Neutralising Antibody Titer Against SARS-CoV-2 (Ancestral Strain +D614G) (ARCT-154-J01 PPS-1)

Day	Treatment	N	Baseline GMT	At the visit GMT	GMFR[a]		
					GMFR[a]	95%CI[b]	
						Lower	Upper
Day 29	ARCT-154	385	813.1	5447.9	6.70	5.97	7.53
	Comirnaty	374	865.6	3786.0	4.37	3.98	4.80

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from index strain with D614G mutation).

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; LLOQ, lower limit of quantitation; N, number of participants whose neutralising antibody titer was not missing for both baseline and the visit; NAT, neutralising antibody titer; PPS-1, per protocol set 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a The ratio of neutralising antibody titer at the visit and at baseline (NAT at the visit / NAT at baseline).
b Confidence interval was calculated using t-distribution

Table 15: Summary Statistics of Geometric Mean Fold Rise in Neutralising Antibody Titer Against SARS-CoV-2 (Omicron BA.4/5 Strain) (ARCT-154-J01 PPS-1)

Day	Treatment	N	Baseline GMT	At the visit GMT	GMFR[a]		
					GMFR[a]	95%CI[b]	
						Lower	Upper
Day 29	ARCT-154	385	275.4	2193.3	7.96	7.00	9.06
	Comirnaty	374	291.7	1654.6	5.67	5.02	6.42

Neutralising titers were determined by monogram/Labcorp luminescent pseudovirus assay (spike protein from omicron BA.4 and BA.4 strains; these omicron lineages share identical spike protein sequences).

Abbreviations: CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; LLOQ, lower limit of quantitation; N, number of participants whose neutralising antibody titer is not missing for both baseline and the visit; PPS-1, per protocol set 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
If a measured antibody titer is < the quantitation limit, the value of "the quantitation limit divided by 2" will be imputed into the calculation.
a The ratio of neutralising antibody titer at the visit and at baseline (NAT at the visit / NAT at baseline)
b Confidence interval was calculated using t-distribution

- **Outcomes and estimation, secondary immunogenicity data, durability of responses**

Through days 29-181 after the boosters, waning of circulating virus-neutralising antibodies was seen for ARTC-154 as well as Comirnaty, albeit more pronounced for Comirnaty.

Specifically, for neutralising antibodies against the index strain, through days 29-181 in 18–59-year-old and ≥ 60-year-old vaccinees, levels declined by respectively approximately 1.3-fold and 1.2-fold for ARCT-154 vaccinees, and respectively approximately 2.1-fold and 2.4-fold for Comirnaty vaccinees (see Figure 15 below).

For neutralising antibodies against the omicron BA.4/BA.5 strain, through days 29-181 in 18–59-year-old and ≥ 60-year-old vaccinees, levels declined by respectively approximately 2.0-fold and 1.4-fold in ARCT-154 vaccinees, and approximately 3.5-fold and 5.0-fold in Comirnaty vaccinees (see Figure 15 below).

The number of vaccinees ≥ 60 years of age is likely too low for conclusions to be drawn regarding durability of neutralising antibodies in this age group (Figure 15 below).

However, for 18-59 year old vaccinees through days 29-181 post boost, the interim data indicates that compared to Comirnaty, circulating neutralising antibodies induced by ARCT-154 are approximately 2.1/1.3=1.6 fold more durable measured against the vaccine-matched index strain, and approximately 3.5/2.0=1.7-fold more durable measured against the vaccine-mismatched omicron BA.4/BA.5 strain

(see first figure below). Similar findings were seen for a smaller dataset for more contemporaneous variants (see Figure 16 below).

There was no overall indication in differences in the breadth of responses (neutralising titer ratios between the ARCT-154 and Comirnaty boosters were overall comparable irrespective of virus strain). See the Figure 15 and Figure 20 below.

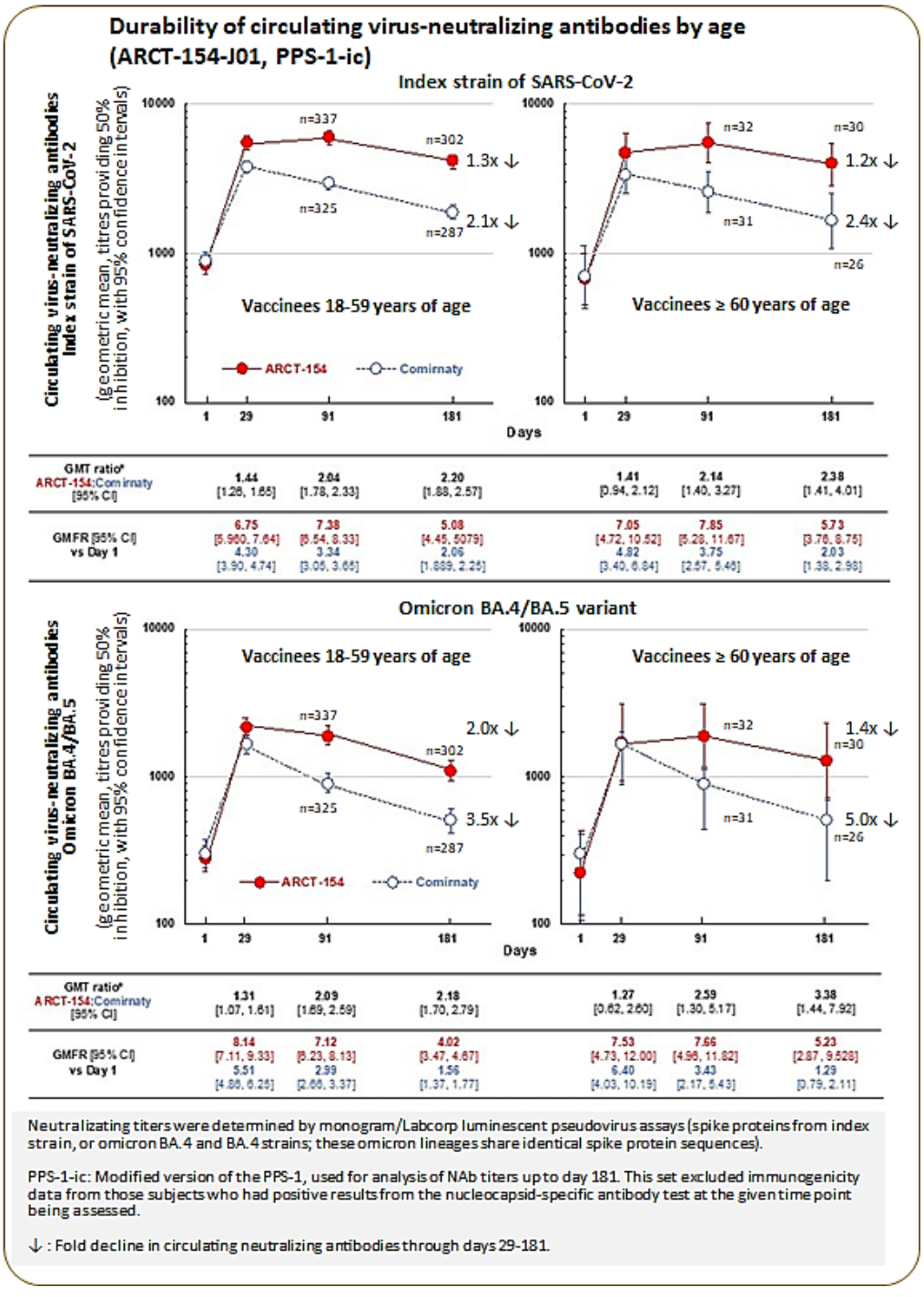


Figure 15: Durability of circulating virus neutralising antibodies by age (ARCT-154-J01, PP-1-ic)

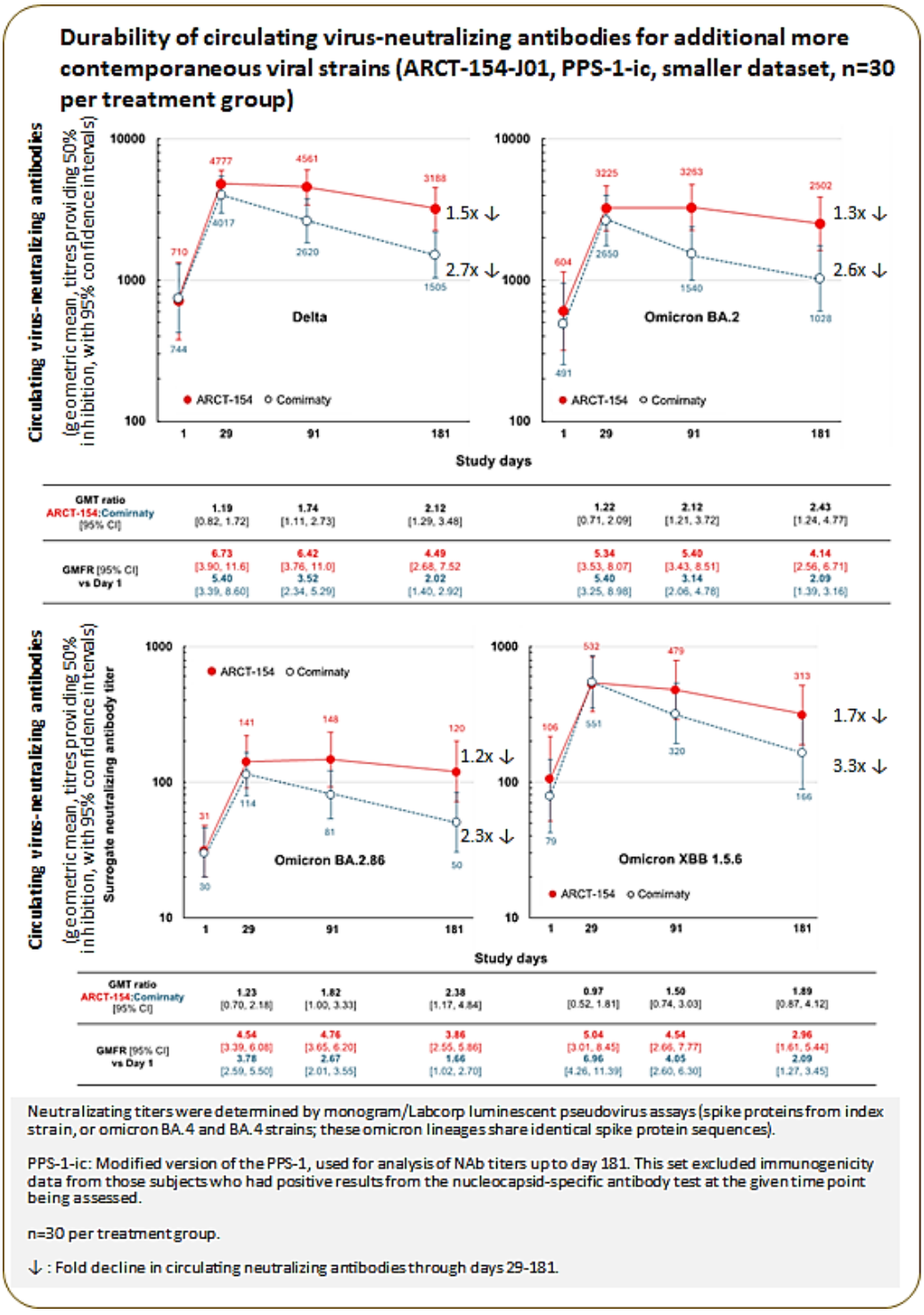


Figure 16: Durability of circulating virus-neutralising antibodies for additional more contemporaneous viral strains (ARCT-154-J01, PSS-1-ic, smaller dataset, n+30 per treatment group)

- **Outcomes and estimation, anti-nucleocapsid sero-status**

In both groups, >90% of the participants remained negative for anti-nucleocapsid antibodies through days 1-181.

Table 16: Nucleocapsid Antibody on Day 1, Day 29, Day 91 and Day 181 (FAS)

Nucleocapsid Antibody on Day 1, Day29, Day91, and Day181 (FAS)

Day	Treatment	N	Nucleocapsid antibody	n	%
Day 1	ARCT-154	417	positive	29	7.0
			negative	388	93.0
	COMIRNATY	408	positive	27	6.6
			negative	381	93.4
Day 29	ARCT-154	417	positive	26	6.2
			negative	391	93.8
	COMIRNATY	407	positive	25	6.1
			negative	382	93.9
Day 91	ARCT-154	412	positive	16	3.9
			negative	396	96.1
	COMIRNATY	401	positive	14	3.5
			negative	387	96.5
Day 181	ARCT-154	391	positive	25	6.4
			negative	366	93.6
	COMIRNATY	372	positive	22	5.9
			negative	350	94.1

Abbreviations: N, number of subjects, n, number of subjects with positive/negative nucleocapsid antibodies
Positivity: based on the criteria in the assessment vendor.

- **Ancillary analyses**

For the categories gender and participants predefined as requiring caution in vaccination, there was a reasonable number of participants in the respective subgroups (male vs. female, requiring caution vs. not requiring caution; > 100 participants/subgroup), and there were no meaningful differences between subgroups as regards neutralising antibody levels (measured against index as well as omicron BA.4/BA.5 strains).

Regarding the category brand of COVID-19 vaccines used for primary immunisation, there were sufficient numbers of participants in the 2 subgroups comprising Comirnaty primary immunisation (i.e., 2 primary immunisations with Comirnaty original followed by Comirnaty booster; N=306 and 298 in ARCT-154 and Comirnaty arms) and Spikevax primary immunisation (i.e. 2 primary immunisations with Spikevax original followed by Comirnaty original booster; N=78 and 76 in ARCT-154 and Comirnaty arms). There were no meaningful differences between these 2 subgroups as regards neutralising antibody levels (measured against index as well as omicron BA.4/BA.5 strains). This agrees with the fact that mRNA vaccines are approved for boosting of individuals who received a primary series with another mRNA vaccine or adenovirus-vectored vaccine.

For the categories age, time since last COVID-19 vaccination and neutralising antibody titer against SARS-CoV-2 before study administration (i.e. before the ARCT-154 and Comirnaty boosters), there was few participants in subgroups, limiting the strength of the data (participants ≥ 65 years old: N=11 and 8 in ARCT-154 and Comirnaty arms, respectively; N=8 and 3 participants with <5 months elapsed since last COVID-19 vaccination in ARCT-154 and Comirnaty arms, respectively; N=5 and 3 participants negative for anti-index neutralising antibody in ARCT-154 and Comirnaty arms before boosting; the latter is expected, as all participants were primary-immunised with COVID-19 vaccines, and had received a first Comirnaty booster).

- **Summary of main efficacy results**

This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 17: Summary of efficacy for trial ARCT-154-J01 trial (pivotal heterologous booster, Japan)

Title: A randomised, multicentre, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA COVID-19 vaccine) in healthy subjects			
Study identifier: Japan Registry for Clinical Trials jRCT 2071220080			
Design	Phase 3 randomised, observer-blind, immunobridging study, designed to evaluate non-inferiority of heterologous boost with ARCT-154 at 5 µg dose versus homologous boost with Comirnaty original at 30 µg dose in healthy Japanese adults (18-77 years of age) who had previously received three immunisations with mRNA vaccines (primary series and first boost with mRNA vaccines, with the boost given at least 3 months before enrollment).		
Duration	Duration of main phase:		The boosters were given day 1; in the interim report, immunogenicity analyses up to day 29 are presented.
	Duration of run-in and extension phases:		Not relevant
Hypothesis	Non-inferiority: The trial is considered successful if the non-inferiority of ARCT-154 to Comirnaty is verified in both neutralising antibody titers and SRR against SARS-CoV-2 (index strain) on day 29 for PPS-1.		
Treatments groups	ARCT-154 vaccine		The content of a vial was diluted with 10 mL of saline, and participants were vaccinated with a single IM dose of 0.5 mL (5 µg). 420 participants randomised; 420 participants received ARCT-154 booster; 417 completed day 29 visit.
	Comirnaty original vaccine		The content of a vial was diluted with 1.8 mL of saline, and participants were vaccinated with a single IM dose of 0.3 mL (30 µg). 408 participants randomised, 408 received the Comirnaty booster; 408 completed day 29 visit.
Endpoints and definitions	Co-primary endpoint	Geometric mean titer (GMT), neutralising antibodies, index strain	Co-primary as well as secondary endpoints were all assessed by validated pseudovirus neutralisation assays. Non-inferiority: day 29, compared to Comirnaty.
	Co-primary endpoint	SRR, neutralising antibodies, index strain	Non-inferiority: day 29, compared to Comirnaty.
	Secondary endpoint	GMT and SRR, neutralising antibodies, omicron BA.4/5 strain	Non-inferiority: day 29, compared to Comirnaty.
	Secondary endpoint	GMT, neutralising antibodies, index and omicron BA.4/5 strains	Durability/time profile; on day 1, 29, 91, 181 and 361. Only day 1 and 29 data provided in interim report.

Title: A randomised, multicentre, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA COVID-19 vaccine) in healthy subjects			
Study identifier: Japan Registry for Clinical Trials jRCT 2071220080			
	Secondary endpoint	SRR, neutralising antibodies, index and omicron BA.4/5 strains	Durability/time profile; on day 29, 91, 181 and 361. Only day 1 and 29 data provided in interim report.
	Secondary endpoint	GMFR, neutralising antibodies, index and omicron BA.4/5 strains	Durability/time profile, on day 29, 91, 181 and 361 relative to day 1. Only day 1 and 29 data provided in interim report.
	Exploratory endpoints	Not listed here, as they are not considered to be of main relevance for the conclusions on immunogenic noninferiority.	
Database lock	The first participant enrolled on 13 December 2022. The predefined co-primary endpoints were based on assessment of immunogenicity at day 29 (boosters given day 1). For this assessment, an interim report was provided (version 1, 21 June 2023, day 29 cut off), with a safety addendum (version 1, 09 August 2023).		

Results and Analysis

Analysis description	**Primary Analysis: Non-inferiority of GMT and SRR after heterologous ARCT-154 booster, compared to homologous Comirnaty booster, day 29**		
Analysis population and time point description	PPS-1 population, validated pseudovirus neutralisation assay, day 29 after booster.		
Descriptive statistics and estimate variability	**Treatment group**	**ARCT-154**	**Comirnaty original**
	Number of subjects	385 (PPS-1 set)	374 (PPS-1 set)
	GMT, index strain	5640.7	3933.6
	95% CI	4321.2, 7363.2	2993.4, 5169.1
	SRR, index strain	65.2	51.6
	95% CI	60.2, 69.9	46.4, 56.8
	GMT, omicron BA.4/BA.5	2551.1	1958.3
	95% CI	1686.5, 3858.9	1281.3, 2993.0
	SRR, omicron BA.4/BA.5 (%)	69.9	58.0
	95% CI	65.0, 74.4	52.8, 63.1
	GMFR, index strain (fold rise)	6.70	4.37
	95% CI	5.97, 7.53	3.98, 4.80
	GMFR, omicron BA.4/BA.5 (fold rise)	7.96	5.67
	95% CI	7.00, 9.06	5.02, 6.42
Effect estimates per comparison	Co-primary endpoint, GMT index strain	Comparison groups	ARCT-154 versus Comirnaty
		GMT ratio, index strain (ARCT/Comirnaty)	1.43
		95% CI	1.26, 1.63
	Co-primary endpoint, SRR index strain	Comparison groups	ARCT-154 versus Comirnaty
		Difference between SRR percentages, index strain (ARCT-Comirnaty)	13.6
		95% CI	6.8, 20.5

Title: A randomised, multicentre, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA COVID-19 vaccine) in healthy subjects			
Study identifier: Japan Registry for Clinical Trials jRCT 2071220080			
	Secondary endpoint, GMT omicron BA.4/BA.5	Comparison groups	ARCT-154 versus Comirnaty
		GMT ratio, omicron BA.4/BA.5 (ARCT/Comirnaty)	1.30
		95% CI	1.07, 1.58
	Secondary endpoint, SRR omicron BA.4/BA.5	Difference between SRR percentages, omicron BA.4/BA.5 (ARCT-Comirnaty)	11.6
		95% CI	4.9 18.3
	Secondary endpoint, GMFR index strain	GMFR, index strain	
		Point estimate and 95% CI, ARCT-154	6.70 (5.97, 7.53)
		Point estimate and 95% CI, Comirnaty original	3.98 (3.98, 4.80)
	Secondary endpoint, GMFR omicron BA.4/BA.5	GMFR, omicron BA.4/BA.5	ARCT-154 versus Comirnaty
		Point estimate and 95% CI, ARCT-154	7.96 (7.00, 9.06)
		Point estimate and 95% CI, Comirnaty original	5.67 (5.02, 6.42)
Notes	The prespecified non-inferiority success criteria for the co-primary endpoints comprising day 29 GMT and SRR for the index strain were met (lower bound of 95% CI for GMT ratio >0.67, SRR difference > -10). The prespecified non-inferiority as well as superiority success criteria for the secondary endpoint comprising day 29 GMT for omicron BA.4/BA.5 was met (lower bound of 95% CI for GMT ratio >0.67 and >1, respectively). GMFR of neutralising antibodies against SARS-CoV-2 (index and omicron BA.4/5 strains) in ARCT-154 group were statistically significantly higher than that in Comirnaty group. Through days 29-181 after the boosters, waning of circulating virus-neutralising antibodies was seen for ARTC-154 as well as Comirnaty, albeit more pronounced for Comirnaty.		

2.5.5.3. Clinical studies in special populations

No studies in special populations were submitted. The number of elderly participants who received the ARCT-154 vaccine across all performed studies is shown in the Table 18 below.

Table 18: Participants who received ARCT-154

Participants who received ARCT-154								
	ARCT-154-01, Phase 1/2/3a/3b			ARCT-154-01 Phase 3c, Any Dose	ARCT-154-J01	ARCT-165-01, Received ARCT-154	ARCT-021-04, Booster ARCT-154,	Total
Age Category	ARCT-154-01, Any Dose*	ARCT-154-01, Dose 1 or 2	ARCT-154-01, Dose 3 or 4					
N	16395	8813	8070	1186	420	12	42	18055
Age ≤64	15375 (93.78%)	8256 (93.68%)	7590 (94.05%)	1013 (85.41%)	408 (97.14%)	12 (100.00%)	36 (85.71%)	16844 (93.29%)
Age 65 – 74	920 (5.61%)	505 (5.73%)	432 (5.35%)	156 (13.15%)	11 (2.62%)		3 (7.14%)	1090 (6.04%)

Participants who received ARCT-154								
	ARCT-154-01, Phase 1/2/3a/3b			ARCT-154-01 Phase 3c, Any Dose	ARCT-154-J01	ARCT-165-01, Received ARCT-154	ARCT-021-04, Booster ARCT-154,	Total
Age Category	ARCT-154-01, Any Dose*	ARCT-154-01, Dose 1 or 2	ARCT-154-01, Dose 3 or 4					
Age 75 – 84	94 (0.57%)	50 (0.57%)	44 (0.55%)	16 (1.35%)	1 (0.24%)		2 (4.76%)	113 (0.63%)
Age ≥85	6 (0.04%)	2 (0.02%)	4 (0.05%)	1 (0.08%)			1 (2.38%)	8 (0.04%)

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The study designs are considered to be in overall agreement with scientific advice provided to the Applicant, and to largely reflect current regulatory expectations to COVID-19 vaccine trials.

Posology for primary series

There is dose-response immunogenicity data available from 4 supportive studies (ARCT-021-01, ARCT-021-02, ARCT-021-04 and ARCT-165-01).

It should be taken into account that the ARCT-021 vaccine which was included in the supportive studies encodes a spike protein which is not stabilized in the prefusion conformation, which could impact extrapolability of the data from ARCT-021 to ARCT-154.

The Applicant's position that the ARCT-165-01 study provides evidence of the durability of immune responses following a heterologous boost with ARCT-154 in individuals previously immunised with a non-replicating mRNA COVID-19 vaccine is not supported.

Nevertheless, overall, these supportive studies are considered to (i) provide proof of concept for the Applicant's self-replicating mRNA COVID-19 vaccine platform, (ii) confirm the expected superiority of the prefusion-stabilized immunogen employed in ARCT-154, and (iii) support the selection of the 5 µg dose for the pivotal studies.

Efficacy for primary series

Pivotal efficacy data for primary series was generated in a large phase 3b study of ARCT-154-01 that included 7562/7256 participants and 200/440 COVID-19 cases in ARCT-154/placebo groups, respectively.

Supportive efficacy data is available from the phase study 3c of ARCT-154-01, where efficacy relative to ChAdOx1 was explored (1145/1128 participants and 20/28 COVID-19 cases in ARCT-154 and ChAdOx1 groups, respectively).

