THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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SUPPLEMENTARY APPENDIX:
Safety and Immunogenicity of an anti-Middle East Respiratory Syndrome Coronavirus DNA Vaccine: an Open-Label, Dose-Ranging Phase 1 Clinical Trial

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Figure S1: Unsolicited adverse events.

Unsolicited adverse events reported as part of the WRAIR-2274 study are shown. Investigations included 15 participants with elevations of CPK, two with decreased hemoglobin, two with decreased neutrophils, and one with an increased respiratory rate.

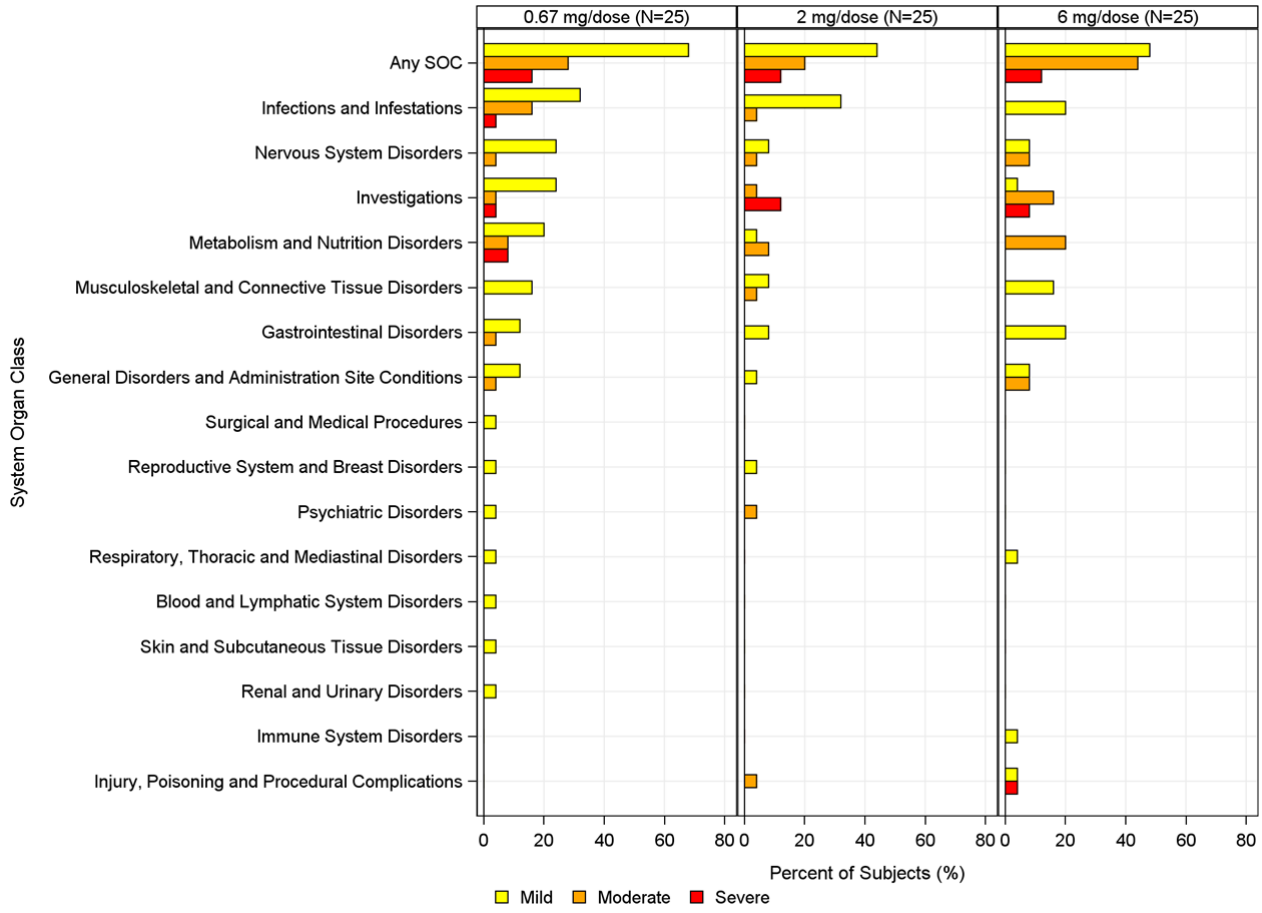


Figure S2: Solicited adverse events.
Solicited systemic and local adverse events reported as part of the WRAIR-2274 study are shown.

