ZIKA-001

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5700 ADMINISTERED ID FOLLOWED BY ELECTROPORATION IN DENGUE VIRUS-NAÏVE ADULTS

Sponsored by:

GeneOne Life Science Inc.

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Version 1.2

PHASE I, OPEN-LABEL, DOSE-RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5700 ADMINISTERED ID FOLLOWED BY EP IN DENGUE VIRUS-NAÏVE ADULTS

Drug:	GLS-5700
Protocol Number:	ZIKA-001
Sponsor:	GeneOne Life Science, Inc. 1040 DeKalb Pike, Suite 200 Blue Bell, PA 19422
Medical Monitor:	Joel Maslow, MD PhD MBA FACP
Version and Date:	Version Draft 1.2; 1 July 2016

CONFIDENTIAL

PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and receive approval or a favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____	_____
Investigator's printed name and signature	Date
	1 July 2016
_____	_____
Medical Monitor	Date

Protocol Number: ZIKA-001
Site Number: xxx
Version Number: Final 1.2/Version Date: 1 July 2016

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CLINICAL PROTOCOL SYNOPSIS

Title of Study: Phase I, open-label, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5700, administered ID followed by EP in dengue virus-naïve adults.

Estimated Number of Study Centers and Countries/Regions: 3 sites US and Canada

Study Phase: I

Research Hypothesis: GLS-5700 administered by intradermal (ID) injection followed by electroporation (EP) will be well tolerated and immunogenic in dengue virus naïve adults.

Primary Objective:

- Evaluate the safety and tolerability of GLS-5700 when administered by ID injection followed by EP in healthy dengue-virus naïve adult subjects to 14 days from final vaccine administration

Primary Safety Endpoints:

- Incidence of adverse events classified by system organ class (SOC), preferred term (PT) severity, and relationship to study treatment and schedule to 14 days post-vaccination
- Administration (injection) site reactions (described by frequency and severity grade) and administration site pain to 14 days post-final vaccination
- Changes in safety laboratory parameters described by frequency and severity grade (e.g., liver panel tests, vital signs)

Secondary Objectives:

- Evaluate the safety to 1 year post vaccination of GLS-5700 in dengue-virus naïve adults.
- Evaluate cellular and humoral responses of GLS-5700 when delivered ID and followed by EP in dengue-virus naïve adults

Secondary Immunologic Endpoints:

- Binding antibody titers to the Zika envelope (E) protein as measured by ELISA
- Neutralizing antibody titers against Zika virus as measured in viral neutralization assay
- Antigen specific cellular immune responses to Zika virus as determined by Interferon-gamma (IFN-γ) ELISpot and/or Intracellular Staining (ICS) assays

Exploratory Objectives:

- Explore whether end point antibody titers are dose related.
- Explore the immunogenicity and longevity of GLS-5700 vaccination
- Explore the time to onset and longevity of immune responses, both humoral and cellular
- Explore if increasing dose levels of GLS-5700 more rapidly induce cellular and humoral immunity
- Explore the epitope specificity for T cell reactions of GLS-5700 to Zika virus

Exploratory Endpoints:

- Comparison of ELISA, neutralization titers, IFN-γ ELISpot and/or ICS across different vaccine regimens
- Other analyses as indicated to assess protective mechanisms against Zika virus.
- Epitope mapping of CD4+ and CD8+ T lymphocyte responses

Table S1: Dosing Arms and Regimens

Group	Vaccine	Schedule	*n*	Route	No. injections per dose	Dose (mg)
1	GLS-5700	0-4-12 weeks	20	ID	1	1
2	GLS-5700	0-4-12 weeks	20	ID	2	2
	TOTAL		40			

Study Design:

This Phase I clinical trial will evaluate whether GLS-5700 administered via ID injection and followed by electroporation (EP) is safe, tolerated and able to generate an immune response against Zika virus in dengue virus-naïve participants and whether immune reactivity is dose-dependent. Injections will be given in the deltoid muscle followed immediately by EP with the CELLECTRA®-3P device.

GLS-5700 contains plasmid pGX7201 that encodes for a consensus sequence of the pre-membrane (prM) and envelope (E) proteins of Zika virus.

Currently there are no approved treatments or prophylactic vaccines for Zika virus. Nor have any vaccine candidates for Zika virus been advanced into human trials.

Evaluation of ID administration of GLS-5700:
There are two arms for ZIKA-001. Participants (n=20 per group) will be administered GLS-5700 at one of two dose levels: 1 mg or 2 mg DNA/dose. Vaccine will be administered as 0.1 ml ID injections followed by EP with the CELLECTRA®-3P device. Participants will receive one or two injections into the deltoid region at vaccination at 0, 4, and 12 weeks (3 vaccination series).

Safety assessment: Participants will be monitored for adverse events utilizing the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix B)" with labs assessed as per site normal values. Pain will be assessed immediately after EP and at 30 minutes post-EP. Laboratory safety assessments will be obtained at screening, 1 week following the 1st vaccination, and 2 weeks following the 2nd and 3rd vaccinations. Adverse events, including assessment of injection site reactions, will be monitored through 12 months after the final vaccination.

In the event that a stopping criterion is reached (Section 7.3.2), the study will not continue until a full discussion has been conducted with the Medical Monitor, Principal Investigator, and IRB/CER (if applicable).

Immunogenicity assessment: Blood will be obtained for Zika immune responses at baseline; at weeks 1, and 4; at 2 and 8 weeks following the 2nd and 3rd vaccinations; and at study weeks 36 and 60. Serum will be separated and sent for analysis for humoral responses (neutralizing and binding antibody titers). Whole blood will be processed to obtain peripheral blood mononuclear cells (PBMC) for ELISpot and/or ICS analysis.

Study Population:

Inclusion Criteria:

a. Age 18-65 years;

b. Able to provide consent to participate and having signed an Informed Consent Form (ICF);

c. Able and willing to comply with all study procedures;

d. Women of child-bearing potential agree to use medically effective contraception (oral contraception, barrier methods, spermicide, etc.) or have a partner who is sterile from enrollment to 3 months following the last injection, or have a partner who is medically unable to induce pregnancy.

e. Sexually active men who are considered sexually fertile must agree to use either a barrier method of contraception during the study, and agree to continue the use for at least 3 months following the last injection, or have a partner who is permanently sterile or is medically unable to become pregnant;

f. Normal screening ECG or screening ECG with no clinically significant findings;

g. Screening laboratory must be within normal limits or have only Grade 0-1 findings;

h. No history of clinically significant immunosuppressive or autoimmune disease.

i. No history of dengue virus vaccination or illness; no history of yellow fever vaccination.

j. Dengue seronegative at baseline by screening laboratory evaluation

k. Not currently or within the previous 4 weeks taking immunosuppressive agents (excluding 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).

Study Population Continued:

Exclusion:

a. Administration of an investigational compound either currently or within 30 days of first dose;
b. Previous receipt of an investigational product for the treatment or prevention of Zika virus except if participant is verified to have received placebo;
c. Administration of any vaccine within 4 weeks of first dose;
d. Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose
e. Administration of any blood product within 3 months of first dose;
f. Pregnancy or breast feeding or plans to become pregnant during the course of the study;
g. Positive serologic result for dengue virus (any serotype) or history of receipt of either dengue virus or yellow fever virus vaccination at any time in the past;
h. Positive serologic test for HIV, hepatitis B surface antigen (HBsAg); or any potentially communicable infectious disease as determined by the Principal Investigator or Medical Monitor;
i. Positive serologic test for hepatitis C (exception: successful treatment with confirmation of sustained virologic response);
j. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 (CKD Stage II or greater);
k. Baseline screening lab(s) with Grade 2 or higher abnormality, except for Grade 2 creatinine;
l. Chronic liver disease or cirrhosis;
m. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;
n. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or prednisone at a dose greater than 10 mg/day or steroid dose-equivalent);
o. Current or anticipated treatment with TNF-α inhibitors such as infliximab, adalimumab, etanercept;
p. Prior major surgery or any radiation therapy within 4 weeks of group assignment;
q. Any pre-excitation syndromes, e.g., Wolff-Parkinson-White syndrome;
r. Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator (AICD)
s. Metal implants within 20 cm of the planned site(s) of injection;
t. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition at the planned site(s) of injection.
u. Prisoner or participants who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness;
v. 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; or
w. Not willing to allow storage and future use of samples for Zika virus related research
x. 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.

Table S2. Schedule of Events: 3 vaccinations

Tests and Observations	Screen (Day -7 to -30)	Day0	Day1	Wk1 (±2d)	Wk4 (±5d)	Wk6 (±5d)	Wk12 (±5d)	Wk14 (±5d)	Wk20 (±10d)	Wk36 (±10d)	Wk60 (±10d) / Early termination
Clinical Assessments											
Consent	X										
Med history	X	X									
Demographics	X										
Travel hx [a]	X										
Medications [b]	X	X		X	X	X	X	X	X	X	X
Phys Exam [c]	X	X		X	X	X	X	X	X	X	X
Vital signs [c]	X	X		X	X	X	X	X	X	X	X
Laboratory Assessments											
12-lead ECG	X										
CBC w/diff	X			X		X		X			
Chemistries [d]	X			X		X		X			
Serologies [e]	X										
Pregnancy [f]	X	X			X		X				
Serum [g]		X		X	X	X	X	X	X	X	X
PBMCs [g]		X		X	X	X	X	X	X	X	X
Blood Vol. per visit (mL)	15	70		80	70	80	70	80	70	70	70
Study Related Procedures											
Vaccine + EP		X			X		X				
EP Data [h]		X			X		X				
Memory aid [i]		X			X		X				
AEs		X	X [j]	X	X	X	X	X	X	X	X

[a] Travel history to Central America, South America, Caribbean Islands, and South Pacific Islands at any time in past
[b] Prior and concomitant, new medications will be recorded at all study visits (Day 0 through study discharge)
[c] 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; Vital signs will be performed pre and post vaccination at week 0, 4, and 12 week visits; height and weight will be recorded at screening.
[d] Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), glucose, BUN, Cr, ALT, AST, CPK
[e] HIV antibody or rapid test, HBsAg, HCV antibody, dengue, West Nile, and chikungunya virus antibodies
[f] Serum pregnancy test at screening and urine pregnancy test thereafter
[g] Collect **4 tubes** whole blood in ACD (yellow top) tubes for PBMCs; and 3 tubes of whole blood (red top) to obtain ~10 mL serum at the indicated time points
[h] Download EP data within 48 hours of dose and transfer to GeneOne or its designee
[i] Provide memory aid to study participants and review on next visit
[j] Detail AEs assessed via telephone.