The social distancing lockdown measures employed in Vietnam during the COVID-19 pandemic were typical for other parts of the world included Europe, but perhaps particularly effective, such that despite the ARCT-154-01 study being conducted approximately 2 years into the COVID-19 pandemic, recruitment into phases 1/2/3a and 3b preceded the main pandemic peak in Vietnam.

However, during the efficacy surveillance period of ARCT-154 phase 3b, a surge of COVID-19 cases caused by the delta variant was observed, contemporaneous to delta surges in other countries, albeit particularly severe in Vietnam, perhaps due to the low level of preexisting population immunity.

In phases 3b and 3c, efficacy was determined based on participants who had no evidence of SARS-CoV-2 infection after completion of the primary series.

In phases 3b and 3c, only participants at high risk for SARS-CoV-2 exposure were recruited (defined as individuals who had social contacts with others at work or in public places as a part of their daily activities; individuals who worked from home and avoided public places and any social activities were not eligible for enrolment). Phases 3b and 3c included relatively few participants with significant comorbidities (approximately 5.5% and 10.9%, respectively), but a higher proportion of individuals ≥ 60 years of age (approximately 17% and 27% in phase 3b and 3c, respectively).

For the reasons above, the efficacy results from ARCT-154-01 phases 3b and 3c represent vaccine-induced protection against heterologous SARS-CoV-2 variants, with the delta variant dominating in the pivotal phase 3b generally considered as having relatively high virulence, in a primarily SARS-CoV-2-naïve population with high risk of SARS-CoV-2 exposure, and a reasonable proportion of individuals at risk for severe COVID-19.

Efficacy against severe endpoints was markedly higher than against milder endpoints (approximately >90% versus approximately 54%).

This is a general phenomenon for spike protein-based COVID-19 vaccines, and while it is positive that ARCT-154 follows the same trend, efficacy against the milder endpoint of symptomatic COVID-19 is considered the most sensitive parameter for comparison to other COVID-19 vaccines.

In this regard, the delta variant was dominant during the phase 3b study period, and for the primary series of the original index-strain versions of the currently approved vaccines, efficacy in controlled trials as well as effectiveness in post-marketing observational studies against symptomatic disease due to the delta variant has been reported as being in the 50%-90% range. Thus, the 56% efficacy reported for ARCT-154 against the delta variant might be thought to be on the low side.

However, the delta wave was particularly severe in Vietnam on a global scale (likely due to successful containment of the preceding index and alpha variant waves, and low vaccination coverage), and this unique epidemiological context (high infection pressure in the community) might be expected to have provided a worst-case scenario for ARCT-154 efficacy.

While point estimates indicated higher efficacy of ARCT-154 than of ChAdOx1, the magnitude of this was relatively low (30% relative early after the primary series, declining to 20% at later timepoints), and statistical significance was reached only for the 20% relative vaccine efficacy estimate. Nevertheless, seen in the context of the pivotal phase 3b efficacy data, and considering also that the phase 3c data reflects efficacy against viral variants which were very mis-matched to the index strain-based vaccines (omicron BA.2 and BA.5), the phase immunogenicity and efficacy data is considered positive.

Further, for ChAdOx1, immunogenicity as well as efficaciousness data for the index strain-based vaccine is available against a variety of SARS-CoV-2 variants, worldwide, including also comparative data against alternative vaccine platforms. Thus, the ARCT-154-01 phase 3c immunogenicity and efficacy data is considered to support the understanding of the generalizability of the therapeutic effect of the primary series seen in Vietnam to the EU population.

For the primary efficacy endpoint (efficacy against COVID-19, days 36-92, mITT), for all subgroups analysed, the 95% CI for VE excluded 30% except for participants who were ≥ 60 years old (N=1361/1329 and 28/56 COVID-19 cases in ARCT-154 and placebo groups, respectively; VE=53.5%, 95% CI: 26.8% to 70.5%).

The applicant argued that this finding may be due to a wider CIs for this subgroup due to the smaller sample size and the relatively low number of COVID-19 cases in this subgroup and also in any case,

while COVID-19 severity is increased in the elderly, primary immunisation is no longer considered a priority for this group in the EU.

In summary, the ARCT-154-01 phase 3b data, supported by the phase 3c data, is considered to provide adequate documentation for the efficacy of the ARCT-154 primary series.

Immunogenicity for primary series

Immunogenicity for the primary series was examined in phases 1/2/3a and 3c of the ARCT-154-01 trial (some data on a homologous boost was also generated in the crossover part of the trial).

To support the national emergency use authorisation application in Vietnam, immunogenicity data from the ACE2-blocking ELISA was pivotal. However, data from the validated pseudovirus neutralisation assay (i.e. VAC62 assay) is considered pivotal for the MAA in the EU.

Irrespective of the assay validation status, for inferring efficacy of COVID-19 vaccines, neutralising antibodies should be determined by cell-based pseudovirus and/or authentic virus neutralisation assays, and while data from ACE2 blocking ELISAs are often found to correlate with cell-based virus neutralisation assays, this needs to be confirmed on a case-by-case basis. Therefore, the applicant's position to prioritize data from the VAC62 pseudovirus neutralisation assay is considered appropriate.

In any case, both assays are index spike-based (i.e. matched to ARCT-154), and the applicant provided data showing that there was a reasonable correlation between data from the assays. Accordingly, the key immunogenicity endpoint of seroconversion rate day 57 was met for both assays.

By the VAC62 assay, at the time of expected maximal neutralising antibody responses after the primary series, anti-index strain neutralising antibody levels were approximately 145 IU/mL, declining to approximately 107 IU/mL at day 92. A homologous Kostaive boost at day 92 provided an approximately 6.5-fold boost neutralising antibody levels (measured at day 120).

The abovementioned circulating neutralising antibody levels in ARCT-154 vaccines correspond to approximately 15% to 70% of the neutralising antibody titer in strongly seropositive convalescent COVID-19 patients. Also, in phase 3c, the primary series induced circulating neutralising antibody levels up to approximately 3-fold higher than the primary ChAdOx1 series.

Neutralising titers such as those described above for the primary series are below those typically obtained with non-replicating mRNA vaccines.

For another index-strain based self-replicating mRNA COVID-19 vaccine which is similar to Kostaive, a similarly relatively low immunogenicity was also reported for the primary series. However, importantly, the primary-series-immunogenicity assessment above does not apply to the use of ARCT-154 for heterologous boosting.

Immunogenicity (inferred efficacy) for heterologous boost

The heterologous boost indication is supported by a smaller study (ARCT-154-J01; 385 and 374 participants in ARCT-154 and Comirnaty original groups, respectively).

At day 29, the study met the predefined primary and secondary immunogenicity endpoints. For the heterologous ARCT-154 boost, immunogenicity against the index strain was non-inferior to the homologous Comirnaty original boost, and immunogenicity against omicron BA.4/5 was superior to Comirnaty original.

Also, based on the interim 6-month data, while waning of circulating neutralising antibodies is seen post boost, this appears less pronounced than for the Comirnaty comparator. Similar findings were seen for a smaller dataset for more contemporaneous variants (omicron BA.2.86 and XBB.1.5).

Neutralising antibody responses are considered to be predictive for efficacy of COVID-19 vaccines, and the clinical efficacy of the comparator vaccine is established.

As such, the immunobridging data from the ongoing ARCT-154-J01 study allows inferring of the magnitude and clinical relevance of protective responses provided by Kostaive in a heterologous boost setting.

For similar self-replicating mRNA COVID-19 vaccines, immunogenicity also appeared to be better in a heterologous boost setting than in a primary series setting, and good immunogenicity was seen in the heterologous boost setting at doses similar to the 5 µg Kostaive dose. Further, in the ARCT-154-J01 trial, , heterologous boost with 5 µg ARCT-154 induced similar to slightly higher levels of virus-neutralising antibodies than did a homologous boost with 30 µg Comirnaty (GMT ratios ARCT-154/Comirnaty 1.43 and 1.30 for index and omicron BA.4/BA.5 strains, respectively). Comirnaty was used also as comparator in booster studies for approved protein-based COVID-19 vaccines, and for those, at comparable times post-boost, GMT ratios to Comirnaty for the index strain were in the 0.8 - 1.4 range.

As such, the interim ARCT-154-J01 data is plausible, and given the novelty of the replicating RNA platform, this is reassuring.

Data on immunogenicity of a heterologous ARCT-154 booster in the elderly is very limited (only 11 and 8 participants ≥ 65 years of age in the ARCT-154 and Comirnaty groups, respectively).

The applicant provided further subgroup analyses performed across stratified age bands in > 50-year-old of relevance for COVID-19 vaccine boosters. In the <50, ≥ 50, ≥ 60 and ≥ 65 years of age groups, there were approximately 224, 160, 31 and 12 participants available for immunogenicity analysis, through the currently available 6-month observation period.

The higher immunogenicity of the heterologous ARCT-154 booster compared to the Comirnaty booster in the general population remained essentially identical across all these age bands (approximately 4-fold and 2-fold higher immunogenicity of ARCT-154, days 29 and 181 after booster, respectively, measured against the index strain; similar results measured against omicron BA.4/BA.5).

Also, the applicant informed that in the ARCT-2303-01 immunogenicity/safety study planned for Q2 2024 (monovalent omicron XBB.1.5 vaccine), 480 participants of 65 years of age or older are planned to be enrolled.

In summary, the available ARCT-154-J01 immunobridging data is considered to provide adequate documentation for the efficacy of ARCT-154 in the proposed heterologous boos setting.

Incomplete understanding of immunological mechanisms, lack of T-cell immunity data

The innate antiviral responses triggered by self-replicating mRNA vaccines may be beneficial or detrimental for immunogenicity (may promote mRNA degradation and shut down translation of the spike protein but may also provide immune-stimulatory / adjuvant-like effects). The outcome of this balance is human-specific (not well predicted by preclinical models, as was also observed for Kostaive) and immunologically complex. These issues are not fully understood for self-replicating mRNA vaccines, including Kostaive. This obviously adds another layer of variability to individual vaccine responses, and another layer of complexity as regards to the extrapolation of immunogenicity and efficacy from one context of Kostaive use to another.

There is currently no data available for T-cell immunity induced by Kostaive from the pivotal studies, and the T-cell immunity data for Kostaive from the supportive studies is very limited.

On one hand, it is well established that for spike protein-based COVID-19 vaccines such as Kostaive, anti-spike antibody responses are predictive for efficacy.

On the other hand, the product is first-in-class and the applicant's self-replicating RNA platform exhibits unique aspects which might confer immunogenicity characteristics to antigens expressed from this platform which are distinct from the immunogenicity characteristics of non-replicating mRNA vaccines.

Thus, information of T-cell responses might be seen as particularly relevant in this case, to better understand the immunological mechanisms triggered by this novel vaccine platform, of relevance for safety (e.g. Th1/Th2 balance) as well as efficacy (T-cell responses are also involved in protection against COVID-19, likely especially in situations of low neutralising antibody responses and in the context of severe disease, and in any case, the magnitude, breadth and durability of antibody responses are modulated by T cell responses).

The applicant informed that evaluation of T-cell responses will be extended in ARCT-154-J01 and ARCT-2301-J01 phase 3 studies (heterologous boosters with respectively the monovalent index strain-based ARCT-154 and the bivalent index and omicron BA.4/5 ARCT-2301 vaccines).

Path forward for primary series indication and variant-updating

It is expected that Kostaive (ARCT-154) will be updated for vaccination campaigns following the current regulatory recommendations. The applicant informed that ARCT-154 is planned to be variant-updated in a timely manner to ensure vaccine availability in time for the start of the autumn/winter booster campaigns.

2.5.7. Conclusions on the clinical efficacy

Efficacy for the primary series with Kostaive was shown in a large, placebo-controlled study performed in Vietnam when the delta variant was dominating, and efficacy for the heterologous booster indication can be inferred from a smaller immunobridging study performed in Japan.

The data overall supports the efficacy of ARCT-154, in primary series as well as heterologous booster settings.

2.5.8. Clinical safety

The safety data are based on data from the ARCT-154-01 study. The study included a Phase 1, 2, 3a, 3b, and 3c part (See tabular overview of clinical studies in Section 2.5.1.). In the initial submission the applicant submitted the 6-month interim CSR and later during the assessment the final CSR for all phases with the analyses after all participants had completed their last study visit on Day 394. The final CSR also includes new reactogenicity/safety results for the Phase 3c cohort.

Further, safety data from supportive studies (i.e. ARCT-021-01, ARCT-021-02, ARCT-021-04) were also included in the safety package.

Beside of the above studies for primary series, the 6-month interim CSR of study ARCT-154-J01 was provided with data for booster immunisation. The applicant commits to submit the final CSR of this study when available.

Data from ARCT-165-01 cohort B was also presented as supportive study for booster immunisation.

Analysis sets

In Study ARCT-154-01 Phase 3b, the RAS included all participants who received any dose of study vaccine. In this submission, the applicant reported the solicited AEs (local and systemic) and unsolicited AEs after dose 1 (D1) and dose 2 (D29) for both groups (ACRT 154 and placebo), but the

solicited AEs and unsolicited AEs after Switchover were not reported. The reactogenicity profile is based on the initial 2-dose vaccination series (D1 and D29) from phases 1/2/3a, 3b, 3c and ARCT-154-J01 and is considered sufficient.

The SAS in Study ARCT-154-01, ARCT-154-J01, ARCT-165-01 and ARCT-021-04 included all participants who received at least one dose of study vaccine. The RAS included all participants who received a dose of study vaccine (i.e., ARCT-154, ARCT-021, ARCT-165 or placebo) and provided at least one partially completed reactogenicity diary report. For both analyses sets safety data from Phase 1, Phase 2, and Phase 3a participants in Study ARCT-154-01 were combined, whereas safety data from Study ARCT-154-01 from Phase 3b and 3c were presented separately.

Definitions of AE categories

AEs were categorised as solicited and unsolicited AEs. Solicited AE were defined as events that occurred within 7 days. They were classified as local (i.e. injection-site erythema, injection-site pain, injection-site swelling, and injection-site tenderness) or systemic (i.e. arthralgia, chills, diarrhoea, fatigue, fever, headache, myalgia, and nausea/vomiting), and graded by the participant.

In Study ARCT-154-01 participants recorded solicited AEs in a symptom diary daily for 7 days after vaccination/placebo (hence from Day 1 and from Day 29). In all other studies solicited AEs a symptom diary for 7 days following each study vaccination.

All solicited AEs were per se considered vaccine-related AEs, in all studies, except in the booster study ARCT-154-J01, where a causality assessment of all systemic solicited AEs was performed by the investigators.

Solicited AEs were graded for severity according to scales defined in the US FDA's Centre for Biologics Evaluation and Research Guidance: Toxicity grading scale for healthy volunteers enrolled in preventative vaccine clinical trials (DHHS 2007).

An unsolicited AE was defined as any event that does not fall under the category of solicited AEs among AEs occurring between the dose of study vaccine and the Day 29 observation. For all studies, unsolicited AEs were graded (i.e. mild, moderate, or severe) and determined whether or not to be related to study vaccine by the investigator.

MAAEs, SAEs and AEs leading to early study discontinuation, were reported up to Day 210 (6-month safety follow-up).

Baseline characteristics

ARCT-154-01 Phase 3b Overall age, gender, height, weight and BMI were comparable between the two groups. Stratification was done for <60 years old and healthy, <60 years old and at risk, or ≥60 years old. Median age was 48 years. Around half of the participants were female in both groups.

17.4% were 60 years or above in both groups, and per definition "at risk", whereas82.6% were under the age of 60 and of those, 47.7% were "healthy" and 34.9% were "at risk". Reasons for being "at risk" of severe COVID-19 were with decreasing frequency: Current or former smoker (31%), others (mainly participants 60 years of age and above) (16%), cardiovascular conditions (15%), diabetes (2.5%), obesity (2%), liver disease (1%), cerebrovascular disease (0.3%), chronic obstructive pulmonary disease (COPD) (0.3%), asthma (0.1%). With regards to median BMI, it was well-balanced between groups. In total of 746 participants (<5%) in the Phase 3b cohort had BMI < 18. Overall, the safety profiles were balanced between participants with BMI < 18 as compared to the overall Phase 3b population.

No cases of COVID-19 were reported in the medical history of the participants. Approximately, 100 participants were positive for anti-nucleocapsid antibodies at baseline (54 participants [0.7%] in ARCT-

154 and 49 participants [0.6%] in placebo). In the overall safety database, the possible contribution of seropositive participants on the safety profile is not considered as relevant, as the number of seropositive participants included was small.

In ARCT-154-01 Phase 3b, concomitant medications were used by approximately half of all participants in Phase 3b. The proportion of participants who used concomitant medications in the study was comparable for ARCT-154 versus placebo (47.2% and 44.8%, respectively). The most common concomitant medications used were analgesics (21.8% and 17.6%, respectively), antibacterials for systemic use (7.2% and 7.5%, respectively), vitamins (5.9% and 6.4%, respectively), unspecified herbal and traditional medicine (5.9% and 5.7%, respectively), and sex hormones and modulators of the genital system (5.7% and 5.6%, respectively). Further antihypertensive medications were also represented, calcium channel blockers (5.8% and 5.8%), agents acting on the renin-angiotensin system (3.0% and 2.9%). Antidiabetics was used in 2.2% and 2.2%, respectively. It is noted that 1167 participants in the ARCT-154 group and 1062 participants in the placebo group received a non-study vaccine. Overall, the concomitant medication reflects the relatively healthy population included.

Demographics for ARCT-154-01 Phase 3b are shown in Table 19

Table 19: Demographics (Phase 3b, SAS)

	ARCT-154 (N=8059)		Placebo (N=8041)	
Age, median (range)	48.0	(18-89)	48.0	(18-86)
Age category, n (%)				
≥18 to <60	6656	(82.6)	6643	(82.6)
≥60	1403	(17.4)	1398	(17.4)
Risk group, n (%)				
≥18 to <60, "healthy"	3841	(47.7)	3835	(47.7)
≥18 to <60, "at risk"	2815	(34.9)	2808	(34.9)
≥60	1403	(17.4)	1398	(17.4)
Female, n (%)	4100	(50.9)	4086	(50.8)
Height, cm, median (range)	158.0	(134-190)	158.0	(128-190)
Weight, kg, median (range)	56.0	(30.0-110.0)	56.0	(29.0-136.0)
BMI, kg/m², median (range)	22.58	(13.8-42.4)	22.52	(13.3-47.6)

Abbreviations: BMI, body mass index; N, total number of participants in each column; n, number of participants contributing to the summary; SAS, Safety Analysis Set.

Medical history in ARCT-154-01 Phase 3b are provided in Table 20.

Table 20: Overview of (Medical) Conditions Associated with Increased Risk of Severe COVID-19 in Phase 3b Participants.

Category	**ARCT-154 (Initial) N=8056 n(%)**	**Placebo (Initial) N=8044 n(%)**	**Total n**
Asthma (Moderate-TO-Severe)	8 (0.1)	12 (0.1)	20
Cancer	11 (0.1)	16 (0.2)	27
Cardiovascular Conditions	1193 (14.8)	1167 (14.5)	2360
Cerebrovascular Disease	25 (0.3)	25 (0.3)	50
Chronic Kidney Disease	1 (0.0)	2 (0.0)	3
Chronic Obstructive Pulmonary Disease	23 (0.3)	16 (0.2)	39

Category	ARCT-154 (Initial) N=8056 n(%)	Placebo (Initial) N=8044 n(%)	Total n
Current or Former Smoker	2530 (31.4)	2509 (31.2)	5039
Current or Recent Substances Abuse Disor	18(0.2)	16 (0.2)	34
Cystic Fibrosis	3(0.0)	2 (0.0)	5
Dementia or Alzheimer's	0(0.0)	1(0.0)	1
Liver Disease (such as Cirrhosis, Non-Al)	73 (0.9)	80 (1.0)	153
Obesity	173 (2.1)	154 (1.9)	327
Other*	1301 (16.1)	1311 (16.3)	2612
Pulmonary Fibrosis	2 (0.0)	2 (0.0)	4
Pulmonary Hypertension	3 (0.0)	2(0.0)	5
Sickle Cell Disease or Other Hemoglobin	1(0.0)	2(0.0)	3
Type 1 or Type 2 Diabetes Mellitus	198(2.5)	201(2.5)	399

* OTHER includes mainly participants 60 years of age and above; one participant may have multiple risks.

ARCT-154-01 Phase 1/2/3a

Overall demographic characteristics were balanced between the treatment groups. Participants were stratified by risk group (<60 and healthy, <60 and at risk, or ≥60). All participants in the Phase 1 were healthy and <60 years old, and overall, in the combined set of Phase 1/2/3a population few participants were > 60 years old (10.7% in ARCT group and 11.5% in placebo group), and therefore median age were a bit younger than in the Phase 3b study.

The most frequent medical event was gastrointestinal disorders, 17.4%, of participants in the ARCT-154 and placebo groups (most gastritis and gastrooesophageal reflux disease, reported by 9.5% and 2.5% of participants, respectively). Concomitant medications were used by 61.3% in the Phase 1/2/3a group of participants. The most common concomitant medications used were analgesics, unspecified herbal and traditional medicine, antibacterials for systemic use, and vitamins.

ARCT-154-J01

808 (97.6%) participants were <65 years and 20 (2.4%) participants were ≥65 years of age (only 12 participants in ARCT-154 group). Age, gender and underlying disease were well balanced between ARCT-154 and the Comirnaty groups. More than half the participants had an underlying disease, and the proportions of the underlying diseases were comparable between groups. But, the most frequent underlying diseases in the ARCT-154 group was: (SOC) Immune system disorder (23.1%)(driven by the PT "Seasonal allergy" 22.9%), SOC Eye disorder (10.7%), SOC Metabolism and nutrition disorders (10%)(driven by PT "dyslipidaemia" 7%), SOC Nervous system disorders (9.8%) (driven mainly by PT "Headache" 6.9%), Respiratory, thoracic and mediastinal disorders (8.6%) (driven mainly by PT "Rhinitis allergic" 5.7%), and Reproductive system and breast disorders (8.3%).

Time since the last vaccination was ≥5 months in most of the participants (98.2%) and 6.8% of all participants had positive results for antibodies against SARS-CoV-2 nucleocapsid protein before

administration of the study vaccine. Both were well balanced between ARCT-154 and the Comirnaty groups.

Concomitant medication for participants in study ARCT-154-J01 were balanced between study groups. Approximately half of the participants received concomitant medication. However, the most frequently concomitant treatments in the ARCT-154 group were antipyretics, analgesics and anti-inflammatory agents (8.6%); Loxoprofen sodium (NSAID) (8.2%); Paracetamol (5.3%) and overall the concomitant medication reflects the relatively healthy population included.

Demographics for ARCT-154-J01 are shown in Table 21 and numbers and proportion of participants with underlying medical condition are shown in Table 22.

Table 21: Demographic and Other Baseline Characteristics (Analysis Set for Safety)

Item	Level/ Statistic	ARCT-154	Comirnaty	Total
Participants in the analysis set		420	408	828
Age [Years]	Min	18	18	18
	Median	47.5	49.0	48.0
	Max	77	76	77
	< 65 years old	408(97.1)	400(98.0)	808(97.6)
	≥ 65 years old	12(2.9)	8(2.0)	20(2.4)
Gender	Male	172(41.0)	169(41.4)	341(41.2)
	Female	248(59.0)	239(58.6)	487(58.8)
Period from last (3rd) vaccination	< 5 months	11(2.6)	4(1.0)	15(1.8)
	≥ 5 months	409(97.4)	404(99.0)	813(98.2)
Participants Requiring Caution in Vaccination	No	268(63.8)	269(65.9)	537(64.9)
	Yes	152(36.2)	139(34.1)	291(35.1)

Table 22: Numbers and Proportions of Participants with Underlying Medical Conditions, by Group (Study-ARCT-154-J01 Safety Analysis Set)

	ARCT-154 (N=420)		COMIRNATY (N=408)	
	n	Proportion (%)	n	Proportion (%)
Number of participants with at least one underlying disease	242	57.6	232	56.9
Blood and lymphatic system disorders	2	0.5	3	0.7
Cardiac disorders	2	0.5	2	0.5
Congenital, familial and genetic disorders	1	0.2	0	0.0
Ear and labyrinth disorders	2	0.5	3	0.7
Endocrine disorders	3	0.7	2	0.5
Eye disorders	45	10.7	43	10.5
Gastrointestinal disorders	23	5.5	26	6.4
General disorders and administration site conditions	0	0.0	1	0.2
Hepatobiliary disorders	19	4.5	6	1.5
Immune system disorders	97	23.1	109	26.7
Infections and infestations	1	0.2	5	1.2
Injury, poisoning and procedural complications	5	1.2	1	0.2
Investigations	0	0.0	3	0.7
Metabolism and nutrition disorders	42	10.0	41	10.0

Table 22: Numbers and Proportions of Participants with Underlying Medical Conditions, by Group (Study-ARCT-154-J01 Safety Analysis Set)

	ARCT-154 (N=420)		COMIRNATY (N=408)	
	n	Proportion (%)	n	Proportion (%)
Musculoskeletal and connective tissue disorders	30	7.1	24	5.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	1.2	4	1.0
Nervous system disorders	41	9.8	37	9.1
Psychiatric disorders	4	1.0	8	2.0
Renal and urinary disorders	5	1.2	4	1.0
Reproductive system and breast disorders	35	8.3	32	7.8
Respiratory, thoracic and mediastinal disorders	36	8.6	26	6.4
Skin and subcutaneous tissue disorders	26	6.2	19	4.7
Surgical and medical procedures	0	0.0	1	0.2

ARCT-021-04

In Study ARCT-021-04, the majority of participants were White (429 [74.0%] participants). Demographic characteristics for the priming vaccination period were similar across vaccine groups. Around half of the participants were male, and the mean age was 48.8 (range 18 to 86) years. 44% were ≥56 years and in this older age cohort mean age was 63.4 years. The majority of participants were included in United States. Of the 228 participants in the booster vaccination period, half were male participants and mean age was 51.6 (range 18 to 86) years. A greater percentage of participants (51.3%) were ≥56 years old compared to the priming vaccination period (44.1%), and the majority of participants were White (81.6%). In the ARCT-021-04 study 85.0% of the participants reported any medical history. The majority of reported events were in the SOCs of surgical and medical procedures (36.9%), immune system disorders (26.7%), psychiatric disorders (24.5%), and musculoskeletal and connective tissue disorders (23.1%).

