THEMBA II T-CELL VACCINE: A PHASE 1/2 STUDY OF THE SAFETY, REACTOGENICITY, AND IMMUNOGENICITY OF VACCINATION WITH saRNA COVID-19 VACCINES

Study Number:	COVID-4.015
IND Sponsor:	ImmunityBio, Inc.
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Protocol Version	**Date**
Version 1	21 January 2022
Version 2	17 February 2022
Version 3	17 March 2022
Version 4	27 October 2022

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with applicable local regulatory requirements, Good Clinical Practice (GCP) as described in the International Conference on Harmonization (ICH) Guideline for GCP (E6 [R2]), United States (US) Code of Federal Regulations (CFR) applicable to clinical studies and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB/IEC, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ImmunityBio, Inc.	
Name of Investigational Products: 1. AAHI -SC2 self-amplifying RNA (saRNA) against SARS-CoV-2 Spike protein delivered by nanostructured lipid carrier (NLC) Vaccine 2. AAHI-SC3 self-amplifying RNA (saRNA) against SARS-CoV-2 nucleocapsid protein delivered by nanostructured lipid carrier (NLC) Vaccine *Note that AAHI-SC3 is now comprised of saRNA against SARS-CoV-2 nucleocapsid protein only while in previous versions of this protocol, AAHI-SC3 was comprised of saRNA against SARS-CoV-2 nucleocapsid and Spike proteins.*	
Name of Active Ingredients: 1. AAHI-SC2 Vaccine 2. AAHI-SC3 Vaccine	
Title of Study: Themba II T-Cell Vaccine: A phase 1/2 Study of the Safety, Reactogenicity, and Immunogenicity of Vaccination with saRNA COVID-19 Vaccines	
Study Number: COVID-4.015	
Study Phase: Phase 1/2	
Study Objectives	**Study Endpoints**
Phase 1	
Phase 1 Primary Objective	
Safety: To determine the safety and reactogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines.	• Incidence of medically-attended adverse events (MAAEs) and serious adverse events (SAEs) through 1 week post final vaccine administration • Incidence of MAAEs and SAEs through 30 days post final vaccine administration • Incidence of MAAEs and SAEs through 6 months post final vaccine administration • Incidence and severity of solicited local reactogenicity AEs through 1 week after each vaccine dose • Incidence and severity of solicited systemic reactogenicity AEs through 1 week after each vaccine dose

	• Incidence and severity of unsolicited AEs through 1 week post final vaccine administration Incidence and severity of unsolicited AEs through 30 days post final vaccine administration Incidence of abnormal changes of laboratory safety examinations Changes in vital signs
Phase 1 Secondary Objective	
Immunogenicity: To determine immunogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines, as determined by changes in humoral and cellular response.	*Humoral Immunogenicity:* • Geometric mean titer (GMT) of S-specific and N-specific IgG antibodies against 2019 novel coronavirus tested by ELISA in serum • GMT of neutralizing antibody *Cellular Immunogenicity:* • T cell activity against SARS-CoV-2 S protein and N protein as assayed by ELISpot
Phase 2	
Phase 2 Primary Objective	
Immunogenicity: To determine immunogenici y of homologous and heterologous vaccination with saRNA COVID-19 vaccines, as determin d by changes in humoral and cellular response	*Humoral Immunogenicity:* • GMT of S-specific and N-specific IgG antibodies against 2019 novel coronavirus tested by ELISA in serum • GMT of neutralizing antibody *Cellular Immunogenicity:* • T cell activity against SARS-CoV-2 S protein and N protein as assayed by the ELISpot assay
Phase 2 Secondary Objectives	
Safety: To determine the safety and reactogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines.	• Incidence of MAAEs and SAEs through 30 days post final vaccine administration • Incidence of MAAEs and SAEs through 6 months post final vaccine administration • Incidence and severity of solicited local reactogenicity AEs through 1 week after each vaccine dose • Incidence and severity of solicited systemic reactogenicity AEs through 1 week after each vaccine dose

	• Incidence and severity of unsolicited AEs through 30 days post final vaccine administration

Study Design:

This is a phase 1/2 open-label study assessing the safety, reactogenicity, and immunogenicity of saRNA COVID-19 boost vaccines in participants that have been previously vaccinated against or previously infected with COVID-19. Participants enrolled will include individuals previously vaccinated against COVID-19 or previously infected with COVID-19 > 3 months prior to enrollment. Previously unvaccinated/vaccinated status and previously uninfected/infected status will be established by medical history and by SARS-CoV-2 serology assessed in the prescreening visit.

The phase 1 study is a single arm, open-label study. The phase 2 and study is a randomized open-label study. For the phase 2 study, laboratory analyses of immunogenicity assessments will be performed blind to participants' vaccine treatment on study. In all study phases, SARS-CoV-2 serological status will be assessed in a prescreening visit.

Participants will be ≥ 18 years of age who are healthy or have medically-stable chronic diseases. The treatment regime is described in the sections that follow. The study schema is shown in Figure 1.

Phase 1

In the phase 1 study, up to 60 previously vaccinated/infected participants will be enrolled in 6 separate cohorts to receive a single vaccine boost consisting of either the AAHI-SC2 or AAHI-SC3 vaccines. Dosing schedule, mode of administration, and dosage for phase 1 are indicated in the table below.