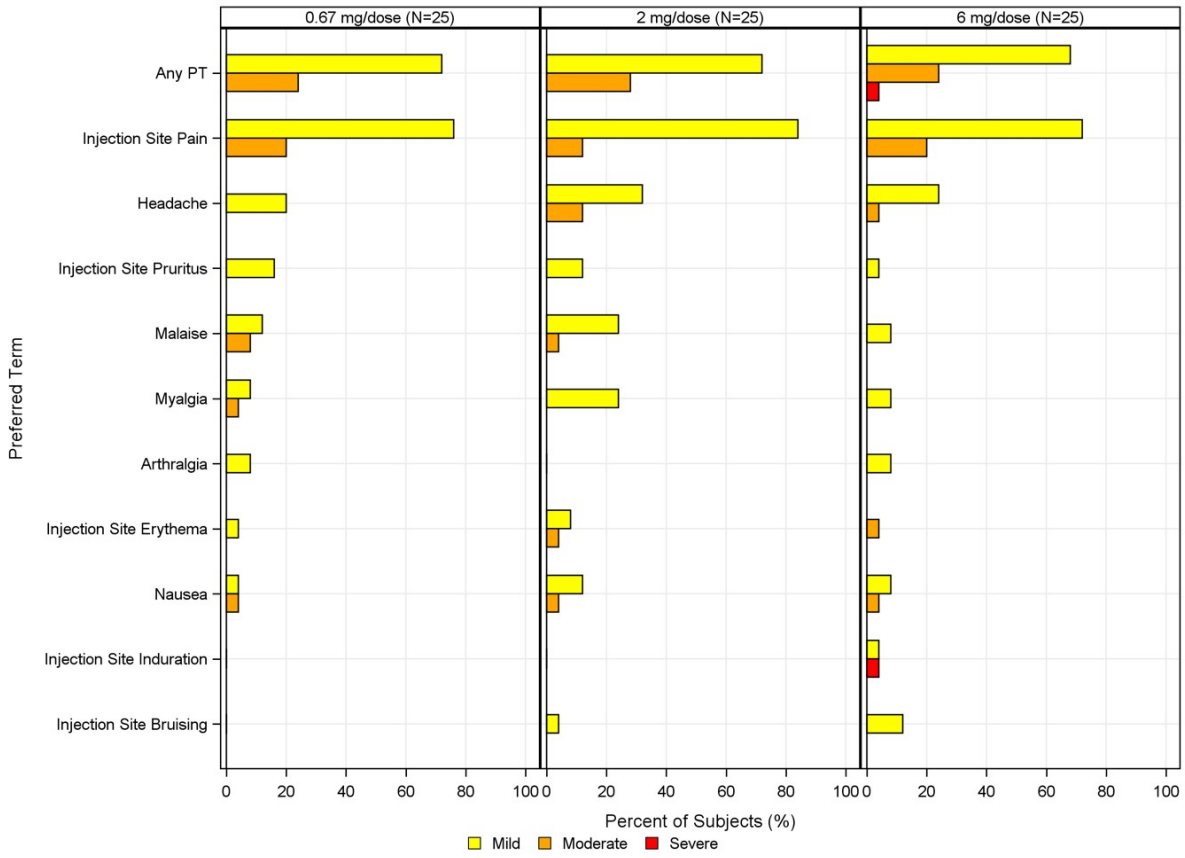
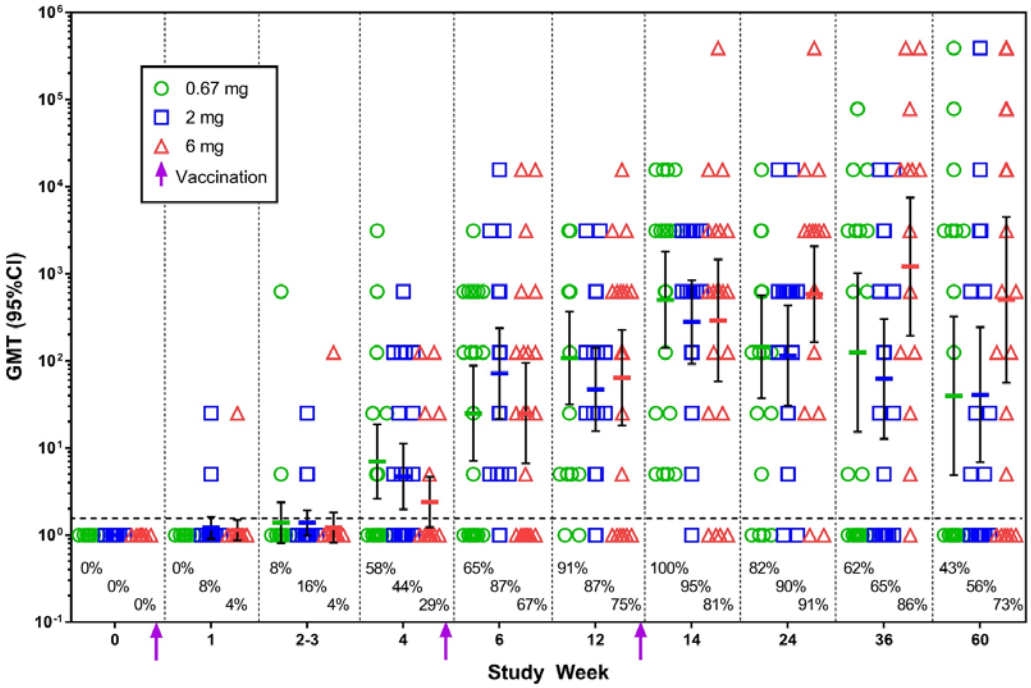


Figure S3: Vaccine Associated Antibody Responses using the fl-S-ELISA
Results of fl-S-ELISA for each dose level are shown for available specimens (mITT data set). Panel A the GMT (95%CI) and percent of participants that demonstrated antibodies against MERS-CoV as determined by fl-S-ELISA. Positive responses defined as an end-point titer ≥5. Panel B shows the correlation of S1-ELISA and fl-S-ELISA to the EMC-2012/Vero neutralization assay as determined by Pearson's coefficient.

S3-A.



S3-B.