Demographics for ARCT-021-04 are shown in Table 23.

Table 23: Demographics Characteristics for the Priming Vaccination Period - SAS

	Group A (N=145)	Group B (N=144)	Group C (N=145)	Group D (N=146)	Total (N=580)
Sex, n (%)					
Male	75 (51.7)	73 (50.7)	85 (58.6)	81 (55.5)	314 (54.1)
Female	70 (48.3)	71 (49.3)	60 (41.4)	65 (44.5)	266 (45.9)
Age (years)					
Mean (SD)	48.9 (16.15)	49.9 (15.16)	48.2 (17.08)	48.2 (15.59)	48.8 (15.99)
Min, Max	18, 86	19, 81	19, 81	18, 77	18, 86
Number of participants ≥18 to <56 (years), n (%)	82 (56.6)	80 (55.6)	81 (55.9)	81 (55.5)	324 (55.9)
Number of participants ≥56 (years), n (%)	63 (43.4)	64 (44.4)	64 (44.1)	65 (44.5)	256 (44.1)
Race, n (%)					
White	108 (74.5)	107 (74.3)	109 (75.2)	105 (71.9)	429 (74.0)
Black or African American	4 (2.8)	7 (4.9)	8 (5.5)	15 (10.3)	34 (5.9)
Asian	28 (19.3)	23 (16.0)	19 (13.1)	23 (15.8)	93 (16.0)
American Indian or Alaska Native	0	2 (1.4)	0	1 (0.7)	3 (0.5)
Multiple	1 (0.7)	2 (1.4)	3 (2.1)	1 (0.7)	7 (1.2)
Not reported	4 (2.8)	3 (2.1)	6 (4.1)	1 (0.7)	14 (2.4)
Country, n (%)					
Singapore	19 (13.1)	16 (11.1)	16 (11.0)	15 (10.3)	66 (11.4)
United States	126 (86.9)	128 (88.9)	129 (89.0)	131 (89.7)	514 (88.6)

Abbreviations: Group A, ARCT-021 7.5 mcg - Placebo; Group B, ARCT-021 5.0 mcg - ARCT-021 5.0 mcg; Group C, ARCT-021 7.5 mcg - ARCT-021 7.5 mcg; Group D, Placebo - Placebo; Max, maximum; Min, minimum; N, total number of participants in each column; n, number of participants contributing to the summary; SAS, Safety Analysis Set; SD, standard deviation.
Note: Percentages were based on the Safety Analysis set within each treatment group and overall.

2.5.8.1. Patient exposure

Overall exposure to ARCT-154 across studies is presented in Table 23. In total, 16395 participants received ARCT-154 in the ARCT-154 studies (Phase 1, 2, 3a, 3b). Including also ARCT-154-J01, ARCT-165-01 Cohort B, and ARCT-021-04, in total 16869 received at least one dose of ARCT-154, 15139 participants received 2 doses of ARCT-154, and 483 participants received 3 doses of ARCT-154. In addition, in the ARCT-154-01 Phase 3c, 1186 participants were exposed to at least 1 dose of ARCT-154 and 1171 to two doses.

In the Phase 3b study, 15414 participants received at least 1 dose of ARCT-154 during the primary vaccination series or after switchover, and 14662 participants received 2 doses of ARCT-154. Overall, 11954 (74.2%) of the Phase 3b study participants completed the last study visit at the cut-off date (12 January 2023) and 13895 (86.2%) completed the Day 120 visit. Solicited AE and Unsolicited AE are available only for participants after first and second dose, and not after switchover.

Table 24: Overall Exposure to ARCT-154

Study	1 Dose	2 Doses	3 Doses	At Least 1 Dose
ARCT-154-01 Phase 1/2/3a/3b	773[a]	15139	483	16395[a]
ARCT-154-J01	420	0	0	420
ARCT-165-01 Cohort B	12	0	0	12
ARCT-021-04	42	0	0	42
TOTAL	**1247**	**15139**	**483**	**16,869**

a Two study participants (405-0593 and 409-0088) in Phase 3b [Placebo (Dose 1 and 2) / ARCT-154 (Dose 3 and 4)] only received Dose 4 but not Dose 3 of ARCT-154. These 2 are included as they received 1 dose.

Vaccine exposure is provided in Table 25 for Phase 3b.

Table 25: Vaccine Exposure (Phase 3b, SAS)

Vaccine Exposure	ARCT-154 (Dose 1 and Dose 2)/Placebo (Dose 3 and Dose 4) (N=8059)		Placebo (Dose 1 and Dose 2)/ARCT-154 (Dose 3 and Dose 4) (N=8041)	
	n	(%)	n	(%)
Received Day 1 dose vaccination	8059	(100.0)	8041	(100.0)
Received Day 29 dose vaccination	7872	(97.7)	7828	(97.4)
Received Day 92 dose vaccination	7462	(92.6)	7353	(91.4)
Received Day 120 dose vaccination	6961	(86.4)	6790	(84.4)

Abbreviations: N, total number of participants in each column; n, number of participants contributing to the summary; SAS, Safety Analysis Set.

In the ARCT-154-01 Phase 3c, 1186 participants were exposed to at least 1 dose of ARCT-154 and 1171 to two doses.

In ARCT-154-J01, 420 participants received ARCT-154 5.0 mcg for the booster vaccination, while 408 participants received Comirnaty 30 mcg for the booster vaccination. A total of 417 participants who received ARCT-154 and 408 participants who received Comirnaty completed their Day 29 visit.

Overall exposure to ARCT-021 is presented in Table 26. In total 600 participants received at least one dose of ARCT-021, and hereof 343 received 2 doses.

Table 26: Overall Exposure of ARCT-021

Study and Group Assignment	1 Dose	2 Doses	3 Doses	At Least 1 Dose
ARCT-165-01 Cohort B	12	0	0	12
ARCT-021-01 and ARCT-021-02	30	60	0	90
ARCT-021-04	183	283	44	498
TOTAL	**225**	**343**	**44**	**600**

2.5.8.2. Adverse events

Solicited AEs

ARCT-154-01 Phase 3b

Solicited AEs within 30 minutes were comparable for ARCT-154 versus placebo. Any systemic reaction occurred in 0.5% of participants after first and after second dose in the ARCT-154 versus 0.3 and 0.6% in placebo (initial). All of the events were Grade 1 or Grade 2. Within 30 minutes after vaccination dizziness and headache were the most frequently reported systemic events and occurred with comparable frequencies in both ARCT-154 and placebo.

Solicited systemic AEs were reported higher in the ARCT-154 group than in the placebo group after the first dose and second dose. Overall, in ARTC-154 group, the frequencies of solicited systemic AEs were slightly higher after the 1st dose (48.1%) than after the 2nd dose (41.7%). The most frequently solicited systemic AEs reported after any dose were fatigue, headache and myalgia. Fever was reported with low frequency after any dose (5.3% after 1st dose and 6.6% after 2nd dose).

The majority of solicited local AEs were mild (Grade 1) or moderate (Grade 2) in severity and were transient and generally resolved in the 2-day period after dosing. The severity of solicited events did not increase with dose 2 compared with dose 1. Per definition, all solicited AEs were deemed related to study vaccine. Frequency of solicited AEs within 7 days for Study ARCT-154-01 Phase 3b are shown below:

Table 27: Solicited Local Adverse Events Within 7 days After Dose 1 and Dose 2 (Phase 3b, RAS)

Category • Event Grade	Dose 1				Dose 2			
	ARCT-154 (N=7940)		Placebo (N=7898)		ARCT-154 (N=7727)		Placebo (N=7670)	
	n	(%)	n	(%)	n	(%)	n	(%)
Any solicited local AE	3474	(43.8)	858	(10.9)	2400	(31.1)	584	(7.6)
Grade 1	3169	(39.9)	832	(10.5)	2259	(29.2)	562	(7.3)
Grade 2	265	(3.3)	26	(0.3)	131	(1.7)	21	(0.3)
Grade 3	40	(0.5)	0	(0.0)	10	(0.1)	1	(0.0)
• Injection Site Tenderness	3003	(37.8)	659	(8.3)	2042	(26.4)	430	(5.6)
Grade 3	32	(0.4)	0	(0.0)	7	(0.1)	1	(0.0)
• Injection Site Pain	3031	(38.2)	676	(8.6)	2062	(26.7)	467	(6.1)
Grade 3	29	(0.4)	–	–	7	(0.1)	–	–
• Injection Site Erythema	80	(1.0)	18	(0.2)	36	(0.5)	8	(0.1)
Grade 3	1	(0.0)	–	–	–	–	–	–
• Injection Site Swelling	224	(2.8)	29	(0.4)	79	(1.0)	9	(0.1)
Grade 3	2	(0.0)	–	–	1	(0.0)	–	–

Abbreviations: AE, adverse event; RAS, RAS, Reactogenicity Analysis Set.

Table 28: Solicited Systemic Adverse Events Within 7 days After Dose 1 and Dose 2 (Phase 3b, RAS)

Category • Event Grade	Dose 1				Dose 2			
	ARCT-154 (N=7940)		Placebo (N=7898)		ARCT-154 (N=7727)		Placebo (N=7670)	
	n	(%)	n	(%)	n	(%)	n	(%)
Any Solicited Systemic AE	3818	(48.1)	2500	(31.7)	3212	(41.6)	1796	(23.4)
Grade 1	3234	(40.7)	2261	(28.6)	2665	(34.5)	1607	(21.0)
Grade 2	469	(5.9)	204	(2.6)	435	(5.6)	166	(2.2)
Grade 3	115	(1.4)	35	(0.4)	112	(1.4)	23	(0.3)
• Dizziness	1051	(13.2)	720	(9.1)	848	(11.0)	444	(5.8)
Grade 3	10	(0.1)	6	(0.1)	8	(0.1)	0	(0.0)
• Fatigue	2344	(29.5)	1309	(16.6)	1925	(24.9)	901	(11.7)
Grade 3	27	(0.3)	9	(0.1)	26	(0.3)	4	(0.1)
• Headache	1926	(24.3)	1237	(15.7)	1649	(21.3)	836	(10.9)
Grade 3	19	(0.2)	7	(0.1)	24	(0.3)	3	(0.0)
• Myalgia	1615	(20.3)	693	(8.8)	1196	(15.5)	550	(7.2)
Grade 3	13	(0.2)	3	(0.0)	7	(0.1)	2	(0.0)
• Nausea	247	(3.1)	171	(2.2)	195	(2.5)	108	(1.4)
Grade 3	0	(0.0)	1	(0.0)	1	(0.0)	0	(0.0)
• Arthralgia	1430	(18.0)	910	(11.5)	1170	(15.1)	678	(8.8)
Grade 3	23	(0.3)	4	(0.1)	17	(0.2)	4	(0.1)
• Chills	1492	(18.8)	558	(7.1)	1344	(17.4)	386	(5.0)
Grade 3	19	(0.2)	4	(0.1)	17	(0.2)	1	(0.0)
• Vomiting	94	(1.2)	54	(0.7)	73	(0.9)	32	(0.4)
Grade 3	–	–	1	(0.0)	1	(0.0)	–	–
• Diarrhea	318	(4.0)	242	(3.1)	166	(2.1)	134	(1.7)
Grade 3	2	(0.0)	3	(0.0)	2	(0.0)	1	(0.0)

Category • Event Grade	Dose 1				Dose 2			
	ARCT-154 (N=7940)		Placebo (N=7898)		ARCT-154 (N=7727)		Placebo (N=7670)	
	n	(%)	n	(%)	n	(%)	n	(%)
• Fever (≥38°C)	419	(5.3)	102	(1.3)	508	(6.6)	92	(1.2)
Grade 3	53	(0.7)	12	(0.2)	63	(0.8)	11	(0.1)

Abbreviations: RAS, Reactogenicity Analysis Set. Grade 1=mild; Grade 2=moderate; Grade 3=severe. No Grade 4 reactions were reported in the study.

The majority of solicited AEs within 7 days of dose 1 and dose 2 in the RAS were Grade 1 or 2 in severity; there were (≤3.0%) Grade 3 events and no Grade 4 events in either the ARCT-154 or placebo groups.

Solicited AEs in ARCT-154-01 Phase 3c

Participants with any local solicited AE reported within first 7 days was 47.9% in the ARCT-154 group and 40.0% in the ChAdOx1 group. Injection site tenderness and injection site pain were the most frequent local symptoms reported after the first dose by 33.0% (390/1182) of ARCT-154 recipients and 30.8% (362/1176) of ChAdOx1 recipients. Solicited systemic AEs were reported by 63.6% in the ARCT-154 group and 61.6% in the ChAdOx1 group. Fatigue and headache were the most frequent systemic symptoms. Fatigue was reported by 35.2% and 36.5% in ARCT-154 recipients and 36.5% ChAdOx1 recipients, respectively. Headache in 25.9% and 32.7%, respectively.

Solicited AEs in ARCT-154-01 Phase 1/2/3a

The pattern of solicited AEs (local and systemic) after the primary 2-dose vaccination was similar in Phase 1/2/3a and Phase 3b. However, the incidences of solicited local and systemic AEs were much higher in Phase 1/2/3a than in Phase 3b.

The difference in the demographic and baseline characteristics between the participants in Phase 1/2/3a and Phase 3b as well as the difference in the number of subjects recruited in Phases 1/2/3a and Phase 3b, could explain these data.

Solicited AEs in ARCT-154-J01

Local solicited AEs were reported in 94.8% in the ARCT-154 group and 96.8% in the Comirnaty group. The most frequently reported solicited local AEs both in the ARCT-154 group and the Comirnaty group were injection site tenderness (92.4% and 95.8%, respectively), followed by injection site pain (83.8% and 87.7%, respectively). Also, injection site erythema, injection site swelling, and injection site induration occurred less in the ARCT-154 group compared to in the Comirnaty group. Most of the local AEs in the ARCT-154 group were reported within 1 to 2 days and resolved within 4 to 5 days after onset. Grade 3 or higher local AEs were reported in 3 participants (0.7%) in the ARCT-154 group and 4 participants (1.0%) in the Comirnaty group. Overall, the local solicited AEs are comparable between ARCT-154 group and the Comirnaty group, an almost equal high percentage has injection site tenderness and injection site pain, but there is a tendency towards fewer injection site erythema, injection site swelling, and injection site induration in the ARCT-154 group.

Solicited systemic AEs occurred in 64,3% in the ARCT-154 group and 62.3% in the Comirnaty group and included pyrexia, arthralgia, chills, diarrhoea, dizziness, headache, malaise, nausea, vomiting, and myalgia. Of the AEs, 65.2% in the ARCT-154 group and 62.0% in the Comirnaty group were deemed related to study vaccine by investigators. Most of the solicited systemic AEs in the ARCT-154 group occurred within 1 to 3 days after study vaccination and resolved within 2 to 3 days after onset. Solicited systemic AEs of grade 3 were reported in 6 participants (1.4%) in the ARCT-154 group and 7 participants (1.7%) in the Comirnaty group. No Grade 4 reactions were reported in the study. Overall, the systemic solicited AEs are comparable between ARCT-154 group and the Comirnaty group.

Frequency and grade of solicited AEs within 7 days for Study ARCT-154-J01 are shown in Table 29 below:

Table 29: Solicited AEs by Grade Within 7 Days After Booster Dose (Analysis Set for Safety) (ARCT-154-J01)

Category Event	ARCT-154 (N=420)		Comirnaty (N=408)	
	N	(%)	N	(%)
Local (Any)				
Any Grade	397	94.5	395	96.8
Grade 1	333	79.3	309	75.7
Grade 2	61	14.5	82	20.1
Grade 3	3	0.7	4	1.0
Injection Site Tenderness				
Any Grade	388	92.4	391	95.8
Grade 1	342	81.4	349	85.5
Grade 2	45	10.7	41	10.0
Grade 3	1	0.2	1	0.2
Injection Site Pain				
Any Grade	352	83.8	358	87.7
Grade 1	307	73.1	316	77.5
Grade 2	44	10.5	42	10.3
Grade 3	1	0.2	0	0.0
Injection Site Induration				
Any Grade	21	5.0	49	12.0
Grade 1	18	4.3	30	7.4
Grade 2	2	0.5	19	4.7
Grade 3	1	0.2	0	0.0
Injection Site Erythema				
Any Grade	26	6.2	54	13.2
Grade 1	21	5.0	24	5.9
Grade 2	5	1.2	27	6.6
Grade 3	0	0.0	3	0.7
Injection Site Swelling				
Any Grade	34	8.1	69	16.9
Grade 1	24	5.7	38	9.3
Grade 2	9	2.1	30	7.4
Grade 3	1	0.2	1	0.2
Systemic (Any)				
Any Grade	270	64.3	254	62.3
Grade 1	191	45.5	182	44.6

Category Event	ARCT-154 (N=420)		Comirnaty (N=408)	
	N	(%)	N	(%)
Grade 2	73	17.4	65	15.9
Grade 3	6	1.4	7	1.7
Dizziness				
Any Grade	25	6.0	13	3.2
Grade 1	16	3.8	11	2.7
Grade 2	9	2.1	1	0.2
Grade 3	0	0.0	1	0.2
Fatigue				
Any Grade	188	44.8	176	43.1
Grade 1	134	31.9	133	32.6
Grade 2	51	12.1	39	9.6
Grade 3	3	0.7	4	1.0
Headache				
Any Grade	165	39.3	125	30.6
Grade 1	129	30.7	97	23.8
Grade 2	33	7.9	25	6.1
Grade 3	3	0.7	3	0.7
Myalgia				
Any Grade	123	29.3	100	24.5
Grade 1	100	23.8	75	18.4
Grade 2	21	5.0	22	5.4
Grade 3	2	0.5	3	0.7
Nausea				
Any Grade	21	5.0	16	3.9
Grade 1	17	4.0	12	2.9
Grade 2	4	1.0	4	1.0
Grade 3	0	0.0	0	0.0
Arthralgia				
Any Grade	112	26.7	113	27.7
Grade1	86	20.5	88	21.6
Grade2	25	6.0	23	5.6
Grade3	1	0.2	2	0.5
Chills				

Category Event	ARCT-154 (N=420)		Comirnaty (N=408)	
	N	(%)	N	(%)
Any Grade	126	30.0	103	25.2
Grade1	95	22.6	66	16.2
Grade2	29	6.9	33	8.1
Grade3	2	0.5	4	1.0
Vomiting				
Any Grade	2	0.5	2	0.5
Grade 1	2	0.5	2	0.5
Grade 2	0	0.0	0	0.0
Grade 3	0	0.0	0	0.0
Diarrhoea				
Any Grade	28	6.7	17	4.2
Grade1	23	5.5	14	3.4
Grade2	5	1.2	3	0.7
Grade3	0	0.0	0	0.0
Fever (≥38°C)				
Any Grade	36	8.6	38	9.3
Grade1	23	5.5	29	7.1
Grade2	11	2.6	7	1.7
Grade3	2	0.5	2	0.5

Abbreviations: AE, adverse event; N, number of participants; n, number of participants with reaction reported.
Note: Grade 1=mild; Grade 2=moderate; Grade 3=severe. No Grade 4 reactions were reported in the study. Any Grade = Grade 1, 2, 3 or 4. Grade 0 reactions (erythema, swelling, fever) were not included in any reactions.

ARCT-021-04

Solicited AEs in study ARCT-021-04 in the overall population were 91.5%, 88.0%, and 91.7% of participants in Groups A, B, and C, respectively, and 50.0% of participants in Group D (Placebo). Most of the AEs were Grade 1 or Grade 2. Grade 3 solicited AE occurred in 27 (4.7%) of participants and Grade 4 solicited AE occurred in 1 (0.2%) participant (in Group A). The most common solicited local AEs overall were injection site tenderness (64.3%) and injection site pain (41.6%).

Solicited systemic AEs (after the first vaccination) occurred in 63.4% of participants vaccinated with ARCT-021 5.0 mcg (Group B) and 72.5% to 67.4% of participants vaccinated with ARCT-021 7.5 mcg (Groups A and C, respectively), compared to 40.4% in the placebo group. The most common solicited systemic AEs were fatigue (36.1%), headache (34.0%), myalgia (30.1%), and chills (17.6%). After the second vaccination the most common solicited systemic AEs were fatigue (28.5%), headache (25.1%), myalgia (22.1%), and arthralgia (13.6%).

In the Booster Reactogenicity Set, 95.3%, Groups E1 (ARCT-021 Priming - ARCT-021 Booster, n=43) and 92.1% in F1 (ARCT-021 Priming - ARCT-154 Booster, n=38) reported any solicited AEs. The majority of events were Grade 1 or Grade 2 in severity, n=15 (12.4%) had a Grade 3 AE.

Unsolicited AEs

ARCT-154-01 Phase 3b

Incidence of unsolicited AEs within 28 days after first and second dose were comparable for ARCT-154 versus placebo. For Dose 1, 14% in the ARCT-154 and 13.7% in placebo. For Dose 2, 13.9% in the ARCT-154 and 15.9% in placebo. Most AEs were mild. The frequency of moderate events was low overall but was slightly higher after the second dose than the first for both ARCT-154 (4.3% versus 5.3%, respectively), the same picture was seen for placebo. The incidence of severe events was overall 0.2% and similar between ARCT-154 and placebo.

Type of AE by MedDRA PT were generally consistent after dose 1 and dose 2. Most common unsolicited AEs in within 28 Days After Dose 1 and Dose 2 were: tachycardia, influenza, arthralgia, headache, cough, hypertension, dizziness, diarrhoea, gastritis, oropharyngeal pain, toothache, fatigue, pyrexia, COVID-19, nasopharyngitis, backpain, myalgia, and pruritus. All most all occurred at comparable frequencies in ARCT-154 and Placebo, and after first and second dose. Pyrexia occurred a bit more often in the ARCT-154 than in placebo (0,2% vs 0.1%) as well as fatigue (0.3% vs 0.2%). Hypersensitivity occurred in 7 participants in the ARCT-154 vs 2 participants in placebo, 2 of the events in the ARCT-154 group were moderate.

Severe unsolicited AEs were generally comparable for ARCT-154 and placebo, and the overall incidence was similar for doses 1 and 2. After first dose 0.1% of the AEs were severe in the ARCT-154 group vs 0.2% in the placebo group. After second dose 0.2% of the AEs were severe in the ARCT-154 group vs 0.2% in the placebo group. The only severe AE (PT) that occurred in more than 1 participant in the vaccination group was hypertension (4 in ARCT-154 vs 3 in placebo after first dose and arthralgia that occurred in 2 participants in the ARCT-154 after second dose vs none in the placebo group.

Few of the AEs were deemed related to study vaccine and were similar in frequency between participants receiving ARCT-154 and placebo (2.5% and 2.3% after dose 1 and 1.7% and 1.4% after dose 2, respectively). The most common (≥7 participants in any group) related AEs across all groups were hypertension, arthralgia, tachycardia, myalgia, headache, fatigue, and pyrexia. After a thorough analysis of tachycardia and hypertension, these events are not seen as related to the vaccine, and therefore not included in the SmPC. Furthermore, also dizziness was deemed related to study vaccine and occurred in 0.1% in the ARCT-154 and 0% in placebo. Also, hypersensitivity, Type IV

hypersensitivity and urticaria occurred more often in ARCT-154 (12 participants vs 3 participants 1. And 2. Dose combined).