Phase	Cohort	Participants	Vaccine	D sing Schedule	Dosage
PHASE 1	1A	10	AAHI-SC2	Day 1	25 µg IM
	1B	10	AAHI-SC2	Day 1	50 µg IM
	1C	10	AAHI-SC2	Day 1	70 µg IM
	2A	10	AAHI-SC3	Day 1	25 µg IM
	2B	10	AAHI-SC3	Day 1	50 µg IM
	2C	10	AAHI-SC3	Day 1	85 µg IM

Safety will be assessed for all participants and will include monitoring of vital signs, and incidence and severity of AEs. Blood samples will be collected for hematology and chemistry analyses and urine samples will be collected for urinalysis. Toxicities will be graded using the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

For each cohort in phase 1, after all 10 participants have completed the toxicity assessment period, the SRC will review safety results to determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

Solicited local and systemic reactogenicity AEs will be collected using diaries for 7 days following study intervention (ie, administration of vaccine). Unsolicited AEs will be recorded in a diary from time of vaccination until 30 days after study intervention. MAAEs and SAEs will be recorded for 6 months after study intervention (related MAAEs and SAEs will be recorded at any time).

Immunogenicity analyses will be conducted by collecting serum and peripheral blood mononuclear cell (PBMC) samples from individual participants before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed.

Phase 2

In the phase 2 study, up to 120 previously vaccinated/infected additional participants will be enrolled. Participants in phase 2 will be randomized 1:1:1:1 to receive Janssen or Pfizer-BioNTech vaccine (control arm), the AAHI-SC2 vaccine (experimental arm 1), or the AAHI-SC3 vaccine (experimental arms 2 and 3). Dose levels for the AAHI-SC2 and AAHI-SC3 vaccines will be as determined in the phase 1 study. Randomization will be stratified by age (18 to 55 years or > 55 years), by previous infection (previously infected or not), and by HIV status (positive or negative). Treatment arms are shown in the table below:

Treatment Arm	Participants	Vaccine	Dosing schedule	Dosage
Control arm	30	Emergency Use Authorization (EUA) or approved vaccine	Day 1	Per prescribing information
Experimental arm 1	30	AAHI-SC2	Day 1	TBD: As determined in phase 1 study
Experimental arm 2	30	AAHI-SC3	Day 1	TBD: As determined in phase 1 study
Experimental arm 3	30	AAHI-SC3	Day 1 and day 29	TBD: As determined in phase 1 study

In addition to dosing visits described above, all participants in all phases of the study will have follow-up study visits for data collection.

The SRC will provide ongoing safety review in the phase 2 study. If a possible safety signal is detected, the SRC will determine if the event warrants stopping the trial, modifying the trial, or continuing without modification.

Solicited local and systemic reactogenicity AEs will be collected using diaries for 7 days following study intervention (ie, administration of vaccine). Unsolicited AEs will be recorded in a diary from time of vaccination until 30 days after study intervention. MAAEs and SAEs will be recorded for 6 months after study intervention (related MAAEs and SAEs will be recorded at any time).

Immunogenicity analyses will be conducted by collecting serum and PBMC samples from individual participants before and after vaccinations to test for humoral- and cell-mediated immune responses. Neutralizing antibodies will be assessed.

Enrollment (planned):

Initially up to 180 participants will be enrolled in this study (60 participants in phase 1 and 120 participants in phase 2).

Eligibility Criteria:

Inclusion Criteria:

1. Healthy adults ≥ 18 years of age at time of enrollment.
2. Vaccinated with an EUA or approved vaccine against COVID-19 ≥ 3 months prior to enrollment on study or infection with COVID-19 ≥ 3 months prior to enrollment on study.
3. Able to understand and provide a signed informed consent that fulfills the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC) guidelines.

4. Agrees to the collection of biospecimens (eg, nasopharyngeal [NP] swabs) and venous blood per protocol.
5. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
6. Temperature < 38°C.
7. Agreement to practice effective contraception for female participants of childbearing potential and non-sterile males. Female participants of childbearing potential must agree to use effective contraception while on study until at least 1 month after the last dose of vaccine. Non-sterile male participants must agree to use a condom while on study until at least 1 month after the last dose of vaccine. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm), intrauterine devices (IUDs), oral contraceptives, injectable contraceptives, patches, implants and abstinence.
8. HIV-positive participants must have been on anti-retroviral therapy for ≥ 4 weeks and have HIV-1 viral load < 1,000 copies/mL at the time of enrollment.

Exclusion Criteria:

1. Serious adverse reaction to any vaccine, any unrelated medication or any component of the investigational vaccine, including a history of anaphylaxis and symptoms of a severe allergic reaction and history of allergies in the past.
2. Confirmed current COVID-19, previous SARS-CoV-2 infection in the last < 3 months, or PCR positive for SARS-CoV-2 at screening
3. Vaccinated with an EAU-approved vaccine against COVID-19 in the last < 3 months.
4. Pregnant or breastfeeding women
5. Any participants with a history of myocarditis or pericarditis.
6. Chronic lung disease (included COPD) as evidenced by one or more exacerbations requiring a course of steroids in the last year, or the requiring chronic low dose oral steroids to prevent exacerbations. Uncontrolled asthma, defined as requiring reliever inhaler (short-acting beta agonist or ipratropium bromide) more than twice a week is also excluded.
7. Bone marrow or organ transplant recipient
8. Extreme obesity (defined as BMI of 40 kg/m^2 or higher).
9. Chronic kidney disease requiring dialysis.
10. History of liver disease.
11. Any disease associated with acute fever, or any infection.
12. Participants with acquired or hereditary immunodeficiencies other than well-controlled HIV are excluded from enrollment.
13. Current diagnosis of active tuberculosis.
14. History of hereditary, idiopathic or acquired angioedema.