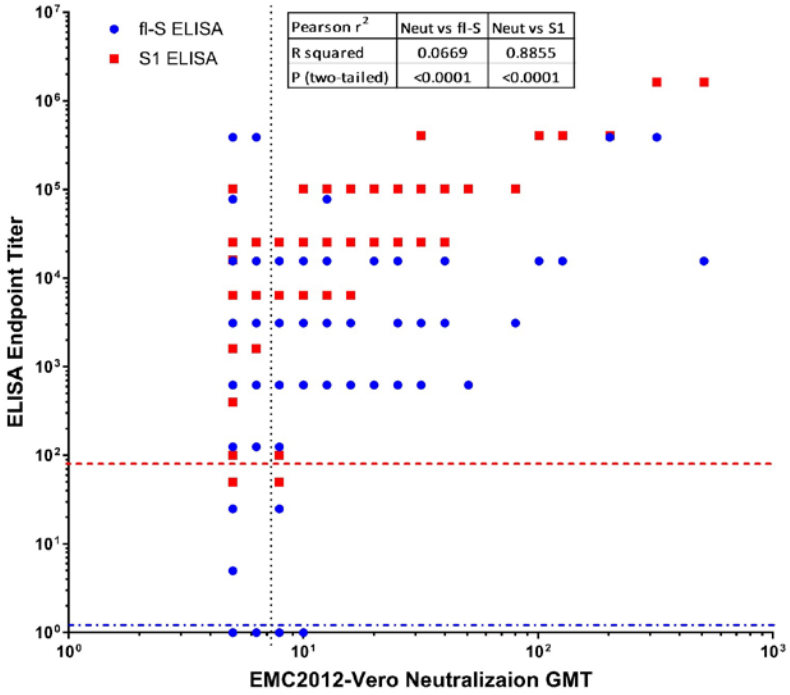
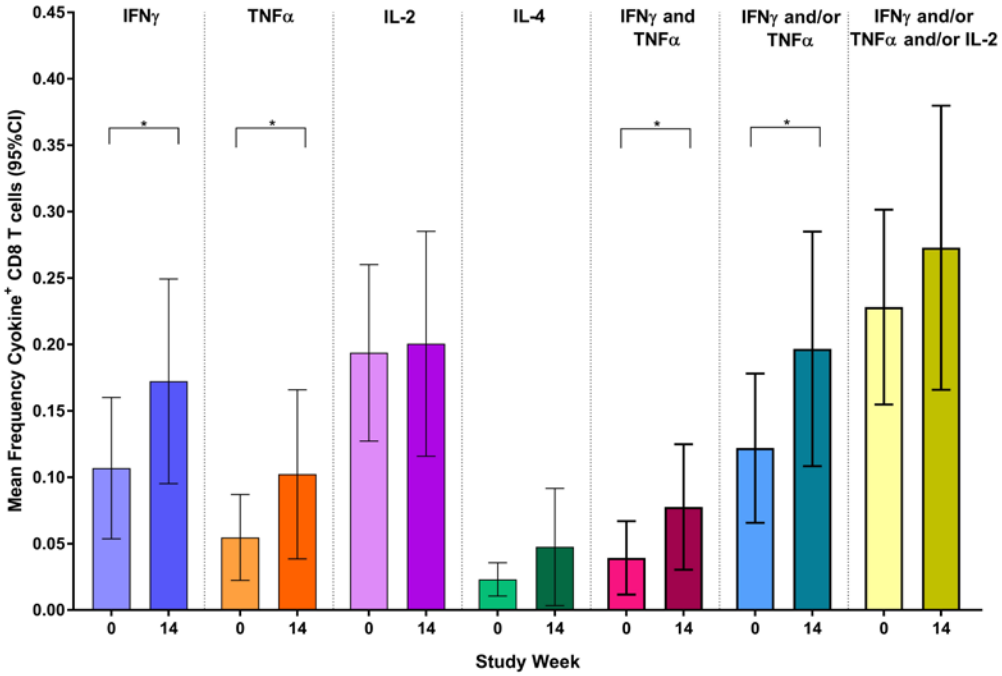


Figure S4: CD8+ and CD4+ T-cell TNFα and IFNγ Responses
Mean frequency with 95%CI of TNFα, IFNγ, IL-2, IL-4 and multiple cytokine combinations are shown for CD8+ (Panel A) and CD4+ (Panel B) T-cells following stimulation against peptides spanning the S glycoprotein as measured by multi-parameter ICS flow cytometry.

S4-A.



S4-B.