Solicited AEs (e.g., arthralgia, myalgia, headache, fatigue, pyrexia and dizziness) were considered ADRs and are included in SmPC section 4.8.

The causality assessment of other reported related AEs concluded a potential association between ARCT-154 and the occurrence of hypersensitivity, rash, and urticaria. Therefore, hypersensitivity (e.g., rash, urticaria, allergic dermatitis, type IV hypersensitivity) were included in SmPC Section 4.8, which is acceptable.

With regards to hypertension and tachycardia, overall frequencies were similar for ARCT-154 and Placebo in the Phase 3b study after all doses, as well as in study Phase 1, 2, 3a, 3b combined. There were however imbalance of SAE of hypertension and hypertensive crisis. In the Phase 1/2/3a/3b study, there were 2 SAEs of hypertension in the ARCT-154 group, and 0 in the placebo group. There were 4 SAEs of hypertensive crisis in the ARCT-154 group, and 2 in the placebo group. In the Phase 3c part of the study there was 1 SAE of hypertension in the ARCT-154 group, vs none in the ChAdOx1 group.

Overview of hypertension and tachycardia in study ARCT-154-J01 and ARCT-154-01 Phase 3c were provided. Three participants in study ARCT-154-J01 had unsolicited AE of palpitations in the ARCT-154 group vs none in the Comirnaty group. In Phase 3c unsolicited AEs of hypertension occurred in 3.7% and 3.6% in ARCT-154 vs ChAdOx after first dose and in 3.2% and 1.8% after second dose. Unsolicited AEs of tachycardia in Phase 3c occurred with low frequency in both groups (0.3%).

Related severe AEs occurred in 3 participants (0.0%) in the ARCT-154 group and 5 participants (0.1%) after dose 1, and in 5 participants (0.1%) in the ARCT-154 group and 2 participants (0.0%) in the placebo group after dose 2.

The overview of unsolicited AEs are provided in Table 30 below.

Table 30: Overview of Unsolicited AEs Within 28 Days after Dose 1 and Dose 2 (Phase 3b, SAS)

Category	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)	n	(%)	n	(%)
AEs	1125	(14.0)	1001	(13.7)	1096	(13.9)	1241	(15.9)
Related AEs	202	(2.5)	184	(2.3)	130	(1.7)	107	(1.4)
AE by worst severity								
Mild	767	(9.5)	767	(9.5)	665	(8.5)	780	(10.0)
Moderate	348	(4.3)	316	(3.9)	418	(5.3)	444	(5.7)
Severe	10	(0.1)	18	(0.2)	13	(0.2)	17	(0.2)
MAAEs	226	(2.8)	232	(2.9)	359	(4.6)	418	(5.3)

Category	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)	n	(%)	n	(%)
Related MAAEs	56	(0.7)	41	(0.5)	35	(0.4)	20	(0.3)
SAEs	38	(0.5)	48	(0.6)	40	(0.5)	61	(0.8)
Related SAEs	5	(0.1)	5	(0.1)	6	(0.1)	0	(0.0)
AE leading to discontinuation of vaccine	3	(0.0)	5	(0.1)	4	(0.1)	0	(0.0)
AE leading to withdrawal from study	2	(0.0)	5	(0.1)	3	(0.0)	5	(0.1)
AE with death as an outcome	2	(0.0)	4	(0.0)	1	(0.0)	1	(0.0)
AE with COVID-related death as outcome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Abbreviations: AE, adverse event; COVID, coronavirus disease; MAAE, medically attended adverse event; N, total number of participants in each column; n, number of participants contributing to the summary; SAE, serious adverse event; SAS, Safety Analysis Set.
Note: For very low numbers of AEs, rounding in calculations of percentage created "0.0%" with some nonzero numbers.

Unsolicited AEs by MedDRA PT are shown in Table 31.

Table 31: Unsolicited AEs in ≥15 Participants in Any Group within 28 Days after Dose 1 and Dose 2 by MedDRA SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=7867)		Placebo (N=7822)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with at least one AE	1125	(14.0)	1101	(13.7)	1096	(13.9)	1241	(15.9)
Cardiac disorders	106	(1.3)	81	(1.0)	86	(1.1)	78	(1.0)
Dizziness	20	(0.2)	12	(0.1)	15	(0.2)	15	(0.2)
Tachycardia	67	(0.8)	52	(0.6)	48	(0.6)	46	(0.6)
Gastrointestinal disorders	150	(1.9)	173	(2.2)	136	(1.7)	163	(2.1)
Diarrhea	16	(0.2)	24	(0.3)	10	(0.1)	7	(0.1)
Gastritis	17	(0.2)	22	(0.3)	18	(0.2)	19	(0.2)
Oropharyngeal pain	31	(0.4)	38	(0.5)	23	(0.3)	49	(0.6)

MedDRA SOC MedDRA PT	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=7867)		Placebo (N=7822)	
	n	(%)	n	(%)	n	(%)	n	(%)
Toothache	27	(0.3)	35	(0.4)	29	(0.4)	32	(0.4)
General disorders and administration site conditions	53	(0.7)	39	(0.5)	68	(0.9)	51	(0.7)
Fatigue	21	(0.3)	17	(0.2)	28	(0.4)	24	(0.3)
Pyrexia	17	(0.2)	5	(0.1)	16	(0.2)	7	(0.1)
Infection and infestations	197	(2.4)	201	(2.5)	276	(3.5)	382	(4.9)
COVID-19	13	(0.2)	24	(0.3)	61	(0.8)	156	(2.0)
Influenza	107	(1.3)	86	(1.1)	80	(1.0)	94	(1.2)
Nasopharyngitis	9	(0.1)	6	(0.1)	15	(0.2)	7	(0.1)
Pharyngitis	31	(0.4)	40	(0.5)	53	(0.7)	54	(0.7)
Upper respiratory tract infection	4	(0.0)	3	(0.0)	19	(0.2)	26	(0.3)
Musculoskeletal and connective tissue disorders	127	(1.6)	131	(1.6)	127	(1.6)	159	(2.0)
Arthralgia	54	(0.7)	54	(0.7)	59	(0.7)	69	(0.9)
Back pain	23	(0.3)	21	(0.3)	22	(0.3)	31	(0.4)
Myalgia	13	(0.2)	13	(0.2)	16	(0.2)	14	(0.2)
Nervous system disorders	151	(1.9)	164	(2.0)	150	(1.9)	155	(2.0)
Headache	129	(1.6)	148	(1.8)	129	(1.6)	133	(1.7)
Respiratory, thoracic and mediastinal disorders	111	(1.4)	112	(1.4)	107	(1.4)	123	(1.6)
Cough	63	(0.8)	69	(0.9)	59	(0.7)	72	(0.9)
Rhinorrhea	30	(0.4)	32	(0.4)	38	(0.5)	32	(0.4)
Skin and subcutaneous tissue disorders	42	(0.5)	34	(0.4)	44	(0.6)	34	(0.4)
Pruritus	22	(0.3)	19	(0.2)	27	(0.3)	27	(0.3)
Vascular disorders	239	(3.0)	222	(2.8)	125	(1.6)	120	(1.5)
Hypertension	230	(2.9)	214	(2.7)	115	(1.5)	116	(1.5)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants in each column; n, number of participants contributing to the summary; PT, preferred term; SAS, Safety Analysis Set; SOC, system organ class.
Note: MedDRA Version 24.0 was used.

Related unsolicited AEs in study ARCT-154-01 Phase 3b are seen in Table 32. Note that per definition all solicited AEs in the study were related to study vaccine.

Table 32: Unsolicited AEs Related to Study Vaccine in ≥2 Participants in Any Group with Onset Within 28 Days After Dose 1 and Dose 2 by MedDRA SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=7867)		Placebo (N=7822)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with at least one AE	202	(2.5)	184	(2.3)	130	(1.7)	107	(1.4)
Cardiac disorders	21	(0.3)	15	(0.2)	21	(0.3)	14	(0.2)
Chest discomfort	0	(0.0)	1	(0.0)	2	(0.0)	3	(0.0)
Chest pain	1	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)
Dizziness	6	(0.1)	3	(0.0)	4	(0.1)	3	(0.0)
Tachycardia	14	(0.2)	9	(0.1)	13	(0.2)	7	(0.1)
Gastrointestinal disorders	3	(0.0)	9	(0.1)	0	(0.0)	2	(0.0)
Constipation	0	(0.0)	2	(0.0)	0	(0.0)	0	(0.0)
Diarrhea	0	(0.0)	4	(0.0)	0	(0.0)	1	(0.0)

Table 33: Unsolicited AEs Related to Study Vaccine in ≥2 Participants in Any Group with Onset Within 28 Days After Dose 1 and Dose 2 by MedDRA SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=7867)		Placebo (N=7822)	
	n	(%)	n	(%)	n	(%)	n	(%)
Nausea	2	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	15	(0.2)	15	(0.2)	17	(0.2)	10	(0.1)
Chills	5	(0.1)	4	(0.0)	3	(0.0)	2	(0.0)
Fatigue	6	(0.1)	6	(0.1)	7	(0.1)	3	(0.0)
Pyrexia	7	(0.1)	1	(0.0)	6	(0.1)	4	(0.1)
Immune system disorders	5	(0.1)	3	(0.0)	7	(0.1)	0	(0.0)
Hypersensitivity	2	(0.0)	1	(0.0)	2	(0.0)	0	(0.0)
Type IV hypersensitivity reaction	0	(0.0)	0	(0.0)	2	(0.0)	0	(0.0)
Urticaria	3	(0.0)	1	(0.0)	2	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	2	(0.0)	2	(0.0)	3	(0.0)	4	(0.1)
Injection site bruising	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Injection site pain	1	(0.0)	2	(0.0)	3	(0.0)	1	(0.0)
Musculoskeletal and connective tissue disorders	30	(0.4)	25	(0.3)	37	(0.5)	32	(0.4)
Arthralgia	17	(0.2)	17	(0.2)	29	(0.4)	23	(0.3)
Arthritis	2	(0.0)	3	(0.0)	0	(0.0)	1	(0.0)
Myalgia	10	(0.1)	7	(0.1)	6	(0.1)	6	(0.1)
Nervous system disorders	15	(0.2)	10	(0.1)	13	(0.2)	10	(0.1)
Headache	11	(0.1)	8	(0.1)	12	(0.2)	10	(0.1)
Hypoesthesia	4	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	12	(0.1)	4	(0.0)	8	(0.1)	5	(0.1)
Pruritus	5	(0.1)	2	(0.0)	5	(0.1)	4	(0.1)
Rash	5	(0.1)	1	(0.0)	1	(0.0)	0	(0.0)
Vascular disorders	118	(1.5)	106	(1.3)	36	(0.5)	34	(0.4)
Hypertension	112	(1.4)	104	(1.3)	33	(0.4)	33	(0.4)
Hypertensive crisis	2	(0.0)	2	(0.0)	1	(0.0)	1	(0.0)

Table 34: Unsolicited AEs Related to Study Vaccine in ≥2 Participants in Any Group with Onset Within 28 Days After Dose 1 and Dose 2 by MedDRA SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=7867)		Placebo (N=7822)	
	n	(%)	n	(%)	n	(%)	n	(%)
Hypotension	3	(0.0)	1	(0.0)	2	(0.0)	0	(0.0)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants in each column; n, number of participants contributing to the summary; PT, preferred term; SAS, Safety Analysis Set; SOC, system organ class.

Note: MedDRA Version 24.0 was used.

Note: For very low numbers of AEs, rounding in calculations of percentage created "0.0%" with some nonzero numbers.

ARCT-154-01 Phase 1/2/3a

Overall unsolicited AEs within 28 days after dose 1 and dose 2 in the SAS were comparable for ARCT-154 versus placebo. Except for the gastrointestinal disorders SOC, where after the first dose, 7.0% of ARCT-154-01 participants experienced an AE compared to 4.3% for placebo, and after second dose 2.6% and 1.6%, respectively. This was mainly caused by diarrhoea and oropharyngeal pain. Overall, most AEs were mild or moderate. One severe AE was reported (in an ARCT-154 participant after dose 1 had toothache graded severe). There were no fatal AEs. No events of myocarditis or pericarditis were reported. No severe unsolicited AEs were reported during Phase 1/2/3a after dose 3 or dose 4.

The overall incidence of participants with AEs related to the study vaccine was similar between the ARCT-154 and placebo groups, except for the SOC term of vascular disorders, PT hypertension, and headache that consistently showed a higher incidence in the ARCT-154 group. Headache is considered an ADR.

ARCT-154-01 Phase 3c

Unsolicited AE was reported by 35.6% of ARCT-154 recipients and 34.9% of ChAdOx1 recipients. The most frequently reported unsolicited AEs by PT in the ARCT-154 and ChAdOx1 groups were influenza (7.0% versus 5.7%), hypertension (6.7% versus 5.1%), and headache (4.6% versus 6.1%). Related unsolicited AE was reported in 6.6% of ARCT-154 group and 5.9% in ChAdOx1 group. The most frequently reported related unsolicited AE by PT in the ARCT-154 and ChAdOx1 groups was hypertension (3.0% versus 2.9% after dose 1, and 2.4% and 1.5% after dose 2, respectively).

ARCT-154-J01

19.3% in the ARCT-154 group and 27.2% in the Comirnaty group experienced unsolicited AEs in the booster study. Incidence of 1% or higher in the ARCT-154 group and the Comirnaty group were injection site pruritus (4.5% and 8.1%, respectively), nasopharyngitis (1.2% and 1.7%, respectively), rhinorrhoea (1.2% and 0.5%, respectively), and back pain (1.0% and 2.7%, respectively).

Most of the AEs were mild in severity. One participant in the ARCT-154 group and 6 in the Comirnaty group had severe AE. In the ARCT-154 group it was hepatic function abnormal. In the Comirnaty group, pyrexia (1 participant), nasopharyngitis (3 participants), ankle fracture (1 participant), and foot deformity (1 participant).

AEs related to study vaccine were reported in 55 participants (13.1%) in the ARCT-154 group and 68 participants (16.7%) in the Comirnaty group. Incidence of 1% or higher in the ARCT-154 group and the Comirnaty group were injection site pruritus and back pain. The related AEs rhinorrhoea, hypoaesthesia, and soft faeces occurred more often in the ARCT-154 group that in Comirnaty.

One Grade 3 unsolicited AE on Day 29 post-vaccination was deemed to be related to the study vaccine by the investigator. An adult female in the ARCT-154 arm, developed increase in AST (118, normal range 10-40), ALT (214 (normal range 5-40), γ-GTP: 60 (normal value< 30), and ALP: 135 (normal range is 38-113). It is noted that ALT also in general was higher in the ARCT-154 arm as compared to the Comirnaty arm, but this is most likely due to baseline differences. Regarding the PT of `Pruritus´, the incidence was low and similar in both primary and booster studies, and there was no imbalance between ARCT-154 group and control groups (placebo and Comirnaty). Therefore, pruritus is not included in SmPC section 4.8. However, injection site pruritus occurred more often in the ARCT-154 group is included in SmPC section 4.8.

Unsolicited AEs in study ARCT-154-J01 are provided in Table 35:

Table 35: Overview of AEs (Analysis Set for Safety) (ARCT-154-J01)

Category	Booster dose			
	ARCT-154 (N=420)		Comirnaty (N=408)	
	N	(%)	n	(%)
Unsolicited AEs (Days 1-28)	81	(19.3)	111	(27.2)
Related unsolicited AEs (Days 1-28)	55	(13.1%)	68	(16.7)
AE by worst severity (Day 1-28)				
Mild	76	(18.1)	96	(23.5)
Moderate	4	(1.0)	9	(2.2)
Severe	1	(0.2)	6	(1.5)
Medically significant AEs	0	(0.0)	0	(0.0)
Related medically significant AEs	0	(0.0)	0	(0.0)
SAEs	3	(0.7)	4	(1.0)
Related SAEs	0	(0.0)	0	(0.0)
AE leading to withdrawal from study	0	(0.0)	0	(0.0)
AE with death as an outcome	0	(0.0)	0	(0.0)

Note: Safety data are presented for 90-day follow-up period after study vaccination, with the exception of those with a shorter reporting period (Days 1-28).

Incidences of Unsolicited AEs in study ARCT-154-J01 are shown in Table 36.

Table 36: Incidences of Unsolicited Adverse Events Occurring in 4 or More Participants in Any Group (Analysis Set for Safety) (ARCT-154-J01)

MedDRA SOC MedDRA PT	ARCT-154 (N=420)		Comirnaty (N=408)	
	n	(%)	n	(%)
Unsolicited adverse events	81	19.3	111	27.2
Blood and lymphatic system disorders	2	0.5	7	1.7
Lymphadenopathy	0	0.0	4	1.0
Gastrointestinal disorders	11	2.6	13	3.2
Abdominal pain	2	0.5	4	1.0
Abdominal pain upper	3	0.7	4	1.0
Faeces soft	4	1.0	1	0.2
General disorders and administration site conditions	28	6.7	47	11.5
Injection site pruritus	19	4.5	33	8.1
Axillary pain	0	0.0	4	1.0
Infections and infestations	7	1.7	14	3.4
Nasopharyngitis	5	1.2	7	1.7
Investigations	5	1.2	6	1.5
Blood creatine phosphokinase increased	3	0.7	4	1.0
Musculoskeletal and connective tissue disorders	10	2.4	15	3.7
Back pain	4	1.0	11	2.7
Nervous system disorders	11	2.6	9	2.2
Hypoaesthesia	4	1.0	1	0.2
Respiratory, thoracic and mediastinal disorders	8	1.9	8	2.0
Rhinorrhoea	5	1.2	2	0.5
Skin and subcutaneous tissue disorders	6	1.4	5	1.2

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants in each column; n, number of participants contributing to the summary; PT, preferred term; SOC, system organ class.
Note: MedDRA Version 26.0 was used.

Table 37: Incidences of Unsolicited Adverse Events Related to Study Vaccine Occurring in 4 or More Participants in Any Group (Analysis Set for Safety) (ARCT-154-J01)

MedDRA SOC MedDRA PT	ARCT-154 (N=420)		Comirnaty (N=408)	
	n	(%)	n	(%)
Unsolicited adverse events	55	13.1	68	16.7
Blood and lymphatic system disorders	2	0.5	7	1.7
Lymphadenopathy	0	0.0	4	1.0
Gastrointestinal disorders	10	2.4	6	1.5
Faeces soft	4	1.0	0	0.0
General disorders and administration site conditions	26	6.2	46	11.3
Injection site pruritus	19	4.5	33	8.1
Axillary pain	0	0.0	4	1.0
Musculoskeletal and connective tissue disorders	5	1.2	5	1.2
Back pain	2	0.5	5	1.2
Nervous system disorders	8	1.9	6	1.5
Hypoaesthesia	4	1.0	1	0.2
Respiratory, thoracic and mediastinal disorders	6	1.4	4	1.0
Rhinorrhoea	4	1.0	2	0.5

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, population size; n, number of participants who experienced the adverse event; PT, preferred term; SOC, system organ class.
Note: MedDRA Version 26.0 was used.
Proportion of participants showed by the first decimal place, being rounded to the second decimal place.

One unsolicited AE (i.e. hepatic function abnormal) of Grade 3 or higher was assessed as related to study vaccine by the investigator in the ARCT-154 arm.

ARCT-021-04

One hundred sixteen (20.0%) and 92 (16.9%) participants reported at least 1 unsolicited AE up to 28 days following the first and second vaccinations, respectively. After first dose any unsolicited TEAEs were reported in 20.3% of the Cohort A, B and C vs 19.2% of Cohort D (placebo). The majority of unsolicited AEs were mild or moderate in severity. No unsolicited severe AEs were reported following the first vaccination, following the second study vaccination 1 participant in Group A (receiving placebo) reported an unsolicited severe AE. Most common AEs in participants following the first vaccination were diarrhoea (1.7%), blood creatine phosphokinase increased (1.2%), headache (1.2%), and hyperkalaemia (1.0%). Following the second vaccination, the most common unsolicited AEs were diarrhoea (1.1%) and fatigue (1.1%).

Related AEs occurred in 6.2% in Cohort A, B and C and in 4.1% in Cohort D (placebo). Related AEs reported in >2 participants vaccinated with ARCT-021 after first vaccination include diarrhoea (4 participants) and urticaria (3 participants). It is noted that the overall incidence of AEs is higher in study ARCT-021-04 than in ARCT-154-01 (phase 3b) as discussed above.

2.5.8.3. Serious adverse event/deaths/other significant events

ARCT-154-01

SAEs occurring in 3 or more participants in any group in ARCT-154-01 are shown in Table 38

Table 38: SAEs ≥3 Participants in Any Group from Day 1 to Day 92, Switchover, or Further Study Vaccine by MedDRA SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	ARCT-154 (N=8059)		Placebo (N=8041)	
	N	(%)	n	(%)
Participants with any SAE	118	(1.5)	201	(2.5)
Ear and labyrinth disorders	3	(0.0)	5	(0.1)
Vestibular disorder	3	(0.0)	5	(0.1)
Gastrointestinal disorders	9	(0.1)	13	(0.2)
Gastritis	2	(0.0)	6	(0.1)
Infections and infestations	54	(0.7)	140	(1.7)
Appendicitis	4	(0.0)	2	(0.0)
COVID-19	39	(0.5)	127	(1.6)
Pneumonia	2	(0.0)	4	(0.0)
Nervous system disorders	6	(0.1)	5	(0.1)
Cerebral infarction	3	(0.0)	0	(0.0)
Vascular disorders	7	(0.1)	3	(0.0)
Hypertensive crisis	4	(0.0)	2	(0.0)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants in each column; n, number of participants contributing to the summary; PT, preferred term; SAE, serious adverse event; SAS, Safety Analysis Set; SOC, system organ class.
Note: MedDRA Version 24.0 was used.
Note: For very low numbers of AEs, rounding in calculations of percentage created "0.0%" with some nonzero numbers.

In study Phase 3b, SAEs with onset from switchover/further study vaccine to Day 210 for participants occurred in 88 out of 7458 participants (1.2%) in the ARCT-154 group and 91 out of 7349 participants (1.2%) in the placebo group. In one participant the SAE was related to the vaccine.

Below in Table 39, the summary of cerebral infarction is included.

Table 39: Summary o fall SAEs with PT 'Cerebral Infraction, "Reported in Study ARCT-154-01

Subject ID (Phase)	PT	Start date	End Date	Days after last vaccination	Days after last dose of ARCT-154	Severity	Relatedness	Outcome
404-0270 (Phase 3b)	Cerebral infarction	03-Aug-2022	22-Aug-2022	168 days post-Dose 4	168 days	Moderate	Not related	Resolved with sequelae
406-0465 (Phase 3b)	Cerebral infarction	21-Dec-2021	27-Dec 2021	28 days post-Dose 2	28 days	Severe	Not related	Resolved with sequelae
407-0287 (Phase 3b)	Cerebral infarction	18-Apr-2022	04-May 2022	62 days post-Dose 4	150 days	Moderate	Not related	Resolved
407-0290 (Phase 3b)	Cerebral infarction	27-Apr-2022	05-May 2022	73 days post-Dose 4	162 days	Moderate	Not related	Resolved
407-0464 (Phase 3b)	Cerebral infarction	23-Nov 2021	29-Nov 2021	29 days post-Dose 1	29 days	Moderate	Not related	Resolved with sequelae
407-1237 (Phase 3b)	Cerebral infarction	06-Jan 2022	14-Jan 2022	45 days post-Dose 2	45 days	Moderate	Not related	Resolved with sequelae
	Cerebral infarction	16-May 2022	07-Jul 2022	175 days post-Dose 2	175 days	Moderate	Not related	Resolved with sequelae
407-1440 (Phase 3b)	Cerebral infarction	03-Nov 2022	16-Dec 2022	246 days post-Dose 4	246 days	Moderate	Not related	Resolved with sequelae
416-0099 (Phase 3b)	Cerebral infarction	08-May 2002		78 days post-Dose 4	169 days	Moderate	Not related	Resolving
504-0567 (Phase 3c)	Cerebral infarction	27-Sep 2022		301 days post-Dose 2	301 days	Moderate	Not related	Resolved
517-1313 (Phase 3c)	Cerebral infarction	20-Nov-2021	05-Dec 2021	12 days post-Dose 1	12 days	Severe	Related	Resolved with sequelae

Related SAEs reported between Day 1 and Day 92 are shown in Table 40. One related SAE (i.e. anaphylactic reaction) with onset from Day 92 to Day 210 was reported in Phase 3b. Thromboembolic events are overviewed below under AESIs.

