SARS-CoV-2-dMAB01

A PHASE 1, OPEN-LABEL, SINGLE-CENTER, DOSE ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF MAB AZD5396 AND MAB AZD8076 DELIVERED AS DMABS IN HEALTHY ADULTS

INVESTIGATIONAL PRODUCT(S):		dMAb AZD5396 and dMAb AZD8076 CELLECTRA™ 2000 with side port needle
STUDY NUMBER(S):	**IRB Number**	850355
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ABBREVIATIONS

ADA	Anti-drug antibodies
ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBC	Complete Blood Count
Cl	Chloride
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
Cr	Creatinine
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
dMAb™	DNA-encoded Monoclonal Antibody (Inovio proprietary)
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ECM	Extracellular Matrix
eCRF	Electronic Case Report Forms
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	International Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular

IND	Investigational New Drug Application
INOVIO	Inovio Pharmaceuticals Inc.
IP	Investigational product
IRB	Institutional Review Board
ISO	International Organization for Standardization
MAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NCS	Not Clinically Significant
NHP	Non-human Primates
NLT	No Less Than
OHRP	Office for Human Research Protections
pDNA	Plasmid DNA
PI	Principal Investigator
PHI	Protected Health Information
PK	Pharmacokinetic
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
RBC	Red blood cell
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SID	Participant Identification Number
SAP	Statistical Analysis Plan
DSMB	Data Safety Monitoring Board / Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
SSC	Saline Sodium Citrate
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
VAS	Visual Analog Scale
WBC	White blood cell
WOCBP	Women of Child-Bearing Potential

1 STUDY SUMMARY

1.1 Synopsis

Title:	A Phase 1, Open-Label, Single Center, Dose Escalation Study of the Safety and Pharmacokinetics of mAb AZD5396 and mAb AZD8076 delivered as dMAbs in Healthy Adults
Short Title:	dMAbs for Prevention of COVID-19
Study Description:	This is a Phase 1, open-label, single center, dose escalation study to evaluate the safety, tolerability and pharmacokinetic profile of mAb AZD5396 and mAb AZD8076 following delivery of optimized dMAb AZD5396 and dMAb AZD8076 with Hylenex® Recombinant, administered by intramuscular injection (IM) followed immediately by electroporation (EP) using the CELLECTRA™ 2000 with Side Port needle device, in a 2- to 4-dose regimen (Days 0, 3, 28, and 31) in healthy adults. Our hypothesis is that the administration of dMAb AZD5396 and dMAb AZD8076 will be safe and associated with expression of mAb AZD5396 and mAb AZD8076 in serum.
Objectives:	**Primary Objectives:** • Describe the safety profile of all subjects in each study group • Describe the pharmacokinetics of mAb AZD5396 and mAb AZD8076 (delivered by the administration of dMAb AZD5396 and dMAb AZD8076 with Hylenex® administered IM followed by EP with the CELLECTRA™ 2000 device). **Exploratory Objective:** • To determine the antiviral activity of plasma of participants in the study when tested in an animal model of SARS-CoV-2 virus infection 28 days after the administration of dMAb AZD5396 and dMAb AZD8076. • To evaluate the incidence of new SARS-COV-2 infection for the duration of the study
Primary Endpoints:	**Primary Endpoints:** **Safety** Safety will be described for all subjects: • Occurrence, nature (MedDRA systemic organ class [SOC] and preferred term [PT]), time to onset, number of days of occurrence, intensity, and relationship to investigational product of injection site reactions and systemic reactions occurring up to 7 days after administration of the investigational product • Occurrence, nature (MedDRA SOC and PT), time to onset, relationship to investigational product and outcome of SAEs throughout the study • Visual analogue scale (VAS) and (see comment) scores for injection site pain up to 7 days after administration of the investigational product • Occurrence of out-of-range from baseline biological test results up to 7 days post-last dose **Pharmacokinetics** • Detection of mAb AZD5396 and mAb AZD8076 serum following administration of dMAb AZD5396 and dMAb AZD8076 with Hylenex® delivered IM followed by EP with the CELLECTRA™ 2000 device.

	Exploratory Endpoints: • Neutralizing antibody titers measured with the neutralization assay • Neutralizing antibody titer against SARS-COV-2 during the study • Frequency of SARS-COV-2 infection in animal models treated with passive transfer of serum from participants. • Frequency of new SARS-COV-2 infection among participants in the study
Study Population:	Up to 50 healthy adults, 18 to 60 years of age, to get the numbered of required evaluable participants in each cohort
Phase:	Phase I
Enrolling Sites:	University of Pennsylvania
Description of Study Intervention:	Administration of dMAb AZD5396 and dMAb AZD8076 with Hylenex® delivered intramuscularly (IM) using the side port needle followed by electroporation (EP) with the CELLECTRA™ 2000 device
Participant Duration:	18 Months

2 INTRODUCTION AND RATIONALE

2.1 Background

2.1.1 SARS-CoV-2 Virus Epidemiology and Clinical Illness

The COVID-19 disease pandemic is a global health crisis. COVID-19 is characterized by a mild-to-severe respiratory illness including fever, cough, and difficulty breathing, and in the most severe cases can require mechanical ventilation or even lead to death. In the US alone, as of June 17, 2023, there were > 103,436,829 confirmed cases of COVID-19 and > 1,132,872 related deaths.[24] The COVID-19 pandemic has had a severe impact on the health system and will likely have lasting social and economic impact. Medical countermeasures are urgently needed.

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness.

2.1.2 Current Treatment

Several interventions and drugs have proven effective to prevent and treat COVID-19 and several of them have received Emergency use authorization (EUA) by the FDA.

Management of non-hospitalized patients with acute COVID-19 includes providing supportive care, reducing the risk of transmission to others and advising patients on when to contact a health care provider to seek an in-person evaluation.

Anti-SARS-CoV-2 mAbs have proven useful for both prevention of disease (PEP) for people who have risk factors for infection and progression to severe COVID-19 after an exposure and also for treatment of COVID-19 among those who are not sick enough to require hospitalization and are at high risk of progressing to severe COVID-19.

Bamlanivimab plus etesevimab and casirivimab plus imdevimab received EUA for use as post exposure prophylaxis (PEP), and both products, sotrovimab and bebtelovimab, also received EUA for treatment of patients with COVID-19 that do not require hospitalization and can be treated in the outpatient setting. Subsequently, with the spread of the Omicron strain, none of them presently retain the authorization to be used in the US. Astra Zeneca also received an EUA for their mAb combination product (Evusheld, the combination of the two long-acting antibodies AZD8895 and AZD1061, tixagevimab with cilgavimab) use as pre-exposure prophylaxis (prevention) of COVID-19 in certain adults and pediatric patients (December 8th, 2021, modified on 2/24/2022). The Evusheld EUA was revised in January 2023 given lack of efficacy against >90% of newer SARS-CoV-2 variants. If variants of a particular virus regain sensitivity to Evusheld, then Evusheld would be the only effective preventive measure before exposure. In such a scenario, the emergency use authorization (EUA) for other prophylactic measures might be reconsidered or reviewed.

Monoclonal antibodies have not been approved for the management of hospitalized patients with COVID-19; for these types of patients the antiviral remdesivir, the corticosteroid dexamethasone, the JAK inhibitor baricitinib (and tofacitinib), and the IL-6 antagonists tocilizumab or sarilumab are used alone or in combinations for the treatment of the most severe cases of the disease.

2.1.3 Broadly Neutralizing Antibodies against SARS-CoV-2

Neutralizing antibodies (nAbs) are specific types of antibodies that can prevent transmission by blocking virus entry into the uninfected target cells by blocking the virus receptor interaction and via additional mechanisms like antibody dependent cell-mediated cytotoxicity (ADCC).

Monoclonal antibodies that target the spike protein of SAR-CoV-2 have been shown to have a clinical benefit in treating SARS-CoV-2 infection. Preliminary data suggest that monoclonal antibodies may play a role in preventing and treating SARS-CoV-2 infection in household contacts of infected patients and during skilled nursing and assisted living facility outbreaks.

Several anti-SARS-CoV-2 monoclonal antibody products currently have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization: bamlanivimab plus etesevimab; casirivimab plus imdevimab, sotrovimab and bebtelovimab. With the spread of the Omicron strain, as of March 2023, none of them retain the authorization to be used in the US. An EUA does not constitute FDA approval.

AstraZeneca has identified and characterized 2 lead mAb biologic candidates that will be developed into dMAbs. The two candidates (AZD8895 and AZD1061, tixagevimab with cilgavimab) were isolated from B cells derived from two COVID-19 convalescent patients and specifically target the SARS-CoV-2 spike protein receptor binding domain (RBD). They demonstrate nanogram per mL potency in neutralization assays using live SARS-CoV-2 virus and do not compete with one another as they bind to distinct epitopes on the RBD. The two mAbs demonstrate synergistic activity in vitro and protect

animals from a live virus challenge in both an Adenovirus-ACE-2 mouse and a mouse-adapted virus challenge models.

Recently the results of the Astra Zeneca's PROVENT Phase III pre-exposure prophylaxis trial showed AstraZeneca's AZD7442 (Evusheld, the combination of the two long-acting antibodies AZD8895 and AZD1061, tixagevimab with cilgavimab) achieved a statistically significant reduction in the incidence of symptomatic COVID-19, the trial's primary endpoint.

Evusheld reduced the risk of developing symptomatic COVID-19 by 77% (95% CI 46- 90), compared to placebo. AZD7442 was optimized using YTE substitution to increase its half-life and the TM substitution that reduced Fc receptor and complement C1q binding, theoretically reducing the risk of antibody dependent enhancement. In the study, there were no cases of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442. In the placebo arm, there were three cases of severe COVID-19, which included two deaths.

AZD7442 (Evusheld) is the first antibody combination (non-vaccine) modified to potentially provide long-lasting protection that has demonstrated prevention of COVID-19 in a clinical trial. Evusheld received Emergency Use Authorization (EUA) in the US in December 2021 for pre-exposure prophylaxis (prevention) of COVID-19 in people with moderate to severe immune compromise due to a medical condition or immunosuppressive medications and who may not mount an adequate immune response to COVID-19 vaccination, as well as those individuals for whom COVID-19 vaccination is not recommended. Subsequently (2/24/2022), the US Food and Drug Administration has amended the Emergency Use Authorization. The revised authorized dosage regimen in the US is an initial dose of 300mg of tixagevimab and 300mg of cilgavimab, delivered in two consecutive, sequential intramuscular (IM) injections.

The early data, generated by pseudovirus testing of the full Omicron variant spike against the combination of tixagevimab with cilgavimab, the antibodies that comprise Evusheld, add to the growing body of evidence demonstrating that Evusheld retains activity against all tested variants of concern to date, including early Omicron lineages. However, the Evusheld EUA was revised in January 2023 given lack of efficacy against >90% of newer SARS-CoV-2 variants. If variants of a particular virus regain sensitivity to Evusheld, then Evusheld would be the only effective preventive measure before exposure. In such a scenario, the emergency use authorization (EUA) for other prophylactic measures might be reconsidered or reviewed.

2.1.4 AZD8076 and AZD5396

AZD8895 and AZD1061 (Evusheld, the combination of the two long-acting antibodies AZD8895 and AZD1061, tixagevimab with cilgavimab) are the parent antibodies of AZD8076 and AZD5396. The only difference between the two is the TM substitution that reduces Fc receptor and complement C1q binding was reverted to wild type. The reason for this reversion is that anti SARS-Cov-2 antibodies that have effector function like Bamlanivimab plus etesevimab and casirivimab plus imdevimab have proven safe and effective in the treatment of patients with COVID-19 and their use have not been associated with ADE.

Early during the COVID-19 pandemic, there was the concern for potential antibody dependent enhancement (ADE) with mAb biologics. To-date is little evidence of ADE with mAb biologics in clinical trials, with COVID-19 vaccines or with natural infection in people. Individuals who have

received COVID-19 vaccines are displaying less severe disease if they subsequently become infected with diverging SARS-CoV-2 variants of concern.

Multiple groups are highlighting the importance of mAb Fc effector function for optimal protective and therapeutic efficacy against SARS-CoV-210-12.

2.1.5 Limitations of Monoclonal Antibodies

Although antibodies can be highly effective for prevention of infectious diseases, they have limited prophylactic use due to biologic half-life and the complexities of IV administration. Monoclonal antibodies (mAbs) have a proven track record in the clinic for many years for antineoplastic, immunological indications and for the prevention and treatment of infectious diseases. However, to maintain protective levels of mAbs, repeated high dose bolus injections are required. For example, palivizumab (Synagis®), a recombinant mAb indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients, not only requires dosing of subjects prior to beginning of the RSV season but also monthly thereafter throughout the active season to be effective. More recently, half-life extended mAbs with t1/2 ranging from 70 to 130 days have been shown to be safe[1-3] and, nirsevimab, a high-potency RSV mAb has been shown to be effective in preventing RSV medically attended lower respiratory tract infections[4]. Additionally, production of recombinant mAb biologics in bioreactors is time intensive and costly, making their use prohibitive in low resource settings such as field clinics and during deployment, especially during a pandemic. Therefore, alternative approaches should be evaluated.

In practice, despite the EUA approval of monoclonal antibodies to treat and prevent COVID-19, hospitalization and death, this resource has been underutilized because of both logistical (number of available infusion beds and nurses able to administer the product) and supply constraints (enough availability of product). Intravenous mAb delivery can require several hours, and high doses for infusion and follow up are significant obstacles for quick administration. Additional solutions to deliver these life-saving biologics are needed.

2.1.6 The dMAb Platform

The dMAb platform represents a novel application of DNA plasmid technology that could change mAb delivery as an approach for protection and treatment of infectious diseases. Plasmid DNA (pDNA) is engineered to encode immunoglobulin heavy and light chain genes for direct delivery into animal or human tissue, resulting in in vivo expression of dMAb (Figure 1). The enabling delivery technology of in vivo electroporation (EP) is employed to efficiently transport pDNA into the muscle tissue. This innovative approach simplifies mAb administration by utilizing the body's cells as biological factories to produce and secrete mAbs directly into circulation to control infection. pDNA is non-integrating, non-infectious, and does not induce immune responses directed against the vector backbone. The resulting dMAbs are therefore nonpermanent, enabling transient in vivo gene-encoded mAb production. We recently demonstrated that biologically relevant levels of functional dMAbs can be achieved in vivo that protect in several infectious disease models in small animals[5-9]. Initial NHP pharmacokinetic (PK) studies demonstrate in vivo dMAb expression for up to 56 days. In one study, protection against virus infection was demonstrated following dMAb delivery[7]. Key optimizations in dMAb design, delivery, formulation, and validation are included to improve in vivo dMAb expression to tackle the challenge of preventing SARS-CoV-2 infection.