15. No spleen or functional asplenia.
16. Chronic use (more than 14 continuous days) of any medications that may be associated with impaired immune responsiveness including, but not limited to, systemic corticosteroids exceeding 10 mg/day of prednisone equivalent, allergy injections, immunoglobulin, interferon (IFN), or immunomodulators. The use of low dose topical, ophthalmic, inhaled and intranasal steroid preparations will be permitted.
17. According to the judgement of the investigator any medical, psychiatric, psychological, social, occupational or other conditions that could affect the participants ability to sign informed consent, provide safety assessment data or comply with the requirements of the study protocol.
18. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

Duration of Treatment:

For most participants, treatment will be confined to study day 1. For participants in experimental arm 3 of the phase 2 study, treatment will occur on day 1 and day 29.

Duration of Follow-up:

Participants who receive study treatment will be followed by a health care professional until either death (by any cause) or for 1 year past first administration of vaccine.

Reference Therapy, Dosage, and Mode of Administration:

Janssen or Pfizer-BioNTech vaccine.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of treatment-emergent MAAEs, SAEs, reactogenicity AEs, unsolicited AEs, safety laboratory tests and vital signs. Toxicities will be graded using the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

Immunogenicity: Immunogenici y endpoints will include GMT of IgG binding antibodies and GMT of neutralizing antibodies. T-Cell activity against SARS-CoV-2 will be assessed.

Statistical Methods:

The purpose of this phase 1/2 study is to determine the safety, reactogenicity, and immunogenicity of saRNA COVID-19 boost vaccines in participants that have been previously vaccinated against or previously infected with COVID-19. Participants enrolled will include individuals previously vaccinated against COVID-19 or previously infected with COVID-19 > 3 months prior to enrollment.

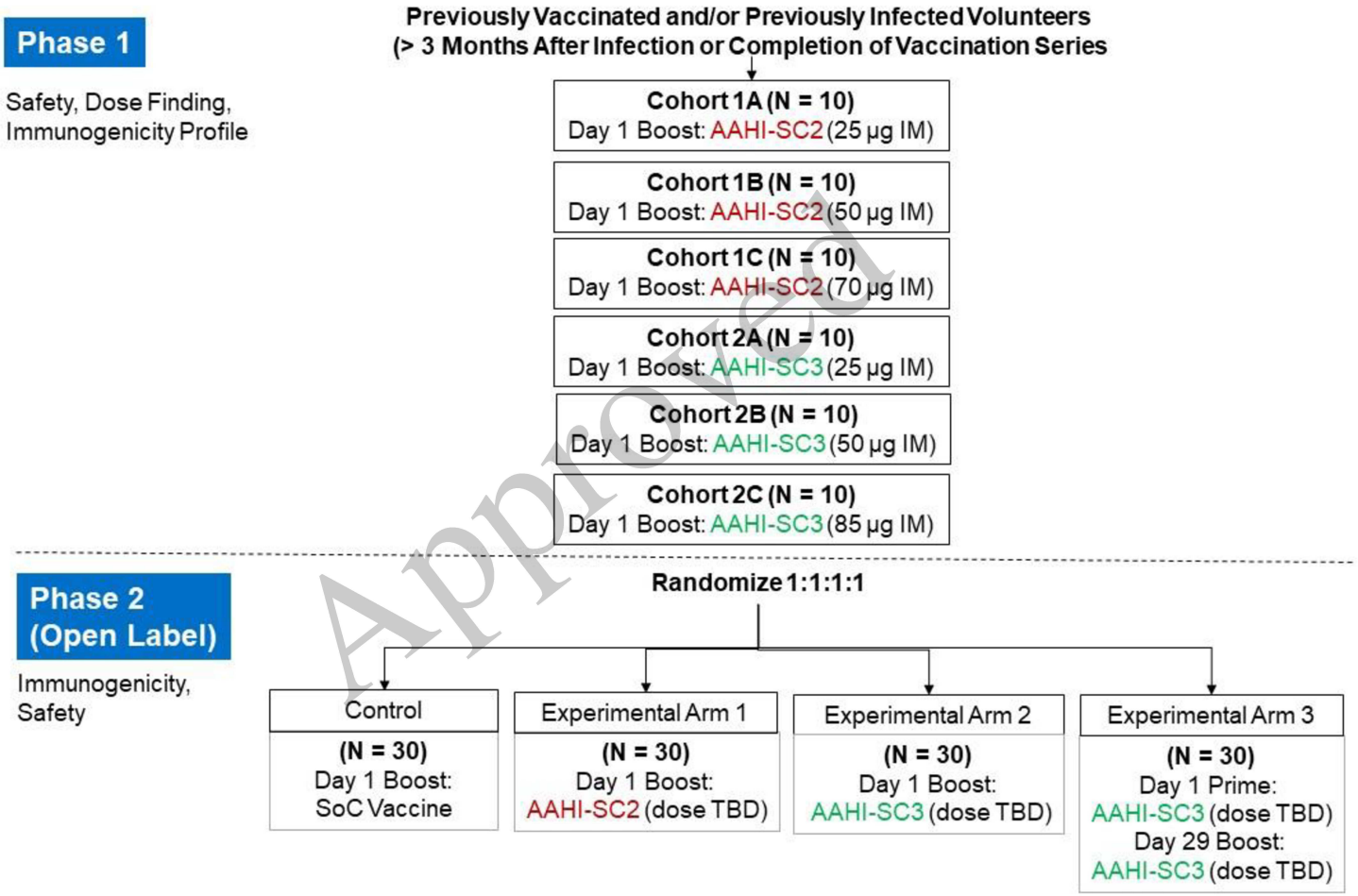
The phase 1 study is a single arm, open-label study. The phase 2 study is a randomized open-label study. For the phase 2 study, laboratory analyses of immunogenicity assessments will be performed blind to participants' vaccine treatment on study. Results for phase 1 will be summarized by cohort and results for phase 2 will be summarized for each randomized arm.