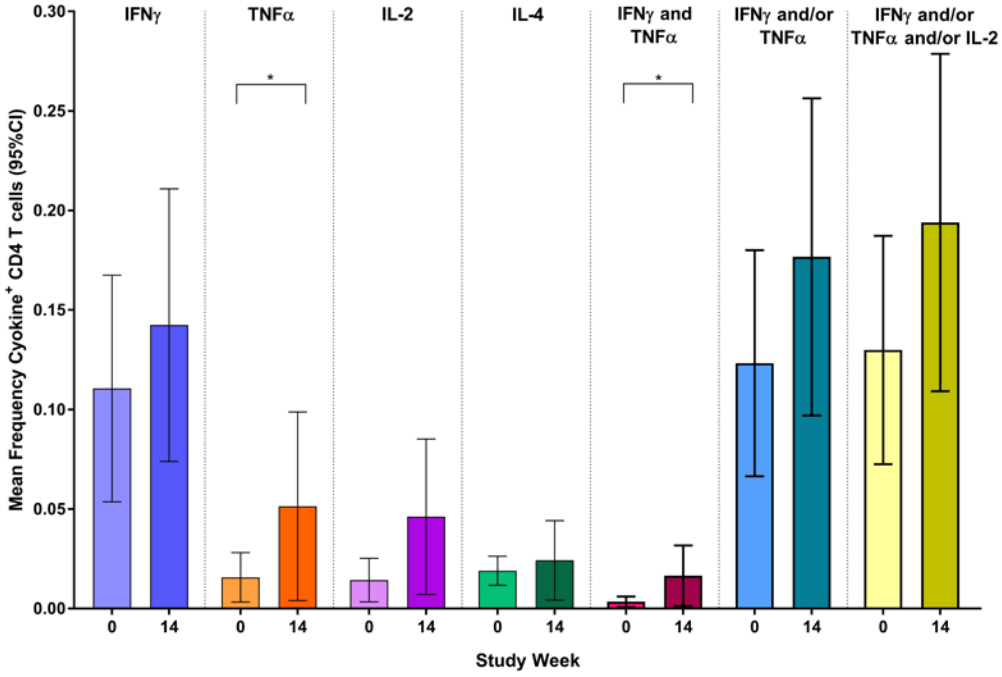
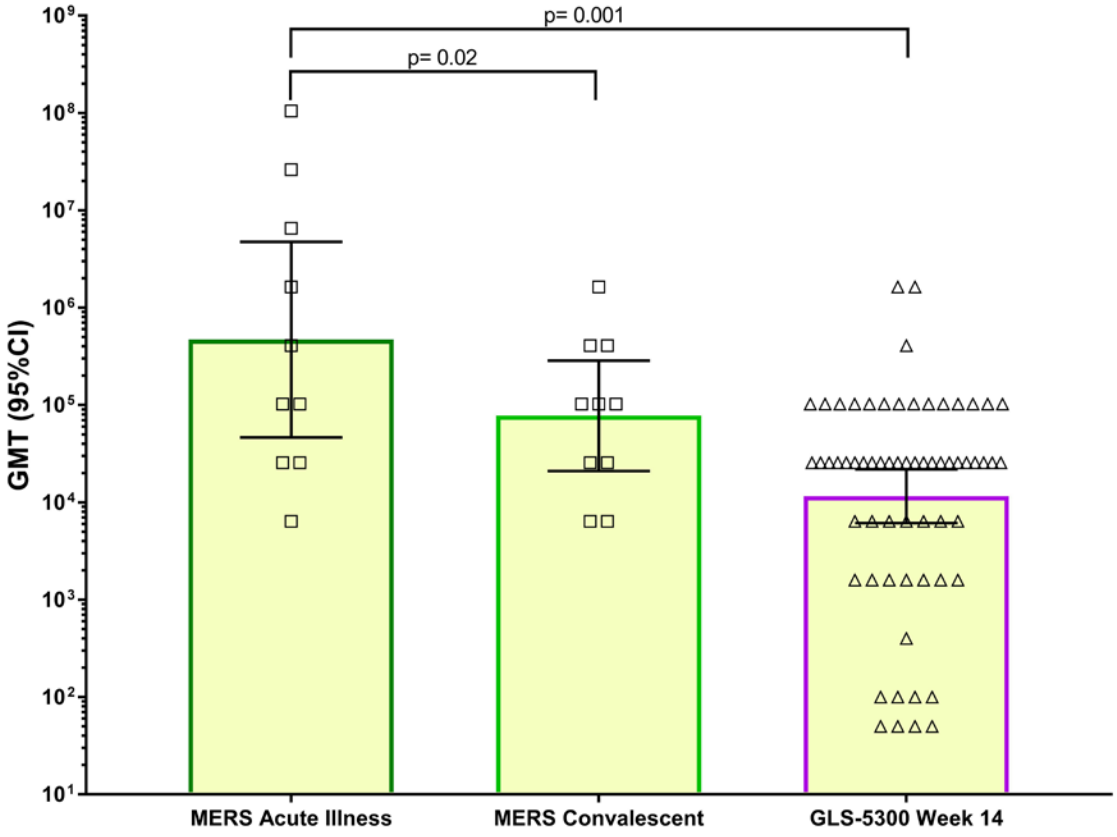


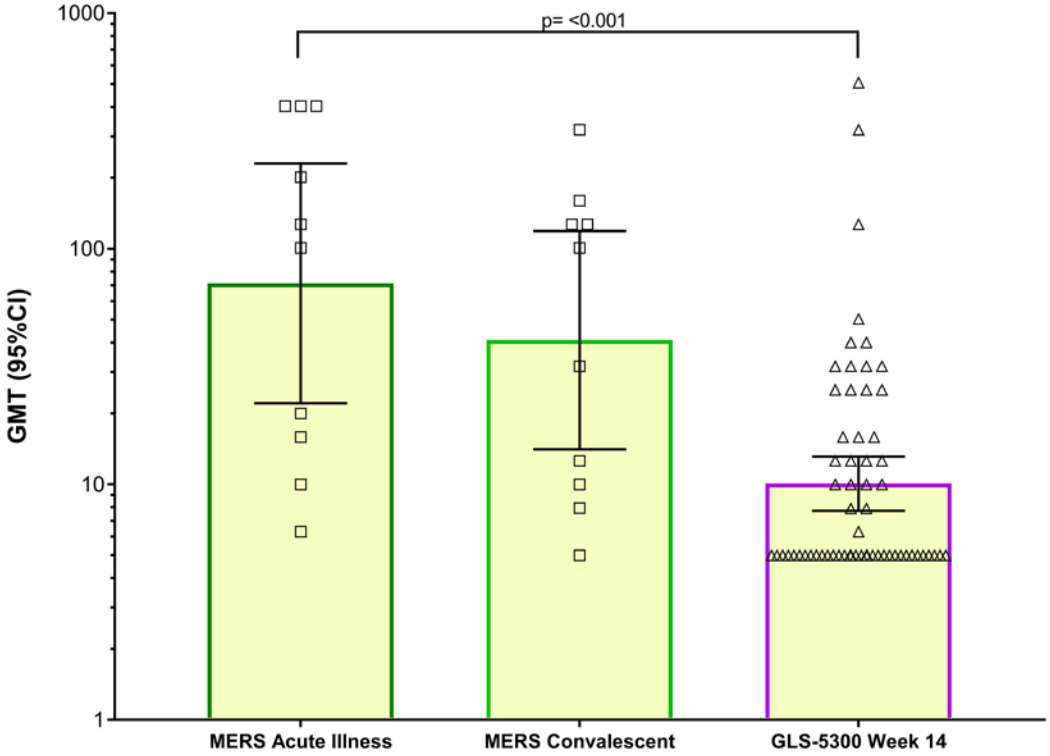
Figure S5: Immune responses of patients recovered from MERS-CoV infection.

Serum and PBMCs were collected and analyzed from 10 patients post-recovery from MERS-CoV natural infection. Panel A shows GMTs (95%CI) of the end-point titers of MERS-CoV antibodies as determined by S1-ELISA for acute and convalescent samples. Panel B shows GMTs (95%CI) of the MERS-CoV neutralizing antibodies as determined by EMC-2012/Vero assay for acute and convalescent samples. Panel C shows total SFU/million PBMCs as a stacked bar graph of mean responses to each peptide pool. In each figure, corresponding mean of all available week 14 assay results in GLS-5300 recipients are shown for comparison.