Figure 1. Overview of in vivo dMAb expression

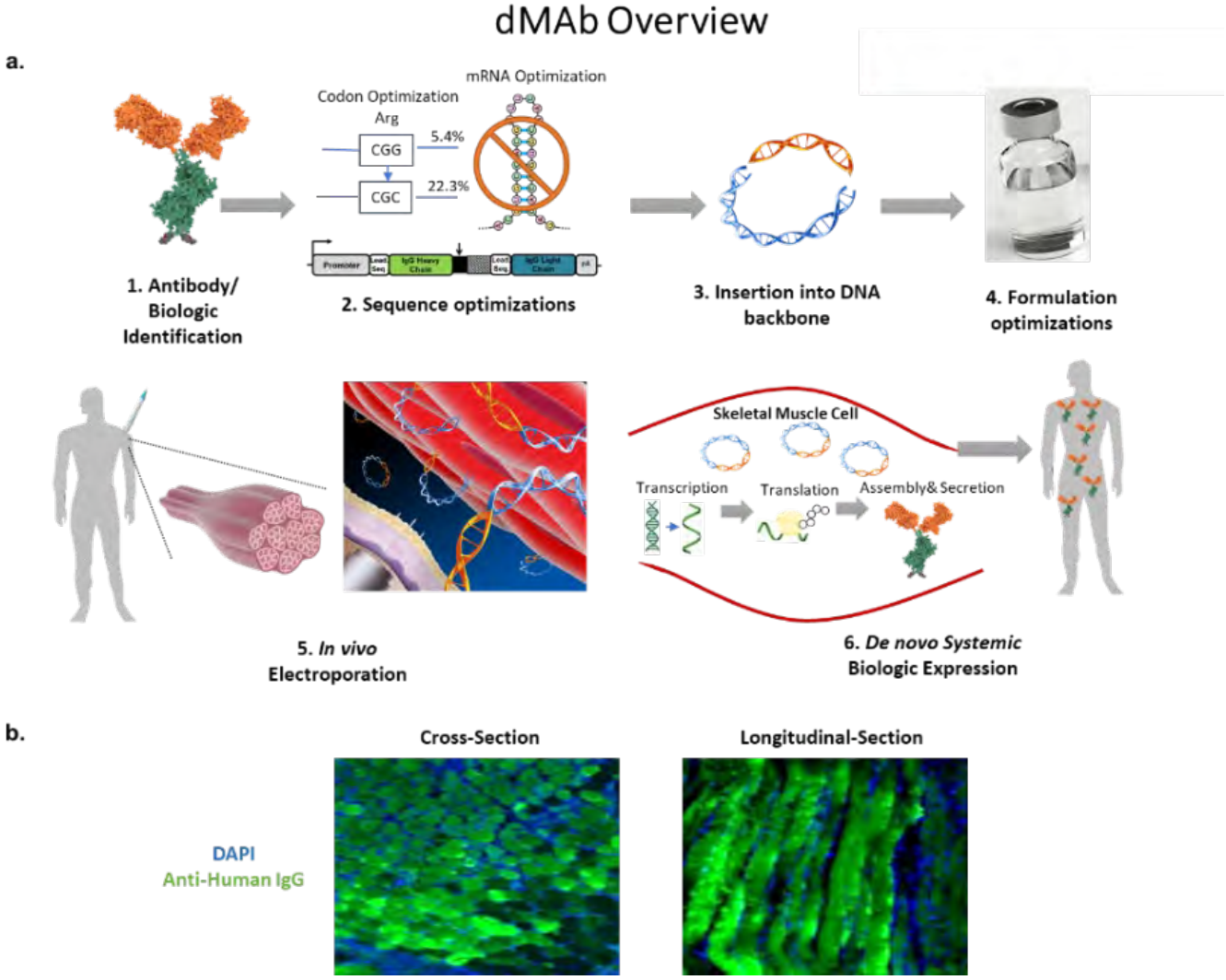


Figure 1: Overview of in vivo dMAb expression. A.1) A protective mAb is identified. 2) The sequence undergoes amino acid and nucleotide optimization to enhance in vivo expression. 3) The optimized sequences is inserted into a pDNA expression vector and 4) formulated for delivery. 5) dMAb-encoding DNA is delivered in vivo via injection and in vivo electroporation. 6) dMAbs are expressed and secreted into circulation. B. Example of in vivo dMAb expression in mouse muscle sections.

2.1.7 Prior Human Experience with dMAbs

A first in human safety and proof-of-concept study of a dMAb targeted against Zika virus has completed enrollment. In this Phase 1, open label, single center, dose escalation study, we evaluated the safety, tolerability and PK profile following delivery of INO-A002 with Hylenex® delivered IM followed by EP with the CELLECTRA™ 2000 device in 30 healthy adult Dengue naive volunteers 18 to 60 years of age (NCT03831503). The administration of INO-A002 A002 has been well-tolerated to date. This study used Inovio's initial plasmid design, early formulation, and single needle delivery. In more recent NHP studies, using second generation plasmids, Ig design, and improved formulations with device

modifications, 10-30 µg/ml human dMAb expression was detected in NHP studies. Our proposed studies utilize these advances and will build on additional developments for clinical advancement.

Although vaccines will be the ultimate prevention approach to COVID-19 disease, the limitation of vaccines is the lag time between the immunization and the development of a protective immune response which could take several weeks. This lag time is not ideal during the exponential growth phase in a pandemic situation, or for urgent situations. A solution is dMAb delivery in combination with COVID-19 vaccine which has the potential to provide both immediate and long-lasting (persistent) protection against COVID-19. DNA vaccines are not neutralized by serology; therefore, they can be uniquely advanced as a combined modality. Published preclinical data with the DNA platform from our team supports that this combination is effective in viral models.

2.2 Study Rationale

This trial proposes the use of DNA-encoded monoclonal antibodies (dMAbs) to provide pre-exposure prophylaxis against SARS-CoV-2. dMAbs are a unique synthetic nucleic acid platform for in vivo delivery of protective mAb providing a broad countermeasure for COVID-19 infection.

2.2.1 dMAbs for COVID 19 prevention

Achieving consistent, high in vivo expression levels is the major technical challenge with most gene-encoded antibody platforms. To address this challenge, our team has invested significant resources in the areas of 1) sequence optimization[9,10]; 2) formulation optimization[11]; and 3) delivery optimizations in large animal models such as non-human primates (NHPs) and pigs. As part of SARS-CoV-2 dMAb preclinical development, we will employ these three strategies to ensure high levels of in vivo expression.

This study directly addresses the need for preventative medical countermeasures against SARS-CoV-2. dMAbs have the potential to be delivered as pre-exposure prophylaxis to at-risk populations such as the warfighter and other military personnel, health-care workers, and other vulnerable populations such as the elderly, also in combination with vaccination. In addition to prevention, dMAbs may be a treatment option for exposed individuals.

2.2.2 Dosing Rationale

The optimal dose and dosing regimen for dMAb AZD5396 (mAb AZD2130 encoded via DNA plasmid) and dMAb AZD8076 (mAb AZD2196 encoded via DNA plasmid) are as yet uncharacterized. In addition to safety, this study will assess 4 different doses to evaluate the pharmacokinetic profile of mAb AZD5396 and mAb AZD8076 expression following administration of dMAb AZD5396 and dMAb AZD8076. Preclinical studies of dMAb AZD5396 and dMAb AZD8076 in rhesus macaques assessed a 2 mg dose and demonstrated clinically detectable levels of mAb AZD5396 and mAb AZD8076 in the circulation for up to 49 days following the last dose of AZD5396 and AZD8076.

The dose was selected to deliver the maximum amount of plasmid DNA within the volume and concentration limitations of the final product and available animal data. Five doses will be tested, ranging from 0.25 to 4 mg, in 8 cohorts.

Electroporation using the CELLECTRA™ 2000 device with side port needle will follow seconds after injection of the dose.

2.2.3 Rationale for Electroporation

Several groups are developing methods to improve the expression of DNA-based therapeutic proteins and vaccines, using genetic optimization (including use of highly concentrated DNA formulations, multiple RNA optimizations, and addition of improved leader sequences) and alternative cellular delivery (i.e. EP)[12]. Electroporation is a physical process that exposes the target tissue to a brief electric field pulse that induces temporary and reversible pores in the cell membrane to enhance the cellular uptake of large molecules such as DNA. By temporarily increasing the permeability of cell membranes, EP has been shown to be an efficient way to introduce DNA into cells[13,14] and to increase the expression level of antigens encoded by DNA[15]. This technology has been used for more than three decades by molecular biologists for in vitro cell transfection and is now being employed by Inovio in the clinic for delivery of plasmid DNA vaccines and immunotherapies.

The CELLECTRA™ EP device can efficiently transfer plasmid DNA into cells to enable gene expression. This method of delivery has great potential for gene transfer and prophylactic and therapeutic vaccination, as has been demonstrated in animal studies[16]. EP has been extensively used in large animal species, such as dogs, pigs, cattle, and NHP, to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens[17] that can activate both cellular and humoral responses in animal models[16,18]. The IM delivery of DNA with EP is well studied, and optimum conditions for plasmid uptake and expression are described for therapeutics, vaccines and tumor animal model systems[19,20]. Inovio Pharmaceuticals has developed the CELLECTRA™ 2000 device which utilizes a novel constant current process for IM EP[17].

2.3 Risk/Benefit Assessment

In accordance with the International Conference on Harmonization (ICH), this study has been designed to minimize risk to study participants. Potential risks of study products and administration from studies using similar plasmids with the identical DNA backbone are listed in Table 1.

The potential side effects of treatment with the investigational products may include but are not limited to discomfort related to the inoculation administration and electroporation technique such as local edema, swelling, or pain. Systemic side effects observed with vaccines based on the identical backbone have been demonstrated to be generally minimal in more than 3500 participants. The potential benefit is to determine whether this inoculation could generate immune responses with potential to be sufficient as prophylactic treatment for those at risk for SARS-CoV-2 virus infection.

Table 1. Expected Risks of dMAb AZD5396 and dMAb AZD8076 and Hylenex® Recombinant (Hyaluronidase) Delivered IM with EP using CELLECTRA™ 2000 with side port needle

Frequency [a]	Event
Very Common (≥10%)	Mild Injection site pain or tenderness Moderate Injection site pain or tenderness Injection site erythema or redness Injection site swelling, hardness, or scabbing Injection site pruritus Not feeling well (fatigue, muscle aches, joint pain or headache)
Common (≥1% to <10%)	Pyrexia
Uncommon (≥0.1% to <1%)	Severe Injection site pain or tenderness Injection site bruising Nausea, lightheadedness or dizziness
Rare (≥0.01% to <0.1%)	None
Very Rare (<0.01%)	Allergic reaction

[a] Defined per CIOMS

For further details, see the Investigator Brochure.

There are insufficient data currently available to determine severity expectedness. Of all data generated to date with plasmids other than dMAb AZD5396 and dMAb AZD8076 using similar backbone, most events have been mild to moderate with few reported as severe. There may be side effects and discomforts that are not yet known.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives

1. Describe the safety profile of all subjects in each study group
2. Describe the pharmacokinetics of mAb AZD5396 and mAb AZD8076 (administered as dMAb AZD5396 and dMAb AZD8076) with Hylenex® given IM followed by EP with the CELLECTRA™ 2000 device.)

3.2 Primary Safety Endpoints

Safety will be described for all subjects:

1. Occurrence, nature (MedDRA systemic organ class [SOC] and preferred term [PT]), time to onset, number of days of occurrence, intensity, and relationship to investigational product of injection site reactions and systemic reactions occurring up to 7 days after administration of the investigational product
2. Occurrence, nature (MedDRA SOC and PT), time to onset, relationship to investigational product and outcome of SAEs throughout the study

3. Visual analogue scale (VAS) and (see comment) scores for injection site pain up to 7 days after administration of the investigational product
4. Occurrence of out-of-range from baseline biological test results up to 7 days post-last dose

3.3 Primary Pharmacokinetic Endpoint

1. Detection of mAb AZD5396 and mAb AZD8076 serum following administration of dMAb AZD5396 and dMAb AZD8076 with Hylenex® delivered IM followed by EP with the CELLECTRA™ 2000 device.

3.4 Exploratory Objectives

1. To determine the Neutralizing SARS-COV-2 antibody titers of participants during the study.
2. To determine the antiviral activity of plasma of participants in the study when tested in an animal model of SARS-CoV-2 virus infection after the administration of dMAb AZD5396 and dMAb AZD8076.
3. To evaluate the incidence of new SARS-COV-2 infection for the duration of the study.

3.5 Exploratory Endpoint

1. Neutralizing antibody titer against SARS-COV-2 during the study
2. Frequency of SARS-COV-2 infection in animal models treated with passive transfer of serum from participants.
3. Frequency of new SARS-COV-2 infections for the duration of the study.

4 STUDY PLAN

4.1 Study Design

This will be a Phase 1, open label, single center, dose escalation study to evaluate the safety, tolerability, and pharmacokinetic profile of mAb AZD5396 and mAb AZD8076 following delivery of optimized dMAb AZD5396 and dMAb AZD8076 with different doses of Hylenex® Recombinant, administered by intramuscular injection (IM) followed immediately by electroporation (EP) using the CELLECTRA™ 2000 with side port needle device, in a five-dose (8 cohort) regimen in healthy adults.

Up to 50 healthy volunteers 18 to 60 years of age will be enrolled in this study and evaluated across eight cohorts (n=3 to 6 per cohorts A1, A2, B, C, and D; n=5 per cohorts E, F, and G). Participants will be administered dMAb AZD5396 and dMAb AZD8076 at a five-dose level of each plasmid:

0.5 mg single-dose (cohort A1),

1 mg single-dose (cohort A2),

1 mg two-dose (cohorts B and F),

2 mg two-dose (cohort C),

0.25 mg two-dose (cohort D),

4 mg two-dose (cohort E), and

2 mg four-dose (cohort G).

Participants will receive two injections (one per dMAb) into the arm (deltoid)/leg (quadriceps) region at Day 0 alone (groups A1 and A2) or on day 0 and 3 (groups B-F) or on days 0, 3, 28, 31 (cohort G). Injections may be given in different arms or in an arm (deltoid) and a leg (quadriceps). If preferred or needed both doses can be done in the deltoid region or the lateral quadriceps, although the injections should be in different areas separated by at least 2 cm. The Day 3 injections may repeat an area already used on Day 0 as long as separated by at least 2 cm. The Day 31 injections may repeat an area already used on Day 28 as long as separated by at least 2 cm. The Day 28 injections may repeat an area already used on Day 0 or Day 3 injections with no separation required given the time span between injections.

This study will adhere to a dose escalation scheme as described in Figure 2.

Participants will be enrolled sequentially beginning with Cohort A1. The first participant in cohort A1 will be dosed 0.5 mg of each product once on Day 0 following confirmation of eligibility criteria. If no stopping event (DLT) is observed (see Section 10.10) after 14 days of the initial dose, the remaining two participants in that cohort A1 will be dosed three days apart. If there are 0 DLT events after 14 days of the initial dosing of the third subject, cohort A2 will open and will follow the same schedule. Same process will be followed for the next cohorts with a total of 6 participants enrolled in each of cohort B to C (See Figure 2), 1 sentinel participant will be enrolled initially and, after 14 days of observation, the additional 5 participants will be enrolled three days apart each. If there are 0 DLT events past 14 days after the initial dosing of the last participant, the next cohort will open. Because cohorts D F, & G are a similar or lower dose and the safety profile have been already established in previous cohorts, the 14-day waiting periods will not apply to Cohorts D, F, or G. Even though the levels of expression observed in cohorts A-D are way below the levels seen when the monoclonal antibodies are given as protein, Cohort E will receive a higher dose which will require a 14 day waiting period after the dosing of the first participant at this level. Every participant in Cohort E following the 14 day waiting period will be dosed 3 days apart as done in other cohorts. Any DLT will be reported to the FDA in an expedited manner.