1. INTRODUCTION

1.1 Background and Rationale

1.1.1 Zika Virus Epidemiology and Clinical Illness

Zika virus was discovered in 1947 during a survey to map the extent of yellow fever in the Entebbe region of Uganda. The virus was cultured from the serum of a sentinel macaque placed in the Zika forest that developed fever but was otherwise well. Initially restricted to equatorial regions of Africa and Asia, Zika started to spread eastward across the Pacific Ocean with an outbreak on Yap Island, Micronesia in 2007 [1], in French Polynesia in 2014 [2], and reaching Brazil in late 2014 or early 2015 [3, 4]. Although cases of Guillain Barré syndrome (GBS) were documented in the French Polynesian Zika outbreak [5], it was not until cases of microcephaly were documented in October 2015 during the outbreak in Brazil that global awareness of Zika disease was raised. Epidemiologic studies since then have documented a rate of GBS of approximately 1 in 5000 following Zika virus infection [6] and microcephaly affecting 1-2% of fetuses infected during pregnancy.

Zika virus infection presents similarly to dengue or chikungunya with fever in most, rash, malaise, myalgias, conjunctivitis and retroorbital pain but may present with few, if any, discernable symptoms [7]. The propensity for neurologic sequelae coupled with the rapid spread across South America, Central America, and the Caribbean has raised international alarm [8]. Moreover, alternative non-mosquito-borne routes of Zika virus spread include through blood transfusion, breast milk [9], sexual transmission [10-12], and may include urine and saliva [13, 14].

Zika virus is spread primarily through *Aedes* species mosquitoes, mainly *Aedes aegypti,* but can be carried and transmitted by many other mosquito species [15]. *Aedes* species mosquitoes also transmit other arboviruses such as dengue and chikungunya. In fact, these infections are co-endemic in most regions and may cause concurrent infections [16-18]. Most commercial flavivirus diagnostic assays are based on the NS1 protein, however, there is significant cross-reactivity between the NS1 proteins of yellow fever, dengue, and Zika. Whether prior exposure to any other arbovirus may affect the clinical response to Zika virus, or vice versa, is unknown.

1.1.2 Current Treatment

There are no approved therapies or vaccines for Zika virus infection, nor have any products advanced into clinical testing. Moreover, while many companies and academic groups have announced development plans for Zika virus vaccines, none have been published to date.

There have been a number of vaccines developed for other flavivirus infections. Live virus vaccines utilizing chimeric viral constructs have been approved for use for yellow fever and dengue. DNA vaccines have been developed and published for dengue [19, 20], West Nile virus [21-24], and Japanese encephalitis virus [23]. Notably, DNA vaccines

targeting West Nile virus [21, 22] and Dengue virus [20] have been tested as part of Phase I clinical trials without vaccine associated toxicity.

1.1.3 Pre-clinical experience with GLS-5700

The immunogenicity of pGX7201, the DNA plasmid that is the component comprising GLS-5700, has been studied in mice, guinea pigs, rabbits, and rhesus macaques. As of this writing, challenge trials are in progress. Details are presented in the Investigators Brochure and are summarized below.

pGX7201 encodes for the pre-membrane and envelope (prME) structural proteins of the Zika virus. The coding sequence is a synthetic compilation based on a statistical average of the amino acid sequence of African and Asian lineage strains published prior to December 2015, weighted towards the Asian lineage. The prME sequence is expressed from a modified pVAX1 expression vector, pGX0001. Expression, identity, and specificity were first determined in *E. coli* following transfection into tissue culture. The genetic structure of pGX7201 is such that prior work with West Nile virus and other flaviviruses has shown that proper folding of the envelope region occurs by inclusion of the premembrane region.

Mice were immunized intramuscularly (IM) into the quadriceps muscle with either 12.5 μg/dose or 25 μg/dose of pGX7201 at 0, 2, and 4 weeks. Injection of vaccine was immediately followed by EP using the CELLECTRA-3P device. Seroconversion was seen following a single vaccination with endpoint titers reaching ~1:10,000 following the third immunization. Immunization also induced neutralizing antibodies titers of ≥1:80, (neutralizing titers ≥1:10 are considered as protective for other viruses). pGX7201 also induced broad based, high-level T cell responses; ≥ 400 SFU/10^6 peripheral blood mononuclear cells (PBMCs). Based on the predicted crystal structure of the Zika virus mature pre-membrane and envelope proteins, mapping of the T cell response demonstrated responses to multiple envelope domains (DI, DII, and DIII, and the carboxy terminal region) with minimal to no reactivity to the pre-membrane and membrane region.

Specificity of the response was assessed by determining cross-reactivity of serum from pGX7201 (Zika virus vaccine) immunized mice against the envelope proteins of the four dengue serotypes; the Zika virus prME protein complex served as a positive control. There was no reactivity detected against any of the flavivirus dengue serotypes. Additional experiments to determine whether there was any cross-reactivity against the chikungunya envelope (chikungunya is an α arbovirus) similarly showed no reactivity over baseline at any titer. Thus, pGX7201 reactivity was specific to Zika virus with no cross-reactivity to the dengue flavivirus or other arboviruses such as chikungunya.

These data demonstrate that the vaccine was able to generate levels of antibody and T-cell responses that would be predictive of protection from infection. Since the pre-membrane and membrane regions would be predicted to be conserved across flaviviruses, the lack of reactivity to this region would further support a Zika-specific response for GLS-5700 based on pGX7201.

pGX7201 was also administered to guinea pigs and rabbits with similar B and T cell responses, demonstrating its utility across multiple mammalian species.

Non-human primates were immunized with pGX7201 at either low dose (0.5 mg/vaccination) or high dose (2 mg/vaccination) for three vaccinations spaced 3 weeks apart by either intradermal (ID) or IM injection and followed by electroporation (EP). These experiments are still in progress. Notably, after a single vaccination, 7 of 10 NHPs administered pGX7201 via ID injection and followed by EP developed robust B cell responses versus only 1 of 10 animals dosed IM (5 animals in each dose group (0.5 and 2 mg)). All animals, whether injected ID or IM seroconverted after 2 injections. Neutralizing activity has been detected with a single ID injection; quantification of the magnitude of the response has not yet been completed. pGX7201 also generated T cell responses in NHPs; quantification of response is in progress.

Importantly, as Zika virus circulates with dengue and chikungunya, and uses the same mosquito vectors to spread the disease, co-immunization experiments are underway to assess the immunogenicity of a single vaccine composed of DNA plasmid components against the Zika virus prME (pGX7201), the four dengue serotypes, and chikungunya virus in both guinea pigs and non-human primates.

Challenge studies to assess whether pGX7201 is protective in mouse and primate models of disease are underway. IFNAR mice (IFNα and IFNβ receptor knockouts) were first shown to be susceptible to Zika virus infection with mortality observed in approximately 7 days. IFNAR mice have been used successfully to assess a DNA vaccine against the Usutu flavivirus [27]. Histopathology of IFNAR mice infected with Zika virus following SQ administration demonstrates abnormalities restricted to the central nervous system, mimicking human disease. AG129 mice (IFN α, β, γ receptor knockouts) have also been shown to represent a lethal model for dengue virus [28], as well as for Zika virus infection (unpublished). While this mouse strain has been utilized to assess the response against a live-virus chimeric dengue virus vaccine [29], its response to a DNA vaccine has been questioned because of the complete loss of IFN responsiveness.

1.1.4 Target population for Zika virus vaccines and therapies

As reviewed above, Zika virus infection typically causes a self-limited illness that is minimally symptomatic for many. However, the occurrence of severe neurologic complications has focused development efforts. The most publicized and dramatic complications of infection are those occurring during fetal development and include microcephaly, intra-uterine growth retardation, cerebral calcifications, ocular calcifications, and other ocular abnormalities – with an attack rate estimated at 1 – 2% of women who become infected during pregnancy. The rate of Zika virus-induced fetal loss resulting in spontaneous miscarriage is, however, unknown. In adults, the most common complication of Zika virus infection is Guillain Barré syndrome occurring at an estimated rate of 1 in 5,000 cases. Additional complications include encephalomyelitis and acute demyelinating encephalomyelitis (ADEM). Zika has also resulted in deaths among adults with and without other complicating factors.

Key target groups for a vaccine are therefore women of child-bearing potential, men who have sexual relations with women of child-bearing potential, non-immune women who become pregnant, and adults in general – especially those with underlying severe disease. Additional implied groups are non-immune travelers to Zika endemic regions both to

prevent primary and secondary (via sexual transmission) cases, especially those returning to regions with permissive mosquito populations, to limit the spread of the virus globally.

This clinical study will assess the safety and immunogenicity of GLS-5700 in a dengue virus naïve population. Other studies will assess the safety and immunogenicity in a dengue-virus seropositive population.

1.1.5 Human experience with GLS-5700

There is no clinical experience with GLS-5700.

The safety of GLS-5700 can be informed from past experience with similar DNA vaccine candidates that are in, or have completed, human clinical trials. Specific examples of DNA vaccine human experience include: Phase I and 2 trials of INO-3100, targeting the human papilloma virus (HPV) that incorporates the HPV E6 and E7 proteins of HPV 16 and 18 [25, 26]; and current studies of VGX-6150 Hepatitis C vaccine in patients with chronic infection (NCT02027116), INO-4212 Zaire Ebola virus vaccine (NCT02464670), and GLS-5300 against the Middle East Respiratory syndrome coronavirus (MERS-CoV, NCT02670187). Each of these vaccine products use the same plasmid backbone but with different pathogen-specific antigen inserts. All of these products have been well tolerated and without vaccine associated serious adverse events (SAEs).

1.1.6 Administration of similar DNA plasmids by Electroporation (EP)

Experience with DNA vaccines using the modified pVAX1 plasmid backbone by Inovio Pharmaceuticals and GeneOne Life Science is extensive. Ongoing collaborative clinical trials between Inovio Pharmaceuticals and GeneOne Life Science include a prophylactic vaccines against MERS-CoV (NCT02670187) and the Zaire strain of Ebola virus (NCT02464670); and a therapeutic vaccine against genotype 1 hepatitis C virus (NCT02027116). Prior studies have also examined a DNA plasmid based vaccine against H5N1 Avian influenza (NCT01184976). Each vaccine construct has a similar structure: utilizing a pVAX1 expression vector with an insert comprising a portion of the viral DNA representing a consensus sequence not found in nature. All of these vaccine constructs have been administered either ID or IM and followed by electroporation with vaccine formulated in sterile water or sterile saline salt citrate (SSC) buffer. In each case, there have been no vaccine-associated safety concerns; the primary adverse events reported are transient injection site reactions.