Descriptive statistics will be presented for all study endpoints. No statistical comparisons of the phase 2 arms is planned.

Safety Analyses: Safety will be assessed by the incidence of treatment-emergent MAAEs, SAEs, and solicited local and systemic reactogenicity AEs, and unsolicited AEs for the time period of interest, overall and by grade using the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). Clinically significant changes in safety laboratory tests and vital signs also will be summarized.

Immunogenicity Analyses: GMTs and their associated 95% confidence intervals (CIs) will be computed by exponentiation of the corresponding log-transformed means and 95% CIs. T cell activity will be summarized.

Figure 1: Study Schema – Previously Vaccinated/Infected Participants



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

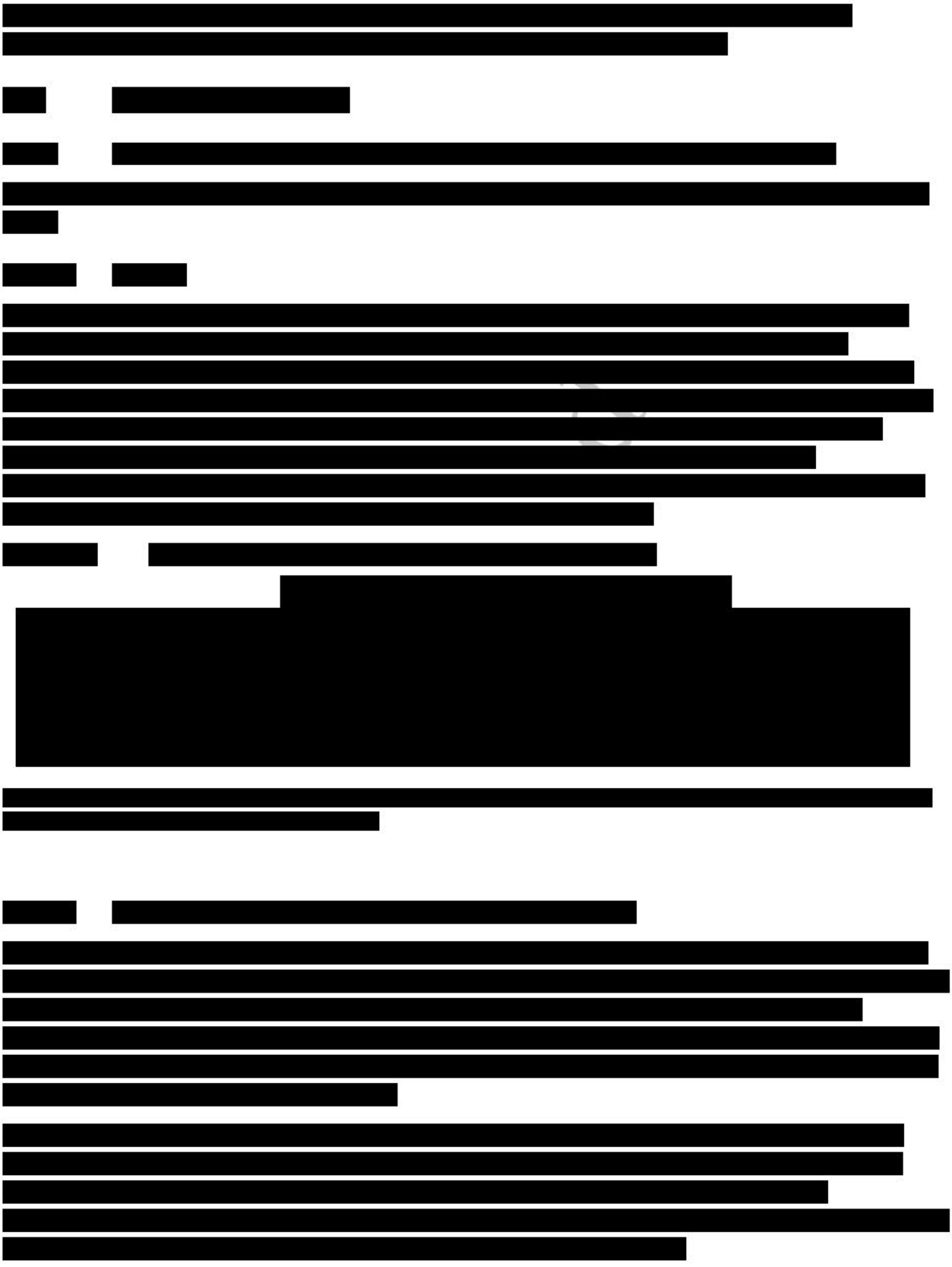
Abbreviation or Specialist Term	Explanation
β-HCG	β-Human chorionic gonadotropin
ACE2	Angiotensin converting enzyme 2
Ad5	Adenovirus serotype 5
ARDS	Acute respiratory distress syndrome
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAU	Binding antibody units
BSL	Biosafety level
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CMI	Cell mediated immunity
COVID-19	Coronavirus disease 2019
CRF	C se report form
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunosorbent spot assay
EOS	End of study
ETSD	Enhanced T cell stimulation domain
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
hAd5	Human adenovirus serotype 5