Table 2. Dosing Arms and Regimens

Cohort	Study Product	Dose Schedule	n	No. injections per dose (dose formulation in mg) 2 injections are given on each day	Hylenex dose per injection	Final volume per injection	EP parameters	Total dose of each dMAb (mg)
A1	dMAb AZD5396 and dMAb AZD8076	Day 0	3	1x (0.5 mg dMAb AZD5396) + 1x (0.5 mg dMAb AZD8076)	68U	0.5 mL	OpBlock 0078	0.5 mg dMAb AZD5396 + 0.5 mg dMAb AZD8076
A2	dMAb AZD5396 and dMAb AZD8076	Day 0	3	1x (1mg dMAb AZD5396) + 1x (1 mg dMAb AZD8076)	135U	1 mL	OpBlock 0078	1 mg dMAb AZD5396) + 1 mg dMAb AZD8076
B	dMAb AZD5396 and dMAb AZD8076	Day 0, 3	6 (3+3)	2x (0.5 mg dMAb AZD5396) + 2x (0.5 mg dMAb AZD8076)	66.5U	0.5 mL	OpBlock 0078	1 mg dMAb AZD5396 + 1 mg dMAb AZD8076
C	dMAb AZD5396 and dMAb AZD8076	Day 0, 3	6 (3+3)	2x (1 mg dMAb AZD5396) + 2x (1 mg dMAb AZD8076)	135U	1 mL	OpBlock 0078	2 mg dMAb AZD5396 + 2 mg dMAb AZD8076
D	dMAb AZD5396 and dMAb AZD8076	Day 0, 3	6 (3+3)	2x (0.25 mg dMAb AZD5396) + 2x (0.25 mg dMAb AZD8076)	34U	0.25 mL	OpBlock 0078	0.5 mg dMAb AZD5396 + 0.5 mg dMAb AZD8076
E	dMAb AZD5396 and dMAb AZD8076	Day 0, 3	5	2x (2 mg dMAb AZD5396) + 2x (2 mg dMAb AZD8076)	75U (0.5 mL)	0.70 mL	OpBlock 0078	4 mg dMAb AZD5396 + 4 mg dMAb AZD8076
F	dMAb AZD5396 and dMAb AZD8076	Day 0, 3	5	2x (0.5 mg dMAb AZD5396) + 2x (0.5 mg dMAb AZD8076)	75U (0.5 mL)	0.55 mL	OpBlock 0070	1 mg dMAb AZD5396 + 1 mg dMAb AZD8076
G	dMAb AZD5396 and dMAb AZD8076	Day 0, 3, 28, 31	5	4x (0.5 mg dMAb AZD5396) + 4x (0.5 mg dMAb AZD8076)	75U (0.5 mL)	0.55 mL	OpBlock 0078	2 mg dMAb AZD5396 + 2 mg dMAb AZD8076
	TOTAL		**44-50[d]**					

[a] All subjects will receive the study product by IM route of administration. All doses of optimized dMAb AZD5396 and dMAb AZD8076 will be prepared with Hylenex® less than 4 hours before dosing of subjects. Doses of Hylenex will vary depending on the cohort to allow for a different volume per injection

[b] Use of CELLECTRA™ 2000 with Side Port needle, OpBlock 0078 and 5P-IM Side Port Array or Profusion Therapeutic Infusion needle (G47574) for Cohorts A-E & G.

[c] Use of CELLECTRA™ 2000 with Side Port needle, OpBlock 0070 and 5P-IM Side Port Array for Cohort F.

[d] Note that the n is defined as evaluable participants. Due to partial doses or early dropouts, we may dose up to 50 participants total to reach enough evaluable participants in each cohort. See Protocol section 8.2 which describes replacing participants.

The decision to open new cohorts in the clinical trial is justified by several key factors. Firstly, ensuring safety is of utmost importance in any clinical trial. By introducing additional cohorts, we will gather more data on the safety profile of the investigational product.

Secondly, evaluating the levels of expression of dMAbs is crucial for assessing the efficacy of this approach. The expression levels directly impact the therapeutic potency and effectiveness in vivo. By expanding the cohorts, we will gather a larger sample size and thereby obtain more reliable data on the expression levels of dMAbs in different individuals. This broader understanding of expression levels will aid in determining optimal dosages and predicting the treatment's potential success.

Lastly, exploring different approaches to enhance the expression levels of dMAbs in vivo is a logical step forward. By opening new cohorts, we will introduce and test various strategies aimed at increasing the expression levels. These approaches may include novel delivery methods that will evaluate the tolerability of electroporation using alternative parameters and modified formulations. This exploration of different avenues increases the chances of finding innovative solutions to optimize the expression levels of dMAbs, potentially enhancing the treatment's efficacy and therapeutic impact.

In conclusion, opening new cohorts in the clinical trial is justified by the need to ensure safety, assess the expression levels of dMAbs, and explore diverse strategies to increase expression levels in vivo. This multifaceted approach strengthens the research process and provides a more comprehensive understanding of the investigational treatment, ultimately paving the way for improved therapeutic outcomes. The rationale for redosing participants with a DNA-encoded monoclonal antibody (dMAb) after 52 weeks is to evaluate the long-term efficacy and potential for sustained antibody presence in the system. This interval is strategically chosen based on the expected duration of dMAb-induced antibody production, hypothesizing that a yearly boost could reinforce the therapeutic effects.

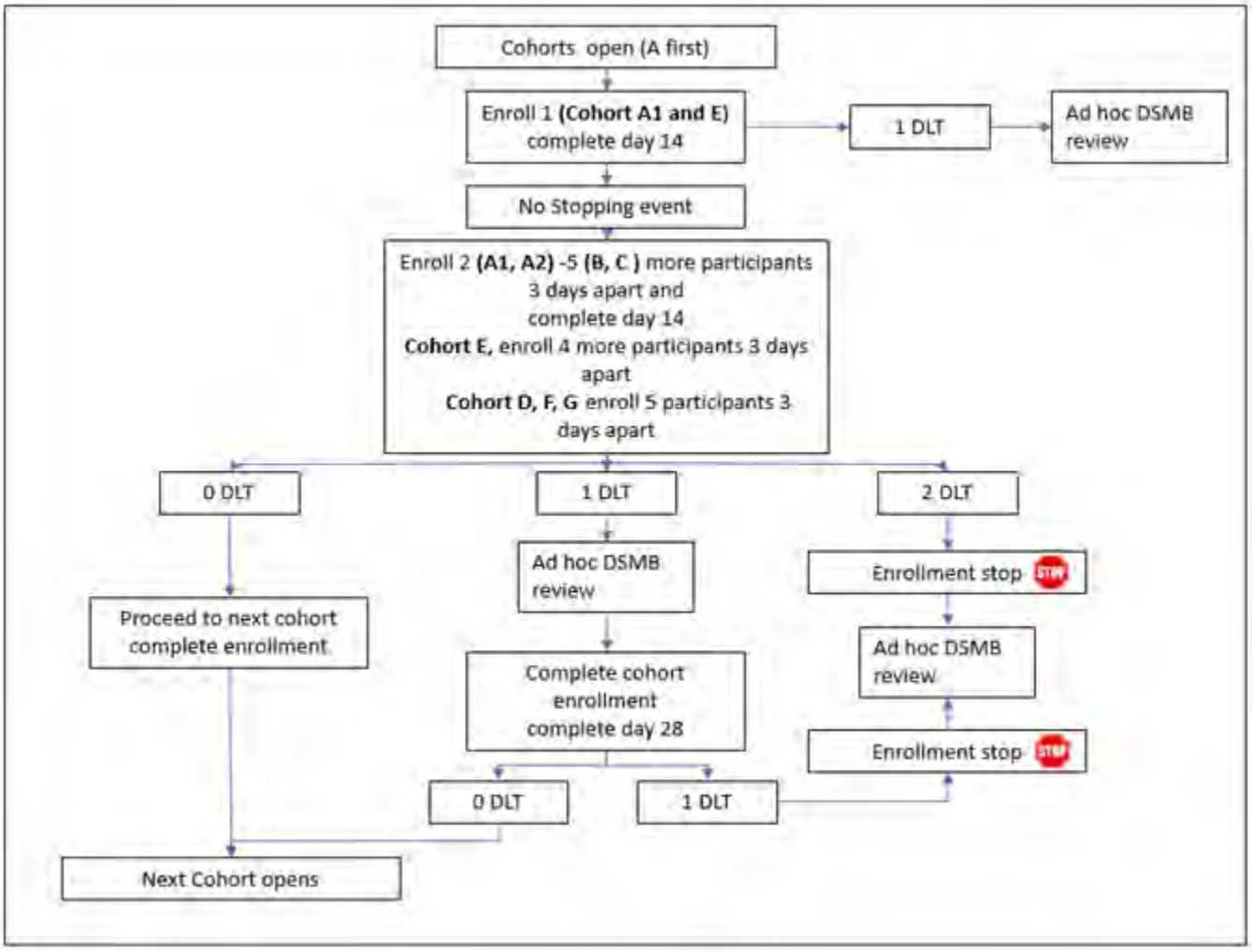
4.2 Dose Escalation Scheme

The study will apply a single ascending dose (SAD) modified 3+3 design. This study will adhere to a dose escalation scheme as described in Figure 2. Participants will be enrolled sequentially beginning with Cohort A1. The first participant in cohort A1 will be dosed on Day 0 following confirmation of eligibility criteria. If no stopping event (DLT) is observed (see Section 10.10) after 14 days of the initial dose, the remaining two participants in that cohort will be dosed. If there are 0 DLT events after 14 days of the initial dosing of the third subject, enrollment will be completed, and then cohort A2 will open. Same process will be followed for cohorts B and C. Because cohorts D, F, & G are a similar or lower dose and the safety profile would have been already established in previous cohorts, the 14-day waiting periods will not apply to Cohorts D, F, or G. Even though the levels of expression observed in cohorts

A-D are way below the levels seen when the monoclonal antibodies are given as protein, Cohort E will receive a higher dose which will require a 14 day waiting period after the dosing of the first participant at this level. Every participant in Cohort E following the 14 day waiting period will be dosed 3 days apart as in other cohorts.

If one dose limiting toxicity (DLT) is observed in the first three participants enrolled in any cohort, an ad hoc DSMB will review the event and make a decision if the study should continue. If the DSMB agrees that the study should continue, the remaining participants will be enrolled in the cohort and dosed but the next cohort will not open until the 28-day period of safety is completed. However, if any additional DLT occurs (i.e., >1 DLT in 6 total participants in a given cohort), then that dose will be deemed not tolerated.

Figure 2. Dose Escalation Scheme



Doses of Investigational product will be administered intramuscularly in ~0.5 mL/dose volume in cohorts A1, B, F, & G; ~1 mL/dose volume in cohorts A2 & C; ~0.25 mL/dose volume in cohort D; and ~2 mL/dose volume in cohort E, followed immediately by EP with the CELLECTRA^{TM} 2000 with Side Port needle device. It is recommended that the investigational product be administered such that the injection is delivered slowly using the side port needle in muscle. The side port needle should be fully

inserted prior to the injection, held in place for a moment, then removed prior to EP. Firm pressure should be used to complete injection and then the needle removed prior to EP.

Safety will be reviewed by the DSMB. Progression to the next cohort is dependent on an acceptable safety profile of all 3, 5, or 6 participants completing, at a minimum, the Day 14 after the first dose, except for Cohort D (or 28 days after the last dose, if DLT observed). Following the first review, all subsequent reviews will include data from all enrolled participants.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Age 18-60 years.
2. Able to provide consent to participate and having signed an Informed Consent Form (ICF).
3. Able and willing to comply with all study procedures.
4. Body mass index (BMI) between 20 and 31, inclusive.
5. Screening laboratory must be within normal limits or have only Grade 0-1 findings.
6. Normal screening ECG or screening ECG with no clinically-significant findings.
7. Women of child-bearing potential agree to one of the following:
   a. use medically effective contraception (oral contraception, barrier methods, spermicide, etc.)
   b. have a partner who is sterile from enrollment to 6 months following the last injection
   c. have a partner who is medically unable to induce pregnancy

   Abstinence is acceptable per Investigator discretion and as long as it is documented that the subject will use medically effective contraception when engaging in sexual activities and notifies the study team.
8. Sexually active men who are considered sexually fertile must agree to one of the following:
   a. use a barrier method of contraception during the study and continue its use for at least 6 months following the last injection
   b. have a partner who is permanently sterile or is medically unable to become pregnant
9. No history of clinically significant immunosuppressive or autoimmune disease. Individuals with HIV infection who have been virologically suppressed for more than 1 year and with current CD4 cell count entry greater than 500 cells/ul will be allowed into the study.

5.2 Exclusion Criteria

1. Administration of an investigational compound either currently or within 6 months of first dose.
2. Administration of any vaccine within 4 weeks of first dose.
3. Administration of a SARS-CoV-2 vaccine in the last 14 days or plans to have any standard of care vaccines within 14 days form the last administration of study products.
4. Positive SARS-CoV-2 infection at screening visit.
5. Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose.

6. Administration of any blood product within 3 months of first dose.
7. Co-morbid conditions including poorly-controlled diabetes (HbA1C > 7), poorly-controlled hypertension (BP > 140/95 repeatedly), asthma, and any cardiovascular disease.
8. Pregnancy or breast feeding or plans to become pregnant during the course of the study.
9. Positive serologic test for hepatitis B surface antigen (HBsAg); or any potentially communicable infectious disease as determined by the Principal Investigator or Medical Director.
10. Positive serologic test for hepatitis C (exception: successful treatment with confirmation of sustained virologic response);
11. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 mg/dL (CKD Stage II or greater);
12. Baseline screening lab with Grade 2 or higher abnormality, except for Grade 2 creatinine.
13. Chronic liver disease or cirrhosis.
14. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation.
15. Current or anticipated concomitant immunosuppressive therapy (inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or prednisone at a dose less than 10 mg/day or steroid dose-equivalent are not exclusionary).
16. Current or anticipated treatment with TNF-α inhibitors such as infliximab, adalimumab, etanercept.
17. Prior major surgery or any radiation therapy within 6 months of first dose.
18. Any pre-excitation syndromes, e.g., Wolff-Parkinson-White syndrome.
19. Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator (AICD)
20. Fewer than two acceptable sites available for IM injection and EP considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    a. Tattoos, keloids or hypertrophic scars located within 2 cm of intended administration site.
    b. Implantable-Cardioverter-defibrillator (ICD) or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist).
    c. Any metal implants or implantable medical device within the electroporation site.
21. Prisoner or participants who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness.
22. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements or assessment of immunologic endpoints.
23. Not willing to allow storage and future use of samples for SARS-CoV-2 virus related research.
24. Any illness or condition that in the opinion of the investigator may affect the safety of the participant or the evaluation of any study endpoint.
25. Participants with known bleeding diatheses or that are using blood thinners for 30 days before study enrollment including warfarin, heparin, Clopidogrel, Apixaban (Eliquis), Dabigatran

(Pradaxa), Edoxaban (Savaysa), Rivaroxaban (Xarelto). The use of low dose aspirin (81 mg daily) is acceptable.

26. Participants with concomitant intramuscular medications.

5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once at the Investigator's discretion.

6 STUDY INTERVENTION

6.1 Investigational Products dMAb AZD5396 and dMAb AZD8076

dMAb AZD5396 contains plasmids pGX93321 and pGX93311 that encodes for the heavy and the light Ig chains of optimized mAb AZD5396; dMAb AZD8076 contains plasmids pGX93322 and pGX93315 that encodes the heavy and the light Ig chains of optimized mAb AZD8076 monoclonal antibody against SARS-CoV-2 virus.

6.1.1 Acquisition and Accountability of dMAb AZD5396 and dMAb AZD8076

dMAb AZD5396 and dMAb AZD8076 will be provided by the manufacturer to the University of Pennsylvania Investigational Drug Service (IDS).

Study product accounting will be performed continuously during the study. Details on study product volume, administration, and accountability are documented in the applicable study documents, i.e. CRF and on respective pharmacy forms.