Many groups have also published on DNA plasmid-based vaccine trials. Use of DNA vaccines for treatment of advanced HIV infection was first published in 1998 [30] with a recent review summarizing HIV related studies of greater than 1200 participants with no serious DNA-vaccine associated adverse events [31, 32]. Other notable studies include Phase I trials of DNA plasmid vaccines against Ebola virus [33-35], HPV [25, 26], HIV [36], and influenza [37]. In fact, a DNA vaccine for HPV has completed Phase II and demonstrated the ability to reverse pre-cancerous changes of the cervix causing regression of cervical intraepithelial neoplasia (CIN) grades 2 and 3, and clearance of chronic HPV infection in affected women [26]. Thus the DNA-based vaccine in this study, INO-3100, is the first vaccine to achieve clearance of a chronic viral infection.

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) and intradermal (ID) routes of administration. Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the plasmid DNA into the target site for antigen production: muscle or dermal cells. Following cellular uptake, there is efficient production of the defined pathogen-specific antigen proteins encoded by the DNA plasmid expression system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed [38]. EP has been extensively used in large animal species, such as dogs, pigs, cattle, and NHPs to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens [38], resulting in the activation of both cellular and humoral responses in these animal models [39, 40]. Importantly, antigen-specific immune responses for DNA vaccines delivered with EP are far superior to administration without EP [40]. The IM delivery of DNA with EP is well studied and optimum conditions for plasmid uptake and expression are described for therapeutic indications, vaccines, and tumor animal model systems [41, 42]. ID delivery with EP has also been shown to yield similar, if not superior results, and may be better tolerated. [43].

As of this writing, more than 800 human participants have undergone electroporation with the CELLECTRA® IM or ID devices in approximately 20 studies **(Table 1.1)**. More than 2000 doses of DNA have been administered. The most significant finding has been moderate but self-resolving administration site pain. Evaluation of CPK for muscle damage with IM delivery and ECG for cardiac conduction abnormalities has been unremarkable and no significant EP-related safety issues have been identified.

Table 1.1: Total Participants and Total DNA Doses Administered with IM and ID followed by EP with the CELLECTRA® Device

IM + EP Studies	# Subject	# Dose	ID + EP Studies	# Subject	# Dose
CEL-001	10	10	CEL-002	10	10
HPV-001	18	54	FLU-002	22	39
HPV-002	13	13	FLU-101	105	307
HPV-003 active	125	360	FLUPRIME	40	94
HPV-003 placebo	42	124	FLUPRIME placebo	10	20
FLU-001	32	56	FLUPRIME extension	32	32
FLU-001K	30	59	EBOV-001	15	42
HIV-001	12	48	HVTN098	39	232
HVTN 080	40	117			
HVTN 080	8	22			
RV262 A	7	14			
RV262 B	42	75			
VGX-6150-01	18	71			
HPV-004	1	4			
HPV-005	12	41			
HPV-006	1	4			
EBOV-001 (Ebola)	60	180			
WRAIR-2274 (MERS)	75	225			

1.2 GLS-5700

GLS-5700 contains a single plasmid, pGX7201, in sterile saline salt citrate buffer (SSC).

Common name: pGX7201

Chemical name: pGX7201 is a circular, double stranded, deoxyribonucleic acid plasmid consisting of 5066 base pairs.

Distinguishing name: This is a eukaryotic expression plasmid containing DNA encoding for pre-membrane and envelope (prME) proteins of the Zika virus. pGX7201 incorporates a consensus prME sequence of published Zika virus clinical isolate strains. The prME sequence has been codon optimized for mammalian expression. The transcription unit is controlled by a synthetic CMV promoter and elements required for replication and selection in *E coli*, namely a pUC origin of replication (pUC-Ori) and kanamycin resistance gene (KanR), respectively.

1.3 Dose and Regimen Rationale

The optimal dose and dosing regimen for GLS-5700 are as yet uncharacterized. In addition to safety, this study will assess two different doses of vaccine to evaluate optimal humoral and cellular immune responses to Zika prME. Based on prior experience with other DNA vaccines, there may be a plateau effect above 2 mg for DNA vaccines administered by EP. Preclinical studies of pGX7201 (the plasmid that comprises GLS-5700) in rhesus macaques assessed high (2 mg/vaccination) and low (0.5 mg/vaccination) doses with similar immunogenicity. No significant difference was seen in mice between doses of 12.5 μg and 25 μg/dose. Additionally, robust antibody and T-cell immune responses in humans were elicited with a dose of 2 mg/vaccination with a similar DNA construct in a Phase I dose-ranging study for the treatment of cervical dysplasia related to HPV cervical infection [25, 26]. Assessment of antibody and T-cell responses following each vaccination will determine the immune response to vaccination. Follow-up after the primary vaccination series will determine the longevity of immunogenicity of the vaccine.

1.4 Risks/Benefit Assessment

In accordance with the International Conference on Harmonisation (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 1.4**.

The potential side effects of treatment with the investigational products may include but not limited to discomfort related to the vaccine 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 725 participants. Since the volunteers in this clinical trial have unknown risk for exposure to Zika virus, no direct benefit is expected. The potential benefit is to determine whether this vaccine could generate immune responses with potential to be sufficient as prophylactic treatment for those at risk for Zika virus infection.

Table 1.4: Summary of Reported Adverse Events of DNA Vaccines Delivered IM+EP or ID+EP with CELLECTRA®

Common	• Mild to moderate administration site pain, erythema, tenderness, swelling, induration • Malaise/fatigue, myalgia, or headache in the first few days following injection • Visible lesion(s) at the injection site, such as erythematous papules with eschar, hypopigmentation, hyperpigmentation, or scar (ID administration only)
Less common	• Administration site bruising/ecchymosis, hematoma or pruritus • Arthralgia or nausea • Injection site hematoma, bruising/ecchymosis, laceration, other transient lesions, or bleeding related to the injection procedure
Uncommon or rare	• Administration site, laceration, other transient lesions, or bleeding related to the injection procedure • Severe administration site pain or tenderness • Rash following injection/EP • Scar formation (ID administration) • Vasovagal reaction/lightheadedness/dizziness related to the injection/EP procedure • Transient changes in clinical laboratory values
Unknown frequency or theoretical potential risks	• Severe localized administration site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including urticaria, angioedema, bronchospasm, or anaphylaxis • Chills, flu-like syndrome • Muscle damage at the administration site • Autoimmune disease • Electrical injury • Disruption of function of implanted electronic medical devices • Exacerbation of cardiac arrhythmia • Effects on the fetus and on pregnancy

The full safety monitoring plan is described in detail in the Evaluation of Safety and Management of Toxicity section below (Section 7).

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

GLS-5700 administered intradermally (ID) followed by EP will be safe, well tolerated and immunogenic in dengue virus-naïve adults.

2.2 Primary Objectives

- Evaluate the safety and tolerability of GLS-5700 when administered by ID injection followed by EP in healthy dengue virus-naïve adult participants within 14 days post final vaccination.

Primary Safety Endpoints

- Incidence of adverse events classified by system organ class (SOC), preferred term (PT) severity, and relationship to study treatment and schedule to 14 days post final vaccination in dengue virus-naïve adults
- Administration (injection) site reactions (described by frequency and severity grade) and administration site pain to 14 days post final vaccination
- Changes in safety laboratory parameters described by frequency and severity grade (e.g., liver panel tests, vital signs)

2.3 Secondary Objectives

- Evaluate the safety to 1 year post vaccination of GLS-5700 in dengue virus-naïve adults
- Evaluate the cellular and humoral response of GLS-5700 when delivered ID followed by EP in dengue virus-naïve adults

Secondary Immunologic Endpoints

- Binding antibody titers to the Zika envelope (E) protein as measured by ELISA
- Neutralizing antibody titers against Zika virus as measured in viral neutralization assay
- Antigen specific cellular immune responses to Zika virus as determined by Interferon-gamma (IFN-γ) ELISpot and/or Intracellular Staining (ICS) assays

2.4 Exploratory Objectives

- Explore whether end point antibody titers are dose related.
- Explore the time to onset and longevity of immune responses, both humoral and cellular
- Explore if increasing dose levels of GLS-5700 more rapidly induce cellular and humoral immunity
- Explore the epitope specificity for T cell reactions of GLS-5700 to Zika virus

Exploratory Endpoints

- Comparison of ELISA, neutralization titers, IFN-γ ELISpot, and ICS responses across different vaccine regimens
- Other analyses as indicated to assess protective mechanisms against Zika virus.
- Epitope mapping of CD4+ and CD8+ T lymphocyte responses

3. STUDY DESIGN

This is a Phase I open-label, dose-ranging study to assess the safety, tolerability, and immunogenicity of GLS-5700 in dengue virus-naïve adults. Eligible participants who consent to participate will be administered GLS-5700 via ID injection followed immediately by EP using the CELLECTRA® 3P Adaptive Constant Current Electroporation device.

Prospective participants who read and sign the ICF will be screened for eligibility for up to 30 days prior to their first dose. Screening evaluation will consist of a medical history, vital signs including height and weight, ECG, and laboratory evaluations. Participants without a history of exclusionary conditions, not clinically significant or normal ECG, and Grade 0-1 laboratory values (per the Toxicity Grading Scale for Healthy Adults Appendix B) for CBC, serum chemistry, and CPK, will be eligible for participation in the trial.

Evaluation of ID administration of GLS-5700:
Group 1 Participants (n=20) will be administered 1 mg GLS-5700 DNA/dose given as an ID injection followed by EP with the CELLECTRA®-3P device. Participants will receive a 3-dose series with immunizations at 0, 4, and 12 weeks.

Group 2 Participants (n=20) will be administered 2 mg GLS-5700 DNA/dose given as two ID injections per immunization followed by EP with the CELLECTRA®-3P device. Participants will receive a 3-dose series with immunizations at 0, 4, and 12 weeks.

See **Tables S1 and S2** for a summary of study treatments and dosing schedule.

Safety assessments: All participants will be monitored for

- Local and systemic adverse events (AE's) at each study visit.
- Laboratory related AE's following each vaccination.

Immunogenicity assessments:

The study will explore humoral and cell mediated immune responses in blood samples collected at the following times:

- Day 0 (prior to 1st dose of vaccine)
- Week 1 and week 4 post 1st vaccination
- Week 6 and 12 (2 and 8 weeks post 2nd vaccination)
- Week 14 and 20 (2 weeks and 8 weeks post 3rd vaccination)
- Weeks 36 and 60

3.1 Treatment Progression Scheme / Interim Safety Monitoring

This study will utilize a treatment progression scheme similar to WRAIR-2274 (assessment of GLS-5300 against MERS CoV) to assess and ensure the safety of each dose level of vaccine as follows.