Table 40: SAEs Related to Study Vaccine with Onset from Day 1 to Day 92, Switchover, or Further Study Vaccine by SOC and PT (Phase 3b, SAS)

MedDRA SOC MedDRA PT	ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)
Number of participants who received study vaccine	8059		8041	
Participants with at least one SAE	10	(0.1)	5	(0.1)
Ear and labyrinth disorders	0	(0.0)	1	(0.0)
Vestibular disorder	0	(0.0)	1	(0.0)
General disorders and administration site conditions	1	(0.0)	1	(0.0)
Administration related reaction	0	(0.0)	1	(0.0)
Injection site reaction	1	(0.0)	0	(0.0)
Immune system disorders	5	(0.1)	0	(0.0)
Dermatitis contact	1	(0.0)	0	(0.0)
Hypersensitivity	1	(0.0)	0	(0.0)
Type IV hypersensitivity reaction	2	(0.0)	0	(0.0)
Urticaria	1	(0.0)	0	(0.0)
Nervous system disorders	1	(0.0)	1	(0.0)
Cerebrovascular disorder	0	(0.0)	1	(0.0)
Headache	1	(0.0)	0	(0.0)
Vascular disorders	4	(0.0)	2	(0.0)
Deep vein thrombosis	1	(0.0)	0	(0.0)
Hypertension	1	(0.0)	0	(0.0)
Hypertensive crisis	2	(0.0)	2	(0.0)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants in each column; n, number of participants contributing to the summary; PT, preferred term; SAE, serious adverse event; SAS, Safety Analysis Set; SOC, system organ class.
Note: MedDRA Version 24.0 was used.
Note: Percentages were computed based on the number of participants in SAS who received the study vaccine in the specified period.
Note: For participants who received a nonstudy vaccine, safety data were presented prior to the time of receipt of the nonstudy vaccine.
Note: If a participant experienced more than 1 event in a given category, that participant was counted only once in that category.
Note: Unsolicited events included solicited events that were ongoing >7 days after injection.

Table 41: Study ARCT-154-01 – SAEs in ≥3 Participant in the ARCT-154 Group from Day 92 (Switchover) to the Study End (Phase 3b, SAS) by SOC and PT

• **SOC** **PT**	**ARCT-154 (Initial)/ Placebo (Dose 3 and 4) (N=7458)**		**Placebo (Initial)/ ARCT-154 (Dose 3 and 4) (N=7350)**	
	n	**(%)**	**n**	**(%)**
Participants with at least 1 SAE	168	(2.3)	173	(2.4)
• Cardiac Disorders	8	(0.1)	8	(0.1)
• Ear and labyrinth disorders	11	(0.1)	10	(0.1)
Vestibular disorder	10	(0.1)	9	(0.1)
• Eye disorders	3	(0.0)	4	(0.1)
• Gastrointestinal disorders	18	(0.2)	17	(0.2)
Gastritis	3	(0.0)	2	(0.0)
Gastrooesophageal reflux disease	3	(0.0)	0	(0.0)
Pancreatitis acute	0	(0.0)	5	(0.1)
• General disorders and administration site conditions	6	(0.1)	0	(0.0)
• Hepatobiliary disorders	5	(0.1)	4	(0.1)
Cholelithiasis	4	(0.1)	0	(0.0)
• Infections and infestations	46	(0.6)	54	(0.7)

Table 41: Study ARCT-154-01 – SAEs in ≥3 Participant in the ARCT-154 Group from Day 92 (Switchover) to the Study End (Phase 3b, SAS) by SOC and PT

• **SOC** **PT**	**ARCT-154 (Initial)/ Placebo (Dose 3 and 4) (N=7458)**		**Placebo (Initial)/ ARCT-154 (Dose 3 and 4) (N=7350)**	
	n	**(%)**	**n**	**(%)**
Appendicitis	5	(0.1)	8	(0.1)
COVID-19	13	(0.2)	16	(0.2)
Pneumonia	5	(0.1)	5	(0.1)
Viral infection	2	(0.0)	3	(0.0)
• Injury, poisoning and procedural complications	18	(0.2)	13	(0.2)
Limb injury	3	(0.0)	1	(0.0)
• Metabolism and nutrition disorders	4	(0.1)	7	(0.1)
Hyperglycaemia	0	(0.0)	3	(0.0)
• Musculoskeletal and connective tissue disorders	9	(0.1)	9	(0.1)
• Neoplasms benign, malignant and unspecified	15	(0.2)	13	(0.2)
Breast cancer	2	(0.0)	3	(0.0)
Lipoma	0	(0.0)	3	(0.0)
Lung neoplasm malignant	4	(0.1)	2	(0.0)
• Nervous system disorders	14	(0.2)	11	(0.1)
Cerebral infarction	3	(0.0)	2	(0.0)
Cerebrovascular accident	3	(0.0)	2	(0.0)
Cerebrovascular disorder	2	(0.0)	3	(0.0)
• Renal and urinary disorders	3	(0.0)	8	(0.1)
Nephrolithiasis	1	(0.0)	4	(0.1)
Ureterolithiasis	0	(0.0)	3	(0.0)
• Reproductive system and breast disorders	4	(0.1)	3	(0.0)
Ovarian cyst	3	(0.0)	2	(0.0)
• Respiratory, thoracic and mediastinal disorders	2	(0.0)	7	(0.1)
Chronic obstructive pulmonary disease	1	(0.0)	4	(0.1)
• Vascular disorders	4	(01)	3	(0.0)

Abbreviations: COVID-19, Coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants receiving treatment; n, number of participants with event; PT, preferred term; SAE, serious adverse event; SAS, Safety Analysis Set; SOC, system organ class.
Adverse Events are coded using MedDRA version 24.0.

In study phase 3c, from Day 1 to Day 92, 22 (1.9%) participants in the ARCT-154 group and 35 (3.0%) participants in the ChAdOx1 group reported at least one SAE. The most frequently reported SAE by PT was COVID-19 (5 in the ARCT-154 group and 8 in the ChAdOx1 group). For cardiac disorders, 1 participant in the ARCT-154 group and 3 participants in the ChAdOx1 group reported SAEs. No cases of myocarditis or pericarditis were reported.

Three of the SAEs were deemed related in the ARCT-154 group and 4 in the ChAdOx1 group. The three related SAEs in the ARCT-154 group were angina pectoris, polyarthritis, and cerebral infarction.

From Day 92 to Day 394, 5.5% in the ARCT-154 group 4.5% in the ChAdOx1 group had at least one SAE. No SAE was assessed as related to the study vaccination in the period from day 92 to day 394.

ARCT-154-J01

From Day 1 and up to 181 days after study vaccination, 10 SAEs occurred in 9 participants. Five of them occurred in ARCT-154 (i.e. enterocolitis, osteoarthritis, haemorrhoids, retinal detachment, and myelopathy) and five in four participants receiving Comirnaty. None of the SAEs were assessed as related to the study vaccines. The participant with myelopathy was an adult woman with a history of cervical spinal stenosis. Two months after vaccination the participant had an event of cervical spondylosis myelopathy. The investigator assessed the event of cervical spondylosis myelopathy as serious (hospitalisation), unexpected, and not related to the study vaccine.

SAEs in Study ARCT-154-J01 between Day 1 and Day 181 post booster are figured in Table 42.

Table 42: Frequencies and Percentages of Serious Adverse Events other than Death

	ARCT-154 (N=420)		COMIRNATY (N=408)	
SOC	n	Proportion	n	Proportion
PT		%		%
Frequencies and percentages of adverse events	5	1.2	4	1.0
Eye disorders	1	0.2	1	0.2
Cataract	0	0.0	1	0.2
Retinal detachment	0	0.0	1	0.2
Rhegmatogenous retinal detachment	1	0.2	0	0.0
Gastrointestinal disorders	2	0.5	0	0.0
Enterocolitis	1	0.2	0	0.0
Haemorrhoids	1	0.2	0	0.0
Infections and infestations	0	0.0	1	0.2
Severe invasive streptococcal infection	0	0.0	1	0.2
Injury, poisoning and procedural complications	0	0.0	1	0.2
Meniscus injury	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders	1	0.2	1	0.2
Osteoarthritis	1	0.2	0	0.0
Foot deformity	0	0.0	1	0.2
Nervous system disorders	1	0.2	0	0.0
Myelopathy	1	0.2	0	0.0

Analysis Set for Safety up to Day 181.
MedDRA/J (V26.0).
n = number of subjects reporting an SAE.

ARCT-021-04

No SAEs were reported following the first vaccination. One participant in Group A reported an SAE (i.e. hip fracture) following the second vaccination, three participants in Group B experienced SAEs (i.e. cholecystitis, small intestinal obstruction and atrial fibrillation) and one participant in Group C experienced an SAE (i.e. chronic lymphocytic leukaemia). One participant in Group D (placebo) experienced a related SAE (i.e. ischemic stroke). Following the booster vaccination, one participant had an SAE (i.e. urticaria).

Other studies

In study ARCT-021-01 one SAE (cellulitis, related to an insect bite) occurred in a placebo recipient. In ARCT-021-02 one participant experienced a SAE (ischemic stroke), which was judged as unlikely related by the investigator and not related by the sponsor. In Study ARCT-165-01, one SAE (depression) occurred, assessed as unrelated.

Death

In ARCT-154-01 phase 3, 5 participants died in the ARCT-154 group from Day 1 to Day 92. (PT: hypoglycaemia, pancreatitis, COVID-19, lung neoplasm malignant, pharyngeal cancer metastatic). Sixteen participants died in the placebo group in the same period. From Day 1 to Day 210, one death was reported in Phase 1/2/3a study participants. From Day 92 to Day 210 in Phase 3b study, 9/7458 (0.1%) deaths were reported in participants who received placebo as dose 3 and dose 4 and in 4/7349 (0.1%) participants who received ARCT-154 as dose 3 and dose 4. Seven participants had AE onset leading to death >Day 210. None of the death were considered to be related to the study vaccine.

Deaths from day 1 to day 92 in ARCT-154-01 Phase 3b are shown in Table 43.

Table 43: AEs with Outcome of Death from Day 1 to Day 92, Switchover, or Further Study Vaccine (Phase 3b, SAS) by SOC and PT

MedDRA SOC MedDRA PT	ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	N	(%)
Participants with any AE with outcome of death	5	(0.1)	16	(0.2)
Blood and lymphatic system disorders	0	(0.0)	1	(0.0)
Lymphadenopathy	0	(0.0)	1	(0.0)
Endocrine disorders	1	(0.0)	0	(0.0)
Hypoglycaemia	1	(0.0)	0	(0.0)
Gastrointestinal disorders	1	(0.0)	0	(0.0)
Pancreatitis	1	(0.0)	0	(0.0)
Hepatobiliary disorders	0	(0.0)	1	(0.0)
Hepatic cirrhosis	0	(0.0)	1	(0.0)
Infections and infestations	1	(0.0)	12	(0.1)
COVID-19	1	(0.0)	9	(0.1)
Pneumonia	0	(0.0)	1	(0.0)
Pneumonia acinetobacter	0	(0.0)	1	(0.0)
Septic shock	0	(0.0)	1	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.0)	1	(0.0)
Hepatic cancer	0	(0.0)	1	(0.0)
Lung neoplasm malignant	1	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	1	(0.0)	0	(0.0)
Pharyngeal cancer metastatic	1	(0.0)	0	(0.0)
Vascular disorders	0	(0.0)	1	(0.0)
Aortic dissection	0	(0.0)	1	(0.0)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; n, number of participants contributing to the summary; N, number of participants receiving study vaccine; PT, preferred term; SAS, Safety Analysis Set; SOC, system organ class.
Note: MedDRA Version 24.0 was used.

In the other studies no participants died.

Medically attended adverse events (MAAE)

Participants with at least one MAAE were 12.1% in ARCT-154 and 14.6% in Placebo. For Phase 3b study, the incidence of MAAEs was generally comparable for ARCT-154 versus placebo overall at the SOC and PT level, with some exceptions: The SOC of infections and infestations, where the most common MAAE in both groups was COVID-19, which was more frequent in the placebo group (6.8%) than the ARCT-154 group (3.3%). More MAAE of pyrexia occurred in ARCT-154 group than in Placebo (20 participants vs 10 participants), backpain (22 participants vs 12 participants) and hypertension (96 participants vs 75 participants). No events of myocarditis or pericarditis were reported.

The most common related MAAEs were categorised under SOCs vascular disorders (0.4% ARCT-154 and 0.3% placebo), mostly explained by the PT hypertension, musculoskeletal and connective tissue

disorders (0.2% in each group), general disorders and administration site conditions (0.2% in each group), and nervous system disorders (0.2% ARCT-154 and 0.1% placebo) mostly the PT headache.

MAAEs from Day 92 to Day 210 were similar in pattern and frequency to MAAEs from Day 1 to Day 92.

Adverse events of special interest (AESIs)

The applicant stated that no AESIs were identified for the studies of ARCT-021 and ARCT-154. Based on the identified and potential risks for other COVID-19 vaccines, the following events have been evaluated in this application:

- Myocarditis or pericarditis: No myocarditis or pericarditis events were reported in any studies. Chest pain occurred in some participants in ARCT-154-01, Phase 3, and the incidence was higher in male participants n=4 after first dose and n=6 after second dose, compared to placebo with one participant after each dose. None of these events were related to myocarditis or pericarditis. Based on previous experience with other vaccines against COVID-19 employing a similar technology a warning about the potential risk of myocarditis and pericarditis in section 4.4 of the SmPC was added.

- Vaccine-associated enhanced disease: No vaccine-associated enhanced disease including VAERD events were identified by the Safety Review Committee and/or Data and Safety Monitoring Board. No increase in severity of COVID-19 was observed in the pivotal ARCT-154-01 study or in any of the other studies.

- Anaphylaxis**:** in Study ARCT-154-01, a total of 1 SAEs of anaphylactic reactions and 7 SAEs of hypersensitivity related reactions were reported in the study in the ARCT-154 group. Anaphylaxis and hypersensitivity are added separately in section 4.8 of the SmPC and mentioned in section 4.4.

- Bell's Palsy/Neuropathy: in Study ARCT-154-01, 2 cases of facial paralysis occurred approximately 2 months after the second dose of placebo. Both events were assessed as non-related due to temporal implausibility.

- Thromboembolic events: among the 12 thromboembolic events reported in all studies within 28 days after any study vaccination, 6 events were reported after the study vaccine (5 events after ARCT-154 in study ARCT-154-01 and one event after ARCT-021 in study ARCT-021-02) and 6 events were reported after controls (5 events after placebo dose and 1 event after ChAdOx-1S comparator vaccine in study ARCT-154-01). Also, no specific time pattern was found within the 28 days. As such, no imbalance in the number of cases per group was observed. Most of the 12 participants had risk factors for thromboembolic events such as hypertension, type II diabetes, dyslipidemia, previous episodes of cerebral infarction or traumatic brain injury, smoking. Of the 6 thromboembolic events attributed to LUNAR-COV19 vaccines, 4 were categorized as severe, 1 as moderate, and 1 as mild in severity. Among the 6 events, two participants recovered with sequela, and 1 event had a fatal outcome (see section 2.5.9.). Two events (cerebral infarction and DVT) were assessed as related, whereas and one event in the placebo group was assessed as related by investigators.

2.5.8.4. Laboratory findings

No laboratory assessments were performed in Phase 2, 3a, or 3b of the ARCT-154-01 study.

In studies ARCT-021-01 and ARCT-021-02, transient changes in neutrophil and lymphocyte count (≤Grade 3 lymphopenia and <Grade 2 neutropenia) were observed.

Besides of the above, no notable median changes over time for any of the variables (i.e. alkaline phosphatase, ALAT, ASAT, bilirubin, creatinine, GGT) were observed in ARCT-154-01 phase 1.

However, three participants had high bilirubin at Day 29 in the ARCT-154 compared to none in the placebo group.

In study ARCT-154-J01, clinical laboratory test results (i.e. AST, ALT, CPK, LDH, and Troponin) on Day 1 and Day 29 and proportions of subjects with high cardiac related enzyme values were similar in both groups. But more participants had high ALT and AST values in the ARCT-154 group both at Day 1 and Day 29. One Grade 3 unsolicited AE of increase in ALT and AST on Day 29 post-vaccination was deemed to be related to the study vaccine by the investigator.

Overall, there were no findings regarding vital signs, physical examination and electrocardiograms that suggest a safety concern due to ARCT-154 during clinical studies.

Vital signs, physical findings

Overall, there were no findings regarding vital signs, that suggest a safety concern due to ARCT-154 during clinical studies.

In Study ARCT-154-J01, no physical examination findings were reported as clinically significant by the investigators. In Study ARCT-154-01, physical examination data was collected but not analysed.

ECGs were only performed in the ARCT-021-01 and in ARCT-154-J01. In these studies, no ECG findings were reported as clinically significant by the investigators.

2.5.8.5. Safety in special populations

Elderly

For study ARCT-154-01 Phase 3b solicited AEs (within 7 Days) for participants <60 years and ≥ 60 years were provided. Around 1400 participants were > the age of 60 years. More Local AEs occurred in the participants < 60 years (55.4%) compared to participants ≥ 60 years (38.4%) after first and second dose of ARCT-154. Also, systemic AEs occurred more often in the younger population (63.3%) compared with participants ≥ 60 years (48.2%), similar to what is seen in other COVID-RNA vaccines.

Unsolicited AEs up to 28 days after dose 1 and dose 2 were generally similar between younger population compared to participants ≥ 60 years. The most common (≥1% of participants in either group) unsolicited AEs in ARCT-154 group were the following hypertension, headache, influenza, and tachycardia after first dose. After second dose the most common (≥1% of participants in either group) unsolicited AEs were hypertension, headache, and influenza. Tachycardia occurred in more participants > 60 years (1.7%) than in participants < 60 years (0.6%). Hypertension occurred in more participants > 60 years (4.1%) than in participants < 60 years (2.6%), after first dose. These tendencies were less pronounced after second dose.

For participants <65 years, 65-74 years, 75-84 years and > 85 years for both solicited and unsolicited AEs per treatment group, no notable differences were observed across the different age subgroups. In the ARCT-154-J01 study (booster) only 12 participants were > 65 years of age. No trends were present for increase in unsolicited AEs in participants above 65 years of age.

In study ARCT-021-04, incidences of unsolicited AEs were generally similar between age cohorts (only <56 and >56 years are provided). For this cohort limited information are available for adults > 65 years.

Incidences of solicited AEs for study ARCT-154-01 Phase 3b are shown in Table 44.

Table 44: Overall Summary of Unsolicited ARs up to 28 days following Each Vaccination (Dose 1 and Dose 2) by Age Group (Phase 3b, SAS) (ARCT-154-01)

Category	Dose 1		Dose 2	
	ARCT-154 (N=8059)	Placebo (N=8041)	ARCT-154 (N=8039)	Placebo (N=8021)
	n (%)	N (%)	n (%)	n (%)
Age Group ≥18 to <60 Years Old				
Participants who received study vaccine	6656	6643	6497	6474
Participants with at least 1 AE	918 (13.8)	908 (13.7)	911 (14.0)	1033 (16.0)
Related AEs	161 (2.4)	146 (2.2)	102 (1.6)	87 (1.3)
AE by worst severity				
Mild	626 (9.4)	629 (9.5)	554 (8.5)	668 (10.3)
Moderate	284 (4.3)	267 (4.0)	345 (5.3)	356 (5.5)
Severe	8 (0.1)	12 (0.2)	12 (0.2)	9 (0.1)
MAAEs	190 (2.9)	190 (2.9)	303 (4.7)	351 (5.4)
Related MAAEs	43 (0.6)	30 (0.5)	34 (0.5)	17 (0.3)
SAEs	28 (0.4)	33 (0.5)	31 (0.5)	39 (0.6)
Related SAEs	3 (0.0)	1 (0.0)	5 (0.1)	0 (0.0)
AE leading to premature discontinuation of study vaccine	2 (0.0)	3 (0.0)	4 (0.1)	0 (0.0)
AE leading to withdrawal from study	1 (0.0)	3 (0.0)	3 (0.0)	3 (0.0)
AE with death as an outcome	1 (0.0)	2 (0.0)	1 (0.0)	0 (0.0)
AE with COVID-related death as an outcome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age Group ≥60 Years Old				
Participants who received study vaccine	1403	1398	1370	1348
Participants with at least 1 AE	207 (14.8)	193 (13.8)	185 (13.5)	208 (15.4)
Related AEs	41 (2.9)	38 (2.7)	28 (2.0)	20 (1.5)
AE by worst severity				
Mild	141 (10.0)	138 (9.9)	111 (8.1)	112 (8.3)
Moderate	64 (4.6)	49 (3.5)	73 (5.3)	88 (6.5)
Severe	2 (0.1)	6 (0.4)	1 (0.1)	8 (0.6)
MAAEs	36 (2.6)	42 (3.0)	56 (4.1)	67 (5.0)

Table 45: Overall Summary of Unsolicited ARs up to 28 days following Each Vaccination (Dose 1 and Dose 2) by Age Group (Phase 3b, SAS) (ARCT-154-01)

Category	Dose 1		Dose 2	
	ARCT-154 (N=8059)	Placebo (N=8041)	ARCT-154 (N=8039)	Placebo (N=8021)
	n (%)	N (%)	n (%)	n (%)
Related MAAEs	13 (0.9)	11 (0.8)	1 (0.1)	3 (0.2)
SAEs	10 (0.7)	15 (1.1)	9 (0.7)	22 (1.6)
Related SAEs	2 (0.1)	4 (0.3)	1 (0.1)	0 (0.0)
AE leading to premature discontinuation of study vaccine	1 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)
AE leading to withdrawal from study	1 (0.1)	2 (0.1)	0 (0.0)	2 (0.1)
AE with death as an outcome	1 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)
AE with COVID-related death as outcome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Abbreviations: AE, adverse event; COVID, coronavirus disease; MAAE, medically attended adverse event; n, number of participants contributing to the summary; N, total number of participants in each column; SAE, serious adverse event; SAS, Safety Analysis Set.

Note: Percentages are computed based on the number of participants in Safety Analysis Set who received study vaccine in the specified period.

Note: For very low numbers of AEs, rounding in calculations of percentage created "0.0%" with some nonzero numbers.

Note: For participants who received a nonstudy vaccine, safety data are presented prior to the time of receipt of the nonstudy vaccine.

Note: If a participant experienced more than 1 event in a given category, that participant is counted only once in that category.

Note: At each level of summation (relationship, severity), participants reporting more than one AE are counted only once using the strongest relationship to study vaccine and the greatest severity.

Note: Unsolicited events include solicited events that were ongoing > 7 days after injection.