S5-A.



S5-B.


p= <0.001
1000
100
10
1
GMT (95%CI)
MERS Acute Illness
MERS Convalescent
GLS-5300 Week 14

S5-C.

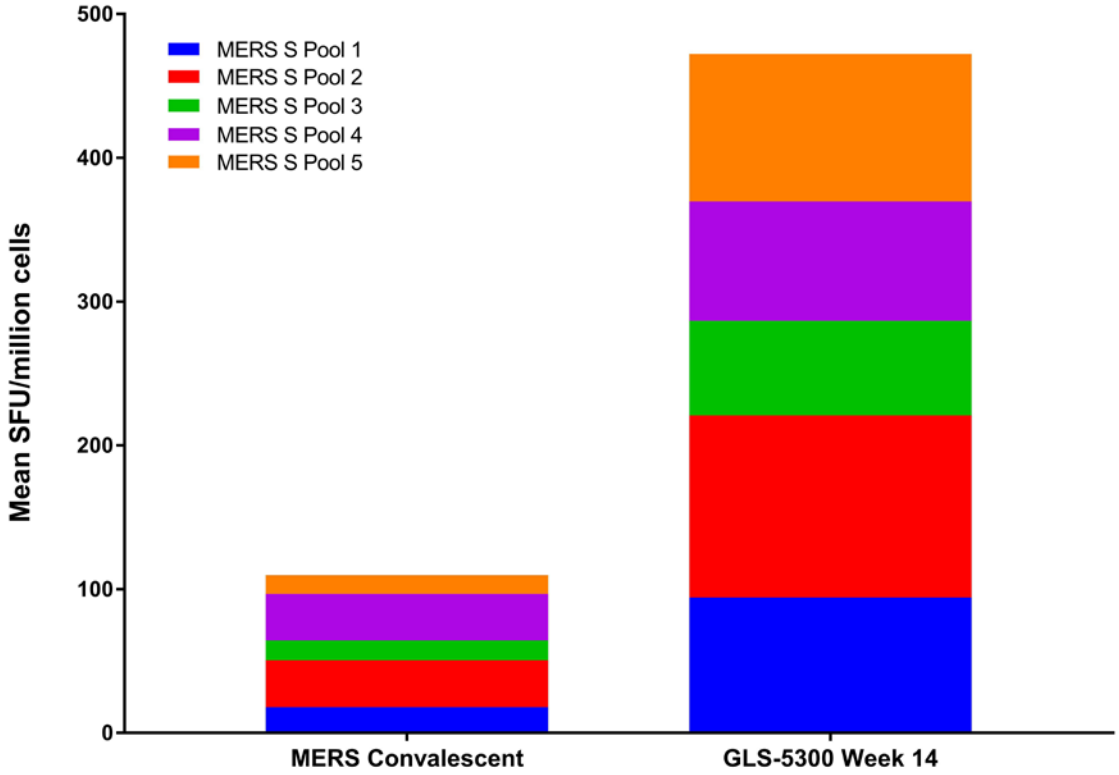

MERS S Pool 1
MERS S Pool 2
MERS S Pool 3
MERS S Pool 4
MERS S Pool 5
500
400
300
200
100
0
Mean SFU/million cells
MERS Convalescent
GLS-5300 Week 14

Figure S6: Comparison of fl-S-ELISA between Convalescent and Vaccine Samples
Figure S4 shows GMTs (95%CI) of the end-point titers of MERS-CoV antibodies as determined by fl-S-ELISA for convalescent samples compared to GLS-5300 week 14 responses.