Participants will be contacted by telephone to report reactions the day following the 1st vaccination to determine whether there are any AE's or other reactions. If no vaccine associated AEs requiring expedited reporting have occurred for the first 5 participants enrolled at 1 mg, then enrollment of the remainder of Group 1 at 1 mg/dose can proceed. Progression to the 2nd dose of vaccine at 1 mg/dose or enrollment of Group 2 at 2 mg/dose will require safety assessment as detailed below.

Safety laboratory assessments will be performed 1 week after the 1st dose of vaccine and 2 weeks after the 2nd and 3rd doses for all study participants, as appropriate. If no vaccine associated Grade 3 or Grade 4 AEs or any Serious Adverse Events (SAE) are encountered for the first 5 participants enrolled at 1 mg dose after review of their safety data, then enrollment into the 2 mg group can proceed. If there are no vaccine associated Grade 3 or 4 or serious safety events noted for the first 5 participants 24 hr post administration of 2 mg, then dosing will continue. Safety labs will be reviewed for the 1st 5 participants at the 2 mg dose by the monitoring committee. Safety labs will be reviewed monthly thereafter.

Review of safety labs will be conducted by a safety monitoring committee consisting of the study medical monitor with input from the site PI. The IRB/CER will be provided a summary statement of each safety review. The Safety Monitoring Committee (SMC) will meet to review safety laboratory assessments after 5 persons have received vaccine at each dose level. The committee will meet between 2-5 business days following the collection of safety labs for all 5 persons at the respective dose level. SMC meetings thereafter will occur on an ad hoc basis in response to any potential safety concerns.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment of Participants

Adult volunteers will be recruited for the study.

4.2 Inclusion Criteria

a. Age 18-65 years;
b. Able to provide consent to participate and having signed an Informed Consent Form (ICF);
c. Able and willing to comply with all study procedures;
d. Women of child-bearing potential agree to use medically effective contraception (oral contraception, barrier methods, spermicide, etc.), or have a partner who is sterile from enrollment to 3 months following the last injection, or have a partner who is medically unable to induce pregnancy.
e. Sexually active men who are considered fertile must agree to use either a barrier method of contraception during the study, and agree to continue the use for at least 3 months following the last injection, or have a partner who is permanently sterile or medically unable to become pregnant;
f. Normal screening ECG or screening ECG with no clinically significant findings;

g. Screening labs must be within normal limits or have only Grade 0-1 findings, except that creatinine may be grade 2 at baseline;

h. No history of clinically significant immunosuppressive or autoimmune disease.

i. No history of dengue virus vaccination or illness; no history of yellow fever vaccination

j. Dengue seronegative at baseline by screening laboratory evaluation

k. Not currently or within the previous 4 weeks taking immunosuppressive agents (excluding 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).

4.3 Exclusion Criteria

a. Administration of an investigational compound either currently or within 30 days of first dose;

b. Previous receipt of an investigational product for the treatment or prevention of Zika virus infection except if participant is verified to have received placebo;

c. Administration of any vaccine within 4 weeks of first dose;

d. Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose

e. Administration of any blood product within 3 months of first dose;

f. Pregnancy or breast feeding or have plans to become pregnant during the course of the study;

g. Positive serologic result for dengue virus (any serotype) or history of receipt of either dengue virus or yellow fever virus vaccination at any time in the past;

h. Positive serologic test for HIV, hepatitis B surface antigen (HBsAg); or any potentially communicable infectious disease as determined by the Principal Investigator or Medical Monitor;

i. Positive serologic test for hepatitis C (exception: successful treatment with confirmation of sustained virologic response);

j. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 (CKD Stage II or greater);

k. Baseline screening lab(s) with Grade 2 or higher abnormality;

l. Chronic liver disease or cirrhosis;

m. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;

n. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or corticosteroids at a dose greater than 10 mg/day or steroid dose-equivalent);

o. Current or anticipated treatment with TNF-α inhibitors such as infliximab, adalimumab, etanercept;

p. Prior major surgery or any radiation therapy within 4 weeks of group assignment;

q. Any pre-excitation syndromes, e.g., Wolff-Parkinson-White syndrome;

r. Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator (AICD)

s. Metal implants within 20 cm of the planned site(s) of injection;

t. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition at the planned site(s) of injection.

u. Prisoner or participants who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness;

v. 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; or

w. Not willing to allow storage and future use of samples for Zika virus related research

x. 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.

4.4 Discontinuation/Withdrawal of Study Participants

A participant will be considered to have completed the study when he/she completes all scheduled study treatments and follow-up visits. If a participant discontinues the study at any time after dosing, the investigator will make every effort to have the participant complete all assessments as indicated in Section 7.1 – Safety Parameters. The investigator will make every effort to have all scheduled immune assessment blood samples collected as indicated in the Schedule of Events, **Table S2**.

Unless a participant refuses to continue participation, all follow-up visits and procedures should be completed as indicated in the Schedule of Events, **Table S2**, following the last dose whether or not the participant has completed all doses.

The reason for any discontinuation of investigational product will be discussed with the Sponsor's Medical Monitor and indicated on the study forms. The primary reason for a participant discontinuing further dosing or withdrawal from the study itself is to be selected from the following standard categories:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator, are grounds for discontinuation for the best interest of the participant. This includes serious and non-serious adverse events regardless of relation to study drug.
- Death: The participant died.
- Withdrawal of Consent: The participant desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawal, it must be recorded on the case report form (CRF). This reason does not allow for further data collection or later study related procedures.
- Protocol Violation: The participant failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of either study treatments or study withdrawal.

- Lost to Follow-up: The participant fails to attend study visits and study personnel are unable to contact the participant after repeated attempts including letter sent by certified mail or its equivalent.
- Physician Decision: The participant was terminated for a reason other than those listed above by the physician caring for the participant.
- Other: The participant was terminated for a reason other than those listed above, such as termination of study by the Sponsor.

5. STUDY PRODUCT

5.1 Investigational Product

GLS-5700, the investigational product to be used in this study, contains a DNA plasmid encoding for the pre membrane and envelope (prME) proteins of Zika virus and is formulated in sterile salt citrate buffer (SSC). GLS-5700 will be provided (**Table 5.1**) at a concentration of 10 mg/ml.

Table 5.1: Investigational Product

GLS-5700	
Recoverable volume per container	0.4 mL minimum
Concentration	10 mg/mL
Container Size and Type	2 mL glass vial

5.2 Packaging and Labeling of GLS-5700

Study product will be supplied in a non-blinded fashion. Study product will be shipped directly from the manufacturer or its designee to the study site. Each vial will be labeled with a single panel label (**Table 5.2**).

Table 5.2: Sample labels for the final drug product components

Biologic Product/ Diluent	Sample Label
GLS-5700 / SSC	GLS-5700 [10 mg/ml] 0.4 mL/Vial Single Use Vial Lot: GLS-5700.xxxxx Date of Manufacture: DD MMM YYYY Final Retest Date DD MMM YYYY Store at 2 - 8ºC CAUTION New Drug – Limited by Federal Law to Investigational Use GeneOne Life Science, Inc. Rev 000

5.3 Handling of GLS-5700

Study product accounting will be performed continuously during the study. Details on study product volume, administration, and accountability are documented in the CRF and on respective pharmacy forms. At completion/termination of the study, all unused and partially used supplies must be returned to GeneOne Life Science, Inc. The investigator, pharmacist/drug administrator and monitor must verify that no drug supplies remain at the site at the time of study close-out. Appropriate records will be maintained in the investigator's site file.

GeneOne Life Science, Inc. will be responsible for assuring the quality of the investigational product is adequate for the duration of the trial. GLS-5700 will be shipped refrigerated. If there the cold packs are at room temperature when the shipment is received, the Sponsor must be contacted immediately.

Investigational product(s) 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. GLS-5700 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.

5.4 Dispensing of GLS-5700

It is the responsibility of the Investigator to ensure that GLS-5700 is only dispensed to study participants. Authorized personnel at the official study site must be the only ones to dispense the product according to local regulations.

The dosing syringe must be labeled with a four-hour expiration date from the time the vial(s) are removed from storage.

Detailed instructions on handling and dispensing of Investigational Product are provided below.

5.5 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 GeneOne Life Science 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.

5.6 Preparation of Investigational Product

GLS-5700 is supplied in single dose 2 mL vials at a concentration of 10 mg/mL at a minimum recoverable volume of 0.4 mL. GLS-5700 is formulated in SSC.

Study drug is to be prepared by site staff who are trained and knowledgeable in mixing and dispensing investigational agents. Documentation of certification will be kept with the pharmacy documents. Study drug should be diluted and prepared in a BioSafety level 2 cabinet. Personnel will wear safety glasses, gloves and lab coat.

Remove investigational product from the refrigerator. Briefly centrifuge the vials between 500-2500 rpm for 3-5 seconds to remove any vaccine from the cap to the bottom of the vials. After centrifugation, maintain the vials in an upright position until use.

5.6.1 Preparation of 1 mg ID Dose

To prepare study drug for 1 mg ID dose, the pharmacy staff should have a 1 mL tuberculin syringe with 25 or 27 gauge needle. Label syringe as “1 mg GLS-5700

Dosing". Withdraw 0.20 mL of study drug (at 10mg/mL) into the syringe and prime to 0.1 mL.

5.6.2 Preparation of 2 mg ID Dose

To prepare study drug for 2 mg ID dose, the pharmacy staff should have two 1 mL tuberculin syringes with 25 or 27 gauge needles. Label both syringes as "2 mg GLS-5700 Dosing". Withdraw 0.20 mL of study drug (at 10mg/mL) into each of the two syringes and prime to 0.1 mL.

Additional instructions for Investigational Product preparation are provided in the Pharmacy Manual.

5.7 Records of Investigational Product Disposition at Site

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried 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;
- Amount destroyed at study site, if applicable.

5.8 Return and Destruction of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to GeneOne Life Science, Inc., or its designee, if not authorized by GeneOne Life Science, Inc. to be destroyed at the site.

All investigational products returned to GeneOne Life Science, Inc., 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 GeneOne Life Science, Inc., 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 GeneOne Life Science, Inc. employee or

designated Study Monitor.Used investigational product must NOT be destroyed until accountability has been completed by the responsible GeneOne Life Science employee or designated Study Monitor.

5.9 Use of CELLECTRA® Electroporation Device

Instructions for use of the CELLECTRA® device are located in the Operations Manual. Each clinical site will receive training for the use of the CELLECTRA® device. The following specifications will be used during the study:

CELLECTRA® 3P-ID

Number of pulses per treatment = 4
Maximum Current Strength = 0.2 Amperes
Voltage Strength = 1 - 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second
EP needle array length (injection depth) = 3 mm (with array guide in place)

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 PI, approved Sub-Investigator, or sponsor in 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 sponsor personnel.
2. The CV and any relevant qualifications of the individual have been reviewed and approved by the sponsor or its designee to perform the procedure.