Solicited AEs by age group for study ARCT-154-01 Phase 3b are shown in Table 46

Table 46: Study ARCT-154-01 Phase 3b – Local and Systemic Solicited AE (Dose 1 or 2), by Grade and by Age Group, per Treatment Group

		<65 years		65-74 years		75-84 years		≥85 years	
Reaction	**Grade**	**ARCT-154 (Initial) (N=7525) n (%)**	**Placebo (Initial) (N=7517) n (%)**	**ARCT-154 (Initial) (N=483) n (%)**	**Placebo (Initial) (N=468) n (%)**	**ARCT-154 (Initial) (N=49) n (%)**	**Placebo (Initial) (N=52) n (%)**	**ARCT-154 (Initial) (N=2) n (%)**	**Placebo (Initial) (N=4) n (%)**
Any Local or Systemic	Mild	4202 (55.8%)	2954 (39.3%)	244 (50.5%)	153 (32.7%)	28 (57.1%)	16 (30.8%)	-	1 (25.0%)
	Moderate	864 (11.5%)	351 (4.7%)	26 (5.4%)	13 (2.8%)	3 (6.1%)	1 (1.9%)	-	-
	Severe	235 (3.1%)	52 (0.7%)	2 (0.4%)	3 (0.6%)	-	-	-	1 (25.0%)
Any Local Reaction	Mild	3569 (47.4%)	1109 (14.8%)	173 (35.8%)	47 (10.0%)	20 (40.8%)	5 (9.6%)	-	1 (25.0%)
	Moderate	341 (4.5%)	43 (0.6%)	3 (0.6%)	1 (0.2%)	1 (2.0%)	-	-	-
	Severe	47 (0.6%)	1 (0.0%)	-	-	-	-	-	-
Injection Site Erythema	Mild	92 (1.2%)	21 (0.3%)	3 (0.6%)	-	-	-	-	-
	Moderate	5 (0.1%)	2 (0.0%)	1 (0.2%)	-	-	-	-	-
	Severe	1 (0.0%)	-	-	-	-	-	-	-
Injection Site Induration/Swelling	Mild	224 (3.0%)	33 (0.4%)	8 (1.7%)	-	-	-		1 (25.0%)
	Moderate	32 (0.4%)	3 (0.0%)	-	-	-	-	-	-
	Severe	3 (0.0%)	-	-	-	-	-	-	-
Injection Site Pain	Mild	3274 (43.5%)	923 (12.3%)	156 (32.3%)	38 (8.1%)	19 (38.8%)	5 (9.6%)	-	-
	Moderate	237 (3.1%)	26 (0.3%)	2 (0.4%)	1 (0.2%)	1 (2.0%)	-	-	-
	Severe	34 (0.5%)	-	-	-	-	-	-	-
Injection Site Tenderness	Mild	3197 (42.5%)	838 (11.1%)	141 (29.2%)	33 (7.1%)	12 (24.5%)	3 (5.8%)	-	-
	Moderate	263 (3.5%)	28 (0.4%)	2 (0.4%)	1 (0.2%)	1 (2.0%)	-	-	-
	Severe	36 (0.5%)	1 (0.0%)	-	-	-	-	-	-
Any Systemic	Mild	3614 (48.0%)	2675 (35.6%)	198 (41.0%)	139 (29.7%)	22 (44.9%)	14 (26.9%)	-	1 (25.0%)
	Moderate	735 (9.8%)	327 (4.4%)	24 (5.0%)	12 (2.6%)	2 (4.1%)	1 (1.9%)	-	-
	Severe	210 (2.8%)	52 (0.7%)	2 (0.4%)	3 (0.6%)	-	-	-	1 (25.0%)
Fever (>=38 °C)	Mild	521 (6.9%)	127 (1.7%)	15 (3.1%)	6 (1.3%)	1 (2.0%)	1 (1.9%)	-	-
	Moderate	167 (2.2%)	31 (0.4%)	5 (1.0%)	1 (0.2%)	1 (2.0%)	-	-	-
	Severe	111 (1.5%)	23 (0.3%)	1 (0.2%)	-	-	-	-	-
Arthralgia	Mild	1684 (22.4%)	1105 (14.7%)	83 (17.2%)	61 (13.0%)	8 (16.3%)	7 (13.5%)	-	1 (25.0%)
	Moderate	226 (3.0%)	113 (1.5%)	8 (1.7%)	10 (2.1%)	-	-	-	1 (25.0%)
	Severe	39 (0.5%)	7 (0.1%)	-	-	-	-	-	-
Chills	Mild	1813 (24.1%)	742 (9.9%)	61 (12.6%)	22 (4.7%)	7 (14.3%)	2 (3.8%)	-	1 (25.0%)
	Moderate	247 (3.3%)	43 (0.6%)	3 (0.6%)	2 (0.4%)	-	-	-	-
	Severe	31 (0.4%)	3 (0.0%)	-	2 (0.4%)	-	-	-	-
Diarrhea	Mild	388 (5.2%)	295 (3.9%)	11 (2.3%)	11 (2.4%)	-	-	-	-
	Moderate	34 (0.5%)	30 (0.4%)	3 (0.6%)	-	-	-	-	-
	Severe	3 (0.0%)	4 (0.1%)	1 (0.2%)	-	-	-	-	-
Dizziness	Mild	1302 (17.3%)	859 (11.4%)	63 (13.0%)	39 (8.3%)	8 (16.3%)	2 (3.8%)	-	1 (25.0%)
	Moderate	128 (1.7%)	56 (0.7%)	3 (0.6%)	3 (0.6%)	-	-	-	1 (25.0%)
	Severe	18 (0.2%)	5 (0.1%)	-	1 (0.2%)	-	-	-	-

		<65 years		65-74 years		75-84 years		≥85 years	
Reaction	**Grade**	**ARCT-154 (Initial) (N=7525) n (%)**	**Placebo (Initial) (N=7517) n (%)**	**ARCT-154 (Initial) (N=483) n (%)**	**Placebo (Initial) (N=468) n (%)**	**ARCT-154 (Initial) (N=49) n (%)**	**Placebo (Initial) (N=52) n (%)**	**ARCT-154 (Initial) (N=2) n (%)**	**Placebo (Initial) (N=4) n (%)**
Fatigue	Mild	2583 (34.3%)	1555 (20.7%)	127 (26.3%)	70 (15.0%)	16 (32.7%)	5 (9.6%)	-	1 (25.0%)
	Moderate	364 (4.8%)	109 (1.5%)	2 (0.4%)	6 (1.3%)	-	-	-	-
	Severe	51 (0.7%)	11 (0.1%)	-	1 (0.2%)	-	-	-	1 (25.0%)
Headache	Mild	2247 (29.9%)	1452 (19.3%)	102 (21.1%)	63 (13.5%)	9 (18.4%)	8 (15.4%)	-	-
	Moderate	288 (3.8%)	129 (1.7%)	3 (0.6%)	4 (0.9%)		-	-	1 (25.0%)
	Severe	42 (0.6%)	8 (0.1%)	-	1 (0.2%)		-	-	-
Myalgia	Mild	1891 (25.1%)	933 (12.4%)	77 (15.9%)	50 (10.7%)	11 (22.4%)	6 (11.5%)	-	1 (25.0%)
	Moderate	214 (2.8%)	59 (0.8%)	4 (0.8%)	4 (0.9%)	1 (2.0%)	-	-	-
	Severe	20 (0.3%)	3 (0.0%)	-	1 (0.2%)	-	-	-	1 (25.0%)
Nausea	Mild	346 (4.6%)	229 (3.0%)	11 (2.3%)	6 (1.3%)	-	-	-	1 (25.0%)
	Moderate	35 (0.5%)	18 (0.2%)	1 (0.2%)	2 (0.4%)	-	1 (1.9%)	-	-
	Severe	1 (0.0%)	1 (0.0%)	-	-	-	-	-	-
Vomiting	Mild	138 (1.8%)	74 (1.0%)	6 (1.2%)	-	-	-	-	-
	Moderate	13 (0.2%)	7 (0.1%)	-	1 (0.2%)	-	-	-	-
	Severe	1 (0.0%)	-	-	1 (0.2%)	-	-	-	-

Abbreviations: AE, adverse event; N, number of participants receiving treatment; number of participants with event.

Unsolicited AES by age group is provided in Table 47:

Table 47: ARCT-154-01 Unsolicited AEs by Age Group (Day 1 – Day 92), per Treatment Group

	< 65 Years		65 - 74 Years		75 - 84 Years		>= 85 Years	
Parameters	**ARCT-154 (Initial) (N = 7525)**	**Placebo (Initial) (N = 7517)**	**ARCT-154 (Initial) (N = 483)**	**Placebo (Initial) (N = 468)**	**ARCT-154 (Initial) (N = 49)**	**Placebo (Initial) (N = 52)**	**ARCT-154 (Initial) (N = 2)**	**Placebo (Initial) (N = 4)**
Number of participants, n (%)	7525 (100.00%)	7517 (100.00%)	483 (100.00%)	468 (100.00%)	49 (100.00%)	52 (100.00%)	2 (100.00%)	4 (100.00%)
Number of Total Adverse Events	3631	3932	193	207	23	19	1	6
Number of Total Serious Adverse Events	110	177	12	30	2	2	-	1
Participants with Serious Adverse Events, n (%)	105 (1.40%)	175 (2.33%)	12 (2.48%)	23 (4.91%)	2 (4.08%)	2 (3.85%)	-	1 (25.00%)
- Fatal, n (%)	3 (0.04%)	12 (0.16%)	1 (0.21%)	4 (0.85%)	1 (2.04%)	-	-	-
- Requires or Prolongs Hospitalization, n (%)	104 (1.38%)	173 (2.30%)	12 (2.48%)	22 (4.70%)	2 (4.08%)	2 (3.85%)	-	1 (25.00%)
- Is Life Threatening, n (%)	1 (0.01%)	1 (0.01%)	-	1 (0.21%)	-	-	-	-
- Persist or Signif Disability/Incapacity, n (%)	-	-	-	-	-	-	-	-
- Congenital Anomaly or Birth Defect, n (%)	-	-	-	-	-	-	-	-
- Other Medically Important Serious Event, n (%)	1 (0.01%)	1 (0.01%)	-	-	-	-	-	-
AE leading to drop out, n (%)[a]	4 (0.05%)	13 (0.17%)	1 (0.21%)	4 (0.85%)	1 (2.04%)	-	-	-
Psychiatric disorders, n (%)[b]	29 (0.39%)	17 (0.23%)	3 (0.62%)	2 (0.43%)	-	-	-	1 (25.00%)
Nervous system disorders, n (%)[b]	344 (4.57%)	358 (4.76%)	9 (1.86%)	9 (1.92%)	2 (4.08%)	-	-	-
Accidents and injuries, n (%)[c]	55 (0.73%)	66 (0.88%)	1 (0.21%)	-	1 (2.04%)	-	-	-
Cardiac disorders, n (%)[b]	288 (3.83%)	254 (3.38%)	22 (4.55%)	22 (4.70%)	4 (8.16%)	5 (9.62%)	1 (50.00%)	-
Vascular disorders, n (%)[b]	593 (7.88%)	594 (7.90%)	56 (11.59%)	40 (8.55%)	4 (8.16%)	4 (7.69%)	-	-
Cerebrovascular disorder, n (%)[d]	7 (0.09%)	2 (0.03%)	-	-	-	-	-	-
Infections and infestations, n (%)[b]	728 (9.67%)	995 (13.24%)	25 (5.18%)	36 (7.69%)	2 (4.08%)	3 (5.77%)	-	1 (25.00%)

	< 65 Years		65 - 74 Years		75 - 84 Years		>= 85 Years	
Parameters	**ARCT-154 (Initial) (N = 7525)**	**Placebo (Initial) (N = 7517)**	**ARCT-154 (Initial) (N = 483)**	**Placebo (Initial) (N = 468)**	**ARCT-154 (Initial) (N = 49)**	**Placebo (Initial) (N = 52)**	**ARCT-154 (Initial) (N = 2)**	**Placebo (Initial) (N = 4)**
Anticholinergic syndrome, n (%)[e]	-	-	-	-	-	-	-	-
Sum of postural hypotension/falls/black outs/syncope/dizziness/ataxia/fractures, n (%)[f]	3 (0.04%)	6 (0.08%)	1 (0.21%)	-	-	-	-	-
Other AE appearing more frequently in older patients, n (%)[g]	574 (7.63%)	578 (7.69%)	54 (11.18%)	39 (8.33%)	4 (8.16%)	4 (7.69%)	-	-

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in group; n, number of participants with event; SMQ, standardised MedDRA query.

[a] Not collected in the study.

[b] Data were based on Body System or Organ Class.

[c] Selected using preferred terms specified for narrow range in Accidents and injuries (SMQ).

[d] Selected using preferred term: Cerebrovascular disorder.

[e] Selected using preferred term: Anticholinergic syndrome.

[f] Selected using preferred terms: Orthostatic hypotension, Fall, Syncope, Loss of consciousness, Dizziness, Ataxia, Fracture bone, Fracture.

[g] Selected using preferred terms: Osteoporosis, Hypertension, Hypercholesterolaemia, Diabetes mellitus.

Note: Percentage is based on Column Total.

Risk group

In ARCT-154-01 phase 3b, solicited AEs (local and systemic) within 7 days after dose 1 and dose 2 were generally higher for participants <60 years old and "Healthy" than in participants <60 years old and "At risk" group and, than in participants ≥60 years. This was mainly driven by injection site tenderness and injection site pain as well as by the systemic AEs of fatigue, headache, myalgia, and chills. Standardized MedDRA queries were used to select populations with significant cardiovascular conditions, diabetes and obesity, liver diseases, COPD, and asthma. The chosen SMQs and PTs were meaningful for reflecting underlying disease. Overall, a minor proportion of the examined participants had significant underlying conditions. In total, 485 participants (5.5%) in study ARCT-154-01 Phases 1/2/3a/3b, 129 participants (10.9%) in study ARCT-154-01 Phase 3c, and 40 participants (9.5%) in study ARCT-154-J01.

Overall unsolicited AEs, severe AEs, SAEs, AEs leading to premature discontinuation of vaccine was similar among the 3 risk group categories. Incidence of AEs by PT were generally similar across the 3 risk groups, with slightly higher incidence in participants ≥ 60 years of age (14.8%) compared to 13,5% in the group < 60 years and "healthy". In the subgroup analysis between participants with underlying medical conditions (corresponding to an 'at risk' population in the EU) and the overall population indicate that the safety profile in a population with these medical conditions is consistent with that of the overall population.

Solicited AEs in participant "at risk" in study ARCT-154-01 Phase 3b are shown in Table 48 and Table 49.

Table 48: Solicited AEs Within 7 Days After Dose 1 and Dose 2 by Risk Group (Phase 3b, RAS) (ARCT-154-01)

Category Event	ARCT-154 (Initial) (N=8059)	Placebo (Initial) (N=8041)
	n (%) / nm	n (%) / nm
Risk Group ≥18 to <60 Years Old and "Healthy"		
Any solicited AE	2921 (77.2) / 3785	1858 (49.2) / 3775
Local	2272 (60.0) / 3785	661 (17.5) / 3775
Injection site erythema	57 (1.5) / 3785	13 (0.3) / 3775
Injection site induration/swelling	148 (3.9) / 3785	19 (0.5) / 3775
Injection site pain	2045 (54.0) / 3785	536 (14.2) / 3775
Injection site tenderness	2016 (53.3) / 3785	511 (13.5) / 3775
Systemic	2563 (67.7) / 3785	1689 (44.7) / 3775
Fever (≥38°C)	459 (12.1) / 3785	99 (2.6) / 3775
Nausea	281 (7.4) / 3785	172 (4.6) / 3775
Vomiting	104 (2.7) / 3785	48 (1.3) / 3775
Diarrhea	245 (6.5) / 3785	179 (4.7) / 3775
Headache	1587 (41.9) / 3785	947 (25.1) / 3775
Fatigue	1731 (45.7) / 3785	949 (25.1) / 3775
Myalgia	1244 (32.9) / 3785	564 (14.9) / 3775
Arthralgia	1097 (29.0) / 3785	666 (17.6) / 3775
Chills	1237 (32.7) / 3785	452 (12.0) / 3775
Dizziness	882 (23.3) / 3785	547 (14.5) / 3775
Risk Group ≥18 to <60 Years Old and "At Risk"		
Any solicited AE	1870 (67.7) / 2762	1131 (41.2) / 2747
Local	1353 (49.0) / 2762	388 (14.1) / 2747
Injection site erythema	29 (1.0) / 2762	9 (0.3) / 2747
Injection site induration/swelling	92 (3.3) / 2762	17 (0.6) / 2747
Injection site pain	1208 (43.7) / 2762	321 (11.7) / 2747

Table 49: Solicited AEs Within 7 Days After Dose 1 and Dose 2 by Risk Group (Phase 3b, RAS) (ARCT-154-01

Category Event	ARCT-154 (Initial) (N=8059)	Placebo (Initial) (N=8041)
	n (%) / nm	n (%) / nm
Injection site tenderness	1196 (43.3) / 2762	288 (10.5) / 2747
Systemic	1579 (57.2) / 2762	1022 (37.2) / 2747
Fever (≥38°C)	274 (9.9) / 2762	60 (2.2) / 2747
Nausea	77 (2.8) / 2762	59 (2.1) / 2747
Vomiting	38 (1.4) / 2762	26 (0.9) / 2747
Diarrhea	141 (5.1) / 2762	126 (4.6) / 2747
Headache	791 (28.6) / 2762	495 (18.0) / 2747
Fatigue	1018 (36.9) / 2762	556 (20.2) / 2747
Myalgia	713 (25.8) / 2762	342 (12.4) / 2747
Arthralgia	651 (23.6) / 2762	415 (15.1) / 2747
Chills	734 (26.6) / 2762	275 (10.0) / 2747
Dizziness	441 (16.0) / 2762	293 (10.7) / 2747
Risk Group ≥60 Years Old		
Any solicited AE	813 (58.9) / 1380	555 (40.7) / 1364
Local	530 (38.4) / 1380	159 (11.7) / 1364
Injection site erythema	16 (1.2) / 1380	2 (0.1) / 1364
Injection site induration/swelling	29 (2.1) / 1380	2 (0.1) / 1364
Injection site pain	470 (34.1) / 1380	136 (10.0) / 1364
Injection site tenderness	440 (31.9) / 1380	104 (7.6) / 1364
Systemic	665 (48.2) / 1380	513 (37.6) / 1364
Fever (≥38°C)	85 (6.2) / 1380	29 (2.1) / 1364
Nausea	36 (2.6) / 1380	27 (2.0) / 1364
Vomiting	16 (1.2) / 1380	9 (0.7) / 1364
Diarrhea	53 (3.8) / 1380	35 (2.6) / 1364
Headache	313 (22.7) / 1380	223 (16.3) / 1364
Fatigue	395 (28.6) / 1380	253 (18.5) / 1364
Myalgia	261 (18.9) / 1380	152 (11.1) / 1364
Arthralgia	301 (21.8) / 1380	224 (16.4) / 1364
Chills	190 (13.8) / 1380	90 (6.6) / 1364
Dizziness	198 (14.3) / 1380	128 (9.4) / 1364

Abbreviations: AE, adverse event; n, number of participants contributing to the summary; N, total number of participants in each column; nm, number of participants with an available answer to the reaction category after the dose; RAS, Reactogenicity Analysis Set.

Note: Percentages are computed based on the number of participants with an available answer to the reaction category after the dose.

Note: If a participant experienced more than 1 event in a given category, that participant was counted only once in that category.

Note: Any reactions occurring after dose 1 and/or dose 2 are considered.

Unsolicited AEs by risk group in study ARCT-154-01 Phase 3b are shown in Table 50.

Table 50: Overall Summary of Unsolicited AEs Within 28 Days After Dose 1 and Dose 2 by Risk Group (Phase 3b, SAS) (ARCT-154-01)

Category	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)	n	(%)	n	(%)
Risk Group ≥18 to <60 Years Old and "Healthy"								
Participants who received study vaccine	3841		3835		3753		3751	
AEs	520	(13.5)	536	(14.0)	546	(14.5)	623	(16.6)
Related AEs	91	(2.4)	75	(2.0)	57	(1.5)	55	(1.5)
AE by worst severity								
Mild	338	(8.8)	365	(9.5)	320	(8.5)	399	(10.6)
Moderate	178	(4.6)	166	(4.3)	222	(5.9)	221	(5.9)
Severe	4	(0.1)	5	(0.1)	4	(0.1)	3	(0.1)
MAAEs	114	(3.0)	100	(2.6)	181	(4.8)	216	(5.8)
Related MAAEs	32	(0.8)	15	(0.4)	24	(0.6)	11	(0.3)
SAEs	20	(0.5)	15	(0.4)	13	(0.3)	20	(0.5)
Related SAEs	3	(0.1)	0	(0.0)	3	(0.1)	0	(0.0)
AEs leading to premature discontinuation of vaccine	2	(0.1)	1	(0.0)	2	(0.1)	0	(0.0)
AE leading to withdrawal from study	1	(0.0)	0	(0.0)	2	(0.1)	3	(0.1)
AE with death as an outcome	1	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
AE with COVID-related death as outcome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Category	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)	n	(%)	n	(%)
Risk Group ≥18 to <60 Years Old and "At Risk"								
Participants who received study vaccine	2815		2808		2744		2723	
AEs	398	(14.1)	372	(13.2)	365	(13.3)	410	(15.1)
Related AEs	70	(2.5)	71	(2.5)	45	(1.6)	32	(1.2)
AE by worst severity								
Mild	288	(10.2)	264	(9.4)	234	(8.5)	269	(9.9)
Moderate	106	(3.8)	101	(3.6)	123	(4.5)	135	(5.0)
Severe	4	(0.1)	7	(0.2)	8	(0.3)	6	(0.2)
MAAEs	76	(2.7)	90	(3.2)	122	(4.4)	135	(5.0)
Related MAAEs	11	(0.4)	15	(0.5)	10	(0.4)	6	(0.2)
SAEs	8	(0.3)	18	(0.6)	18	(0.7)	19	(0.7)
Related SAEs	0	(0.0)	1	(0.0)	2	(0.1)	0	(0.0)
AEs leading to premature discontinuation of vaccine	0	(0.0)	2	(0.1)	2	(0.1)	0	(0.0)
AE leading to withdrawal from study	0	(0.0)	3	(0.1)	1	(0.0)	0	(0.0)
AE with death as an outcome	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
AE with COVID-related death as outcome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Risk Group ≥60 Years Old								
Participants who received study vaccine	1403		1398		1370		1348	
AEs	207	(14.8)	193	(13.8)	185	(13.5)	208	(15.4)
Related AEs	41	(2.9)	38	(2.7)	28	(2.0)	20	(1.5)
AE by worst severity								
Mild	141	(10.0)	138	(9.9)	111	(8.1)	112	(8.3)
Moderate	64	(4.6)	49	(3.5)	73	(5.3)	88	(6.5)
Severe	2	(0.1)	6	(0.4)	1	(0.1)	8	(0.6)
MAAEs	36	(2.6)	42	(3.0)	56	(4.1)	67	(5.0)
Related MAAEs	13	(0.9)	11	(0.8)	1	(0.1)	3	(0.2)
SAEs	10	(0.7)	15	(1.1)	9	(0.7)	22	(1.6)
Related SAEs	2	(0.1)	4	(0.3)	1	(0.1)	0	(0.0)

Category	Dose 1				Dose 2			
	ARCT-154 (N=8059)		Placebo (N=8041)		ARCT-154 (N=8059)		Placebo (N=8041)	
	n	(%)	n	(%)	n	(%)	n	(%)
AEs leading to premature discontinuation of vaccine	1	(0.1)	2	(0.1)	0	(0.0)	0	(0.0)
AE leading to withdrawal from study	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)
AE with death as an outcome	1	(0.1)	2	(0.1)	0	(0.0)	1	(0.1)
AE with COVID-related death as outcome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)

Abbreviations: AE, adverse event; COVID, coronavirus disease; MAAE, medically attended adverse event; n, number of participants contributing to the summary; N, total number of participants in each column; SAE, serious adverse event; SAS, Safety Analysis Set.
Note: Percentages are computed based on the number of participants in Safety Analysis Set who received study vaccine in the specified period.
Note: For very low numbers of AEs, rounding in calculations of percentage created "0.0%" with some nonzero numbers.
Note: For participants who received a nonstudy vaccine, safety data are presented prior to the time of receipt of the nonstudy vaccine.
Note: If a participant experienced more than 1 event in a given category, that participant is counted only once in that category.
Note: At each level of summation (relationship, severity), participants reporting more than one AE are counted only once using the strongest relationship to study vaccine and the greatest severity.
Note: Unsolicited events include solicited events that were ongoing > 7 days after injection.

In ARCT-154-J01 studies, the incidence of solicited local adverse events and solicited systemic adverse events by category of those who requires caution for vaccination is shown in Table 51.

Table 51: Incidences of Solicited Local and Systemic Adverse Events by Category of Persons Requiring Caution for Vaccination (Analysis Set for Safety) (Study ARCT-154-J01)

		ARCT-154 (N=420)			Comirnaty (N=408)		
Category Event	Requires caution for vaccination	N	n	%	N	n	%
Solicited local adverse events	No	268	251	93.7	269	259	96.3
	Yes	152	147	96.7	139	136	97.8
Injection site erythema	No	268	33	12.3	269	51	19.0
	Yes	152	19	12.5	139	34	24.5
Injection site swelling	No	268	35	13.1	269	62	23.0
	Yes	152	24	15.8	139	35	25.2
Injection site induration	No	268	34	12.7	269	49	18.2
	Yes	152	18	11.8	139	32	23.0
Injection site tenderness	No	268	244	91.0	269	257	95.5
	Yes	152	144	94.7	139	134	96.4
Injection site pain	No	268	219	81.7	269	232	86.2
	Yes	152	133	87.5	139	126	90.6
Solicited systemic adverse events	No	268	165	61.6	269	160	59.5
	Yes	152	111	73.0	139	95	68.3
Pyrexia	No	268	49	18.3	269	45	16.7
	Yes	152	35	23.0	139	31	22.3
Arthralgia	No	268	57	21.3	269	69	25.7
	Yes	152	55	36.2	139	44	31.7
Chills	No	268	79	29.5	269	65	24.2
	Yes	152	47	30.9	139	38	27.3
Diarrhoea	No	268	13	4.9	269	10	3.7
	Yes	152	15	9.9	139	7	5.0
Dizziness	No	268	11	4.1	269	9	3.3
	Yes	152	14	9.2	139	4	2.9
Headache	No	268	100	37.3	269	82	30.5
	Yes	152	65	42.8	139	43	30.9
Malaise	No	268	112	41.8	269	112	41.6
	Yes	152	76	50.0	139	64	46.0
Nausea	No	268	8	3.0	269	8	3.0
	Yes	152	13	8.6	139	8	5.8
Vomiting	No	268	0	0.0	269	1	0.4
	Yes	152	2	1.3	139	1	0.7
Myalgia	No	268	71	26.5	269	64	23.8
	Yes	152	52	34.2	139	36	25.9

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; n, number of participants contributing to the summary; N, total number of participants in each column.
Note: MedDRA/J Version 26.0 was used.
Note: The worst severity was used for participants who experienced the same events more than once. Adverse event counts include Grade 0 reactions.