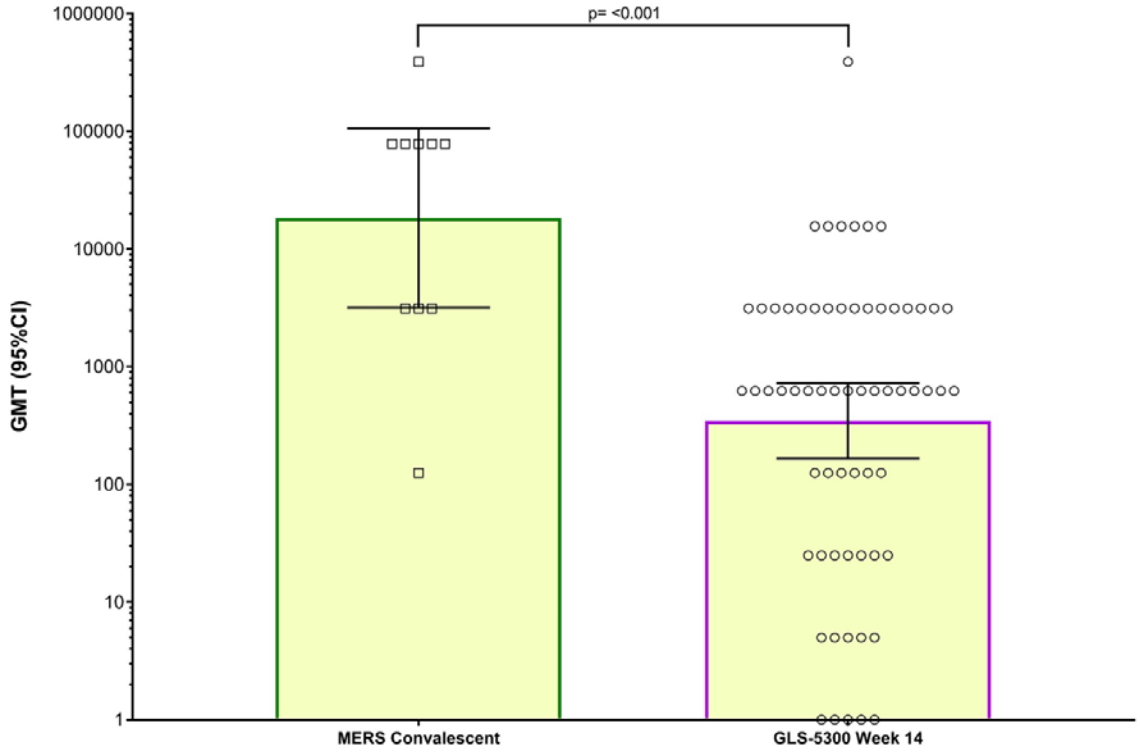


Table S1: Method Descriptions for MERS-CoV Immunology Assays

Assay	Methods and interpretation
S1-ELISA	Recombinant MERS-CoV Spike glycoprotein S1 (amino acids 1-725) portion (Sino Biological) was bound to solid phase 96-well microtiter plates overnight. Plates were washed and blocked then sequentially incubated with (1) four-fold serial dilutions of serum from participants starting at 1:100, in duplicate and (2) horseradish peroxidase enzyme-conjugated anti-human IgG secondary reagent. ABTS® Peroxidase Substrate (Mandel Scientific) was added to plates and optical density at 405 nm was measured on a standard microplate reader. Serum from a MERS-CoV infected rhesus macaque from pre-clinical testing served as a positive control in the assay. The endpoint titer of anti-S1-specific antibody in serum was defined as the reciprocal of the highest serum dilution with measured optical density that is above 0·1 and greater than the plate cut-off value. Positives were defined as endpoint titer ≥100; negatives were reported as 50.
fl-S-ELISA	Same as S1-ELISA except plates were coated with recombinant full-length MERS-CoV S protein (Sino Biological) and the dilution series of participant serum was five-fold starting at 1:5. Positives were defined as endpoint titer ≥5; negatives were reported as 1.
MERS EMC-2012/ Vero cell neutralization assay	Participant serum was serially diluted two-fold,in triplicate starting at 1:10, mixed with 100 plaque forming units of MERS-CoV EMC-2012 strain and incubated to allow for serum antibody and virus interaction. The serum/virus/medium mixtures were added to monolayers of Vero cells. Following incubation, light microscopy was used to evaluate cytopathic effects in wells. Neutralization in this assay was defined as a ≥ 50% reduction of virus-induced cytopathic effects per well (NT_{50}). The titer value for each replicate was defined as the reciprocal of the highest serum dilution at which a 50% reduction in cytopathic effects was observed and results were reported as the GMT of the triplicate NT_{50} measures. Positives were defined as endpoint GMT ≥7·9 (two of three replicates positive); negatives were reported as 6·3 (one of three replicates positive) or 5 (no replicates positive).
IFNγ-ELISPOT	Human IFNγ ELISpotPRO kits (Mabtech) were used as directed. Briefly, frozen participant PBMCs were thawed and rested overnight. Plates pre-coated with IFN-γ specific capture antibody were washed and blocked with media containing 10% FBS. Cells were stimulated for 24 hours with each of five pools (custom synthesis by GenScript; each pool contained 44-45 peptides) of 15-mer peptides, overlapping by 11 amino acids, spanning the entire MERS-CoV S-glycoprotein. Secreted IFNγ was detected with an alkaline phosphatase conjugated antibody and signal was developed using a BCIP/NBT-plus substrate. Spots were counted using a CTL ImmunoSpot plate reader and software. Spot counts for each peptide pool were calculated as background-subtracted SFU/million PBMCs. The total SFU/million PBMC count for 5 peptide pools was reported. Positives were defined as SFU/million PBMCs ≥141, two times the mean total spot counts of all baseline samples.
Multi-parameter intracellular cytokine staining flow cytometry	Thawed PBMCs were incubated for five hours with a single pool of all MERS-CoV S 15-mer peptides (see IFNγ-ELISPOT) in the presence of Brefeldin A. Cells were washed and incubated with live-dead violet stain (Invitrogen) followed by a cocktail of anti-CD4-BV510 and anti-CD8-AP Cy7 antibodies. Cells were washed, fixed and permeabilized, and then incubated with a cocktail of anti-IFNγ-PE, anti-TNFα-AF700, anti-IL-2-APC, anti-IL4-PE D594, anti-CD3-BV650 antibodies (antibodies from BioLegend except anti-IL-2 from BD). Samples were analyzed on FACS LSRII (BD) equipped with four lasers (violet, blue, green and red) and band pass filters to capture 18 colors. Data was analyzed using FloJo v.10 software. Gating strategy: FSC-A/FSC-H singlets-> FSC-A/SSC-A lymphocytes-> Live, CD3+ cells-> [CD8+CD4- cells -> IFNγ+, TNFα+, IL-2+, and IL-4+ populations] or [CD8-CD4+ cells -> IFNγ+, TNFα+, IL-2+, and IL-4+ populations].

Table S2: Reasons for screen failure or non-inclusion into the WRAIR-2274 study

Inclusion / Exclusion Criterion	# ineligible *
Number of participants failing any criteria	45
Screening laboratory abnormality greater than or equal to Grade 2	20
Able and willing to comply with all study procedures	12
Screening BMI greater than or equal to 35	6
PI decision related to illness or condition that may interfere with study requirements	4
Active drug or alcohol use that may affect study requirements	1
History of clinically significant immunosuppressive or autoimmune disease	1
Screening ECG with clinically significant abnormality	1
Pregnancy	1
Eligible for study, but not enrolled	3

* Participants may have more than one criterion for study ineligibility

Table S3: Unsolicited adverse events by MedDRA System organ class by severity and relationship to study vaccine