It is the responsibility of the Investigator to ensure that a current record of investigational products disposition is maintained at the study site where investigational product is inventoried, dispensed and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to each participant, including unique participant identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Amount returned to Sponsor or designee.

- Amount destroyed at study site, if applicable.

At completion/termination of the study, all unused and partially used supplies must be returned to the Sponsor or designee. The investigator, pharmacist/drug administrator and monitor must verify that no drug supplies remain at the site at the time of study closeout. Appropriate records will be maintained in the investigator's site file.

6.1.2 Formulation, Appearance, Packaging, and Labeling of dMAb AZD5396 and dMAb AZD8076

dMAb AZD5396 and dMAb AZD8076 Drug Product is supplied in 2 R vials at a concentration of 10 mg/mL at a minimum recoverable volume of NLT 0.2 mL/vial. It is formulated in saline sodium citrate (SSC).

Appearance: Clear to slightly opalescent (≤RS1; USP <855>), colorless solution (≤Standard A; USP <631>), essentially free of visible particles.

Drug product labels are customized per local regulation, but the following information, at minimum, is included:

- Protocol identifier
- Investigational product name
- Dosage and formulation
- Lot number
- FDA required statement: "Caution: New Drug. Limited by Federal (or United States) law to investigational use."
- Expiration date
- Quantity in container

6.1.3 Product Storage and Stability of dMAb AZD5396 and dMAb AZD8076

The pharmacist at the University of Pennsylvania IDS will be responsible for assuring the quality of the investigational product is adequate for the duration of the trial. dMAb AZD5396 and dMAb AZD8076 will be shipped refrigerated. If the temperature logger is alarmed and displays a temperature deviation when the shipment is received, the Sponsor (Pablo Tebas, MD) and Inovio must be contacted immediately and IP quarantined until cleared for use by the manufacturer.

Investigational products must be stored in a secure area according to local regulations. All study products must be transferred from the shipping container to the appropriate storage conditions upon arrival. dMAb AZD5396 and dMAb AZD8076 must be stored refrigerated at 2 to 8°C.

Refrigerator/freezer temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

6.1.4 Handling, Preparation and Dispensing of dMAb AZD5396 and dMAb AZD8076

Investigational product is to be prepared by site staff who are trained and knowledgeable in mixing and dispensing investigational agents. For details, please review the Pharmacy Manual. Documentation of certification will be kept with the pharmacy documents. Study drug should be prepared in a BioSafety level 2 cabinet. Personnel will utilize proper aseptic technique per institutional guidelines.

It is the responsibility of the Investigator to ensure that dMAb AZD5396 and dMAb AZD8076 and CELLECTRA™ are only dispensed and administered to study participants. Authorized personnel at the official study site must be the only ones to dispense the product according to local regulations.

dMAb AZD5396 (pGX93321 and pGX93311) and dMAb AZD8076 (pGX93322 and pGX93315) drug products are formulated in a saline sodium citrate (SSC) buffer to a concentration of 10 mg/mL plasmid) in 150 mM sodium chloride and 15 mM sodium citrate, which is supplied in 2 R glass vials and stored refrigerated at 5°C. Hylenex® Recombinant (human hyaluronidase injection) will be used for dose preparation at the clinical site. Hylenex® is approved in the US for intramuscular use to increase the dispersion and absorption of other injected drugs. In this Phase 1 clinical study, a 0.5 to 2 mg dose of dMAb AZD5396 and dMAb AZD8076 will be administered intramuscularly.

Dose preparation of each investigational product will occur within 4 hours prior to administration. For details about the preparation of the dose, consult the most current version of the Pharmacy Manual.

6.2 Hylenex® Recombinant

Hylenex® Recombinant is a purified preparation of the enzyme recombinant human hyaluronidase. It is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (P20). Hyaluronidases are a family of enzymes that catalyze the degradation of hyaluronic acid. By catalyzing the hydrolysis of hyaluronic, a constituent of the extracellular matrix (ECM), hyaluronidase lowers the viscosity of hyaluronan, thereby increasing tissue permeability. Pre-treating the muscle with a hyaluronidase dose suitable for rats (0.56 U/g b.w.) prior to plasmid DNA injection increased transfection efficiency of injected plasmid by >200% [22]. It is, therefore, used in conjunction with other drugs to speed their dispersion and delivery. dMAb AZD5396 and dMAb AZD8076 and Hylenex® Recombinant will be administered IM followed by EP to enhance plasmid dispersion in the delivery tissue[23].

Hylenex® Recombinant will have both the original manufacturer's label on individual vials and the carton, and an additional label on the carton indicating the study number.

Refer to FDA approved package insert for additional information.

6.3 Investigational Device CELLECTRA™ 2000 with Side Port Needle

The investigational device used in the study is the CELLECTRA™ 2000 with Side Port Needle.

6.3.1 Acquisition and Accountability

The investigative site is responsible for maintaining investigational device and drug accountability logs. The drugs and device must have full traceability from the receipt of the products through the participant use, disposal or return of the products. The Site must document acknowledgement of receipt and notify Inovio upon receipt of the investigational products. This includes the content shipped and condition upon receipt.

For each participant administration, there must be a record of each product used for that participant, i.e., for the device, Pulse Generator serial number, applicator serial number, and array lot number. The CELLECTRA™ 2000 5P-IM Applicator is intended to be used multiple times on the same participant and then disposed after final use in accordance with accepted medical practice and any applicable local, state, and federal laws and regulations. Once the 5P-IM applicator is assigned to a participant, it may NOT be used on another participant. IM applicators used during device training conducted by Sponsor personnel or self-led refresher training must NOT be used on any participant. The used sterile disposable array attachment must be discarded after use in accordance with institutional policy regarding disposal of sharp needles/instruments.

6.3.2 Packaging and Labeling of Investigational Device

The CELLECTRA™ 2000 with Side Port device, and its components, and the Profusion Therapeutic Infusion needle (G47574) will be shipped directly from Inovio to the study site.

6.3.3 Use of CELLECTRA™ 2000 with Side port Electroporation Device

The treatment/electroporation procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer vaccinations or parenteral drugs to patients (e.g., MD, DO, RN). Non-licensed individuals (i.e., other than an MD, DO, or RN) may perform the treatment/electroporation procedure under both of the conditions below:

1. The non-licensed individual has been trained by the Manufacturer or its designee in intramuscular drug injection followed by EP. The non-licensed individual will perform the procedure under the direct supervision of the Principal Investigator or an approved Sub-Investigator who has already been trained by the Manufacturer or its designee.
2. The CV and any relevant qualifications of the individual have been reviewed and approved by the Sponsor (Pablo Tebas, MD) or its designee to perform the procedure.

All individuals designated to perform the EP procedure must satisfactorily complete device training from the manufacturer or its designee regardless of their qualifications. Any deviation from the above procedures must be approved by the sponsor and manufacturer or respective designee(s).

6.4 Return and Destruction of Investigational Products

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to the Sponsor (Pablo Tebas, MD) or its designee, if not authorized by the sponsor to be destroyed at the site.

All investigational products returned to the Sponsor (Pablo Tebas, MD) or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. It is the Investigator's responsibility to arrange for disposal for all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

If investigational products are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by the Sponsor

(Pablo Tebas, MD) or its designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible Sponsor (Pablo Tebas, MD), employee or designated person/team. Used investigational product must NOT be destroyed until accountability has been completed by the responsible Sponsor (Pablo Tebas, MD) employee or designated person/team.

6.5 Precautions with Investigational Medicinal Product

A dose of the study product known or suspected to have been taken (accidentally or intentionally) in excess of the dose mandated by the protocol, and any misuse or abuse of study products or any other product taken as a concomitant medication, whether or not associated with an adverse experience, must be reported to the Sponsor (Pablo Tebas, MD) within 24 hours. Any clinical sequelae in association with the overdose will be reported as an AE or SAE. Details of signs or symptoms, clinical management, and outcome should be reported, if available

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7 STUDY PROCEDURES

Table 3. Schedule of Events Cohorts A-F

Tests and Observations	Screen Day -1 to -30	Day 0	Day 3 (cohorts B-F) ±1d	Day 7 ±1d	Day 10 (cohorts B-F) ±1d	W2 ±2d	W3 ±2d	W4 ±2d	W5 ±2d	W6 ±4d	W8 ±2d	W12 ±7d	W16 ±7d	W24 ±7d	W32 +8w	W42 ±2w	W52 ±7d	Additional PKs/ADAs, if needed	W72 ±7d	Additional PKs/ADAs, if needed[k]	Early Termination
Consent	X																				
Eligibility criteria	X																				
Demographics	X																				
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Conc. Meds [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Physical Exam [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
CBC w/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Chemistries [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
HbA1c	X																				
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Serologies [e]	X																				
CPK (with fractionation)	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Pregnancy [f]	X	X	X																		
PK & ADA [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
NP swab for SARS-CoV-2	X																				

Tests and Observations	Screen Day -1 to -30	Day 0	Day 3 (cohorts B-F) ±1d	Day 7 ±1d	Day 10 (cohorts B-F) ±1d	W2 ±2d	W3 ±2d	W4 ±2d	W5 ±2d	W6 ±4d	W8 ±2d	W12 ±7d	W16 ±7d	W24 ±7d	W32 +8w	W42 ±2w	W52 ±7d	Additional PKs/ADAs, if needed	W72 ±7d	Additional PKs/ADAs, if needed[k]	Early Termination
Inoculation + EP		X	X																		
EP Data [h]		X	X																		
Memory aid [i]		X	X																		
VAS [j]		X	X																		
Injection Site Reactions		X	X	X	X																
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Prior and concomitant, new medications will be recorded at all study visits (Day 0 through study discharge). Prior treatments, defined as administered up to 8 weeks prior to the time of informed consent, should be recorded in the CRF as prior medications.
b. Full physical examination performed at screening and last visit or early termination only. Perform targeted examinations at other visits as determined by Investigator or per participant complaints. Record history of weight lifting or other significant physical activity.
c. Vital signs will be performed pre and post inoculation at day 0, day 3, day 28, and day 31 visits; height and weight will be recorded at screening and final visit.
d. Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO3), glucose, BUN, Cr, ALT, AST
e. HIV antibody or rapid test, HBsAg, HCV antibody.
f. Serum pregnancy test at screening and urine pregnancy test thereafter
g. Collect 3 tubes of whole blood (red top) to obtain ~10 mL serum at the indicated time points (this includes the PK sampling and ADA formation)
h. Download EP data within 48 hours of dose and transfer to Sponsor or its designee
i. Provide memory aid to study participants and review on next visit
j. Obtain VAS score immediately after EP and at 5 and 10 minutes after injection. This is done after each injection, which are separated by 30 minutes.
k. Up to 2 additional PK/ADA draws may occur up to 6 months after the participant's Week 72 target visit.

Table 4. Schedule of Events Cohort G

Tests and Observations	Screen Day -1 to -30	Day 0	Day 3 ±1d	Day 7 ±1d	Day 10 ±1d	W2 ±2d	W3 ±2d	Day 28 ±1d	Day 31 ±1d	W5 ±2d	W6 ±4d	W8 ±2d	W12 ±7d	W16 ±7d	W24 ±7d	W32 +8w	W42 ±2w	W52 ±7d	Additional PKs/ADAs, if needed	W72 ±7d	Additional PKs/ADAs, if needed[k]	Early Termination
Consent	X																					
Eligibility criteria	X																					
Demographics	X																					
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Conc. Meds [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Physical Exam [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
CBC w/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Chemistries [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
HbA1c	X																					
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Serologies [e]	X																					
CPK (with fractionation)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
Pregnancy [f]	X	X	X					X	X													
PK & ADA [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X		X
NP swab for SARS-CoV-2	X																					
Inoculation + EP		X	X					X	X													
EP Data [h]		X	X					X	X													

Tests and Observations	Screen Day -1 to -30	Day 0	Day 3 ±1d	Day 7 ±1d	Day 10 ±1d	W2 ±2d	W3 ±2d	Day 28 ±1d	Day 31 ±1d	W5 ±2d	W6 ±4d	W8 ±2d	W12 ±7d	W16 ±7d	W24 ±7d	W32 +8w	W42 ±2w	W52 ±7d	Additional PKs/ADAs, if needed	W72 ±7d	Additional PKs/ADAs, if needed[k]	Early Termination
Memory aid [i]		X	X					X	X													
VAS [j]		X	X					X	X													
Injection Site Reactions		X	X	X	X			X	X	X	X											
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Prior and concomitant, new medications will be recorded at all study visits (Day 0 through study discharge). Prior treatments, defined as administered up to 8 weeks prior to the time of informed consent, should be recorded in the CRF as prior medications.
b. Full physical examination performed at screening and last visit or early termination only. Perform targeted examinations at other visits as determined by Investigator or per participant complaints. Record history of weight lifting or other significant physical activity.
c. Vital signs will be performed pre and post inoculation at day 0, day 3, day 28, and day 31 visits; height and weight will be recorded at screening and final visit.
d. Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO3), glucose, BUN, Cr, ALT, AST
e. HIV antibody or rapid test, HBsAg, HCV antibody.
f. Serum pregnancy test at screening and urine pregnancy test thereafter
g. Collect 3 tubes of whole blood (red top) to obtain ~10 mL serum at the indicated time points (this includes the PK sampling and ADA formation)
h. Download EP data within 48 hours of dose and transfer to Sponsor or its designee
i. Provide memory aid to study participants and review on next visit
j. Obtain VAS score immediately after EP and at 5 and 10 minutes after injection. This is done after each injection, which are separated by 30 minutes.
k. Up to 2 additional PK/ADA draws may occur up to 6 months after the participant's Week 72 target visit.

7.1 Screening Evaluations

The assessments performed during screening will determine the participant's eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. Participants' post-menopausal status must meet requirements as specified in the inclusion criteria. The following screening evaluations will be performed within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to the first Study Treatment.

If a participant does not meet an inclusion or exclusion criterion due to a transient and non- clinically significant event at screening, relevant screening evaluations may be repeated within the same 30-day screening period. If the participant fails twice, they will be considered a screen failure.

The following evaluations will be performed during the screening period:

- Signed and dated informed consent.
- Collect demographics, including gender.
- Obtain and document complete medical history, surgical history (including all past procedures), present conditions, and concomitant illnesses.
- Full physical examination.
- Record current concomitant medications/treatments.
- Record vital signs including body weight and height, heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature.
- Perform 12 lead ECG.
- Collect blood for PT(INR) and aPTT, HbA1C, CBC with differential, serum chemistry [sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO3), glucose, blood urea nitrogen (BUN), creatinine (Cr)], AST, ALT, and CPK.
- Collect urine for urinalysis.
- Collect blood for serum pregnancy test.
- Collect serum for HIV, Hepatitis B surface antigen (HBsAg), and Hepatitis C serology.
- Review and confirm all inclusion/exclusion criteria.
- A nasal or nasopharyngeal (NP) swab for a COVID-19 test (note – a combination COVID-19+flu test will be done if required per current hospital policy).

7.2 Dosing and Follow-Up Evaluations

Once eligibility has been confirmed, the participant will be assigned to receive Investigational product. Visit dates and windows must be calculated from Day 0.

7.3 Day 0, Day 3, Day 28, and Day 31

The following evaluations will be performed on Day 0 (all cohorts), Day 3 (cohorts B-G), Day 28 (cohort G), and Day 31 (cohort G) only prior to Investigational product administration:

- Collect all present and/or new or ongoing adverse events (including history of new COVID 19 diagnosis).
- Document any present conditions and concomitant illnesses.
- Record current concomitant medications/treatments.
- Targeted physical examination (driven by symptoms).
- Record vital signs pre injection including heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature.
- Collect urine for urinalysis and urine pregnancy test (if WOCBP).
- Collect blood for PT(INR) and aPTT, CBC with differential, serum chemistry, CPK.
- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation.
- Provide Memory Aid.