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

5.10 Investigational Device Accountability

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the CELLECTRA® serial number, applicator serial number, and array lot number used for treatment/ EP of each participant.

6. STUDY PROCEDURES AND TREATMENTS

See **Table S2** in the Clinical Protocol Synopsis for Schedule of Events showing study procedures and the times at which they are to be carried out.

6.1 Procedure by Visit

6.1.1 Screening Evaluations

The assessments during the screening phase will determine the participants' eligibility for the study and also their ability to comply with protocol requirements by completing all screening assessments. The following additional screening evaluations will be performed within 30 days prior to dosing on Day 0. All screening assessment values must be reviewed prior to study treatment.

- Signed informed consent (Section 6.2.1);
- Review and confirm all inclusion/exclusion criteria (section 4.2, 4.3);
- Collect demographics, including gender, ethnic origin, and travel history;
- Obtain complete medical history (including procedures history), present conditions and concomitant illnesses, and travel history (Section 6.2.2);
- Record concomitant medications/treatments at present and in past 8 weeks;
- Record vital signs (heart rate, blood pressure, oral temperature), body weight, height, heart rate (HR), blood pressure (BP), and oral temperature (Section 6.2.3.3);
- Collect blood for CBC with differential, blood chemistry [Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), glucose, BUN, creatinine, AST, ALT, CPK (Section 6.2.3.6);
- Collect blood for serologic assessment of HIV, Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV), and dengue, West Nile, and chikungunya virus antibodies
- Serum pregnancy (Section 6.2.3.6);
- 12 lead ECG (Section 6.2.3.5);
- Physical Exam (Section 6.2.3.2); and
- Determine proposed site of injection(s)

6.1.2 Study Evaluations

6.1.2.1 Vaccine Administration Visits

The following procedures will be performed at vaccination visits:

The following study evaluations will be performed **prior to dosing**:

- Review of medical history from screening
- Concomitant medications/treatments;
- Vital signs;
- Urine pregnancy test, if applicable
- Collect blood for serum or PBMCs for immune assessment as indicated;
- Targeted physical assessment
- Adverse event assessment

Administer **study treatment followed by EP**

The following study evaluations will be performed **post dose**:
- Pain assessment immediately and 30 minutes after EP;
- Injection site reaction assessment 30 minutes after EP;
- Distribute Participant Reminder Diary;
- Download EP data from device as directed and forward to GeneOne Life Science or its designee

6.1.2.2 Telephone assessment (Day 1 post 1st vaccination)

The following procedures will be performed the day following the 1st vaccination:
- Contact the study participant (either by phone or in person);
- Local and systemic injection site review;
- Adverse and Serious adverse event assessment;

6.1.2.3 Non-vaccination study visits

The following procedures will be performed during non-vaccination visits:
- Concomitant medications/treatments;
- Vital signs;
- Targeted physical assessment;
- Local and systemic injection site review;
- Adverse and Serious adverse event assessment;
- Collect blood for serum or PBMCs for immune assessment as indicated;
- Collect blood for safety laboratory assessment (CBC, serum chemistries, CPK) [as indicated]
- Review Participant memory aids [as indicated]

6.1.2.4 End of Study Visit (Week 60) / Early Termination

The following procedures will be performed 12 months after the end of treatment (week 60 visit):
- Concomitant medications/treatments;
- Vital signs;
- Full physical exam;
- Local and systemic injection site review;
- Adverse event assessment;
- Collect blood for serum or PBMCs for immune assessment as indicated;

6.1.2.5 Premature Withdrawal

Participants may refuse further vaccinations and/or terminate participation in the study at any time. In the event a participant decides to terminate participation prematurely, efforts should be made to perform all study

assessments. Participants may also discontinue participation in the study or have their participation discontinued by the principal investigator if safety and/or tolerability issues are considered intolerable and/or not manageable with symptomatic treatment.

At a minimum, all assessments from Week 14 visit should be performed prior to withdrawal if not already completed.

In the case of a fatal outcome, all relevant information (including cause of death, concomitant medication, and relationship to study treatment or underlying disease) will be collected.

6.2 Timing and Evaluations

6.2.1 Informed Consent

Study personnel will meet with prospective study participants, explain the study, and provide them with an informed consent form (ICF) that describes the screening tests, eligibility criteria for entering the study, and study treatments and follow-up procedures. An informed consent must be signed prior to any study related procedures being performed. A copy of the signed and dated consent form will be given to the participant.

6.2.2 Patient Identification Number and Group Assignments

Each participant who consents will be assigned a unique participant identification designation number (PID#), which identifies the participant for all study-related procedures that occur prior to receiving an allocation number. Once assigned, PID numbers cannot be reused for any reason. Information regarding participant's PID# and screen date will be documented on a screening log.

Study participants will be allocated to each of the two dosing groups such that the initial 5 eligible participants at each of the three study sties will be assigned to Group 1 at 1 mg/dose, the next 5 eligible participants at each study site will be assigned to Group 2 at 2 mg/dose. The final study participants will be allocated to the three study sites with 5 participants assigned to the 1 mg/dose group and allocated in a proportional manner between sites and the final 5 participants assigned to the 2 mg/dose group and similarly allocated in a proportional manner between study sites. Sponsor reserves the right to revise allocations between study sites should unexpected delays occur or any site cannot meet recruitment goals.

Medical History

Investigators should document all significant illnesses that the participant has experienced as Medical History. Illnesses' first occurring or detected during the study and/or worsening of an existing illness(es) that occur after the first vaccination 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, will 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, will be recorded in the CRF as concomitant medications.

Travel History

Investigators should inquire as to travel to any country or region to include the South Pacific Islands, South America, Central America, or the Caribbean.

6.2.3 Safety Assessments

The following patient evaluations for safety will be performed.

6.2.3.1 Patient self-evaluations

Participants record any post treatment reactions (local and systemic) and enter this information in the Post Vaccination Memory Aid (shown in Appendix A) 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 considered the property of the participants and are not collected nor considered as source documents.

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

6.2.3.2 Physical Assessments and Targeted Physical Assessment

A full physical examination will be conducted at screening. A targeted physical assessment will be performed at other visits as determined by the Investigator or directed per participant complaints. The injection site is to be assessed by the study personnel within 30 to 45 minutes after EP, as well as at the follow up visits.

6.2.3.3 Vital Signs

Vital signs including oral temperature, respiration rate, blood pressure and heart rate will be measured at specified visits.

6.2.3.4 Weight and Height

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

6.2.3.5 12-Lead ECGs

An ECG will be performed at screening for all participants to determine eligibility. The ECG should include measurements of ventricular rate, PR, QRS, QT, QT_c with assessment as to whether the ECG is normal or abnormal. Abnormal ECGs will be interpreted as clinically significant or not clinically significant. Dosing will be delayed in the event of a clinically significant abnormal pre-dose ECG until it has been reviewed by the PI, qualified PI designee, Medical Monitor or Sponsor consultant cardiologist and deemed safe to proceed.

6.2.3.6 Laboratory Evaluations

At screening, Week 1, Week 6, and Week 14 (as indicated) blood samples will be taken to be tested for serum chemistry and hematology. Approximately 425 mL of blood will be drawn from each participant during the entire duration of the study.

Hematology

CBC: White blood cell (WBC) count and differential count, Red blood cell (RBC) count, Hemoglobin, Hematocrit, Platelet count;

Serum Chemistry

Serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, AST, CPK;

Serology (screening only):

Antibody to HIV (human immunodeficiency virus), Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), and West Nile virus, chikungunya virus, and dengue virus antibodies;

Pregnancy Test

For female participants of reproductive potential, a serum pregnancy test will be obtained at screening with a negative result. Participants who have a screening pregnancy test that is positive will be considered as ineligible for the study. If a pregnancy test is positive prior to completing the prescribed regimen, additional doses of vaccine must not be given. Every attempt should be made to follow pregnant participants for the remainder of the study and to determine the outcome of the pregnancy and to follow the outcome post-delivery for a year.

6.3 Injection of Investigational Product followed by Electroporation

Participants will receive a 3 -vaccination series.

- Group 1 (n=20) will receive 3 vaccinations of 1 mg GLS-5700 given by ID injection followed by EP with CELLECTRA®-3P at 0, 4, and 12 weeks
- Group 2 (n=20) will receive 3 vaccinations of 2 mg GLS-5700 given by ID injection in two sites (1 mg/site) followed by EP with CELLECTRA®-3P at 0, 4, and 12 weeks

Vaccinations will be delivered ID into the deltoid region, followed immediately by EP (see Section 5.9 - Use of CELLECTRA® Electroporation Device). Vaccinations must not be given within 2 cm of a tattoo, scar, or active lesion/rash. The timing of the initial dose will be designated Day 0 with the subsequent doses scheduled for administration as per the Schedule of Events (**Table S2**). Within 48 hours following each Study Treatment, data should be downloaded from the EP device and sent to the Sponsor (GeneOne Life Science, Inc.) or designee by courier or email.

For individuals assigned to Group 1, injections should be alternated side to side between vaccinations.

For individuals assigned to Group 2 (2 mg per injection), injections should preferentially be given into both deltoid regions, i.e. at each vaccination both arms will have vaccine injections. If, however, one arm cannot be injected due to the reasons cited above, then injections should be given no closer than 3 cm apart.

6.3.1 Management of anxiety and pain due to EP procedure

Participants will be offered an analgesic (e.g. ibuprofen, acetaminophen) after injection/EP or EMLA cream before the procedure; the latter applied at least 15 min prior to vaccination.

Participants who are allergic to or have contraindications for use of ibuprofen or acetaminophen may be offered a suitable alternative.

6.4 Assessment of Laboratory Abnormalities

Blood will be drawn for serum chemistries and hematology assessments at the visits listed in the Schedule of Events, (**Table S2**) and as listed in section 6.2.3.6.

Laboratory AEs will be assessed and graded. See Section 7.1.7 for details.

6.5 Assessment of Clinical Adverse Events

The injection site will be assessed by study personnel prior to and within 30 to 45 minutes after injection/EP. Participants will be given an oral thermometer and instructed to take and record their oral temperature daily (at the same time each day). Participants will also be advised to record local and systemic events for 6 days after vaccination in a Post Vaccination Memory Aid (Appendix A).

Participants will also be queried regarding the occurrence of any adverse events, concomitant medications and new onset chronic disease during their clinic visits. Participants will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study up to and including the final study visit. These events will be recorded on the participant's case report form (CRF).