MedDRA System Organ Class	Incidence	Severity			Relationship to vaccine	
	Number (%)	Mild	Moderate	Severe	Not related	Related
Any SOC *	56 (74·7%)	27 (36%)	19 (25·3%)	10 (13·3%)	30 (40%)	26 (34·7%)
Blood and lymphatic system	1 (1·3%)	1 (1·3%)	0	0	0	1 (1·3%)
Gastrointestinal	11 (14·7%)	10 (13·3%)	1 (1·3%)	0	7 (9·3%)	1 (1·3%)
General disorders	8 (10·7%)	5 (6·7%)	3 (4%)	0	7 (9·3%)	1 (1·3%)
Immune system	1 (1·3%)	1 (1·3%)	0	0	1 (1·3%)	0
Infections and infestations	27 (36%)	21 (28%)	5 (6·7%)	1 (1·3%)	21 (28%)	6 (8%)
Injury, poisoning, procedures	3 (4%)	1 (1·3%)	1 (1·3%)	1 (1·3%)	3 (4%)	0
Investigations	18 (24%)	6 (8%)	6 (8%)	6 (8%)	10 (13%)	8 (10·7)
Metabolism and nutrition	16 (21·3%)	6 (8%)	8 (10·7%)	2 (2·7%)	12 (16%)	4 (5·3%)
Musculoskeletal and Connective tissue	11 (14·7%)	10 (13·3%)	1 (1·3%)	0	9 (12%)	2 (2·7%)
Nervous system	14 (18·7%)	10 (13·3%)	4 (5·3%)	0	10 (13·3%)	4 (5·3%)
Psychiatric	2 (2·7%)	1 (1·3%)	1 (1·3%)	0	1 (1·3%)	1 (1·3%)
Renal and urinary	1 (1·3%)	1 (1·3%)	0	0	0	1 (1·3%)
Reproductive system and breast	2 (2·7%)	2 (2·7%)	0	0	2 (2·7%)	0
Respiratory, thoracic, mediastinal	2 (2·7%)	2 (2·7%)	0	0	0	2 (2·7%)
Skin and subcutaneous	1 (1·3%)	1 (1·3%)	0	0	0	1 (1·3%)
Surgical and medical procedures	1 (1·3%)	1 (1·3%)	0	0	1 (1·3%)	0

* SOC, System Organ Class

Table S4: P-values for Fisher's Exact Tests Comparing MERS S1 ELISA Positive Response between Groups by Study Day, mITT Population

	Positive Response Rate			Fisher's Exact Test Results		
Time Point	**Group I: 0.67 mg/dose (N=25)**	**Group II: 2 mg/dose (N=25)**	**Group III: 6 mg/dose (N=25)**	**Group I vs. Group II**	**Group II vs. Group III**	**Group I vs. Group III**
Day 0	0·0	0·0	0·0	NC	NC	NC
Week 1	4·0	32·0	28·0	**0·0232**	> 0·999	0·0488
Week 2	23·1	33·3	12·5	0·6728	0·6027	> 0·999
Week 3	16·7	61·5	41·2	**0·0414**	0·4621	0·2341
Week 4	50·0	72·0	75·0	0·1482	1·0000	0·1351
Week 6	73·9	87·0	79·2	0·4591	0·7008	0·7400
Week 12	81·8	87·0	87·5	0·6995	> 0·999	0·6943
Week 14	90·9	95·0	95·2	> 0·999	> 0·999	> 0·999
Week 24	86·4	95·0	100·0	0·6079	0·4651	0·1085
Week 36	81·0	87·0	95·5	0·6927	0·6078	0·1853
Week 60	71·4	78·3	86·4	0·7322	0·6995	0·2806

N=Number of participants in the mITT population.

NC=not calculable; because of lack of response across all groups, p-value is not calculable.

Table S5: MERS S1 ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals (CI) by Study Day and Group, mITT population

Time Point	Statistic	Group I: 0.67 mg/dose (N=25)	Group II: 2 mg/dose (N=25)	Group III: 6 mg/dose (N=25)
Day 0	N	25	25	25
	GMT	50.0	50.0	50.0
	95% CI	NC	NC	NC
Week 1	N	25	25	25
	GMT	51.4	82.4	60.7
	95% CI	48.5, 54.4	51.1, 132.9	53.2, 69.2
Week 2	N	13	12	8
	GMT	80.8	112.2	54.5
	95% CI	36.0, 181.4	40.2, 313.1	44.4, 66.9
Week 3	N	12	13	17
	GMT	79.4	179.8	92.2
	95% CI	32.7, 192.8	66.5, 486.2	54.9, 154.7
Week 4	N	24	25	24
	GMT	377.5	389.1	377.5
	95% CI	123.4, 1155.3	170.7, 886.7	152.1, 937.0
Week 6	N	23	23	24
	GMT	1917.1	3398.8	1848.6
	95% CI	558.5, 6580.4	1429.0, 8083.8	573.3, 5960.2
Week 12	N	22	23	24
	GMT	3200.0	3398.8	2769.7
	95% CI	946.4, 10820.3	1329.2, 8690.7	942.5, 8139.1
Week 14	N	22	20	21
	GMT	8770.2	8742.7	20318.7
	95% CI	2433.5, 31608.0	3285.3, 23265.1	6532.9, 63195.6
Week 24	N	22	20	23
	GMT	5822.8	6625.7	14881.7
	95% CI	1841.8, 18408.9	3283.9, 13368.0	6168.6, 35902.0
Week 36	N	21	23	22
	GMT	2377.6	2228.9	5467.2
	95% CI	832.7, 6788.7	950.8, 5225.1	2366.7, 12629.3
Week 60	N	21	23	22
	GMT	1312.5	1081.4	1994.8
	95% CI	478.8, 3597.9	457.0, 2558.8	793.8, 5012.7

N=Number of participants in the mITT population.
NC=not calculable; due to lack of variance in ELISA results for group/day combination
ELISA below limit of detection=50; positive response threshold=100

Table S6: Kruskal-Wallis Test p-values by Time Point for the ELISA S1 Titer Results