Investigational product administration should occur after all the above pre-dose procedures have been completed.

Participants will receive two injections into the arm (deltoid)/leg (quadriceps) region at day 0 (all groups), and on day 3. Injections will be separated by ~30 minutes. Injections may be given in different arms or in an arm (deltoid) and a leg (quadriceps). If preferred or needed both doses can be done in the deltoid region or the lateral quadriceps, although the injections should be in different areas separated by at least 2 cm. The Day 3 injections may repeat an area already used on Day 0 as long as separated by at least 2 cm. For Cohort G, the Day 28 injections may be repeated in an area already used, and the Day 31 injections may repeat an area already used on Day 28 as long as separated by at least 2 cm.

If a participant has a DLT, as outlined in the protocol, the second dose of the product will not be given.

The following evaluations will be performed on Day 0 (all cohorts), Day 3 (cohorts B-G), Day 28 (cohort G), and Day 31 (cohort G) after Investigational product administration:

- Conduct targeted injection site reaction systemic and local assessments 30 min post each injection.
- Record vital signs post each injection including heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature. Participants will be observed for 1 hour after the last injection.
- Perform 12 lead ECG after each injection.
- Collect any new adverse events after each injection.
- Complete VAS score immediately after EP and at 5 and 10 minutes post each injection.
- Download EP Data.
- Before the participant is discharged, we will wait until his or her vital signs are normal or have returned to their baseline before the injection.
- Normal vital sign ranges for the average healthy adult while resting are:
  - Blood pressure: systolic >90 and <140 mmHg, diastolic >60 and <100mmHg
  - Breathing: >9 and <20 breaths per minute

  - Pulse: 60 to 100 beats per minute
  - Temperature: Afebrile

- If the vitals do not return to baseline in 4 hours, the subjects will be maintained for observation in the hospital for continuous monitoring. This hospitalization will not be considered a SAE but a protocol procedure unless the event progresses and places the subject at risk.
- Participants will be reminded of the safety risk information included in the informed consent.

7.4 Day 7 (Week 1)

The following evaluations will be performed at this visit:

- Conduct targeted injection site reaction systemic and local assessment.
- Collect all present and/or new or ongoing adverse events.
- Document any present conditions and concomitant illnesses (including history of new COVID 19 diagnosis).
- Record current concomitant medications/treatments.
- Targeted physical examination.
- Record vital signs including heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature.
- Collect blood for PT(INR) and aPTT, CBC with differential, serum chemistry, CPK.
- Collect urine for urinalysis.
- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation.
- Perform 12 lead ECG.

7.5 Day 10 (cohorts B-G only)

The following evaluations will be performed at this visit:

- Conduct targeted injection site reaction systemic and local assessment.
- Collect all present and/or new or ongoing adverse events.
- Document any present conditions and concomitant illnesses (including history of new COVID 19 diagnosis).
- Record current concomitant medications/treatments.
- Targeted physical examination.
- Record vital signs including heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature.
- Collect blood for PT(INR) and aPTT, CBC with differential, serum chemistry, CPK.
- Collect urine for urinalysis.

- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation.
- Perform 12 lead ECG.

7.6 Week 2, Week 3, Week 4, Week 5, Week 6, Week 8, Week 12, Week 16, Week 24, and Week 52

The following evaluations will be performed at these visits:

- Conduct targeted injection site reaction systemic and local assessment (cohort G, Week 5 and 6).
- Collect all present and/or new or ongoing adverse events.
- Document any present conditions and concomitant illnesses (including history of new COVID 19 diagnosis).
- Record current concomitant medications/treatments.
- Targeted physical examination.
- Record vital signs including heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature.
- Collect blood for PT(INR) and aPTT, CBC with differential, serum chemistry, CPK
- Collect urine for urinalysis.
- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation.
- Perform 12-lead ECG

7.7 Week 32, Week 42, and additional PK/ADA measurements

The following evaluations will be performed at weeks 32 and 42:

- Collect all present and/or new or ongoing adverse events.
- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation.

Participants may be asked to come in for additional PK/ADA monitoring between weeks 52 and 72, at the investigators' discretion.

Participants may be asked to come in for additional PK/ADA monitoring between weeks 72 and 98, at the investigators' discretion.

7.8 Week 72 / Early Termination Visit

The following evaluations will be performed at the visit:

- Collect all present and/or new or ongoing adverse events
- Document any present conditions and concomitant illnesses (including history of new COVID 19 diagnosis)
- Record current concomitant medications/treatments
- Full physical examination

- Record vital signs including body weight and height, heart rate (HR), respiratory rate (RR), blood pressure (BP), oral temperature
- Collect blood for PT(INR) and aPTT, CBC with differential, serum chemistry, and CPK
- Collect urine for urinalysis
- Collect serum for mAb AZD5396 and mAb AZD8076 level assessment and ADA evaluation
- Perform 12 lead ECG

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Clinical laboratory evaluations (CBC, CMP, and any other necessary at the discretion of the PI).
- PK evaluation

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are scheduled for Day 0 but do not receive the study drug may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced at the discretion of the Investigator. Subjects in cohorts B, C, D, E, and F may be replaced if they do not receive both the Day 0 and the Day 3 doses. Subjects in cohort G may be replaced if they do not receive all four of the Day 0, 3, 28, and 31 doses. Subjects in these cohorts who

only receive Day 0 doses and want to continue in the study will be included in the A1 or A2 group for analysis.

8.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for more than 2 scheduled visits and is unable to be contacted by the study site staff. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit immediately and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 STUDY ASSESSMENTS AND PROCEDURES

See Table 3 for Schedule of Events showing study procedures and the times at which they are to be carried out.

9.1 Informed Consent

All participants must sign the informed consent prior to any trial related procedures are performed. The informed consent documentation must be in accordance with applicable regulations and GCP. Qualified trial personnel will meet with prospective trial participants, explain the trial, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the trial, trial dosing schedules and follow-up procedures, in a language understandable to the participant. Explanation of the trial includes, but is not limited to, trial objectives, potential benefits and risks, discomforts/inconveniences, and the participant's rights and responsibilities. The participant is then requested to sign and date the ICF. A copy of the signed informed consent documentation must be provided to the participant. The qualified trial personnel will document the process of obtaining informed consent within the source record. Signed ICFs are maintained in the participant's source records and must be accessible for verification at any time. Signing of the ICF begins the 30-day screening window.

The initial consent will be in person. Re-consenting may be conducted in-person or remotely. The participant and research team will review the amended consent form in detail and be provided with a clear and detailed explanation of the consent changes. The participant will have the opportunity to have all questions answered. If the participant must complete the consent form remotely, the consent form will be sent electronically. Participants will be required to either print, sign, and send a scanned copy of the consent form to the study team or send by mail. The study member(s) obtaining consent will sign the consent form and then provide a copy to the participants. Alternatively, if an MD investigator is unable to sign the consent form in person but able to re-consent remotely, the subject will sign the consent form

and study staff will provide them with a signed copy, when available. Obtaining re-consent signatures through DocuSign may also be an option. The re-consent process will be documented in PennChart.

9.2 Assignment of Participant Identification Numbers

Each participant who consents will be assigned a unique participant identification number (SID), which identifies the participant for all trial-related procedures. SIDs are a combination of a four-digit site code and a four-digit participant number starting with 0001. Once assigned, SIDs cannot be reused for any reason. Information regarding the SID and screen date will be documented on a screening and enrollment log/system and in the eCRF.

Participants meeting eligibility criteria listed in the protocol will be assigned by the site in accordance with the allocation schedule provided by the Sponsor (Pablo Tebas, MD).

9.3 Medical History

All relevant (as judged by the investigator) past and present conditions at screening, as well as prior surgical procedures will be recorded for the main body systems. Illnesses first occurring or detected after the signing of the informed consent, or during the study and/or worsening of an existing illness in severity, frequency or nature after signing of the informed consent are to be documented as AEs on the CRF. Prior treatments, defined as administered up to 8 weeks prior to the time of informed consent, should be recorded in the CRF as prior medications. Concomitant treatments, defined as continuing or new treatments taken at or after the signing of the informed consent, should be recorded in the CRF as concomitant medications.

9.4 Safety Evaluations

The following evaluations for safety will be performed.

9.4.1 Physical Exam and Targeted Physical Assessments

A full physical examination will be conducted during screening and at study discharge. A targeted physical assessment (physical exam focused on the area of specific symptoms) will be performed at other visits as determined by the Investigator or directed per participant complaints.

Injection Site Reaction

Injection site reaction assessed 30 minutes post injection and at all subsequent visits up to Day 10. Systemic and local reaction assessment consists of evaluation of the following:

Systemic: hypotension, hyperhidrosis, erythema, headache, dizziness, myalgia, arthralgia, fever, peripheral edema; and

Local reactions: pain, pruritus, erythema, swelling, scab, infection.

9.4.2 Vital Signs

Vital signs including oral temperature, respiration rate, blood pressure and heart rate will be measured at screening and all other in-person study visits. Vital signs will be performed both pre- and post-inoculation at Day 0, Day 3, Day 28, and/or Day 31 visits (as applicable).

9.4.3 Height, Weight, Handedness

Handedness will be recorded for each participant.

Weight (kg) and height (cm) will be collected at screening and at study discharge.

9.4.4 12-lead ECG

A single 12-lead ECG will be performed at screening, at pre- and post-dosing on Days 0, 3, 28, and 31 (as applicable to each cohort), and at each study visit. The ECG should include measurements of ventricular rate, PR, QRS, QT, and QTc, as well as an assessment of whether the ECG is normal or abnormal. Abnormal ECGs should be interpreted as clinically significant or not clinically significant. For Cohorts Expansion, if applicable, further dosing should be delayed in the event of a clinically significant abnormal post-dose ECG result from Day 0 until it has been reviewed by the PI, qualified PI designee, Medical Director, or Sponsor consultant cardiologist and deemed safe to proceed.

9.4.5 Laboratory Evaluations

At screening and select times during the study, blood samples will be collected for safety assessments. Up to 450 mL of blood will be drawn from each participant over the course of the year-long study. Participants may be asked to come back for additional blood draws if collected blood sample is lost or unevaluable for any reason.

Coagulation

PT(INR) and a PTT will be measured at screening and at visits specified in the Schedule of Events.

Hematology (Complete blood count (CBC) with automated differential):

White blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, lymphocytes, neutrophils, monocytes and platelet count will be measured at Screening and at visits specified in the Schedule of events.

Serum chemistry

Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarbonate (HCO3), Calcium (Ca), Phosphate (PO4)], glucose, BUN (blood urea nitrogen) and Creatinine (Cr), AST, ALT and bilirubin will be measured at Screening and at visits specified in the Schedule of Events.

Creatine Phosphokinase (CPK)

CPK will be measured at Screening and at visits specified in the Schedule of Events.

HbA1c

HbA1c will be measured at Screening only.

Urinalysis

Urine samples will be tested by dipstick for glucose, protein, and hematuria at Screening and at visits specified in the Schedule of Events. If abnormal (presence of protein, hematuria, or glucose ≥ 1+), a microscopic examination should be performed.

Serology

Antibodies to hepatitis B surface antigen (HBsAg), hepatitis C and human immunodeficiency virus will

be measured at screening only.

SARS-CoV-2 (and influenza if required per hospital policy)

A nasal or nasopharyngeal (NP) swab for a COVID-19 test at screening only (a combination COVID-19 +flu may be run if required per current hospital policy).

Pregnancy Testing

For women of child bearing potential (WOCBP), a serum pregnancy test will be obtained at screening and a urine pregnancy test will be performed prior to dosings. A negative result for urine β-HCG (test must have a sensitivity of at least 25 mIU/mL) must be available prior to each administration of Investigational product. If the β-HCG test is positive, indicating that the participant is pregnant prior to completing the specified dose regimen, then no further Investigational product will be administered. Every attempt should be made to follow pregnant participants for the remainder of the study and to determine the outcome of the pregnancy.

9.4.6 Visual Analog Scale

At select times after EP, participants will complete VAS questionnaires. A VAS consists of a horizontal line, 10 cm in length, anchored by word descriptors at each end (no pain = 0 cm; worst pain = 10 cm). Immediately after injection/EP, the participant will be instructed to mark on the line, the point that they feel represents the pain experienced related to the injection/EP procedure. The VAS will be administered immediately after EP and 5 and 10 minutes later after each injection, which are separated by 30 minutes. The VAS score is determined by measuring in centimeters from the left-hand end of the line to the point that the patient marks.

9.5 Injection and Electroporation (EP)

Injections of investigational product are immediately followed by electroporation. Participants in Cohorts A1 and A2 will receive two injections of dMAb AZD5396 and dMAb AZD8076 in the deltoid/quadriceps followed immediately by EP on Day 0. Cohorts B-G will receive two injections of dMAb AZD5396 and dMAb AZD8076 in the deltoid/quadriceps followed immediately by EP on both Days 0 and 3, for a total of 4 injections. Cohort G will also receive two injections of dMAb AZD5396 and dMAb AZD8076 in the deltoid/quadriceps followed immediately by EP on Days 28 and 31, for a total of 8 injections. If preferred or needed, both doses can be done in the deltoid region or the lateral quadriceps on Days 0, 3, 28, and/or 31.

Study Agent must not be given within 2 cm of a tattoo, scar, or active lesion/rash. Also, IM injection followed immediately by EP must not be performed in the muscle of an extremity which has any metal hardware (e.g., surgical rods, pins or joint replacements). The two injections on Days 0, 3, 28, and/or 31 will be given on the same side deltoid and lateral quadriceps (i.e., left side or right side of the body). If preferred or needed, both doses can be done in the deltoid region or the lateral quadriceps.

The side-port needle should be inserted fully with firm pressure until injection is completed, then wait for a few seconds and then removed. Training on this method of injection will be provided.

9.5.1 Management of Anxiety and Pain Due to Electroporation (EP) Procedures

In case of pain, participants may be treated with a non-narcotic analgesic (e.g., ibuprofen, ketorolac) after injection/EP. Participants who are allergic to or have contraindications to EMLA, ibuprofen,

ketorolac may be offered a suitable alternative. Medication taken for anxiety or pain management should be added to the concomitant medications.

Adequate time (~>30 minutes) for pain to subside from prior EP will be allowed for participants receiving 2 EPs/day.

9.5.2 Downloading of EP Data from CELLECTRA™ 2000 Device

Within 24 to 48 hours following each Study Treatment, data will be downloaded from the EP device and the data file that is created should be sent to the Sponsor (Pablo Tebas, MD) or designee (e.g., Inovio). Instructions on how to download the data and Sponsor contact information are provided separately. Training will also be provided.

9.6 Assessment of Laboratory Abnormalities

Blood will be drawn for coagulation, serum chemistry, hematology and CPK at the visits listed in the Schedule of Events. Urinalysis will also be performed at screening and at other specified visits.

Laboratory AEs will be assessed and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued in September 2007.

9.7 Assessment of Clinical Trial Adverse Events

Participants will be queried regarding the occurrence of any adverse events including adverse events related to injection site reactions, concomitant medications and new onset illness or disease during their study visits. Participants will be reminded to contact study personnel and immediately report any event for the duration of the study. All adverse events will be captured from the time of the informed consent to study discharge. These events will be recorded on the participant's CRF.