Immunodeficient

The safety of the vaccine has not been assessed in immunocompromised individuals, including those with a known diagnosis of the HIV or those receiving immunosuppressant therapy.

Sex

Solicited AEs within 7 days after dose 1 and dose 2 in the RAS were lower for male participants compared with female participants for both local and systemic solicited AEs. The same picture was seen in the placebo groups. The most common solicited AEs in participants in the ARCT-154 group were injection site pain male participants (44.8%) and female participants 49.0%), injection site tenderness (44.6% vs 47.5%), fatigue (36.3% vs 42.9%), headache (27.3% vs 40.3%) and dizziness (14.9% vs 23.3%). The reactogenicity of ARCT-154 in female is more frequently and slightly higher in severity than in male and therefore, no reflected in the SmPC.

For unsolicited AEs up to 28 days after dose 1 and dose 2 incidences were generally similar between male (13.5%, 14.6%) and female (14.4%, 15.4%) participants and there were no trends by MedDRA SOC or PT between male and female participants.

In study ARCT-154-J01, incidences of local and systemic solicited AEs were in general higher in females than in males both in ARCT-154 vaccinated and in Comirnaty vaccinated. For most of the systemic events this was highly pronounced (e.g. headache (25.6% in males vs 48.8% in females), malaise (36.6% vs 50.4%), nausea (1.2% vs 7.7%)).

Pregnancy and lactation

Experience with the use of ARCT-154 in pregnant women is limited. In total 76 pregnancies were reported in Study ARCT-154-01 up to July 2023. Before Day 92 of the study, 50 pregnancies were reported (19 cases in ARCT-154 group, 22 cases in the placebo group, and 9 cases remain blinded). After Day 92, 26 pregnancies were reported (11 in ARCT-154 group, 14 in placebo group, and 1 remains blinded). The applicant has overviewed all spontaneous abortions (miscarriage), anembryonic pregnancies, and premature births observed in all of the clinical studies. In total thirteen cases occurred, in all episodes the participant was not pregnant at time of vaccination, in one case the status was unknown. In three of the cases exposures during pregnancy could not be ruled out.

None of the SAEs were assessed as related to the study.

In the Studies ARCT-154-J01, ARCT-165-01, ARCT-021-01, ARCT-021-02, and ARCT-021-04, no pregnancies were reported.

No safety data are provided for participants who was breastfeeding after the vaccination are provided.

Ethnicity and country

An analysis of differences in AEs based on ethnicity and race was performed in study ARCT-021-04. The only study that was conducted in more than 1 country was ARCT-021-04, where around three-fourths of the participants were white. In the study, no trends occurred for solicited AEs by ethnicity and country. For non-hispanic White (US) participants and for Asian (Singapore; US) participants the majority of solicited local, and systemic AEs were mild/Grade 1 or moderate/Grade 2 for both the first and second vaccinations. Also, no trends in unsolicited AEs by ethnicity and country were apparent.

Overall, the most often solicited (local and systemic) were similar in all groups, but incidences differed. Unsolicited AEs occurred more often in the Asian Singapore population. The overall incidence of AEs was higher in study ARCT-021-04 than in ARCT-154-01 (phase 3b) where overall, unsolicited AEs occurred in 14,0% of ARCT-154 and 13.7% placebo after 1. Dose. In ARCT-021-04, overall unsolicited AEs occurred in 20.3% of the Cohort A, B and C vs 19.2% of Cohort D after first dose.

The incidences in study ARCT-021-04, ARCT-0154 (phase 1, 2, 3a) and ARCT-0154-0J were similar, which is reassuring for the incidence of reported AEs in the Vietnamese population. In ARCT-0154 (phase 1, 2, 3a), overall unsolicited AEs occurred in 23,7% of ARCT-154 and 28.1% placebo after 1. Dose. In ARCT-0154-0J, overall unsolicited AEs occurred in 19.3% of ARCT-154 and 27.3% in Comirnaty.

Anti-nucleocapsid antibodies and neutralising antibody titers

For the booster study ARCT-154-J01, solicited AEs by presence of anti-nucleocapsid antibodies and neutralising antibody titers against SARS-CoV-2 ancestral strain and Omicron BA.4/5 variant was provided.

The frequency of any local solicited AEs in negative (participants negative for NAb titres against Omicron BA.4/5) participants was lower than in participants with Nabs against Omicron BA.4/5 and the overall population (89.5% vs 96.1% vs 94.8%, respectively). For solicited systemic AEs there were no differences in frequency. The frequency of severe events was low in both subgroups. The numbers are too low to draw a meaningful conclusion. With regards to anti-nucleocapsid antibodies none of the participants in ARCT-154-01 phase 1, 2, 3a and less than 1% of the participants in phase 3b were positive at baseline (54 participants in ARCT-154 and 49 in placebo at baseline). Therefore, it is not meaningful to make a formal comparison.

Study sites

Participants with at least 1 unsolicited AE with onset during the first 28 days after dose 1 and dose 2 were comparable between ARCT-154 and placebo groups within each study site, except for one site, where 6 AEs occurred in the ARCT-154 group compared to none in the placebo group. The applicant stated that this was mainly driven by a higher rate of respiratory infections at that site.

2.5.8.6. Safety related to drug-drug interactions and other interactions

No interaction studies have been performed. Assuming that antiviral drugs with potential impact on VEEV replication might reduce the efficiency of replicase activity and considering the theoretical risk of co-administration of vaccine with interferons, the applicant proposed the inclusion of this information in SmPC section 4.5.

2.5.8.7. Discontinuation due to adverse events

AEs leading to discontinuation were not a prespecified safety evaluation in this study. However, no participants were withdrawn from the study due to AEs in either group.

In study ARCT-154-01 Phase 3b, AEs leading to discontinuation of study vaccine occurred at a low incidence 14 (0.2%) participants in the ARCT-154 group and 25 (0.3%) participants in the placebo group had at least 1 AE leading to discontinuation of study vaccine. Most of the AE causing discontinuation were serious. SAEs leading to discontinuation occurred in 9 participants in the ARCT-154 group and in 18 participants in the placebo group. The most common AE leading to discontinuation was COVID-19, with 1 participant in the ARCT-154 group and 9 participants in the placebo group. AEs in ARCT-154 group were tachycardia (2 participants), hypoglycaemia, pancreatitis, type IV hypersensitivity, urticaria, pharyngitis, lung neoplasm malignant (2 participants), cerebral infarction, pharyngeal cancer metastatic, induced abortion and hypertension.

Table 52: Overview of AEs Leading to Discontinuation from Day 1 to Day 92, Switchover, or Further Study Vaccine (Phase 3b, SAS)

Category	ARCT-154 (Initial) (N=8059)		Placebo (Initial) (N=8041)	
	n	(%)	n	(%)
Participants with at least one AE leading to discontinuation	14	(0.2)	25	(0.3)
Participants with at least one related AE leading to discontinuation	2	(0.0)	0	(0.0)
Participants with AE leading to discontinuation by worst Severity				
Mild	6	(0.1)	5	(0.1)
Moderate	1	(0.0)	3	(0.0)
Severe	7	(0.1)	17	(0.2)
Participants with at least one MAAE	10	(0.1)	20	(0.2)
Participants with at least one related MAAE	2	(0.0)	0	(0.0)
Participants with at least one SAE leading to discontinuation	9	(0.1)	18	(0.2)
Participants with at least one related SAE leading to discontinuation	2	(0.0)	0	(0.0)

2.5.8.8. Post marketing experience

There is no post-marketing data for this vaccine.

2.5.9. Discussion on clinical safety

The safety data are mainly based on data from the ARCT-154-01 study. The Phase 3b part included 16120 subjects randomised 1:1 to receive ARCT-154 vaccine or placebo. The Phase 1 study included 100 healthy participants (≥18 to <60 years old) randomised 3:1 to ARCT-154 or placebo. The Phase 2 study included 302 healthy and "at risk" adult participants randomised 3:1 to receive ARCT-154 or placebo. The Phase 3a included 600 healthy and "at risk" adult participants randomised 3:1 to ARCT-154 or placebo. In the phase 3c approximately 2,400 participants were randomised 1:1 to receive ARCT-154 or ChAdOx1.

Safety data from Phase 3b were not combined with data from Phases 1, 2, and 3a. In addition, data from phase 2/3a ARCT-154-01 are presented combined as the studied population are comparable, whereas the phase 1 study included younger healthy participants not "at risk".

Furthermore, results from ARCT-021 can be seen as supportive for the safety of the LUNAR-COV19 platform, noted is though that data are limited by numbers of participants in the ARCT-021 study and by study setups. But ARCT-021-04 included White subjects (three-fourths were White) and therefore considered supportive for the safety in a European setting. In addition, data for booster immunisation was presented (ARCT-154-J01). As a supportive study for booster immunisation, data from ARCT-165-01 was presented.

For SAS and RAS, safety data from Phases 1, 2 and 3a participants in Study ARCT-154-01 were combined, whereas safety data from Study ARCT-154-01 from Phase 3b was presented alone. This approach is acceptable for the assessment of AEs etc, but pooling is needed for AEs and frequencies in the SmPC section 4.8, where all safety data for ARCT-154 should be represented.

Definitions of AE categories

The applicant categorised AEs as solicited and unsolicited. All solicited AEs were per se considered vaccine-related AEs, in all studies, except in the booster study ARCT-154-J01, where a causality

assessment of all systemic solicited AEs was performed by the investigators. The strategy is largely endorsed.

As stated in the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) since most adverse reactions to vaccines occur within the first few days after each dose, it is common practise that solicited local and systemic symptoms are collected for approximately 5-7 days after each dose. However, a longer post-dose period of collection of solicited symptoms may be applicable for replication competent live vaccines (e.g. 10-14 days or sometimes more). Due to the self-replicating nature of Kostaive, the applicant was asked to address this and clarified that in all studies most solicited AEs occurred within the first two days after vaccination and resolved within 2-4 days, and therefore collection of solicited AEs for 7 days was adequate, which is acceptable**.**

For the analysis of Solicited AEs within 7 days after ARCT-154, administered as 2-dose primary series 28 days apart, the applicant provided the number and percentage of solicited local and systemic AEs aggregated and by specific AEs after the first and second doses separately and combined as well as, by severity.

Unsolicited AEs were defined as any spontaneously reported or discovered AE. In Study ARCT-154-01 and ARCT-154-J01 unsolicited AEs were recorded up to 28 days after each vaccination. Continuing Solicited AEs that continued after 7 days were also captured as unsolicited AEs and followed until stabilization/resolution.

As stated in the EMA considerations on COVID-19 vaccine approval (EMA/592928/2020) most adverse reactions to vaccines occur within 4-6 weeks from vaccination. As the concentration of sa-mRNA decreases over a 2-week period with only a minimum of sa-mRNA detected after 30-days, and further, as also the frequencies of unsolicited AEs were similar within 28 days after first and second dose and the second vaccination were administered on day 29, the follow-up time for unsolicited AEs is considered acceptable.

For unsolicited AEs leading to discontinuation of study vaccine/withdrawal from the study, MAAEs, and SAEs, were documented until the last study visit (i.e. 1 year after the completion of the initial vaccination series). For the long-term follow-up, it is acceptable that only SAEs and AESIs are captured. In the protocol for study ARCT-154-J01, pericarditis/ myocarditis is pre-specified as an AESI, but not in study ARCT-154-01 and ARCT-021.

Exposure

Overall, the safety package is deemed large enough for meaningful assessment and to allow an assessment of uncommon risks. However, the booster package is limited by numbers of participants, and almost no elderly participants were included.

Demographics, medical history and concomitant medication

ARCT-154-01 Phase 3b

Overall, the "at risk" population in study ARCT-154-01 phase 3b seems mainly driven by current or former smoking, cardiovascular conditions (not specified if it was significant cardiac disease) or being over the age of 60. It is agreed that conditions are well-balanced between the two treatment groups, but very few participants had diabetes, obesity, cerebrovascular disease, COPD and asthma, which is considered a safety limitation that the studied "at risk" population is not corresponding to a "at risk" population in the EU population in which the vaccine will most likely be used, e.g. in European countries diabetes occurs at frequencies of approximately one in every four adults older than 65 years of age.

The applicant clarified that 5.5% of the participants in the booster study had significant underlying disease such as significant cardiovascular conditions, diabetes and obesity, liver diseases, COPD, and asthma. Based on the data provided, though limited, it is agreed that the safety profile can be extrapolated to a population with these medical conditions for which the vaccine is likely to be used. Use in patients with significant, unstable chronic medical conditions remain as missing information in the safety specifications.

No data are available for children and adolescents, which is acceptable since the product is not proposed indicated for this population.

ARCT-154-J01

Based on the outlined underlying diseases the examined population is not reflecting the population for whom the vaccine will most likely be used. E.g. in the booster study SOC cardiac disorders occurred with a frequency of 0.5%, hypertension (4%), diabetes (2.2%), COPD (0.2%) and asthma (1.7%). The applicant clarified that 9.5% of the participants in the booster study had significant underlying disease such as significant cardiovascular conditions, diabetes and obesity, liver diseases, COPD, and asthma. Also, only 2.4% of participants in the booster population were > 65 years of age.

The applicant justified that safety (mainly based on data from primary vaccination) can be extrapolated from the examined population to an elderly population. With regards to a population with underlying diseases in a European setting the safety data provided, though limited, did not raise any specific concerns. Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) remains a safety concern (Missing information). Furthermore, the applicant has specified the proportion of participants with underlying disease in the SmPC section 5.1.

In all the ARCT-154 studies participants were Asian (99.6% in ARCT-154-01 and 99.4% placebo, other 0.4% and 0.6%), which is acceptable.

In conclusion for the ARCT-154 studies the provided demographics are well-balanced between groups. Few participants had significant underlying medical conditions and few participants were > 75 years of age in study ARCT-154-01, and few participants were > 65 years of age in study ARCT-154-J01.

Adverse events

Solicited AEs

Regarding the solicited AEs, there was a higher frequency of solicited local and systemic AEs in Phase 1/2/3a compared to Phase 3b. This could be explained by differences in demographic and baseline characteristics, as well as in different study design (Phase 1/2 vs Phase 3). E.g. slightly more participants were under the age of 60 in the Phase 1, 2, 3a studies than in the Phase 3b, and also for other COVID vaccines solicited AEs occur with a higher frequency in young subjects. Also, for study ARCT-154-J01 the frequency of solicited AEs was higher compared to the frequency in the ARCT-154 Phase 3b study. The applicant contend that this could be related to increased reporting of AEs in Japan in contrast to other nations and provide a reference in support of this. Further, it is reassuring that the frequencies of AEs in the Comirnaty (comparator) group in study ARCT-154-J01 were comparable to those observed with the ARCT-154 group. Also, it is noted that the pattern of solicited AEs (local and systemic) after the primary vaccination was similar in Phase 1/2/3a and Phase 3b, as well as for study ARCT-154-J01.

Unsolicited AEs

Unsolicited AEs in study ARCT-154-01 Phase 3b within 28 days after first dose occurred in 14% in the ARCT-154 and 13.7% in placebo. Most AEs were mild. The frequency of moderate events was low

overall but was slightly higher after the second dose than the first for both ARCT-154 (4.3% versus 5.3%, respectively), the same picture was seen for placebo. The incidence of severe events was overall 0.2% in ARCT-154.

In study ARCT-154-J01 unsolicited AEs occurred in 19.3% in the ARCT-154 group and 27.2% in the Comirnaty group in the booster study. One participant in the ARCT-154 group had a related severe AE of increased liver enzymes. Also, injection site pruritus was deemed related to ARCT-154 vaccine.

The Applicant performed a causality assessment of the reported related AEs and concluded a potential association between ARCT-154 and the occurrence of hypersensitivity, rash, and urticaria and have therefore included hypersensitivity (e.g., rash, urticaria, allergic dermatitis, type IV hypersensitivity) in the list of adverse drug reactions. Furthermore, injection site pruritus is included.

The applicant found that hypertension and tachycardia were not ADR, based on lack of association between ARCT-154 vaccine and these events. On request the Applicant provided an overview of all events off tachycardia and hypertension and demonstrated an equal proportion between the ARCT-154 population and the comparators in the ARCT-154 studies, based on this it is agreed not to include hypertension and tachycardia as ADR.

SAEs

The overall number of participants with SAEs in ARCT-154-01 Phase 3b from Day 1 to Day 92 was higher in the placebo (n=201, 2.5%) than the ARCT-154 (n=118, 1.5%) group. This was mainly explained by serious COVID-19 events in the placebo group.

On request, the applicant provided an overview including more details of all SAEs Cardiac events (angina pectoris, myocardial ischaemia, acute myocardial infarct, unstable angina, cardiac failure and third-degree atrioventricular block) from all studies. In total, in study ARCT-154-01 overall, 12 SAEs were reported within 28 days post vaccination: 1 case of myocardial infarction, 3 cases of angina pectoris, 1 case of unstable angina, 4 cases of myocardial ischemia, and 1 case of each arrhythmia, atrioventricular block complete, and atrial fibrillation. Of these 12 cases, 6 were reported after the ARCT-154 vaccine and 6 cases were reported in the control group. Most of the 12 participants reported underlying medical conditions, including hypertension, dyslipidemia, or other chronic cardiovascular conditions. Of the 6 cardiac events in the ARCT-154 group, 1 was severe and 5 moderate in severity. Three fatal cases due to cardiac events occurred 157 days, 253 days and 258 days after receiving the last dose of ARCT-154. All events were deemed as unrelated to the study vaccine by the investigators. No cases of myocarditis or pericarditis were reported.

In total, 7 SAEs of hypersensitivity were reported in the study. One related SAE of anaphylactic reaction was reported. Type IV hypersensitivity reaction was reported in 2 participants in the ARCT-154 group versus 0 participants in the placebo group. The applicant included hypersensitivity (e.g., rash, urticaria, allergic dermatitis, type IV hypersensitivity) to the SmPC section 4.8 as requested. Anaphylaxis was added to the list of ADRs in the SmPC section 4.8 separately and described in the text as requested.

Nervous system disorder SAE frequency was comparable between the treatment groups in Phase 3b (6 participants in the ARCT-154 compared to 5 in the placebo group. Cerebral infarction occurred more often in ARCT-154 group.

None of related SAEs until D92 were included in the SmPC, except headache that was reported as solicited AEs.

With regards to the SAEs of deep vein thrombosis, cerebral infarction, hypertension and hypertensive crises the applicant provided more details on these cases and discussed possible relation to the vaccine.

In total, 22 SAEs associated with hypertension were identified in the ARCT-154-01 study: 14 cases of hypertension, 6 cases of hypertensive crisis, 1 case of cerebrovascular disorder, and 1 case of pre-eclampsia. No SAEs associated with hypertension were reported in studies ARCT-021-01/02, ARCT-021-04, ARCT-154-J01, ARCT-165-01, and ARCT-2301-J01. Within 28 days 6 events occurred in ARCT-154 compared to 2 events in the control arm. No participant with hypertension or hypertensive crisis experienced cerebral circulatory insufficiency or cerebral infarction.

The applicant performed an analysis of all thromboembolic events reported in all studies. For thromboembolic events, the applicant applied a window of 28 days after any study vaccination, which is endorsed. Within the window of 28 days in study ARCT-154-01, 11 cases with thromboembolic events were reported: 2 cases of cerebral infarction, 4 cases of cerebrovascular accident, one case of cerebrovascular disorder, 2 cases of transient ischemic attack, 1 case of myocardial infarction, and 1 case of deep vein thrombosis. One additional case (ischemic stroke) was reported in study ARCT-021-02.

Among the 12 thromboembolic events reported within 28 days after any study vaccination, 6 events were reported after the study vaccine and 6 events were reported after controls

Two events (cerebral infarction and DVT) were assessed as related, whereas and one event in the placebo group was assessed as related by investigators. One fatal event was not deemed as related by the investigator, and the sponsor agreed. This was an adult female participant with no medical history or concomitant medication, who 20 days after receiving ARCT-154 died because of "stroke" (PT: Cerebrovascular accident). The participant had taken some unknown supplements to improve cerebral blood circulation for a 10-year history of dizziness, light-headedness, and headache. No laboratory tests or scans were provided, and no autopsy was performed. The cause of death was reported as a stroke, but as the participant also had epigastric pain (initially judged as gastritis), it was not possible to rule out chest pain and the investigator noted that the cause of death could also have been a myocardial infarction. Based on the lack of laboratory data, scanning results and autopsy it is not possible to conclude on this event. Overall, the applicant concluded that available data do not support the causal association between ARCT-154 and, hypertension and hypertensive crises, which is acceptable. With regards to the thromboembolic events the uncertainty related to the fatal event and two events deemed related to the vaccine by the investigator, combined with a new vaccine platform, thromboembolic events is included as Important Potential Risk and follow-up measures are proposed to be implemented in the RMP.

The applicant clarified the number of SAEs after switchover that were 88 SAE in ARCT-154 and 91 in placebo. An overview of SAEs (SOC and PT) after switchover in participants who received ARCT-154 at dose 3 and 4 in Phase 3b was provided**.** Overall, SAEs after switchover revealed no new concerns and were similar in frequency and type between ARCT-154 recipients and placebo recipients. No related SAEs with onset from Day 92 to Day 210 were reported in Phase 3b.

Two SAEs in Phase 1,2,3a were deemed related to study drug (atrial fibrillation and urticaria), both in placebo participants. No serious related AEs were noted after dose 3 or dose 4.

Regarding a quality question raised on the lack of potency data for batch used in the pivotal study, the applicant addressed that based on safety data from studies made with batches with potency comparable with the commercial batches (the booster study and preliminary data from an ongoing study). The apparently higher potency levels for commercial batches will not impact the safety of the ARCT-154 drug product.

Deaths

In study ARCT-154-01 Phase 3b and Phase 1/2/3a in total 42 deaths were reported.

None of the death were considered to be related to the study vaccine.

In the other studies no participants died.

Laboratory findings

In studies ARCT-021-01 and ARCT-021-02 transient changes in neutrophil and lymphocyte count (≤Grade 3 lymphopenia and <Grade 2 neutropenia) were observed. No haematology laboratory parameters are available from the Phase 2, 3a, 3b, 3c or from the ARCT-154-J01 to confirm or unconfirm this. As these cases were not associated with any clinical symptoms or assessed as clinically significant, it is acceptable not to include it as an adverse reaction.

Regarding the grade 3 event of increase in AST and ALT occurred in study ARCT-154-J01 in an adult female with no background medical history, the applicant provided further analysis that demonstrate that participants with ALT and AST values above the normal range at baseline was higher in the ARCT-154 group than in the Comirnaty group, and it is agreed that this is most likely the reason for a higher proportion of elevated liver enzymes after vaccination.

High CPK values in 3 subjects in the ARCT-154 group and 4 subjects in the Comirnaty group were reported as unsolicited AEs (grade 1 and not related to the study vaccine). In these participants the possibility of myocarditis or pericarditis were excluded following evaluation by investigator or cardiologist. Other cardiac enzyme test results were not remarkable. Even though it is recognised that no myocarditis or pericarditis events occurred in the ARCT-154-01, the finding of no differences in cardiac related enzyme values between Comirnaty and ARCT-154, is not reassuring, as in Comirnaty myocarditis or pericarditis is a known ADR.

Safety in special population

Regarding immunocompromised individuals the applicant clarified that the replicon is only able to transcribe the gene for Spike proteins, which alone, are incapable of causing an infection, whereas live attenuated vaccines may cause an infection if the host is immunocompromised. ARCT-154 also have a self-regulating mechanism to stop the amplification. Further, since the vaccine antigens are immunogenic (expected that this is to a less extend in immunocompromised subjects), the host's antigen-specific immune response will target and kill antigen producing cells. It is agreed to maintain the warning, but not to strengthen to no use in immunocompromised patients.

Pregnancy and lactation

Overall, there is limited available data of exposure during pregnancy, which is properly reflected in the SmPC. Furthermore, use in pregnancy is stated as Missing information in the safety specifications.

Animal studies (reprostudy in rabbits) conducted with ARCT-021 (same LNP) do not indicate risk for harmful effects on fertility or development of foetus. No animal developmental and reproductive toxicology studies have been conducted with ARCT-154.