6.6 Assessment of Injection Site Reactions

The Study Treatment procedure consists of insertion of the CELLECTRA® electroporation array needles (electrodes) into the dermis, 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,

or swelling) that is observed at or near the site of the Study Treatment procedure to injection of the study drug(s) versus administration of the electroporation pulses will be difficult and is not necessary. Consequently, reactions arising from the Study Treatment 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 components below) and use the grading scale as outlined in Appendix B. Each injection site is considered as separate injection sites. The following observations, including grade of severity, will be recorded on the CRF:

- Time of occurrence relative to dose (e.g., immediately after, 1 day after dose, etc.)
- Site of injection
- Components of administration (injection) site reactions:
  - Tenderness (present or absent and severity)
  - Pruritus (present or absent and severity)
  - Erythema (diameter in cm)
  - Induration/Swelling (diameter in cm)
  - Bruising (diameter in cm)
- Resolution date
- Pain (see Section 6.3.1)

6.7 Handling and shipment of biological specimens

Information regarding collection, handling and shipping of biological specimens for this protocol will be provided by GeneOne Life Science.

6.8 Immunogenicity Assessments

6.8.1 ELISA

A standardized ELISA will be performed to measure the Zika virus binding antibody responses to the envelope protein. Briefly, 96-well enzyme immunoassay plates will be coated with purified recombinant Zika virus envelope protein. Samples will be scored as positive if the average OD is greater than 0.15 absorbance units and greater than the average OD before immunization plus 2.5 times the standard deviation (SD) of the OD before immunization at the same dilution. Results will be presented as end-point titer, i.e. the last dilution where the OD value is above threshold.

6.8.2 Neutralizing antibodies

Neutralizing antibodies against Zika virus will be performed by standard methodology as 50% plaque reduction tittered against immune serum.

6.8.3 ELISPOT

The number of antigen-specific IFN-γ secreting cells will be determined by IFN-γ ELISpot assays in response to stimulation with Zika virus peptides using 15-mer peptides overlapping by 11 amino acids spanning the entire pre-membrane and envelope regions.

The average number of spot forming units (SFU) counted in media control wells will be subtracted from the average in individual Zika virus peptide wells and then adjusted to $1x10^6$ PBMCs for each Zika virus peptide pool.

6.8.4 Flow Cytometry

Additional assessment of cellular immune activity may be performed via flow cytometry if sample volumes allow. Flow cytometric assays will include an examination of the influence of vaccination on the ability of patient T cells to exhibit phenotypic markers associated with cytolytic potential after short-term stimulation by Zika virus (hereafter referred to as "CTL Phenotyping"), the ability of patient T cells to remain active in the presence of long-term antigen exposure and efficiently synthesize proteins used in lytic activity (hereafter referred to as "Lytic Granule Loading"), and the ability of patient T cells to effectively employ Granzyme B for the purposes of lytic degranulation and killing of target cells expressing the S antigen (hereafter referred to as "Killing"). These panels may vary as new information becomes available. CTL Phenotyping will be prioritized while Lytic Granule Loading and Killing will only be run if sufficient patient samples are present.

6.9 Downloading of EP Data from CELLECTRA® Device

As directed by study staff, data will be downloaded from the EP device and forwarded by email or courier on a storage device to the sponsor (GeneOne Life Science, Inc.) or designee. Instructions on how to download the data and contact information will be provided under a separate cover. Training will also be provided.

6.10 Concomitant medications and medical procedures

All medications taken or medical procedures performed within 8 weeks prior to enrollment and during the study that do not affect a participant's eligibility for participation (see Section 4.3 - Exclusion Criteria) must be recorded on the CRFs. Dosage and frequency of immunosuppressive medications will also be recorded.

6.11 Restrictions

Participants must not be vaccinated (e.g. influenza vaccine) or have received polyclonal or monoclonal antibodies within 4 weeks of the first dose or 2 weeks before a subsequent dose of investigational product.

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 Safety Parameters

The safety of GLS-5700 will be measured and graded as outlined in Appendix B.

Throughout the course of the study, all AEs will be monitored and reported on an AE CRF, including the event's seriousness, severity, action taken, and relationship to study drug. If AEs occur, the first concern will be the safety of the study participants. AEs must be followed until resolution or stable and the outcome will be documented on the

appropriate CRF. All AEs must be recorded in standard medical terminology rather than the participant's own words.

7.1.1 Adverse Events (AEs)

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, as Clinical or Laboratory AEs. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment. An unexpected AE is one not identified in the Investigator's Brochure (IB) or otherwise not expected from the characteristics of the clinical material.

Study related AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after Screening (before the administration of study drug)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy; see Section 7.1.8 for additional information
- All AEs that occur from the study Day 0 visit onwards and throughout the duration of the study, including the follow-up of study drug period will be recorded as an AE

Study related AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the first vaccination that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the first vaccination and not related to a protocol associated procedure is not an AE. It is considered to be pre-existing and will be documented on the medical history CRF
- Any laboratory abnormality that is considered as non-significant or considered as related to another non-study related condition
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

7.1.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., participant was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for continued treatment or assessment of a pre-existing condition that has not worsened, does not constitute an SAE. NOTE: Evaluation in a physician's office, or at a hospital or other urgent care setting in an observational, non-admitted status regardless of the time period of observation, does not constitute an SAE;
- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

<u>Clarification of Serious Adverse Events</u>

- Death is an outcome of an AE, and not an adverse event in itself
- The participant may not have been on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the participant was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE

- Inpatient hospitalization means that the participant has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. Observation status or evaluation in an emergency department, urgent care setting, or outpatient office does not constitute an SAE.
- The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution. The reporting period for SAEs is described in Section 9.6.2.

7.1.3 Medically Attended Adverse Events (MAAE)

A medically attended adverse event (MAAE) is defined as an adverse event that leads to an unplanned contact with a health care provider.

7.1.4 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (Investigator's Brochure). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

7.1.5 Assessing Severity (Intensity)

The investigator will grade laboratory AEs and clinical AEs (based on discussions with study participants) as outlined in Appendix B.:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)
- Potentially Life Threatening (Grade 4)

Adverse events will be captured on the CRF at the maximum severity reported.

7.1.6 Causal Relationship of Clinical Material to Adverse Events

A causally related AE is one judged to have a suspected relationship to the administration of the clinical material (GLS-5700), and/or the investigational CELLECTRA® device. An AE may also be assessed as not related to the investigational product or device. The Investigator is responsible for reporting

adverse events and judging the relationship between the administration of the clinical material and a subsequent AE 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 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 will assess the overall safety of the investigational product and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the Study Participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. Causality should be assessed by the Investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is reasonable possibility that administration of the Study Treatment contributed to the event;
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to initiation of study drug;
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Participant or use of concomitant medications known to increase the occurrence of the event.

7.1.7 Abnormal Laboratory Value

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, CBC, CPK) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

Severity will be assessed as detailed in Section 7.1.5.

7.1.8 Procedures for Documenting Pregnancy During Study

Participants who are pregnant or expect to become pregnant during the course of the study will be excluded from participation in the study. Should a participant become pregnant after enrolling in the study, she will not be given any further treatments with GLS-5700. The Investigator will report the event to the study team and medical monitor, or its designee, and to the IRB. 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 study 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 study-related blood collection based on the presence or absence of anemia in each participant. Participants who are not withdrawn will continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of first screening procedure through the follow up visits must be reported. Monitoring of the participant and the outcome of the pregnancy will be followed by the investigator. If the end of the pregnancy occurs after the study has been completed, the outcome will be reported directly to the study team and the medical monitor.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant through till the end of follow-up period. A Pregnancy Form will be completed by the investigator and submitted to the sponsor 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 Study Treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. 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.

Participants who are detected as pregnant as part of the screening laboratory assessment, but who have not received study product, will not be enrolled into the

study and will be deemed as screen failures since the criteria for enrollment have not been met.

7.1.9 Post-Study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for participants on study (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 or termination visit and the event is deemed by the investigator to be probably or possibly related to the study treatment, he/she should promptly document and report the event to the study team and medical monitor.

7.2 Methods and Timing for Collection and Recording of Safety Data

0-6 days after each dose: Study participants will be directly observed by study personnel for 30 minutes after injection of GLS-5700 and contacted by study personnel on Day 1 post vaccination for immediate reactions. The occurrence and severity of any AE during this period or the lack of same will be recorded on the appropriate CRF. After that, participants will be given an oral thermometer and a Participant Memory Aid. They will be asked to take and record their oral temperature daily at the same time and to note and characterize in their own words any local or systemic AEs they experience which are to be reviewed at the next study visit.

Throughout the Study: In addition to the daily record of oral temperature, injection site reactions, and systemic complaints recorded for 7 days after injection of clinical material, study participants will be queried at each clinic visit regarding the occurrence of any SAE or other unexpected AE that may have occurred since the last visit. They will be reminded to contact study personnel and immediately report any such event that happens during the course of the study. These events will be recorded on the CRFs.

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 will 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

7.3 Safety and Toxicity Management

The Medical Monitor will be responsible for the overall safety monitoring of the study. The site PI will be responsible locally for safety. The Safety Monitoring Committee will review safety laboratory studies as delineated in Section 3.1.

Safety assessments include the following:

- Incidence of all adverse events classified by system organ class (SOC), preferred term, severity, and relationship to study treatment
- Changes in safety laboratory parameters (e.g., hematology, serum chemistry, and urinalysis)
- Local and systemic injection site review; special attention will be paid to the examination of the injection site. Administration site reactions and the participant's complaints will be documented.

7.3.1 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) will be defined as any Adverse Event of Special Interest (see section 7.1.3) regardless of intensity or relationship to Study Treatment or any Study Treatment-related adverse events that follow:

- Grade 3 or greater administration site erythema, and/or induration recorded ≥ 2 hours after Study Treatment;
- Grade 4 or greater administration site pain, tenderness recorded ≥ 2 hours after Study Treatment;
- Grade 3 or greater fever;
- Grade 3 or greater systemic symptoms, including generalized pruritus;
- Grade 3 or greater laboratory abnormalities

As per the Toxicity Grade for Healthy Adults (Appendix B). The most severe grade for that particular event is to be documented in the CRFs.

Sites will inform the Sponsor of any ERER within 24 hours to discuss whether dosing to the participant should continue.

7.3.2 Stopping Rules (Criteria for Pausing of Study)

If any of the following situations occur then further enrollment and Study Treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator and the IRB/REC (if applicable):

- One third (1/3) or more participants experience an ERER assessed as related to Study Treatment;
- Three or more participants in the same treatment arm discontinue due to an AE related to the Study Treatment;
- Any participant experiences a potentially life threatening AE, Grade 4 AE or death assessed as related to Study Treatment;
- Two or more participants within a treatment arm experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;
- Seven or more participants across all treatment arms experience the same or similar grade 3 or 4 adverse event, assessed as related to Study Treatment;

- Any report of anaphylaxis of Grade 3 or greater assessed as related to Study Treatment.