9.8 Assessment of Administration (Injection) Site Reactions

9.8.1 Patient Self-Evaluations

Participants record any post treatment reactions (local and systemic) and enter this information in the Participant Memory Aid (shown in Appendix A: Participant Memory Aid) on the evening of each dose and for 7 days post each dose. Local administration site reactions will be recorded using the supplied measuring tool. The study staff will review the memory aid; the reported events will be assessed for clinical significance and recorded on the CRFs as appropriate. Memory aids are collected and considered source documents.

9.8.2 Staff Evaluations

Study staff should evaluate each unique memory aid entry according to "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued in September 2007 (Appendix B: Toxicity Grading Scale). Any memory aid entry determined to meet the criteria for a Grade 1 or higher adverse event must be documented as an adverse event. If the reminder memory aid entry does not meet the criteria of a Grade 1 or higher AE as per the toxicity grading scale, clinical judgment can be used to determine whether the entry should be recorded as an AE. For cases

where the reminder memory aid entry and final AE reporting (i.e., grading) do not agree, the reasoning must be recorded in the source documents.

The Investigational product administration procedure consists of insertion of the CELLECTRA™ 2000 5P-IM electroporation array needles (electrodes) through the skin and into the underlying muscle, and intramuscular injection of the Investigational product followed by delivery of the electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug. Attributing any reaction (e.g., pain, erythema, swelling) that is observed at or near the site of the Investigational product administration procedure to injection of the Investigational product or administration of the electroporation pulses will be difficult and is not necessary. Consequently, reactions arising from the Investigational product administration procedure may be reported as administration site or injection site reactions.

When evaluating administration (injection) site reactions throughout the study, it is most important to be as specific as possible by selecting the most appropriate term (see Table 5 below) and use the grading scale as listed in the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, issued September 2007. Administration (injection) site reactions and administration site pain will be evaluated starting immediately and at 5 and 10 minutes following injection/EP. In addition, other events associated with administration (injection) site reactions (e.g., hematoma, infection or necrosis) should also be reported with preferred terms specific for administration (injection) site reactions. Injection site systemic and local reaction assessment that consists of evaluation of the following: General: hypotension, hyperhidrosis, erythema, headache, dizziness, myalgia, arthralgia, fever, peripheral edema, and local reaction: pain, pruritis, erythema, swelling, scab, infection. Non-injection site AEs will be assessed during the entire time while at the investigator site.

Table 5. Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild (1)	Moderate (2)	Severe (3)	Potentially Life Threatening (4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5-5 cm and no interference w/ activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

b. Should be evaluated and graded using the functional scale as well as the actual measurement.

9.9 Serum Assessments

9.9.1 Pharmacokinetic Assessment

Serum samples will be collected at baseline (Day 0), on Day 3, Day 28 (cohort G), Day 31 (cohort G) prior to dosing, and at all subsequent visits (including unscheduled visits in the event that serum mAb AZD5396 and mAb AZD8076 are detected at the Day 42 (Week 6) visit). Blood will be collected for serum at each specified visit. Details on the process for serum sample collection, storage, and shipment will be provided in the Laboratory Manual. Serum samples will be evaluated to determine the expression kinetics (i.e., pharmacokinetics) of mAb AZD5396 and mAb AZD8076 upon Investigational product administration. The serum concentration–time profile of mAb AZD5396 and mAb AZD8076 (ng/mL) will be evaluated for each participant using all available time points. The maximum serum concentration (Cmax), the minimum serum concentration (Cmin), and the Area Under the Curve (AUC0-t) in the course of the study will be calculated as the data allows. Assays to quantitatively determine mAb AZD5396 and mAb AZD8076 levels in human serum samples are currently under development and will include either a mass spectrometry assay and/or a Meso Scale Discovery (MSD) Electrochemiluminescence (ECL) assay that will be qualified for its intended purpose using the FDA Bioanalytical Method Validation Guidance for Industry as a reference.

Serum Pharmacokinetic Assay Description

A validated assays for quantification of serum concentrations of AZD5396 and mAb AZD8076 will be carried out, using the assay previously developed to assay PK of AZD1061 and AZD8895, respectively.

To measure the AZD7442 (AZD1061 and AZD8895) human serum concentration, an immunoaffinity enrichment using streptavidin magnetic beads coated with biotinylated RBD of SARS-CoV-2 followed by LC-MS/MS approach was used. Because AZD8895 and AZD1061 are too large for practical direct quantitative analysis using LC-MS/MS technology, the captured proteins are subjected to “on-bead” proteolysis with trypsin, following standard protein denaturation, reduction, and alkylation processing steps. As a result of the trypsin digestion, characteristic peptide fragments originating from AZD8895 and AZD1061 are produced. The characteristic peptides are quantified as surrogates for the AZD8895 and AZD1061 serum concentrations.

The assay method is applicable to the quantitation of AZD8895 and AZD1061 human serum concentrations within a nominal range of 0.300 to 30.0 μg/mL in 20 μL neat human serum.

9.10 Anti-Drug Antibody Assessment

The presence of anti-drug antibodies (ADA) will be detected using a validated assay developed for AZD8895 and AZD1061at PPD, which are the parent antibodies of the mAb AZD5396 and mAb AZD8076 and share the same Fab region and cross react.

ADA Assay Description

A multi-tiered testing approach, consisting of validated assays for detection (screening assay), specificity (confirmation assay), and semi-quantification (titer assay), is to be used for the assessment of ADA responses to AZD5396 and mAb AZD8076, using the assay previously developed to detect ADA against AZD1061 and AZD8895 respectively.

All clinical samples are screened for ADA against AZD8895 and AZD1061 separately using an ECL solution-phase bridging method. In the method, diluted samples are incubated in a solution phase with

biotinylated AZD8895 or AZD1061 and ruthenium (sulfo-TAG)-labelled AZD8895 or AZD1061. Bridged biotin drug:ADA:sulfo-TAG drug complexes are subsequently captured onto streptavidin-coated plates (MSD) and measured on the MSD SECTOR S 600 plate reader. Samples are reported screen positive for ADA in the screening assay if the mean ECL value is at or above the ECL value of the plate-specific cut point (CP).

Screen positive samples are retested in a confirmation assay, where samples are analyzed both in the absence and presence of excess drug to determine if the sample's positive response is specific to AZD8895 or AZD1061. Samples generating a percent inhibition value equal to or greater than the confirmatory CP established for the method are reported confirmed positive for ADA. The percent inhibition value was calculated for each sample using the following formula:

$$\% \text{ Inhibition} = (1-(\text{mean ECL with AZD8895 or AZD1061}/\text{mean ECL without AZD8895 or AZD1061})) \times 100\%$$

Titers are measured in confirmed positive samples and will be reported as the reciprocal of the highest 2-fold dilution that measured positive in the assay, before returning a negative response. Titers for negative samples are reported as < 80 for AZD8895 or < 40 for AZD1061 since the minimum required dilution of the assay is 1:80 and 1:40, respectively.

Sensitivity was defined as the lowest ADA control concentration that measured positive with respect to the plate CP. The sensitivity results using the anti-ID ADA controls were 4.40 ng/mL and 8.43 ng/mL for AZD8895 and AZD1061 ADA assays, respectively.

Drug tolerance evaluated the effect of AZD8895 or AZD1061 on the detection of ADA at 3 concentrations and is reported as the highest concentration of drug that does not interfere with the detection of 100 ng/mL of the ADA control. The data indicated that for each screening assay the 100 ng/mL of anti-ID ADA control could be detected in human serum samples containing 100 µg/mL of AZD8895 or AZD1061. For each confirmatory assay the 100 ng/mL of anti-ID ADA control could be detected in human serum samples containing 100 µg/mL of AZD8895 or 50 µg/mL of AZD1061.

9.11 Concomitant Medications/Treatments

All medications (prescription and nonprescription) taken within 8 weeks of signing consent and ongoing from signing of the informed consent to study discharge must be recorded on the case report forms (CRFs).

Actual or estimated start and stop dates must be provided. This information will be obtained from the participant and abstracted from any available medical records. The indication for the medication, dose, and dose regimen will be documented. Medication that is considered necessary for the participant's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

9.12 Restrictions

Participants should not use blood thinners within 2 weeks before any dose of Investigational product.

Participants should not use alcohol or drugs that would interfere with study requirements during the course of the study and should report ALL medications/drugs taken to the Investigator and/or other study personnel.

Participants should refrain from becoming pregnant until 6 months following the last dose of investigational product by using appropriate contraceptive measures.

10 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

10.1 Safety Parameters

The safety of AZD5396 and AZD8076 with Hylenex® Recombinant and CELLECTRA ™ 2000 will be measured and graded in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials," issued September 2007 (Appendix B: Toxicity Grading Scale).

10.1.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition changes.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management.

10.1.2 Definition of Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

10.2 Unexpected Adverse Drug Reactions (ADR) and Expedited Reporting

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose for which a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., there is evidence to suggest a causal relationship between the product and the AE). An AE or ADR is considered unexpected if it is not listed in the applicable product information (Investigator's Brochure, protocol, or User Manual) or is not listed at the specificity or severity which is consistent with the risk information provided. The Sponsor (Pablo Tebas, MD) will assess each serious adverse drug reaction report for expectedness, to determine if it is a suspected unexpected serious adverse reaction (SUSAR) which requires prompt reporting to regulatory authorities and participating Investigators as an expedited report, in accordance with the applicable regulatory requirements. Additional occurrences of the SUSAR will be required to be reported on an expedited basis until the applicable product information is amended.

In addition to single-case reports of SUSARs, the Sponsor (Pablo Tebas, MD) will notify regulatory authorities and participating investigators of information that might materially influence the benefit- risk assessment of a medicinal product, sufficient to consider changes in product administration or overall conduct of a clinical investigation. Examples of such information include a clinically important increase in the rate of occurrence of a serious expected AE, the identification of a significant hazard to the participant population, or a major safety finding from a trial conducted in animals.

10.3 Unanticipated (Serious) Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Per the definition above, a UADE is a type of SAE that requires expedited reporting on the part of the Sponsor (Pablo Tebas, MD). As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor (Pablo Tebas, MD) by the trial Investigator within 24 hours. Sponsor (Pablo Tebas, MD) will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

10.4 Assessing Severity (Intensity)

The Investigator will assess and grade clinical and laboratory AEs or SAEs (based on discussions with trial participants) in accordance with the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials," issued September 2007.

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)
- Death (Grade 5, clinical AE only)

10.5 Causal Relationship of Clinical Material to Adverse Events

A causally related AE is one judged to have a reasonable causal relationship to the administration of the Investigational product and/or the CELLECTRA™ 2000 investigational device. The Investigator will assess causal relationship of the AE separately to the investigational drugs and also the investigational device. An AE may also be assessed as not related to the Investigational product and/or the investigational device. Because the investigator is knowledgeable about the participant (e.g., medical history, concomitant medications), administers the Investigational product, and monitors the participant's response to the Investigational product, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the Investigational product and EP and a subsequent AE. The Investigator is aware of the participant's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor (Pablo Tebas, MD) will assess the overall safety of the Investigational product delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the trial participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP and/or the investigational device and the causal relationship reported "Yes" or "No" accordingly. Causality should be assessed by the Investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there are facts, evidence or arguments that administration of the Investigational product or device or both Investigational product and device contributed to the event.
- No – there are no facts, evidence or arguments that administration of the Investigational product or device or both Investigational product and device contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of Investigational product.
- Course of the event, considering especially the effects of dose reduction, discontinuation of Investigational product, or reintroduction of Investigational product (where applicable).
- Known association of the event with the Investigational product, EP or with similar treatments.
- Presence of risk factors in the trial participant or use of concomitant medications known to increase the occurrence of the event.

10.6 Post-Trial Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for participants on trial (including any protocol-required post-treatment follow up).

Investigators are not obligated to actively seek AEs or SAEs beyond the follow-up period for participants. However, if the Investigator learns of an AE or SAE that occurs after the completion/discharge or termination visit and the event is deemed by the Investigator to be related to the trial treatment, s/he should promptly document and report the event to the Sponsor (Pablo Tebas, MD).

10.7 Procedures for Documenting Pregnancy During the Trial

Participants who are pregnant or expect to become pregnant during the first 6 months of the trial will be excluded from participation in the trial. Should a participant become pregnant after enrolling in the trial, she will not be given any further treatments with the Investigational product. A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor (Pablo Tebas, MD) trial team within 24 hours after learning of the pregnancy. The Investigator will also report this event to the IRB/IEC within 24 hours of becoming aware of the pregnancy. Sites must request the participant's permission to query pregnancy outcome and follow each participant to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Participants who become pregnant at any point during the trial will continue to be followed for safety assessments without receiving further Investigational product. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent trial-related blood collection based on the presence or absence of anemia in each participant.

All pregnancies that occur from the time of first dosing procedure through the follow-up visits must be reported. The Investigator will monitor the participant and follow the outcome of the pregnancy, as well as the health of the baby for up to one year after birth. If the end of the pregnancy occurs after the trial has been completed, the outcome will be reported directly to the trial team.

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up period.

A Pregnancy Form will be completed by the Investigator and submitted to the Sponsor (Pablo Tebas, MD) within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to Investigational product. The pregnant partner will be asked to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy and the health of the baby for up to one year after birth. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy and the baby's health. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

10.8 Methods and Timing of Collection of Safety Data

Non-serious AEs and SAEs (and UADEs) will be collected for each participant from the time when informed consent is obtained, through the duration of their participation. During each Investigational product administration visit, participants will be directly observed by study personnel for at least 30 minutes after administration of Investigational product for immediate reactions. Throughout the study, participants will be queried at each study visit regarding the occurrence of any SAE or other AE that may have occurred since the last study visit. They will be reminded to contact study personnel and immediately report any serious event that occurs during the course of the study.

Sources of AEs include:

- The participant's response to questions about their health (a standard non-leading question such as 'How have you been feeling since your last visit?' is asked at each visit).

- Symptoms spontaneously reported by the participant.
- Evaluations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
- Other information relating to the participant's health becoming known to the investigator (e.g., hospitalization).

All AEs, regardless of severity, seriousness, or presumed relationship to study treatment, must be recorded using medical terminology in source documents and on the CRF. Whenever possible, a diagnosis should be documented, in lieu of symptoms. The source document and the CRF must contain the Investigator's opinion concerning the relationship of the AE to study treatment.

AEs should be described with the following attributes:

- Duration (start and end dates)
- Seriousness
- Severity
- Causality
- Action(s) taken
- Outcome

10.9 Safety and Toxicity Management

The Medical Director will be responsible for the overall safety monitoring of the study. Safety assessments include the following:

- Adverse events utilizing the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", issued September 2007 (Appendix B: Toxicity Grading Scale).
- Local pain immediately after Investigational product administration and at select times using a VAS.
- Clinically significant laboratory abnormalities (e.g., CBC, chemistry, hematology, coagulation, CPK, urinalysis, ECG) compared to baseline.
- Clinically significant changes to vital signs compared to baseline.

10.10 Dose Limiting Toxicity Criteria

Dose limiting toxicities are defined below for the purposes of evaluating the safety of the administered doses of dMAb AZD5396 and dMAb AZD8076. The following Investigational product administration- and/or EP- related adverse events are defined as DLTs:

- Grade 3 or greater local injection site erythema, swelling, and/or induration recorded ≥ 1 hour after Investigational product administration
- Pain or tenderness at the injection site that requires overnight hospitalization despite proper use of non-narcotic analgesics.

- Grade 3 or greater systemic symptoms assessed by the Principal Investigator as related to Investigational product administration.
- Grade 3 or greater clinically significant laboratory abnormalities assessed by the Principal Investigator as related to Investigational product administration.

The most severe grade for that particular event is to be documented on the CRFs for DLT.