Safety related to drug-drug interactions and other interactions

Regarding the assumption that antiviral drugs with potential impact on VEEV replication might reduce the efficiency of replicase activity, it is considered that the current evidence to support a statement in section 4.5 of the SmPC is insufficient, hence this potential drug interaction risks should not be communicated in SmPC section 4.5 at present time. The applicant is therefore invited to evaluate whether it might be possible to generate product-specific data to support evaluation of the magnitude of such risks, and if relevant, a communication of the risks in the SmPC **(REC3).**

2.5.10. Conclusions on the clinical safety

The safety profile for the primary series with Kostaive was adequately described in a large, placebo-controlled study performed in Vietnam, and there are no major concerns related to safety. Furthermore, data from a booster study in Japan, comparing Kostaive and Comirnaty Original, does not reveal major differences in the safety profile between the two vaccines.

The CHMP considers the following post-authorisation measure (REC) necessary to address issues related to safety:

Assuming that antiviral drugs with potential impact on VEEV replication might reduce the efficiency of replicase activity and considering the theoretical risk of co-administration of vaccine with interferons, the Applicant is invited to evaluate whether it might be possible to generate product-specific data to support evaluation of the magnitude of such risks, and if relevant, a communication of the risks in the SmPC.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 53: Summary of the Safety Concerns

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

2.6.2. Pharmacovigilance plan

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

Table 54: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
Category 1				
N/A	N/A	N/A	N/A	N/A
Category 2				
N/A	N/A	N/A	N/A	N/A
Category 3				

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
V206_06: A retrospective post-authorisation safety study to assess the risk of cardiac inflammatory and thromboembolic events following vaccination with sa-mRNA COVID-19 vaccine in adult individuals Planned	To evaluate the risk of myocarditis, myopericarditis, pericarditis, and thromboembolic events following vaccination with Kostaive using a self-controlled risk interval design among individuals aged 18 years and older. To characterise the occurrence of myocarditis, myopericarditis, pericarditis, and thromboembolic events following vaccination with Kostaive in the following subgroups: age groups (<30, 30-59 and ≥60 years), sex (male, female), other characteristics, as applicable.	Myocarditis and pericarditis Thromboembolic events	Draft protocol Clinical study report	6 months following MAA approval (17 August 2025) 6 months following the completion of data collection
V206_05: A phase IIb, single-arm, open label study to evaluate the safety, tolerability and immunogenicity of Kostaive when administered to adults and elderly subjects with immunosuppressive disorders, or receiving immunosuppressive therapies, who are indicated for a booster dose of COVID-19 vaccine. Planned	To assess the safety and tolerability profile of Kostaive in adults and elderly subjects with immunosuppressive disorders (including autoimmune conditions) or receiving immunosuppressive therapies. To evaluate immunogenicity of Kostaive, as determined by virus neutralisation assay for the SARS-CoV-2 variant recommended by WHO in adults and elderly subjects with immunosuppressive disorders (including	Missing information: Use in immunocompromised patients Use in patients with autoimmune or inflammatory disorders	Final protocol Clinical study report	01 February 2027 30 April 2029

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
	autoimmune conditions) or receiving immunosuppressive therapies.			
ARCT-2303-01: Observer-blind, randomised controlled study to evaluate the immunogenicity, reactogenicity, and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in adults Planned	To assess the safety, reactogenicity, and immunogenicity of the study vaccines when given in co-administration or standalone	Missing information: Interaction with other vaccines	Clinical study report	31 April 2025
V206_03: A prospective observational safety study on pregnancy outcomes in persons immunised with Kostaive during pregnancy Planned	To evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunised as part of routine care with Kostaive during pregnancy	Missing information: Use in pregnancy and while breastfeeding	Final protocol Summary report	01 March 2028 30 April 2031
ARCT-165-01: A Phase 1/2 Randomised, Observer-blind Study of the Safety, Reactogenicity, and Immunogenicity of 3 SARS-CoV-2 RNA Vaccine Candidates in Adults Previously Vaccinated and Not Previously Vaccinated Against SARS-CoV-2 Ongoing	To describe the safety and reactogenicity of 3 investigational SARS-CoV-2 self-amplifying RNA vaccines through Final Visit, defined as 365 days after the last study vaccine dose	Missing information: Long-term safety data	Study start Clinical study report	30 August 2021 31 December 2024
ARCT-154-J01: A randomised, multicenter, phase 3, double-blind, active-controlled comparative study to evaluate the safety and immunogenicity of a booster shot of ARCT-154 (a self-amplifying mRNA	To evaluate the safety and immunogenicity of ARCT-154 given as a booster dose in subjects 18 years of age and older who have received 3 doses of approved mRNA COVID-19 vaccine at least 3 months	Missing information: Long-term safety data	Study start Clinical study report	13 December 2022 31 December 2024

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone	Due dates
COVID-19 vaccine) in healthy subjects Ongoing	prior, for up to 12 months after vaccination			
ARCT-154-01: A Randomised, Observer-blind, Controlled Study to Assess the Safety, Immunogenicity and Efficacy of the SARS-CoV-2 Self-Amplifying RNA Vaccine ARCT-154 in Adults Ongoing	Safety follow-up for all participants up to Day 394.	Missing information: Long-term safety data	Study start Clinical study report	11 August 2021 29 January 2024

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

2.6.3. Risk minimisation measures

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

Table 55: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis and pericarditis	Routine risk minimisation measures: SmPC Section 4.4; PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A data capture aid for myocarditis/myopericarditis/pericarditis will be used to collect event specific follow-up information. Additional pharmacovigilance activities: Observational retrospective post-authorisation safety study (V206_06)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thromboembolic events	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A data capture aid for thrombosis/thromboembolism will be used to collect event specific follow-up information. Additional pharmacovigilance activities: Observational retrospective post-authorisation safety study (V206_06)
Use in pregnancy and while breast feeding	Routine risk minimisation measures: SmPC Section 4.6; PL Section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A noninterventional, prospective study (pregnancy exposure study) to monitor the safety of Kostaive when used during pregnancy (V206_03).
Use in immunocompromised patients	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 5.1. PL Section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).
Use in patients with autoimmune or inflammatory disorders	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A post-authorisation safety study to collect additional safety data in immunocompromised individuals (including autoimmune conditions) and patients who are on immunosuppressive therapies (V206_05).
Interaction with other vaccines	Routine risk minimisation measures: SmPC Section 4.5 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: A study of the immunogenicity and safety of Kostaive administered concomitantly with quadrivalent influenza vaccines in an adult population (ARCT-2303-01).
Long-term safety data	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	None Additional pharmacovigilance activities: One-year post-vaccination follow-up of participants in studies ARCT-154-01, ARCT-154-J01, and ARCT-165-01.
Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 November 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kostaive (zapomeran) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

COVID-19 is an infectious disease caused by SARS-CoV-2, that spread worldwide during 2020 causing WHO to declare a pandemic on 11 March 2020. Globally, as of 22 September 2024, there have been over 776 million confirmed cases of COVID-19, including 7 067 260 deaths, reported to the WHO. Since the COVID-19 pandemic started, over 2 million people in the European Region have died from the disease. COVID-19 is no longer a pandemic, but the virus is still present.

The virus infects primarily the airways and causes a broad spectrum of respiratory infections from asymptomatic infection to SARS.

COVID-19 remains a global health threat that still places a burden on healthcare systems, and due to new birth cohorts, waning immunity and antigenic evolution of the virus, there is a recognized need for periodic COVID-19 vaccination.

3.1.2. Available therapies and unmet medical need

The most effective way to prevent COVID-19 is vaccination. There are currently several vaccines authorised in the EU. COVID-19 vaccines have been shown to be very effective in reducing the risk of infection and severe disease from SARS-CoV-2 infection.

Kostaive is a LNP-encapsulated, sa-mRNA COVID-19 vaccine, encoding the full-length, prefusion-stabilized spike protein of the index (Wuhan) SARS-CoV-2 strain. While sharing many similarities with the currently approved non-replicating mRNA COVID-19 vaccines (i.e. LNP encapsulation of mRNA, use of full-length, prefusion-stabilized spike protein immunogen), the product is first-in-class since none of the currently approved mRNA vaccines are self-replicating.

3.1.3. Main clinical studies

Efficacy of a primary series was documented in a large randomised, placebo-controlled, observer-blind study performed in Vietnam (phase 3b of ARCT-154-01). This study included 7562 and 7256 participants, and 200 and 440 COVID-19 cases in ARCT-154/placebo groups, respectively. mITT was set for days 36-92. Supportive efficacy data for the primary series is available from phase 3c of ARCT-154-01, where the efficacy relative to ChAdOx1 was explored. This study included 1145 and 1128 participants, and 20 and 28 COVID-19 cases in ARCT-154 and ChAdOx1 groups, respectively.

The heterologous boost indication is supported by a smaller randomised, observer-blind noninferiority immunobridging study performed in Japan (ARCT-154-J01). This study included 385 and 374 participants in ARCT-154 and Comirnaty original groups, respectively.

The above studies are included in the safety package for primary vaccination, as well as safety data from ARCT-154-01 Phase 1, Phase 2, Phase 3a studies. Furthermore, safety data from four supportive studies (ARCT-165-01, ARCT-021-04, ARCT-021-01 and ARCT-021-02) is also included. As a supportive study for booster immunisation, safety data from ARCT-165-J01 is also presented.

3.2. Favourable effects

ARCT-154-01 study (primary series)

Efficacy against symptomatic COVID-19 occurring days 36-92 (primary immunisation days 1 and 29) was 56.7% (95% CI: 48.8% to 63.4%). Thus, the study met the primary objective according to the predefined success criterion (lower limit of the 95% CI > 30%).

- Efficacy against severe COVID-19 and COVID-19 at any time up to day 92 after the first immunisation was 95.3% (95% CI: 80.5% to 98.9%) and 56.7% (95% CI: 49.3% to 63.1%), respectively. Thus, for these secondary endpoints, the study also met the predefined success criterion (lower limit of the 95% CI > 0%).
- Efficacy against death caused by COVID-19 was 86.3% (95% CI: -8.9% to 98.3%). As the lower bound of the 95% CI was < 0%, this secondary endpoint was not met. This reflects the low number of deaths occurring in the study, and hence large statistical variability (i.e. it is expected that efficacy increases with endpoint severity for spike protein-based COVID-19 vaccines).

ARCT-154-J01 (booster)

Neutralising antibody responses after heterologous ARCT-154 boost were non-inferior to the Comirnaty original boost measured against the index strain, and were superior to the Comirnaty original boost measured against the omicron BA.4/BA.5 strain.

In addition, through approximately 6 months after the booster, waning of circulating virus-neutralising antibodies appears less pronounced for ARCT-154 than for Comirnaty.

3.3. Uncertainties and limitations about favourable effects

ARCT-154-J01 is a small immunobridging study in a young, healthy and COVID-19-naïve population. This limits meaningful subgroup analysis, especially for most relevant criteria such as age. Specifically, while available data on immunogenicity of an ARCT-154 booster in the elderly is positive, it is yet limited. This is of particular relevance for a booster indication, because the elderly are particularly prone to developing severe COVID-19 and thus, typically prioritized for COVID-19 booster campaigns.

There is uncertainty regarding positioning of Kostaive compared to approved COVID-19 booster vaccines. In the ARCT-154-J01 trial, measured at day 29 post boost (time of expected maximal antibody responses), heterologous boost with 5 µg ARCT-154 induced similar to slightly higher levels of virus-neutralising antibodies than the homologous boost with 30 µg Comirnaty. These results met the predefined primary and secondary immunogenicity endpoints. Comirnaty was used also as comparator in booster studies for approved protein-based COVID-19 vaccines, and for those, at comparable times post-boost, GMT ratios to Comirnaty for the index strain were in the 1.3 - 1.4 range. The currently available limited data from ARCT-154-J01 study suggests that in the heterologous

booster setting, the replicating RNA platform may not provide immunogenicity advantages over certain approved protein-based COVID-19 booster vaccines.

There is an incomplete understanding of immunological mechanisms (i.e. lack of data on T-cell immunity). Self-replicating mRNA vaccines including Kostaive trigger human-specific innate immune responses impacting immunogenicity, efficacy and safety. There is incomplete understanding of these issues, adding another layer of complexity as regards of extrapolation of immunogenicity and efficacy from one context of Kostaive use to another. There is currently no data available for T-cell immunity induced by Kostaive from the pivotal studies, and the T-cell immunity data for Kostaive from the supportive studies is very limited.

The product is first-in-class and the self-replicating RNA platform exhibits unique aspects which might confer immunogenicity characteristics to antigens expressed from this platform which are distinct from the immunogenicity characteristics of non-replicating mRNA vaccines.

Information of T-cell responses might be seen as particularly relevant in this case, to better understand the immunological mechanisms triggered by this novel vaccine platform, of relevance for safety (e.g. Th1/Th2 balance) as well as efficacy (T-cell responses are also involved in protection against COVID-19, likely especially in situations of low neutralising antibody responses and in the context of severe disease, and in any case, the magnitude, breadth and durability of antibody responses are modulated by T cell responses).

The applicant indicated their plan to update the composition of Kostaive in line with regulatory recommendations in a timely manner, to ensure vaccine availability for the start of future autumn/winter booster vaccination campaigns. This will generate additional safety and efficacy data (including information on T-cell immunity), which will allow further understanding of the immunological mechanisms mentioned above.

3.4. Unfavourable effects

The safety of ARCT-154 is based on data from ARCT-154-01 study, a Phase 1/2/3, randomised, placebo-controlled, observer-blind study to examine safety of a 2-dose primary series (28 days apart) conduction in Vietnam (99.5% of the participants were the Kinh ethnic). Data from this study are seen as the main safety package, especially prior to switchover. A 12-month follow-up is planned for MAAEs, SAEs, and AEs leading to early study discontinuation. Phase 3c data was provided during assessment of this application. Further, safety data from 4 supportive studies are also included in the safety package.

In addition, to the above studies submitted for the primary series indication, data for booster immunisation is also available from the ARCT-154-J01 study conducted exclusively in Japan. Safety data are available up to day 181.

The majority of the adverse reactions were mild-moderate in severity and generally resolved within 2-days (local) or 3- days (systemic) period after dosing. As observed with other COVID-19 vaccines, reactogenicity was lower in older adults and male participants compared to younger adults and female participants, respectively.

Overall, Kostaive booster has the same reactogenicity profile and pattern as Comirnaty. The reactogenicity incidence was high (especially for local solicited AEs) but not severe (most AEs were grade 1 or 2) and transient.

It is a safety limitation that the studied "at risk" population is mostly not corresponding to a "at risk" population in the EU population in which the vaccine will most likely be used. In study ARCT-154-01,

5.5% and in study ARCT-154-J01 9.5% of the participants had significant underlying disease such as significant cardiovascular conditions, diabetes and obesity, liver diseases, COPD, and asthma.

The incidence of SAEs (others than serious COVID-19 events) was low in both primary and booster immunisation and the incidence of AESIs (no pre-specified) was also low.

In study ARCT-154-01, myocardial ischemia was reported in 2 participants in the ARCT-154 group versus 0 participants in placebo group and a SAE of angina occurred in a participant that received ARCT-154 in the phase 3c part of the study. Three participant of study ARCT-154-01 had a SAE of deep vein thrombosis.

Of the 6 thromboembolic events attributed to ARCT vaccines, 4 were categorized as severe, 1 as moderate, and 1 as mild in severity. For the participant with fatal outcome, based on the lack of laboratory data, scanning results and autopsy it was not possible to conclude on this event. Thus, thromboembolic events is added as an Important Potential Risk in the safety specification of the RMP.

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties remains regarding participants at risk (with underlying diseases). Use in patients with significant, unstable chronic medical conditions (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) remains a safety concern (Missing information), which is endorsed.

Regarding thromboembolic events, uncertainties remain, especially related to the fatal event. The applicant has accepted to include thromboembolic events as an Important Potential Risk in the RMP and proposed follow-up measures in the RMP.

While the data available from other mRNA vaccine manufacturers suggests the rare risk of primarily mild myocarditis or pericarditis without sequelae following vaccination, no cases of myocarditis or pericarditis were reported in any of the studies. However, it remains as an important potential risk.

In addition, assuming that antiviral drugs with potential impact on VEEV replication might reduce the efficiency of replicase activity and considering the theoretical risk of co-administration of vaccine with interferons, the applicant is invited to evaluate whether it might be possible to generate product-specific data to support evaluation of the magnitude of such risks, and if relevant, a communication of the risks in the SmPC.

3.6. Effects table

Table 56: Kostaive COVID-19 vaccine (ARCT-154) for primary vaccination

Effect	Short Description	Unit	Treatment effect		Uncertainties/ Strength of evidence	References
Favourable Effects						
Vaccine efficacy	COVID-19 with first occurrence of onset days 36- 92, included.	% (95% CI)	56.7 (48.8, 63.4)		In phase 3c, relative efficacy of ARCT-154 primary series to ChAdOx1 primary series was 30.7% (95% CI: (-23.0, 61.0) through this time window, declining to approximately 20% at later timepoints.	ARCT-154-01phase 3b
Vaccine efficacy	in ≥ 60-year-olds	cases/N	ARCT-154 28/1361	Placebo 56/1329	Main efficacy endpoint was not met in this subgroup. The wide 95% CI is likely due to the small number of deaths attributed to COVID-19l. The results show a favourable trend for ARCT-154 vaccine versus placebo.	
		% (95% CI)	54.3 (26.8, 70.5)			
Vaccine efficacy	Severe COVID-19 with first occurrence of onset days 36 -92, included	% (95% CI)	95.3 (80.5, 98.9)		Expected for spike protein-based vaccines that efficacy against severe endpoints is better than against milder endpoints.	
Vaccine efficacy	Death due to COVID-19, days 32-92, included	% (95% CI)	86.3% (-8.9, 98.3)		Large statistical variability due to low number of deaths in the study. Based on the documented efficacy against COVID-19 as well as severe COVID-19, the point estimate is plausible.	

Effect	Short Description	Unit	Treatment ARCT-154		Control Placebo		Uncertainties/ Strength of evidence	References
Unfavourable Effects								
Solicited AEs (reactogenicity) < 7 days			Post dose 1	Post dose 2	Post dose 1	Post dose 2	Transient events, majority grade 1. As expected, more events were seen in group 18-60 YoA compared to >60 YoA.	Reactogenicity analysis set (RAS) ARCT-154-01 Phase 3b
	Injection site pain	%	38.2	26.8	8.6	6.1		
	Injection site tenderness		37.9	26.5	8.4	5.6		
SAEs Day 1 – 6 months	Anaphylaxis Hypersensitivity reactions	events	1 7		1 *		*Number of events in placebo is unclear	
	Bell's palsy		0		2			
	Thrombotic events (within 28 days)– stroke, DVT SAEs		5		5		Two events deemed related by investigator (DVT, stroke) Uncertainty of one event of stroke, that could be related.	

Table 57 Kostaive COVID-19 vaccine (ARCT-154) for heterologous booster

Effect	Short Description	Unit	Treatment (ARCT-154)	Control (Comirnaty Original)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immuno-genicity	GMT ratio for neutralising antibodies against index strain - day 29	Fold-factor (95% CI)	1.43 (1.26, 1.63)		Co-primary endpoints. Non-inferiority was shown. Limited data for elderly subgroup. Through 6 months post-boost, neutralising antibodies more durable than for Comirnaty (similar results for index, delta and omicron BA.2, BA.4/5, BA.2.86 and XBB.1.5 variants).	ARCT-154-J01
	SRR difference for neutralising antibodies against index strain	% points - difference between % (95% CI)	13.6 (6.8, 20.5)			
	GMT ratio for neutralising antibodies against omicron BA.4/BA.5 strain - day 29	Fold-factor (95% CI)	1.30 (1.07, 1.58)		Secondary endpoints. Superiority shown for GMT ratio for omicron BA.4/BA.5. Limited data for elderly subgroup.	
	SRR difference for neutralising antibodies against omicron BA.4/BA.5 strain - day 29	% points - difference between % (95% CI)	11.6 (4.9, 18.3)			
	GMFR for neutralising antibodies against index strain - day 29	Fold-factor (95% CI)	6.70 (5.97, 7.53)	3.98 (3.98, 4.80)		
	GMFR for neutralising antibodies against omicron BA.4/BA.5 strain - day 29	Fold-factor (95% CI)	7.96 (7.00, 9.06)	5.67 (5.02, 6.42)		

Effect	Short Description	Unit	Treatment ARCT-154	Control Comirnaty Original	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Solicited AEs (reactogenicity) < 7 days	Injection site pain	%	83.8	87.8	There was a short follow-up period (Day 29)	ARCT-154-J01
	Injection site tenderness	%	92.4	95.8		

Abbreviations: AE: adverse event; GMT, geometric mean titer. GMFR, geometric fold rise. SRR, seroresponse rate. YoA: Years of Age
Notes: In the ARCT-154-J01 study most of the participants had received a primary series with Comirnaty original (approx. 78%), with a minority having received a primary series with Spikevax original (approx. 20%); thus, for the sake of simplicity, the Comirnaty boost is termed homologous in the table

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the placebo-controlled phase 3b of the ARCT-154-01 study, a primary series with Kostaive met the primary objective of protection against COVID-19, despite the antigenic mismatch between the vaccine and the delta strain which dominated in Vietnam at the time of the study. In phase 3c, a Kostaive primary series was more effective than a primary series with ChAdOx1, during a period of omicron BA.2 and BA.4/BA.5 dominance.

While this is clearly positive, in the current post-pandemic situation, it is recognized that due to the generally high level of preexisting population immunity, for individuals older 6 years of age approximately, and irrespective of previous immunisation history, a single dose of COVID-19 vaccine which is variant-updated according to regulatory recommendations and administered as part of periodic vaccination campaigns would suffice to maintain protective immunity against current SARS-CoV-2 strains.

Thus, an indication for a primary ARCT-154 series in individuals 18 years of age and older as currently sought by the applicant is of lesser clinical relevance. However, the efficacy data for the primary series provides a basis for variant-updating of the Kostaive COVID-19 vaccine platform.

In the ongoing ARCT-154-J01 immunobridging study, in individuals who had previously received three immunisations with mRNA vaccines (primary series with approved index strain-based mRNA vaccines Spikevax original or Comirnaty original, and boost with Comirnaty original, with the boost given at least 3 months before enrolment), a heterologous boost with 5 µg Kostaive provided non-inferior neutralising antibody responses, compared to a boost with 30 µg Comirnaty original. Also, waning of circulating virus-neutralising antibodies appeared less pronounced for ARCT-154 than for Comirnaty, measured against index, delta and omicron BA.2, BA.4/5, BA.2.86 and XBB.1.5 strains.

Neutralising antibody responses are considered to be predictive for efficacy of COVID-19 vaccines.

While the study population was young and healthy (in contrast to the main target populations for COVID-19 vaccine boosters), they were also largely COVID-19-naîve, which might be expected to provide a worst-case scenario for immunogenicity. Also, the approved mRNA vaccines such as the one used as comparator are recognized as being amongst the most highly immunogenic of the COVID-19 vaccines currently available.

As such, the immunobridging data from the ongoing ARCT-154-J01 study is considered to provide adequate documentation for the efficacy of Kostaive in a heterologous boost setting.

Overall, the safety profile for primary vaccination and booster is considered satisfactory based on the provided data from the pivotal study ARCT-154-01.

Generally, the safety profile was expected to share class adverse events with other COVID-19 mRNA vaccines.

The incidence of SAEs (others than serious COVID-19 events) was low in both primary and booster immunisation and the incidence of AESIs (no pre-specified) was also low.

Thromboembolic events is included as an Important Potential Risk in the RMP. No cases of myocarditis or pericarditis were reported in any of the studies, but it remains as a potential risk and a warning is included in the SmPC section 4.4.

It is a safety limitation that the studied "at risk" population is not fully corresponding to a "at risk" population in the EU population in which the vaccine will most likely be used. But in the small subgroup with relevant underlying disease, safety was comparable to the full population.

It is acknowledged that primary vaccination was studied in a large population, at a time-point where such study would have been very difficult in Europe.

Limited safety data are available regarding the use of ARCT-154 during pregnancy and lactation. No safety data are available for immunocompromised subjects.

3.7.2. Balance of benefits and risks

The available data from the pivotal ARCT-154-01 and ARCT-154-J01 trials is considered adequate to document the efficacy of Kostaive in primary immunisation as well as heterologous booster settings.

Overall, the safety profile for the primary series and booster with Kostaive was adequately described with no major concerns related to safety.

3.8. Conclusions

The overall benefit/risk balance of Kostaive is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kostaive is favourable in the following indication:

> *Kostaive is indicated 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.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product

within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that zapomeran is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.