Upon conclusion, the sponsor or designee will notify all investigators and IRBs/EC (if required) regarding the outcome of any investigation stemming from a Study Pause.

Any SAE or death assessed as related to Study Treatment will lead to an immediate halt of study enrollment and Study Treatments.

Guidelines for assessing relatedness are detailed in Section 7.1.6.

8. STATISTICAL CONSIDERATIONS

8.1 General Considerations

The statistical analysis of the data will be performed by GeneOne Life Science or its representative. Descriptive statistics will be presented from the data collected in this Phase I study.

For the baseline characteristics, we will present continuous variables as means, medians, standard deviations, and interquartile ranges, and categorical variables as frequencies and percentages.

Analysis populations will include:

Per-protocol (PP) analysis to comprise participants who receive all Study Treatments and have no protocol violations. Participants in this sample will be grouped to treatment arms as randomized.

The modified intention to treat (mITT) analysis includes all participants who receive at least one Study Treatment. Participants in this sample will be grouped to treatment arms as randomized. Analyses on the mITT sample will be considered supportive of the corresponding PP analyses.

The safety analysis set includes all participants who receive at least one Study Treatment. Participants will be analyzed as to the treatment they received.

Participants who do not complete the study will not be replaced.

8.2 Demographic and Other Baseline Characteristics

Demographic and baseline data, vital signs, medical history, concomitant illnesses, and current medications/treatments will be summarized by means of descriptive statistics: continuous variables as mean, median, standard deviation, and interquartile ranges and categorical variables as frequencies and percentages, stratified by treatment arm based on the mITT population.

8.3 Safety Analysis

8.3.1 Adverse events

Treatment emergent AEs will be summarized by estimates of proportions, exact 95% binomial CIs, and 95% CIs. The differences between the groups (proportions

and GMT ratio) will be calculated. We will use the chi-square test to evaluate the significance of the differences in frequency between groups. These frequencies will be presented separately by dose and overall, i.e. based on pooled doses, and will depict overall, by system organ class and by preferred term, the number and percentage of participants affected. Additional frequencies will be presented with respect to maximum severity and to strongest relationship to Study Treatment. Multiple occurrences of the same AE will be counted only once following a worst-case approach with respect to severity and relationship to Study Treatment. All serious AEs and administration site events will also be summarized as above.

For the purpose of summarizing the safety all active vaccine groups will be grouped together. The proportion of participants experiencing grade 3 or grade 4 adverse events following the vaccine will be presented. The precision with which this sample result estimates the rate of similar adverse events in the population represented by the study sample will be reported in terms of 95% confidence intervals (CI) around the sample proportions. This will provide 95% confidence that the rate of severe adverse effects is not greater than the upper limit of the CI around the proportion of participants with grade 3+ events in the study sample.

Table 8.3.1 illustrates the confidence intervals for a range of hypothetical proportions of adverse events. This table shows (e.g.) that a sample finding of no grade 3 or grade 4 adverse events in a total evaluable sample of 40 participants would provide 95% confidence that the rate in the population from which the sample was drawn is no greater than 8.8%.

Table 8.3.2 shows the probability of detecting at least 1 adverse event of a given type and/or level of severity in the study sample, given a range of hypothesized rates in the population from which the sample was drawn. The table demonstrates that the probability of observing one or more events in a sample of 40 participants is ≥70% with events whose population probabilities are at least 2%, while the probability of observing two or more events is ≥34% for events whose population probabilities are at least 3%.

Table 8.3.1: Exact 95% confidence intervals around potential proportions of participants exhibiting Grade 3+ adverse events (total sample and selected subsample sizes)

N	Samples Rate (%)	Lower Limit (%)	Upper Limit (%
40	0	0	8.8
	1	0	10.7
	2	0	12.4
	3	0.1	13.9
	4	0.3	15.5
	5	0.6	16.9
	6	1.0	18.3
	7	1.4	19.7

	8	1.8	21.1
	9	2.3	22.4
	10	2.8	23.7

Table 8.3.2. Probability of detecting Adverse Events

True Event Rate in the Population Represented by the Study Sample	Probability of Observing Event(s) in the Study Sample (N = 40)	
	1 or more Event	2 or more Events
0.5%	18%	2%
1%	33%	6%
2%	55%	19%
3%	70%	33%
4%	80%	48%
5%	87%	60%

The main summary of safety data will be based on events occurring within 14 days of administration of Study Treatment (as specified in Section 9.6.1).

8.3.2 Laboratory Data

Continuous response variables per time point and changes from baseline will be summarized with mean, median, minimum, and maximum values. Categorical response variables will be summarized per time point with percentages. These will be calculated according to treatment arm.

8.4 Immunogenicity analysis

Data classified as positive/negative or responder/non-responder will be analyzed as the frequency of response for each assay within treatment arm at each time point at which an assessment is performed. For secondary immunogenicity outcomes, estimates of proportions and exact 95% binomial CIs and 95% CIs for the differences between the groups (proportions and geometric mean test (GMT) ratio) will be calculated. We will use the chi-square test to evaluate the significance of the differences between groups. For GMT and mean fold increase in GMT, we will calculate the mean and 95% CI for the log10-transformed titers and then transformed back to the original units by exponentiation. We will use the t test to compare the GMTs between groups. The proportion of participants meeting the criteria for immunologic response following vaccination will be presented for each study arm. The precision with which this sample result estimates the rate of immunologic response rates in the population represented by the study sample will be reported in terms of 90% CIs around the sample proportions. This will provide 95% confidence that the rate of immune response is not less that the lower limit of the proportion of study participants meeting immune response criteria. The primary immunogenicity analysis will include all subjects having evaluable data.

Table 8.4.1 illustrates the confidence intervals for a range of hypothetical proportions of immunologic response. This table shows (e.g.) that a sample finding of 30 (75%) responders in the total sample of 40 participants would provide 95% confidence that the rate in the population from which the sample was drawn was no lower than 62%.

The rate of response in arms will be compared using the chi-square test. Comparison between treatment arms will be carried out using a Mann Whitney U test for continuous variables, and a Fisher's Exact Test or Pearson's Chi-square Test for categorical factors. Because the study is small the study is underpowered for comparisons between arms.

Table 8.4.1: Exact 90% confidence intervals around potential proportions of participants achieving immunologic response criteria for each study arm (total sample and selected subsample sizes)

N	Sample rate	Lower Limit	Upper Limit
40	25%	14%	39%
	50%	36%	64%
	75%	61%	86%
	90%	79%	97%
	95%	85%	99%

The primary immunogenicity analysis will include all participants having evaluable data
A secondary qualitative analysis will assess immune responses relative to presence of pre-existing antibodies to other flaviviruses (West Nile or dengue) or chikungunya virus.

8.5 Sample Size

See section 8.3 for a power calculation of the probabilities of observing adverse events and immunological responses in the present trial.

With 40 participants receiving vaccine at any level, the study provides 80% probability of detecting an event if the incidence is greater than 4% in the vaccinated population (**Table 8.4.1**).

8.6 Missing Values

Missing data will not be replaced, and calculations will be done on reported values.

8.7 Interim analyses

No formal interim analyses will be performed for this study.

9. DATA COLLECTION, MONITORING, AND AE REPORTING

9.1 Confidentiality

Information about study participants will be kept confidential to the best of the study site's ability.

In the event that a participant revokes authorization to collect or use personal health information (PHI), the sponsor 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 at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records or clinical findings, 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, participant's diaries 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.

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee. Records for all clinical participants in this trial will be monitored. Monitoring functions and activities are outlined in the separate Monitoring Plan.

9.3 Records to be kept

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

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents as per country regulations: in the US for at least 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 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will inform the investigator/institution as to when these documents are no longer needed to be retained; and 25 years for Canada.

9.5 Safety and Quality Monitoring and Record Availability

Monitoring

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor or the Sponsor designee as outlined in the Monitoring Plan.:

Record availability and auditing

The investigator will make study documents (e.g., ICFs, drug accountability forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, regulatory agencies, GeneOne Life Science, Inc. or its designee for confirmation of the study data.

Participation as an investigator in this study implies acceptance of potential inspection by regulatory authorities and applicable compliance and quality assurance offices.

9.6 Adverse Experience (AE) Reporting

To assure the safety of the participants, information about all AEs (see Section 7.1 Safety Parameters for definitions), whether volunteered by the participant, discovered by investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the participant's source documents and followed as appropriate.

In addition to AE reporting, a summary of the study's overall progress will be forwarded to regulatory agencies according to the local requirements (e.g., every 6 months, annual).

9.6.1 Study Reporting Period of Adverse Events

All solicited and unsolicited adverse events will be collected throughout the study and recorded on the CRFs. The Study Report will analyze and summarize all adverse events throughout the study. Unsolicited AEs will be summarized for the 14 day period following each administration of Study Treatment. See next section for SAEs.

9.6.2 Study Reporting Period of Serious Adverse Events

The reporting period for SAEs (without regard to causality) is the entire period following the signing of the informed consent form until the end of the study.

Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should record this event to GeneOne Life Science within 24 hours of becoming aware of the event. The investigator may also directly report this event to the clinical site IRB/EC per standard operating procedures within 24 hrs.

Expectedness of SAEs will be determined by GeneOne Life Science using reference safety information specified in the Investigator's Brochure. An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related following the guidelines in Section 7.1.4 (Suspected Unexpected Serious Adverse Reaction, SUSAR) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Ethics Committee as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to the study drug, the event will be reported to the Sponsor or its designee.

If the investigator becomes aware of an SAE, an AESI, or an MAAE in a study participant after the last scheduled follow-up visit, and considers the event related to prior Study Treatment, the investigator will report it to GeneOne Life Science.

SAE TELEPHONE AND CONTACT INFORMATION:

MEDICAL MONITOR:	Joel Maslow, MD PhD MBA	MAILING ADDRESS:
PHONE:	(484) 965-9147p; (610) 331-7844 c	GeneOne Life Science, Inc.
SAFETY PHONE:	(215) 703-5843	1040 DeKalb Pike
FACSIMILE:	(877) 464-7787	Suite 200
EMAIL:	INCDrugSafety@INCResearch.com	Blue Bell, PA 19422

The report should contain as much clinical safety information as possible, but at minimum, the initial report must include the following information:

- Event
- Study code
- Participant number, initials and date of birth
- Investigational study product
- Reporter name and contact information

In the case of a "minimum report" (one that is solely comprised of the information bulleted above), a more detailed follow-up report will be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE must be followed up until resolution or stabilization and for a reported death, the investigator will supply GeneOne Life Science and the Ethics Committee with any additional requested information (e.g., autopsy reports and terminal medical reports).