DLT assessment is scheduled for the first 3 to 6 participants for specified cohorts at Day 14 (Week2). Study Investigators are required to conduct clinical assessment and review blood test results performed. The DSMB is responsible for reviewing available safety data for specified cohorts. Refer to Section 4.2 for additional information on DLTs and the dose escalation scheme.

10.11 Stopping Rules (Criteria for Pausing Trial)

Refer to Study Design and Endpoints, for a description of "3+3" design and enrollment sequence of each cohort.

The stopping rules for this study are any of the following:

- If at any time during the study two thirds of participants in a single cohort experience a DLT after product administration
- If 2 or more participants across all enrolled cohorts experience the same grade ≥3 adverse event or grade ≥3 adverse event in the same organ class
- In the event of any unexpected Grade 4 toxicities
- Any SAE, potentially life-threatening AE or death
- Any reported anaphylaxis from dMAb AZD5396 and dMAb AZD8076 and Hylenex® delivered by EP.

The study will be halted for any report of anaphylaxis from dMAb AZD5396 and dMAb AZD8076 and Hylenex® delivered by EP. The study will be halted to enrollment and further dosing will be suspended until a full discussion has been conducted and then reviewed by the DSMB and study resumption is agreed upon.

10.12 Device Complaint

A product complaint/device deficiency is defined as any written, electronic, or oral communication that alleges deficiencies or inadequacies of the device or components related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device or components after it is released for distribution within the clinical investigation. Device deficiencies include malfunctions, use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled or marketed. All product complaints that meet this definition (with the exception of SAEs requiring 24 hr reporting) must be reported to the Sponsor (Pablo Tebas, MD) with 10 days of discovery *(see Appendix C: CELLECTRA™ Error Reporting Form).

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the

treatment procedure must be reported to the Sponsor (Pablo Tebas, MD) or designee immediately for evaluation. The complaint form must be completed and emailed to the Sponsor (Pablo Tebas, MD) at Pablo.tebas@pennmedicine.upenn.edu

10.13 Adverse Event Reporting

10.13.1 Reporting Period

Adverse events will be reported from the time of informed consent until the subject completes the study.

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within 24 hours of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event. Send the SAE report to the sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e., SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

The study sponsor will be responsible for notifying the Health Authority(ies), Food and Drug Administration (FDA), as applicable of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations. In addition, the sponsor must notify Health Authority(ies), FDA, as applicable and all participating investigators of potential serious risks, from clinical trials or any other source, as per the applicable regulation.

10.13.2 Safety Reporting to the FDA

Following 21 CFR 312.32, the sponsor will notify the FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting:

- Serious and unexpected suspected adverse reaction.
- Findings from other studies.
- Findings from animal or in vitro testing.
- Increased rate of occurrence of serious suspected adverse reactions.

In each IND safety report, the sponsor will identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and will analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

The sponsor will submit each IND safety report in an electronic format that FDA can process, review, and archive.

The sponsor will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Any DLT will be reported to the FDA in an expedited manner.

10.13.3 Safety Reporting to the IRB

A reportable event is an adverse event or incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. An incident is determined to be reportable to the IRB when it is both:

- **probably** or **definitely** related to participation in the research
- unexpected in terms of nature, severity, or frequency

Events that meet these criteria, must be submitted to the IRB within 10 business days of discovery. HOWEVER, **if the event involved a death, investigators should report within 3 calendar days.**

If the event does not meet the reporting criteria above, the Investigator will follow the table below to determine whether the event is reportable to the IRB, and if so, when it should be reported.

Relatedness	Expectedness	Reportable to IRB?	When to Report
Unrelated or Unlikely related	Expected and Unexpected	NO	N/A
Possibly, Probably, or Definitely related	Expected	NO	N/A
Possibly related	Unexpected	YES ONLY IF: The event suggests that the research places subjects or others at greater risk than was previously known or recognized	EXPEDITED REPORTING WITHIN 10 business days; summarize at continuing review
Probably or Definitely related	Unexpected	YES	EXPEDITED REPORTING WITHIN 10 business days; Summarize at continuing review
Probably or Definitely related death	Unexpected	YES	EXPEDITED REPORTING WITHIN 3 calendar days. Summarize at continuing review

11 STATISTICAL CONSIDERATIONS

11.1 General Considerations

Descriptive statistics will be presented from the data collected in this phase 1, open-label study to address the main objectives of assessing safety, tolerability and pharmacokinetics of mAb AZD5396 and mAb AZD8076 expression at a maximum tolerated dose of dMAb AZD5396 and dMAb AZD8076. We anticipate the enrollment of up to 50 participants in the 8 cohorts.

11.2 Analytical Populations

Analysis populations include:

- The safety analysis set includes all participants who receive at least one Investigational Product administration and for whom post-dose safety data are available. Participants will be analyzed as to the dose level and cohort they were enrolled in.
- The per-protocol (PP) analysis set comprises all participants who receive all planned Investigational product administration over all planned dosing visits, have no important protocol deviations, and have valid pharmacokinetic endpoint data available until Week 48. These will be documented and tabulated prior to database lock. Participants in this sample will be analyzed as to the administration regimen to which they were enrolled.
- The modified intention-to-treat (mITT) analysis set includes all participants who receive at least one Investigational product administration and have valid pharmacokinetic endpoint data available until Week 48. Participants in this sample will be analyzed as to the dose level to which they were assigned. Analyses on the mITT sample will be considered supportive of the corresponding PP analyses.

11.3 Description of Statistical Methods

11.3.1 Safety Analyses Adverse Events

All solicited and unsolicited AEs/SAEs will be summarized by frequency per cohort and for all cohorts combined. These frequencies will be presented separately by dose and overall, by system organ class and by preferred term, the number and percentage of participants affected. Percentages, along with associated exact 90% Clopper-Pearson confidence intervals, will be based on the number of participants who are members of the safety analysis. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Investigational product administration. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Investigational product. All SAEs and administration site events will also be summarized as above.

The main summary of safety data (treatment emergent) will be based on events occurring within 48 weeks of administration of at least one of the investigational products (as specified in Section 10.12). Safety data will also be summarized based on events occurring any time after administration of Investigational product on Day 0 to week 72.

Laboratory Data and Vital Signs

Continuous response variables per time point and changes from baseline will be summarized with descriptive statistics: mean standard deviation, minimum, median, and maximum values by time point and cohort. Categorical response variables will be summarized per time point and cohort with frequencies and percentages.

11.3.2 Pharmacokinetic Analyses

The number and percentage of participants in which detection of monoclonal antibody mAb AZD5396 and mAb AZD8076 in serum is achieved will be summarized with a point estimate and corresponding

exact 90% Clopper- Pearson confidence interval. These will be summarized per time point within each cohort. We will also estimate the time to 50% decline from peak concentration.

11.3.3 Disposition

Disposition will be summarized by cohort and overall and will include the number and percentage enrolled, the number and percentage who received each planned dose and the number who completed the trial. The number and percentage of participants who discontinued will be summarized overall and by reason. The number in each analysis population will also be presented.

11.3.4 Demographic and Other Baseline Characteristics

Demographic and baseline data, vital signs, medical history, concomitant illnesses, and current medications/treatments will be summarized with descriptive statistics: mean, standard deviation, minimum, median and maximum values for continuous variables, and percentages for categorical variables, by cohort.

11.3.5 Interim Analyses

Interim analyses will be conducted in response to safety events as they emerge. For reasons of futility or safety issues, the DSMB could recommend stopping enrollment at any time.

11.3.6 Missing Values

The study is small, and we will be replacing subjects who do not receive medication per Investigator discretion. Subjects in cohorts B, C, D, E, and F may be replaced if they do not receive both the Day 0 and the Day 3 doses. Subjects in cohort G may be replaced if they do not receive all four of the Day 0, 3, 28, and 31 doses. Subjects in these cohorts who only receive Day 0 doses and want to continue in the study will be included in the A1 or A2 group for analysis. We do not anticipate employing methods for missing data and will report summaries from reported values.

11.4 Sample Size/Power

Our analyses will focus on estimation, and not on hypothesis testing. No formal power analysis is applicable to this study. We will, however, describe the precision available for descriptive statistics used to summarize the data. For proportions, our samples will be either N=3, N=5, N=6, or N=24, with target estimates of 30% DLTs. CI width varies with event frequency, as shown in Table 6. Our 90% CIs will be no wider than 0.694 for the samples of 6, or 0.361 for the overall sample of 24. For continuous measures, samples of 6 and 24 will yield standardized CIs of 1.64 SDs and 0.70 SDs respectively.

Table 6. Width of 95% CIs

Sample	Pr=0.05	Pr=0.1	Pr=0.2	Pr=0.3	Pr=0.4	Pr=0.5
N=3	0.676	0.716	0.785	0.835	0.865	0.875
N=5	0.510	0.562	0.647	0.703	0.734	0.744
N=6	0.456	0.512	0.598	0.653	0.684	0.694
N=24	0.191	0.239	0.300	0.335	0.355	0.361

11.5 Randomization and Blinding

Randomization is not applicable. Blinding is also not applicable because this is an open-label trial, and as such, site personnel, individual participants and the Sponsor (Pablo Tebas, MD) or its representative trial personnel will be aware of all Investigational product allocations.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Investigator and Sponsor Responsibilities

The Investigator and Sponsor (Pablo Tebas, MD) is responsible for ensuring that the clinical trial is performed in accordance with the protocol, the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

12.2 Protection of Human Subjects

12.2.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each participant prior to enrollment into the trial, and/or from the participant's legally authorized representative. The process for obtaining informed consent must also be documented in the participant's medical record (also refer to section 9.1).

12.2.2 Compliance with IRB/IEC Requirements

This trial is to be conducted in accordance with applicable IRB/IEC regulations. The Investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the trial and re-approval or review at least annually.

12.2.3 Compliance with Protocol

Participants are not required to follow special instructions specific to the IP used in this trial. Participants will be provided with Investigator emergency contact information and advised to report all AEs. While every effort should be made to avoid protocol deviations, should a deviation impacting participant safety be discovered, Sponsor Investigator and Medical Director (Pablo Tebas, MD) must be informed immediately.

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor (Pablo Tebas, MD) and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to trial participants, or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).

12.2.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor and PI if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Sponsor and Principal Investigator (S/PI) will promptly inform study participants, the

Institutional Review Board (IRB), and DSMB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12.2.5 Future Use of Stored Specimens and Data

Research samples, including serum and plasma will be collected and stored for follow-up exploration of study findings and/or adverse events (e.g., measurement of immune response, ADAs, measurement of cytokine and chemokine levels or other inflammatory biomarkers) in this or subsequent studies of dMAb AZD5396 and dMAb AZD8076. Any unused sample collected throughout the study for routine lab analysis may also be stored for future research. Research samples will be coded to maintain patient confidentiality and may be stored for up to 20 years for use in research as noted above.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biosample storage may not be possible after the study and/or testing is completed.

13 DATA COLLECTION, MONITORING AND REPORTING

13.1 Confidentiality and Privacy

A report of the results of this trial may be published or sent to the appropriate health authorities in any country in which the trial products are legally marketed or may ultimately be marketed, but the participant's name will not be disclosed in these documents. The participant's name may be disclosed to the trial Sponsor (Pablo Tebas, MD), the governing health authorities or the Food and Drug Administration (FDA), if they inspect the trial records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each participant prior to enrollment into the trial, and/or from the participant's legally authorized representative in accordance with the applicable

privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (HIPAA)).

Information about trial participants will be kept confidential and managed in accordance with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of the research participant to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the Sponsor (Pablo Tebas, MD) retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect vital status (i.e., that the participant is alive), at a minimum, at the end of their scheduled trial period.

14 SOURCE DOCUMENTS

Source data is all information, original records or clinical findings, laboratory results, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in original source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medical records and within information technology systems that are involved in the clinical trial. The Investigator/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents related to this trial.

14.1 Records Retention

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial related records.

CRFs will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by their participant identification number (SID).

It is the Investigator’s responsibility to retain trial essential documents for at least two (2) years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least two (2) years have elapsed since the formal discontinuation of clinical development of the IP. This retention period may be superseded by country requirements. The Sponsor (Pablo Tebas, MD) will inform the Investigator/institution as to when these documents no longer need to be retained.

14.2 Safety and Quality Monitoring

14.2.1 Data Safety Monitoring Board

An independent DSMB will be established to protect participants through analysis of emerging data from the trial. The DSMB for this trial includes three medical experts not affiliated with the Sponsor (Pablo Tebas, MD) nor any participating trial center (including the Principal Investigator). This DSMB will conduct safety reviews prior to dose escalation and will also serve the role as the independent research monitor. In this role, the DSMB will review all unanticipated problems involving risks to participants or others and report all SUSARs to the Sponsor with an assessment of causality and relatedness and comment on whether they agree with the PI/site.

The DSMB will be responsible for reviewing all safety data, including DLTs, stopping rules and SAEs. Since this trial is an open-label trial, participants, the Principal Investigator and the Sponsor (Pablo Tebas, MD) are not blinded as to Investigational product allocation. The DSMB meeting frequency, scope, and other details will be described in a separate DSMB charter.

14.2.2 Clinical Monitoring

Clinical Monitoring of the clinical trial will be performed by experienced Clinical Monitors, who will report to the Sponsor (Pablo Tebas, MD) or the Sponsor designee. Records for all clinical participants in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure the site is qualified and compliant with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed throughout the trial.

The Clinical Monitor will address and document the following trial conduct activities and obligations and will:

- Assure that the trial is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/IEC policies.
- Discuss trial conduct issues and incidents of noncompliance with the Investigator and/or trial personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the Sponsor (Pablo Tebas, MD).
- Remind the Investigator as necessary of the obligation to immediately report all SAEs and provide subsequent follow-up report of the final outcome to the IRB/IEC.
- Throughout the trial, inspect all source documents to ensure they are complete, logical, consistent, attributable, legible, contemporaneous, original, and accurate (ALCOA).
- Assure that the trial facilities continue to be acceptable.
- Compare the trial CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed.
- Assure that investigational drug and device accountability and reconciliation of records are complete and accurate.

- Assure that all participant specimens are being stored and forwarded properly for testing per laboratory manual requirements.