Abbreviation or Specialist Term	Explanation
hAd5 [E1-,E2b-,E3-]	Adenovirus serotype 5 with deletions in E1, E2b and E3
hAd5-Null	Vaccine vector control with no SARS-CoV-2 antigen encoded
hAd5-S-Fusion+N-ETSD	Vaccine containing both full length wild type SARS-CoV-2 spike gene optimized for better spike protein expression, and full length wild type SARS-CoV-2 nucleocapsid gene modified to also contain an enhanced T cell stimulation domain (ETSD) to enhance cell-mediated immunity
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
ICS	Intracellular cytokine staining
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin
IHC	Immunohistochemistry/immunohistochemical
IL	Interleukin
IM	Intramuscular
IP	Investig tional product
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous(ly)
LAMP	Loop-mediated isothermal amplification
MAAE	Medically attended adverse event
MoDC	Monocyte-derived dendritic cell
N	SARS-CoV-2 nucleocapsid antigen
NCI	National Cancer Institute
NHP	Non-human primate
NLC	Nanostructure lipid carrier
PBMC	Peripheral blood mononuclear cell
qPCR	Quantitative polymerase chain reaction
RBD	Receptor binding domain
RT	Reverse transcription
rvRNA	Replicating viral RNA

Abbreviation or Specialist Term	Explanation
S	SARS-CoV-2 spike antigen
SAE	Serious adverse event
SAP	Statistical analysis plan
saRNA	Self-amplifying RNA
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2, the causative agent of the COVID-19 pandemic
SC	Subcutaneous(ly)
SFC	Spot forming cells
SoC	Standard of care
SOP	Standard operating procedure
SRC	Safety Review Committee
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
VE	Vaccine Efficacy
VP	Viral particles
WBC	White blood cell

1. BACKGROUND AND STUDY RATIONALE

[redacted]



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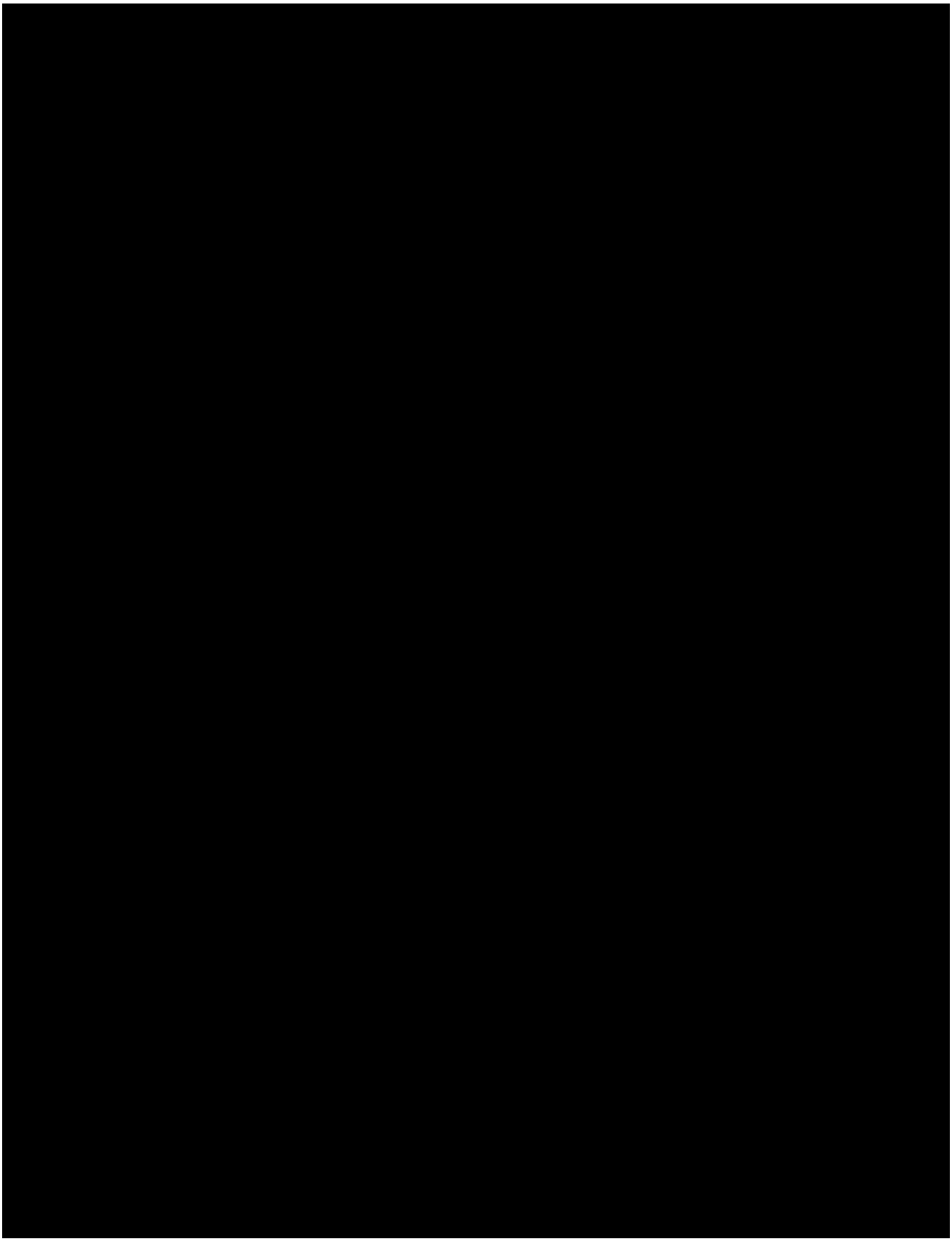