The original SAE form must be kept at the study site. GeneOne Life Science or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

9.6.3 Notifications of Serious Adverse Events

In accordance with local regulations, the Sponsor shall notify the appropriate regulatory authorities, and all participating investigators in a written safety report of any adverse experience associated with the use of the product that is both serious and unexpected (e.g., FDA Form 3500A in the US). Reports of serious adverse events shall be made as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Written notification may be submitted on the form described above or equivalent or in a narrative format and shall bear prominent identification of its contents. Each written notification to regulatory agencies shall be transmitted to the division that has responsibility for review. In each written safety report, the Sponsor shall identify all safety reports previously filed concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of

the previous, similar reports. The Sponsor shall also notify the relevant regulatory authorities by telephone or by facsimile transmission of all deaths regardless of causality and any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to regulatory agencies shall be transmitted to the division that has responsibility for review.

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a Sponsor's event investigation show that an adverse drug experience not initially determined to be reportable is, in fact, reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

In addition to the reporting period for SAEs specified in Section 9.6.2, should the Investigator become aware of an SAE (assessed as related to the investigational product following the guidelines in Section 7.1.6) that occurs within 14 days after stopping the investigational product, the SAE must be reported in accordance with procedures specified in this protocol.

In the event of death, if an autopsy is performed, a copy of the report will be sent to GeneOne Life Science, Inc.

9.7 Reporting of Medically Attended Adverse Events

MAAE will be collected during the entire study through one year following the last Study Treatment. As such, the reporting period for MAAE is the entire period following the signing of the informed consent form until study discharge.

A tabulation of all MAAE and their assessed relationship to Study Treatment will be included in all required periodic reports to regulatory agencies.

9.8 Reporting of Device Related Complaints

Any problems experienced during the treatment procedure including potential malfunctions of the CELLECTRA® device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting form provided in Appendix C must be completed and emailed to the Sponsor, at error@geneonels-us.com and to the Program Manager and study staff as outlined.

9.9 Study Discontinuation

GeneOne Life Science reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study product pertaining to the study must be returned to GeneOne Life Science or its representative.

10. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be allowed. The proposed presentation, abstract and/or manuscript must be made available to GeneOne Life Science, Inc. 60 days prior to submission for publication. GeneOne Life Science, Inc. shall have thirty (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 GeneOne Life Science, Inc. makes such objection, the researcher(s) shall 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).

11. LIST OF ABBREVIATIONS

AdV	Adenovirus
AE	Adverse Reaction
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
Alk Phos	Alkaline Phosphatase
AST	Aspartate Aminotransferase
bGH	Bovine Growth Hormone
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CMV	Cytomegalovirus
CPK	Creatine Phosphokinase
CoV	Coronavirus
Cr	Creatinine
CRF	Case Report Forms
CRO	Clinical Research Organization
CSR	Clinical Study Report
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
eDC	Electronic Data Capture
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation
ERER	Events Requiring Expedited Reporting
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
GP	Glycoprotein
HBsAg	Hepatitis B surface antigen

HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus antibody
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Intradermal
IFN	Interferon
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
INF-γ	Interferon Gamma
IRB	Institutional Review Board
L	Ebola virus RNA polymerase
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MERS	Middle East Respiratory Syndrome
MERS CoV	Middle East Respiratory Syndrome Coronavirus
NP	Ebola virus nucleoprotein
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PHI	Personal Health Information
PID	Participant Identification Number
prME	Pre-membrane and envelope proteins of Zika virus
S protein	MERS Spike protein
SAE	Serious Adverse Event
SSC	Sterile saline salt citrate buffer
SynCon®	Synthetic consensus
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WFI	Water for Injection
WOCBP	Women of Childbearing Potential
ZEBOV	Zaire Ebola virus

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13. APPENDIX

Appendix A: Participant Memory Aid

Protocol	MEMORY AID		Subject number
Zika-001		VACCINATION Day 0 - Day 6	|__|__|__|__|__|__|

LOCAL SYMPTOMS (at injection site)

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Pain (at injection site)	***Other local symptoms***
0: Absent. **1**: Painful on touch. Any pain that does not interfere with or prevent normal everyday activities. **2**: Painful when limb is moved that interferes with normal activities or requires repeated use of pain relievers **3**: Significant pain at rest; prevents normal activities as assessed by inability to attend/do work or school **Please contact your study site when the intensity of your pain is 3 during the 7 day follow-up period for solicited AE's.**	**1**: **Mild:** An adverse event which is easily tolerated, causing minimal discomfort and not interfering with everyday activities. **2**: **Moderate:** An adverse event which is sufficiently discomforting to interfere with normal everyday activities. **3**: **Severe:** An adverse event which prevents normal, everyday activities. (Such an adverse would, for example, prevent attendance at work and would necessitate the administration of corrective therapy).

Redness, Swelling, Bruising at injection site: Please measure the greatest diameter (in cm).

Day 0 = date of vaccination : |__|__||__|__|__||__|__|__|__|

LOCAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Ongoing After Day 6?	Date of last Day of Symptoms (day month year)	Sought medical attention?
Redness → size (cm):	____	____	____	____	____	____	____	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes
Swelling → size (cm):	____	____	____	____	____	____	____	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes
Bruising → size (cm):	____	____	____	____	____	____	____	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes
Pain → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes
Tenderness → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes
Itching/Pruritus → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|	☐ No ☐ Yes

OTHER LOCAL SYMPTOMS (from Day 0 to Day 6)

Description - please specify side(s) and site(s)	Intensity	Start date (day month year)	End date or check box if continuing (day month year)		Sought medical attention?
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐	☐ No ☐ Yes
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐	☐ No ☐ Yes
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐	☐ No ☐ Yes
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐	☐ No ☐ Yes

MEDICATION — Please fill in below if any medication (including vaccination) has been taken <u>since the vaccination</u>

Trade/Generic name	Reason	Total Daily Dose	Start date (day month year)	End date or check box if continuing (day month year)	
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐

Protocol	MEMORY AID		Subject number
ZIKA-001		**VACCINATION Day 0 - Day 6**	_____

GENERAL SYMPTOMS

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature:
Please record temperature every day in the evening. If temperature has been taken more than once a day, please report the highest value for the day. **Please contact your study site when you experience temperature greater or equal to 100.4 °F during the 7 day follow-up period for solicited AE's.**

INTENSITY:

Feeling Unwell/Malaise (*)
0: Normal
1: Symptoms that are easily tolerated
2: Symptoms that interfere with normal activity
3: Symptoms that prevent normal activity or requires repeated use of pain relievers

Headache, Muscle aches (widespread, not limited to the injection site) (*)
0: Normal
1: Symptoms that are easily tolerated
2: Symptoms that interfere with normal activity or requires repeated use of pain relievers
3: Symptoms that prevent normal activity

Arthralgia, Joint Aches, Shivering (*)
0: Normal
1: Symptoms that are easily tolerated
2: Symptoms that interfere with normal activity
3: Symptoms that prevent normal activity

(*) Please contact your study site when the intensity of your Fatigue, Headache, Arthralgia, Muscle aches or Shivering is 3 during the 7 day follow-up period for solicited AE's.

Other general symptoms:
1: **Mild:** An adverse event which is easily tolerated, causing minimal discomfort and not interfering with everyday activities.
2: **Moderate:** An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: **Severe:** An adverse event which prevents normal, everyday activities. (Such an adverse would, for example, prevent attendance at work and would necessitate the administration of corrective therapy).

Day 0 = date of vaccination : __ __ _____ _____

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Ongoing After Day 6?	Date of last Day of Symptoms (day month year)	Medically attended Visit
Temperature [TE] → ☐ °F [O] ☐ Oral	__._	__._	__._	__._	__._	__._	__._	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes
Feeling Unwell/Malaise → intensity:	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes
Headache → intensity:	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes
Joint aches/Arthralgia → intensity:	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes
Muscle aches/Myalgia → intensity:	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes
Nausea → intensity:	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ _____	☐ No ☐ Yes

OTHER GENERAL SYMPTOMS (from Day 0 to Day 6)

Description - please specify side(s) and site(s)	Intensity	Start date (day month year)	End date (day month year)	☐	Medically attended Visit?
	__	__ __ _____	__ __ _____	☐	☐ No ☐ Yes
	__	__ __ _____	__ __ _____	☐	☐ No ☐ Yes
	__	__ __ _____	__ __ _____	☐	☐ No ☐ Yes
	__	__ __ _____	__ __ _____	☐	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __ __ _____

IN CASE OF HOSPITALIZATION, PLEASE INFORM _____ ☎ _____

Appendix B: Toxicity Grading Scale

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007

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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Contains Nonbinding Recommendations

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).

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

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.

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

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

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.

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.

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.

Appendix C: CELLECTRA® Error Reporting Form

Please complete the form and fax to (267) 440-4242 or scan the form to EPerror@inovio.com

Protocol#	**Site#**	**Participant**	**ID Week#**	**Visit Date**

DEVICEINFORMATION
CELLECTRA® Serial No:
Located on label on the front cover
CELLECTRA® Applicator Serial No:
Located on label on the handle
CELLECTRA® Array Lot No:
Located on label on the package

Time of Electroporation: **Location of Treatment/EP:** ☐ Deltoid **R**ight/**L**eft
ϒ Other Location, specify: **Was IM-5PEP guide used?** ☐ YES ☐ NO
If EP Guide was used, please provide reason and include participant's BMI.

Was injection successful? ☐ YES ☐ NO
If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read EP successful? ☐ YES ☐ NO

If NO, please check all complications that led to failure and describe complication below
☐ Impedance Test Error message displayed, fill out Impedance Test Error section below
☐ Electroporation Error message displayed, fill out Electroporation Error section below
☐ EP aborted by trigger or keypad error message displayed
☐ Battery level too low for electroporation message displayed
☐ Difficulty inserting array into muscle or skin
☐ Other, please specify below
Describe device complication below (continue on back if necessary):
Total # of arrays used:

Impedance Test Error
Was the array inserted in participant's arm? ☐ YES ☐ NO # of attempts:
Were all attempts performed on the same day? ☐ YES ☐ NO
(provide other date(s):
Was a different location used for each attempt? ☐ YES ☐ NO
Was a new array used for each attempt? ☐ YES ☐ NO
Please provide any additional information below (continue on back if necessary):

Electroporation Error
Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many
Was the array fully inserted in the participant's arm? ☐ YES ☐ NO
Was the array inserted perpendicular to the participant's skin? ☐ YES ☐ NO
Did the needles of the array appear damaged in any way? ☐ YES ☐ NO
If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.