14.2.3 Publication and Data Sharing Policy

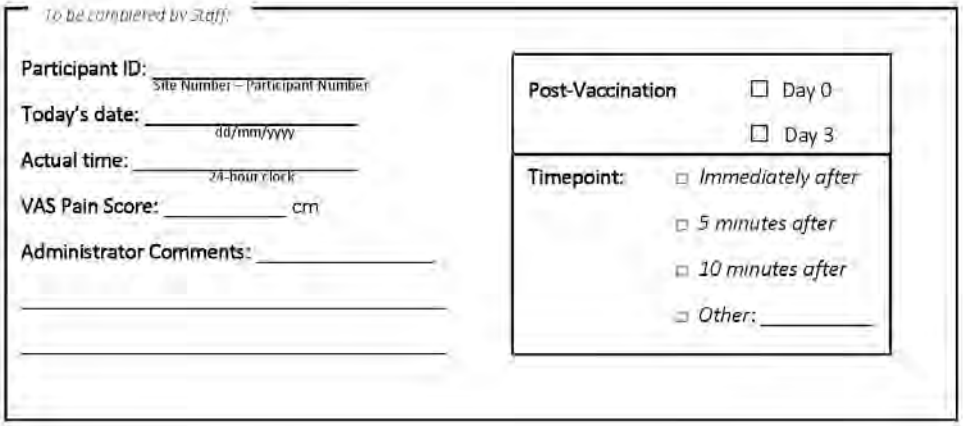
Publication of the results of this trial in its entirety will be allowed. The proposed presentation, abstract and/or manuscript must be made available to the Sponsor 60 days prior to submission for publication. The Sponsor will have 30 days after receipt of the copies to object to the proposed presentation or publication because there is patentable participant matter that needs protection. In the event that the Sponsor makes such objection, the researcher(s) will refrain from making such publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) (directed to the patentable participant matter contained in the proposed publication or presentation) to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

14.2.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

15 APPENDICES

15.1 Appendix A: Participant Memory Aid



To be completed by Staff:

Participant ID: _____
Site Number – Participant Number

Today's date: _____
dd/mm/yyyy

Actual time: _____
24-hour clock

VAS Pain Score: _____ cm

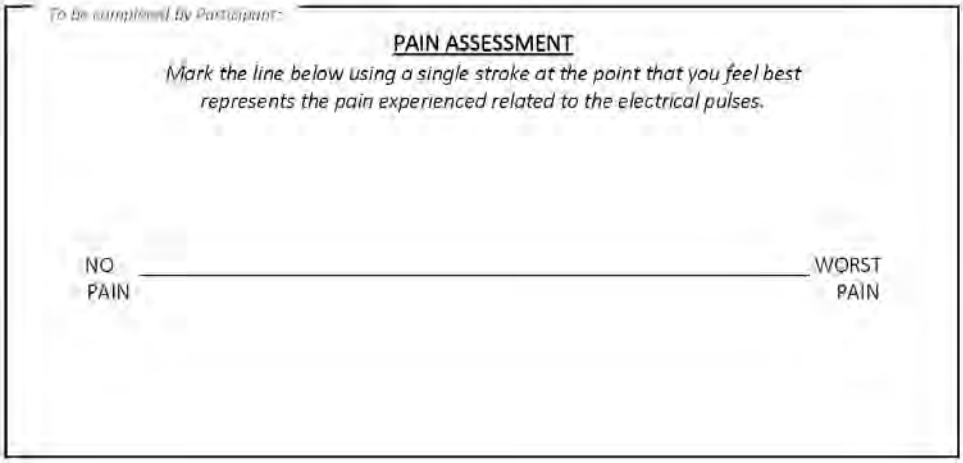
Administrator Comments: _____

_____

_____

Post-Vaccination ☐ Day 0 ☐ Day 3

Timepoint:
- ☐ *Immediately after*
- ☐ *5 minutes after*
- ☐ *10 minutes after*
- ☐ *Other:* _____



To be completed by Participant:

PAIN ASSESSMENT

Mark the line below using a single stroke at the point that you feel best represents the pain experienced related to the electrical pulses.

NO PAIN _____ WORST PAIN

Participant Reminder Diary

SARS-CoV-2-dMAB01

Subject #: _____

Injection Date:_____

Study Arm:_____

Note to Participant:

For questions or problems, please contact your Site Coordinator.

Name:_____

Telephone: ( ) _____

Email (optional): _____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm likealways.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

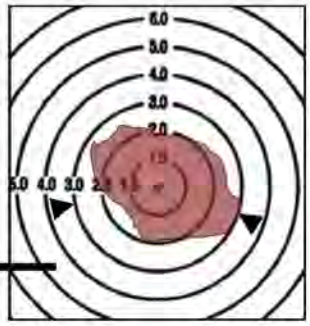
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 0: Evening of Injection Subject #:_____ Date:_____/_____/_____

Sometime during the evening on the day you were injected, fill out the information below. The items on this page refer to the time from your injection to 11:59 p.m. on the day of injection (Day 0). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.:_____ °C or °F (circle one)	Time Taken:_____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst the symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 0). See **General Instructions** on page 2 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 2.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm likealways.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.

General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

☐ **Mild** I only had minor discomfort. I went about my usual activities.

☐ **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.

☐ **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 1: Day After Injection **Subject #:_____** **Date:_____/_____/_____**

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 1). If any of the information changes after you fill out this page but before 11:59 p.m. tonight make any necessary changes below.

Temperature

Evening Temp.:_____ºC or ºF (circle one)	Time Taken:_____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom between midnight and 11:59 p.m. tonight (Day 1). See **General Instructions** on page 4 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 4.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm likealways.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.

General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- ☐ **Mild** I only had minor discomfort. I went about my usual activities.
- ☐ **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- ☐ **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

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Day 2: 2 Days After Injection **Subject #:_____** **Date:_____/_____/_____**

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 2). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.:_____°C or °F (circle one)	Time Taken:_____AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describesyour worst symptom until 11:59 p.m. tonight (Day 2). See **General Instructions** on page 6 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 6.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

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Version 1.0, 22November2021

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General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.

General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 3: 3 Days After Injection Subject #:_____ Date:_____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 3). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.:_____ °C or °F (circle one)	Time Taken:_____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m.tonight (Day 3). See **General Instructions** on page 8 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 8.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.

General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 4: 4 Days After Injection Subject #:_____ Date:_____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 4). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.:_____ °C or °F (circle one)	Time Taken:_____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 4). See **General Instructions** on page 10 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 10.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.

General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 5: 5 Days After Injection Subject #:_____ Date:_____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 5). If any of the information changes after you fill out this page but before 11:59 p.m. tonight, make any necessary changes below.

Temperature

Evening Temp.:_____ °C or °F (circle one)	Time Taken:_____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 5). See **General Instructions** on page 12 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 12.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

General Instructions

Temperature

Take your temperature orally around the same time each evening, using the thermometer provided and record it in the space provided. Also record the time at which you took your temperature. If you recently drank very hot or cold liquids, wait 15 minutes before taking your temperature.

Injection Site Symptoms

Pain and itching

Some people experience pain in the area where they were injected. Some people may also experience itching in the area where they were injected.

- By pain we mean that the place where you were injected hurts even when it isn't touched.

If you experience pain or itching at the injection site, use the following categories to describe how severe these symptoms were. If you don't experience one or more of these symptoms, mark the **NONE** box.

- **Mild** I only had a little discomfort. I could still use my arm like always.
- **Moderate** I noticed the discomfort and didn't use my arm as much as usual.
- **Severe** I really noticed the discomfort. It kept me from doing something I wanted or had to do.

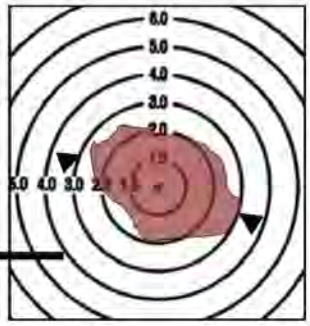
Redness, swelling, and bruising

Some people experience redness, swelling, or bruising in the area where they were injected. If you experience redness, swelling, or bruising, measure the area using the measuring tool you were provided, and record the measurement in the space provided.

To measure the area of redness, swelling, or bruising, do the following:

- Place the measuring tool over the area where you were injected, with the dot over the center of the area.
- Select the circle where the longest part of the area touches the line.
- If the area is in between two circles, select the larger circle.

For example, the area shown to the right measures 3 centimeters (cm) because it is touching the 3cm line.



General and Other Symptoms or Medications

If you have additional symptoms that are not listed, or if you sought medical care for any reason from a health care provider (e.g. doctor's office, emergency room), or if you took any medications, these should be listed in the spaces provided. Please designate any symptoms as Mild, Moderate, or Severe.

- **Mild** I only had minor discomfort. I went about my usual activities.
- **Moderate** I noticed the symptom. It bothered me enough that I didn't do as much as I usually do.
- **Severe** I really noticed the symptom. It kept me from doing something I wanted or had to do.

Day 6: 6 Days After Injection Subject #:_____ Date:_____/_____/_____

The items on this page refer to the time between midnight of last night and 11:59 p.m. today (Day 6). If any of the symptoms you reported on previous pages have not gone away ("resolved"), you will need to let the Site Coordinator or Doctor know.

Temperature

Evening Temp.:_____ °C or °F (circle one)	Time Taken:_____ AM or PM (circle one)

General Symptoms

If you experience any of these symptoms, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Unusually tired/feeling unwell	☐	☐	☐	☐
Muscle aches	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐

Injection Site Symptoms

If you experience an injection site symptom, mark the box that describes your worst symptom until 11:59 p.m. tonight (Day 6). See **General Instructions** on page 14 for more information.

Symptom	None	Mild	Moderate	Severe
Pain	☐	☐	☐	☐
Itching	☐	☐	☐	☐

Redness, Swelling, or Bruising	None	Provide Maximum Measurement
Redness	☐	cm at the longest part
Swelling	☐	cm at the longest part
Bruising	☐	cm at the longest part

Other Symptoms

If you experience symptoms other than the ones above, write them in the space below according to the **General Instructions** on page 14.

Did you experience any other symptoms? ☐ **Yes** ☐ **No**

Symptom or Medical Event	Mild	Moderate	Severe
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Did you take any medications? ☐ **Yes** ☐ **No**

If yes, please list out the name(s) and dosage(s) below:

_____

_____

_____

15.2 Appendix B: Toxicity Grading Scale

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

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Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

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to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

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B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

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Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

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IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

15.3 Appendix C: CELLECTRA™ Error Reporting Form

FORM		
DOCUMENT NO. CDT-FRM-0001	REVISION H	INOVIO POWERING DNA MEDICINES
TITLE: **CELLECTRA 2000 Complaint Reporting Form**		

Instructions:

1. Use this form to report any deficiencies or inadequacies of the CELLECTRA™ 2000 device or components (including its labeling or packaging) related to the identity, quality, durability, reliability, usability, safety, effectiveness or performance of the device or components or download/upload of device data.

   Deficiencies include malfunctions, user/use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The intended performance of a device refers to the intended use for which the device is labeled or marketed.
2. All complaints must be reported to INOVIO immediately following discovery, when possible.
3. Complete all sections below for a CELLECTRA™ 2000 device complaint.
4. Submit the completed form to clinicalcomplaint@inovio.com or fax it to +1 (267) 937-6044.
5. For assistance, call INOVIO's Complaint Line +1 (267) 434-4099.
6. For issues involving a used array, insert the used array into the provided complaint container and quarantine the used array until additional instructions are provided by INOVIO.
7. Direct requests for updated information related to device complaint(s) to clinicalcomplaint@inovio.com.

SECTION 1: QUARANTINE			☐ Not Applicable (N/A)
Check all that apply:	☐ Used Array is Quarantined ☐ Applicator is Quarantined ☐ Pulse Generator is Quarantined	**Date Quarantined** (ddMmmyyyy):	

SECTION 2: ADVERSE EVENT (AE)	
Did an AE occur as a result of this issue? **If Yes, ensure that the AE is recorded in the subject's source documentation and complete the AE electronic Case Report Form (eCRF).**	☐ Yes ☐ No

SECTION 3: CLINICAL TRIAL INFORMATION			
Protocol #:		**Contact Person Name:**	
Clinical Trial Site Name:		**Contact Phone #:**	
Clinical Trial Site #:		**Contact Email:**	

Effective Date: 14 Feb 2023 **CONFIDENTIAL** Page 1 of 4

FORM		
DOCUMENT NO. CDT-FRM-0001	REVISION H	INOVIO POWERING DNA MEDICINES
TITLE: CELLECTRA 2000 Complaint Reporting Form		

SECTION 3: CLINICAL TRIAL INFORMATION			
Clinical Trial Site Address:		**Principal Investigator Name:**	

SECTION 4: PARTICIPANT INFORMATION ☐ N/A			
Subject ID #:		**Dose #/Visit Name:**	

SECTION 5: CELLECTRA™ 2000 DEVICE INFORMATION ☐ N/A	
Pulse Generator Serial Number: (Located on front lid label)	
Pulse Generator Part Number / Reference Number: (Located on front lid label)	

SECTION 6: CELLECTRA™ 2000 APPLICATOR INFORMATION ☐ N/A	
Applicator Serial Number: (Located on handle label)	
Applicator Part Number / Reference Number: (Located on handle label)	

SECTION 7: CELLECTRA™ 2000 ARRAY INFORMATION ☐ N/A		
Array Lot Number: (Located on Array label)		
Array Part Number / Reference Number: (Located on Array label)		
Array Type:	☐ Intramuscular (5P-IM) ☐ Intradermal (3P-ID)	☐ IM Side Port ☐ Intradermal (3PSP ID)

SECTION 8: COMPLAINT INFORMATION		
1. **Was any component of the device damaged prior to use?**		☐ Yes ☐ No
If Yes, describe the damage:		
2. **Were there any deviations from the quick start guide or user manual?**		☐ Yes ☐ No
If Yes, describe the deviation(s):		
3. **Is this complaint related to an issue/error that occurred during subject administration?**		☐ Yes ☐ No
If Yes, proceed to Section 9 and skip Section 10. If No, skip Section 9 and proceed to Section 10.		

FORM		
DOCUMENT NO. CDT-FRM-0001	REVISION H	INOVIO POWERING DNA MEDICINES
TITLE **CELLECTRA 2000 Complaint Reporting Form**		

SECTION 9: ADMINISTRATION ERROR INFORMATION ☐ N/A		
Administration Date (ddMmmyyyy):		
Administration Time (24-hour clock format [e.g., 13:25]):		
Administration Location:	☐ Right Deltoid	☐ Left Deltoid
	☐ Right Anterolateral Quadriceps	☐ Left Anterolateral Quadriceps
	☐ Other (describe location):	
5P IM Side Port ONLY, was the Array Guide Used?	☐ Yes ☐ No ☐ N/A	
If Yes, provide the reason the Array Guide was used:		
5P IM ONLY, was the 2 inch 21 gauge injection needle used for administration?	☐ Yes ☐ No ☐ N/A	
During what step in the process did the issue occur:	☐ During attachment of array to the applicator ☐ While inserting array into tissue ☐ During drug injection ☐ During trigger button press ☐ During EP pulse delivery ☐ While removing the array from the tissue ☐ While removing the array from the applicator ☐ Other (briefly describe the step):	
Did the display on the device read "EP successful"?	☐ Yes ☐ No	
If No, record error message displayed on device screen:		
Were three 3 (IM) or 4 (ID) muscle contractions observed?	☐ Yes ☐ No	
If No, how many muscle contractions were observed?		
Total # of arrays used during administration:		
Was administration ultimately successful?	☐ Yes ☐ No	

SECTION 10: NON-ADMINISTRATION-RELATED, DEVICE ISSUE INFORMATION ☐ N/A		
Date the issue was observed (ddMmmyyyy):		
Time the issue was observed (24-hour clock format [e.g., 13:25]):		
When was the issue observed?	☐ After unpacking the device shipment ☐ During device charging ☐ During download of device data	☐ During upload of device data ☐ Other (briefly describe):

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FORM		
DOCUMENT NO. CDT-FRM-0001	REVISION H	INOVIO POWERING DNA MEDICINES
TITLE **CELLECTRA 2000 Complaint Reporting Form**		

SECTION 10: NON-ADMINISTRATION-RELATED, DEVICE ISSUE INFORMATION ☐ N/A	
Was a device error message observed?	☐ Yes ☐ No ☐ N/A
If Yes, record the error message displayed on device screen:	

SECTION 11: DESCRIPTION OF EVENTS	
List name(s) of clinical trial site staff involved: Provide corresponding clinical trial role(s). Do **NOT** list subject name(s).	
Describe the issue or device error in detail including what happened immediately before and during the issue, and what type of intervention or action took place immediately after the issue (e.g., user error, subject positioning at time of administration, issues with the mechanical or electrical components of the device)**:**	
Print name of person completing this form (first and last)**:**	
Signature of person completing this form:	
Date (ddMmmyyyy)**:**	

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