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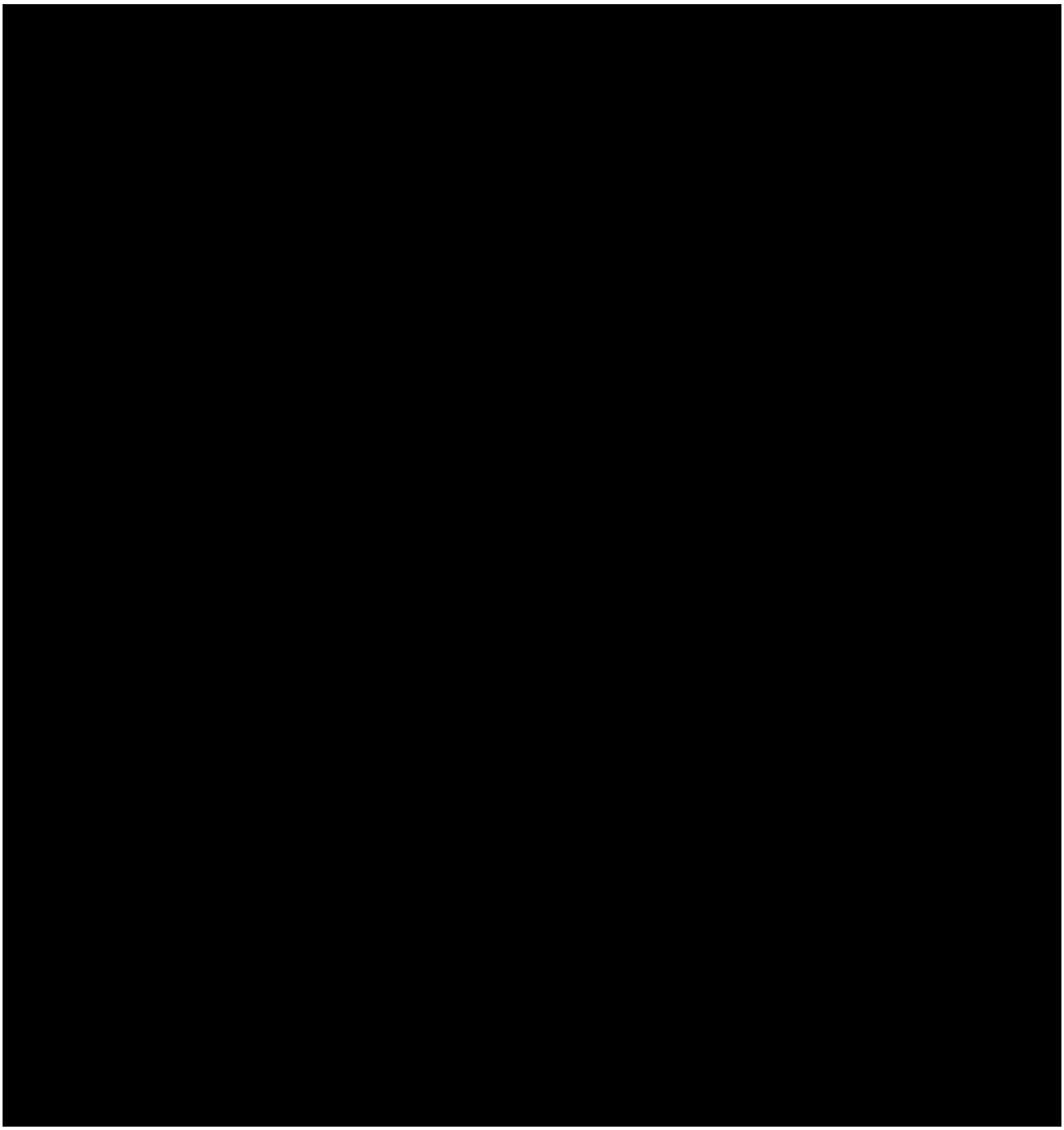

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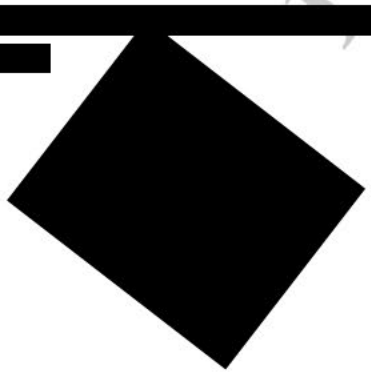

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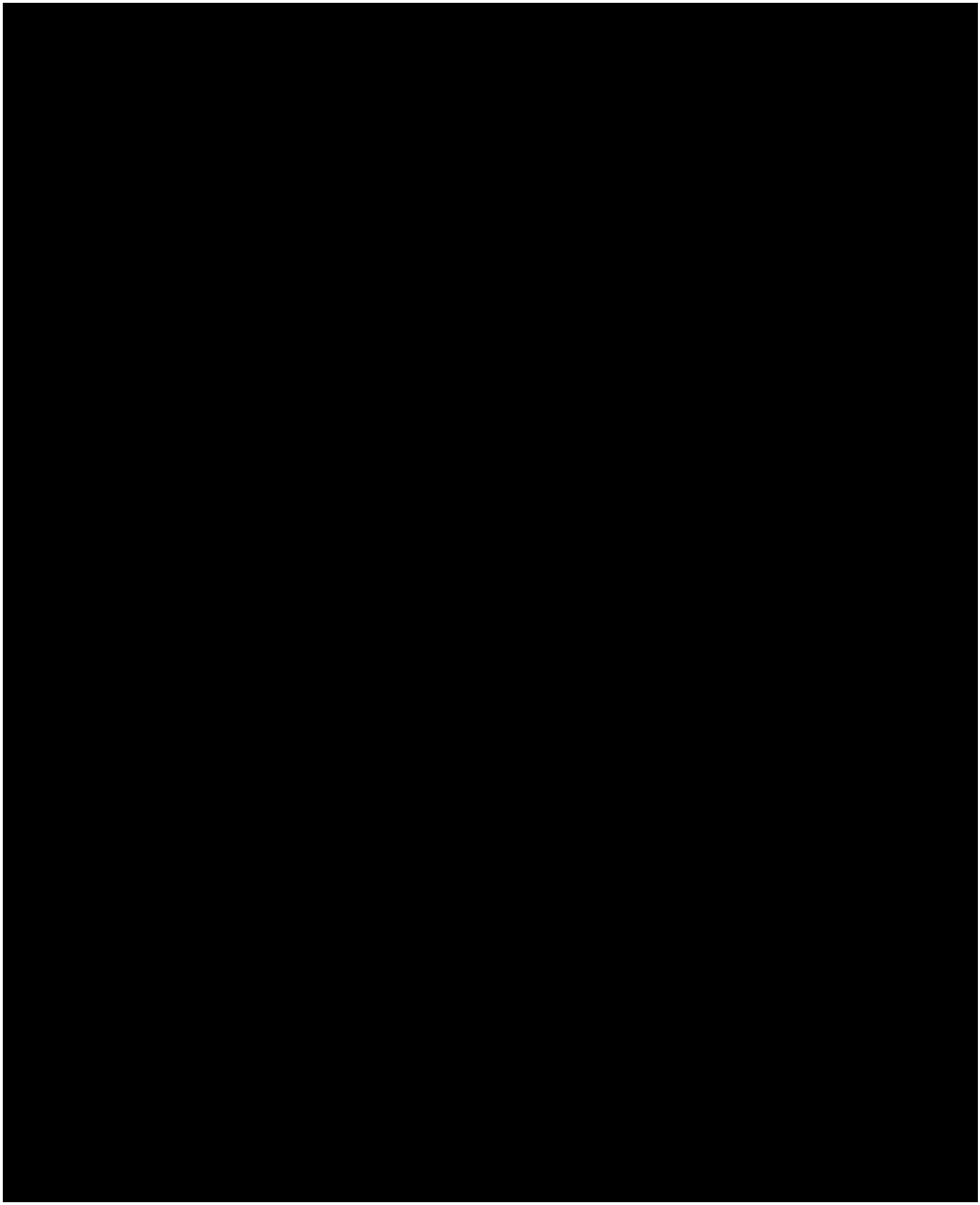

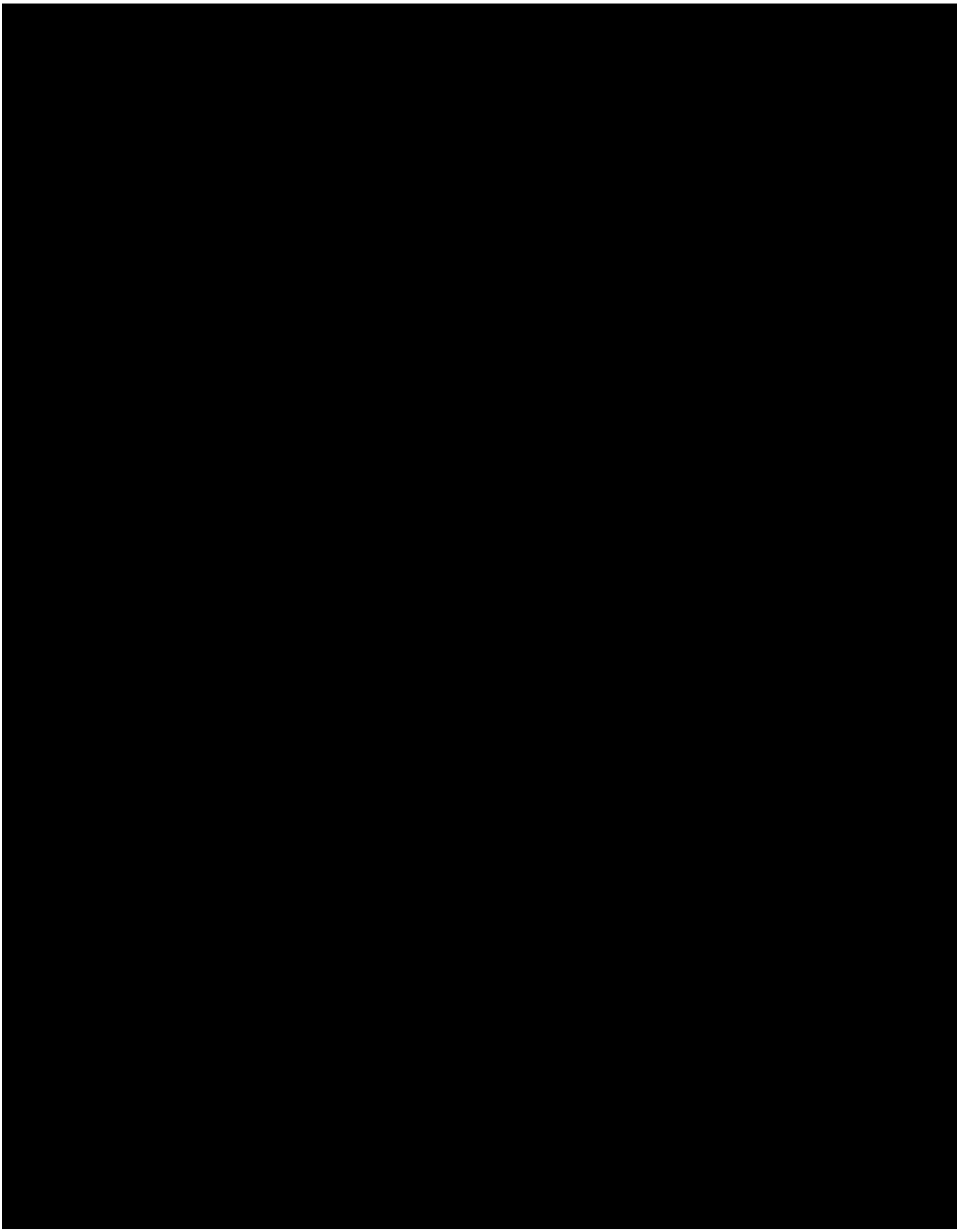

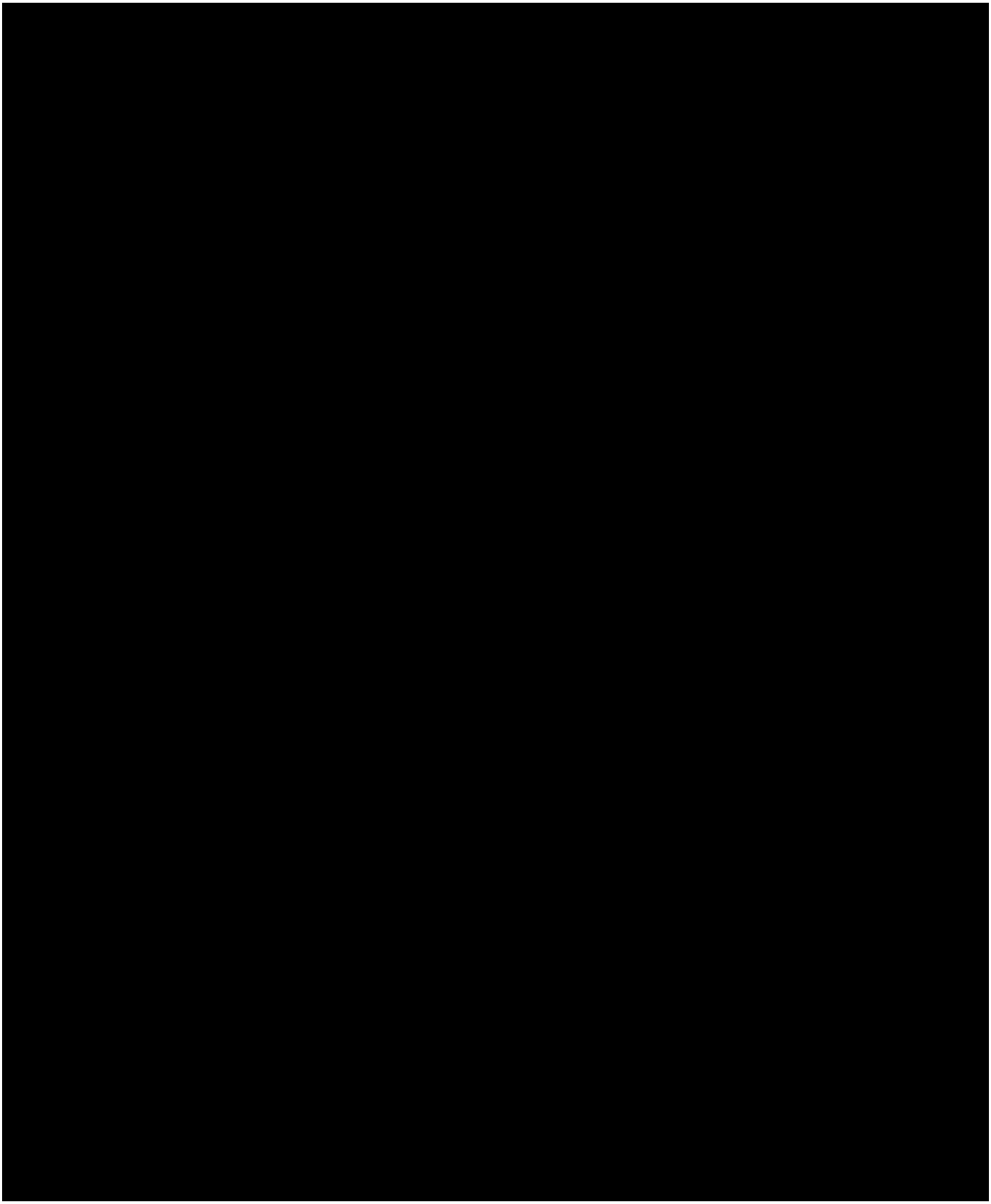

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2. STUDY OBJECTIVES

2.1. Phase 1

2.1.1. Primary Objective

- To determine the safety and reactogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines.

2.1.2. Secondary Objective

- To determine immunogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines, as determined by changes in humoral and cellular response.

2.2. Phase 2

2.2.1. Primary Objective

- To determine immunogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines, as determined by changes in humoral and cellular response.

2.2.2. Secondary Objectives

- To determine the safety and reactogenicity of homologous and heterologous vaccination with saRNA COVID-19 vaccines.