Time Point	P-value*, Kruskal-Wallis Test
Day 0	> 0·999
Week 1	0·032
Week 2-3	0·11
Week 4	0·758
Week 6	0·831
Week 12	0·886
Week 14	0·337
Week 24	0·153
Week 36	0·320
Week 60	0·416

*All p-values are nominal (not pre-specified for inference and not adjusted for multiplicity)

Table S7: T-test Results Comparing Total IFN-γ Means between Groups by Study Day, mITT Population

		Mean IFN-γ SFU/10^6 cells			T-Test Results: t-statistic (p-value)		
Pool	**Time Point**	**Group I: 0.67 mg/dose (N=25)**	**Group II: 2 mg/dose (N=25)**	**Group III: 6 mg/dose (N=25)**	**Group I vs. Group II**	**Group II vs. Group III**	**Group I vs. Group III**
TOTAL	Day 0	30·95 (22)	42·80 (25)	140·65 (25)	-0·81 (0·4200)	-1·73 (0·0954)	-1·92 (0·0663)
MERS S ELISPOT Response (All Pools)	Week 1-4	86·67 (25)	66·63 (25)	126·63 (22)	0·94 (0·3500)	0·95 (0·3500)	1·64 (0·1200)
	Week 6	397·64 (23)	204·24 (22)	278·26 (24)	2·26 **(0·0303)**	-1·04 (0·3031)	1·28 (0·2083)
	Week 12	390·56 (21)	193·67 (22)	303·66 (23)	1·13 (0·2697)	-1·59 (0·1209)	0·48 (0·6360)
	Week 14	652·24 (22)	279·12 (17)	436·45 (19)	1·37 (0·1835)	-1·48 (0·1506)	0·76 (0·4535)
	Week 24	451·00 (20)	269·83 (20)	449·62 (22)	0·99 (0·3321)	-1·59 (0·1229)	0·01 (0·9947)
	Week 36	422·30 (21)	180·51 (23)	340·98 (22)	1·48 (0·1540)	-2·14 **(0·0405)**	0·47 (0·6449)
	Week 60	325·48 (21)	192·25 (23)	342·54 (19)	1·44 (0·1629)	-1·77 (0·0905)	-0·14 (0·8876)

N=Number of participants in the mITT population.

Adjustments for multiple comparisons were not made, therefore all the p-values are nominal.

Table S8: One Way Anova - Tukey's Group Comparison Test between Naturally Infected and Vaccinated Groups

Group Comparison	Mean 1	Mean 2	Mean Diff.	95.00% CI of diff.	P-value
S1 ELISA					
MERS Acute Illness vs. MERS Convalescent	13993600	282880	13710720	4166064 to 23255376	0·002
MERS Acute Illness vs. GLS-5300 Week 14	13993600	91521	13902079	6637066 to 21167093	<0·001
MERS Convalescent vs. GLS-5300 Week 14	282880	91521	191359	-7073654 to 7456373	>0·99
Neutralization					
MERS Acute Illness vs. MERS Convalescent	169·1	90·21	78·9	-22·23 to 180	0·16
MERS Acute Illness vs. GLS-5300 Week 14	169·1	26·5	142·6	65·55 to 219·7	<0·001
MERS Convalescent vs. GLS-5300 Week 14	90·21	26·5	63·7	-13·35 to 140·8	0·13

Clinical Study Documents

WRAIR-2274 Clinical Study Protocol (84 pages)

WRAIR 2274
PROTOCOL V10.0_13

WRAIR 2274, HRPO Log A#19272

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Sponsored by:

GeneOne Life Science Inc.

Funded by:

US Defense Health Program RDT&E

Funding is provided by the Defense Health Program RDT&E through the USAMRMC Principal Assistant for Research and Technology's office. Funding is one time to support execution of a first in human clinical trial. Funding supports the early development of medical countermeasures for emerging infectious diseases threatening deploying Service Members in the CENTCOM and PACOM AOs.

U.S. BB-IND 16711

Version 10.0

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Drug:	GLS-5300
Protocol Number:	WRAIR #2274
Sponsor:	GeneOne Life Science, Inc. 1040 DeKalb Pike, Suite 200 Blue Bell, PA 19422
Principal Investigator	Kayvon Modjarrad, MD, PhD
Sponsor Medical Monitor:	Joel Maslow, MD PhD MBA FACP
Institutional Review Boards	WRAIR Institutional Review Board (IRB) Walter Reed Army Institute of Research 503 Robert Grant Avenue Silver Spring, Maryland 20910-7500 Telephone: 301-319-9940 / Fax: 301-319-9961 Email: usarmy.detrick.medcom-wrair.list.human-subjects-protection@mail.mil FWA#: 00000015; IRB#: 00000794
Version and Date:	Version 10.0 13Nov2017

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 Medical Monitor 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.

_____ 13Nov17_____

Principal Investigator Date

_____ 20 Nov 2017_____

Sponsor Medical Monitor Date

Protocol Number: WRAIR #2274
Version Number: Final 10.0 13Nov2017

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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-5300, administered IM and followed by electroporation in healthy volunteers

Estimated Number of Study Centers and Countries/Regions: 1 site, US

Study Phase: I

Research Hypothesis: GLS-5300 administered by intramuscular (IM) injection followed by electroporation (EP) will be well-tolerated and immunogenic.

Table S1: Dosing Arms and Regimens

Group	Vaccine	Schedule	*n*	Route	Dose (mg)
1	GLS-5300	0-4-12 weeks	25	IM	0.67
2	GLS-5300	0-4-12 weeks	25	IM	2
3	GLS-5300	0-4-12 weeks	25	IM	6
	TOTAL		75		

Study Design:

This is a Phase I open-label dose ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5300. GLS-5300 contains plasmid pGX9101 that encodes for a consensus sequence of the spike (S) protein of the Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV).

Currently there are no approved treatments or prophylactic vaccines for MERS CoV, although a number of products are poised to be advanced into human trials.

This clinical trial will evaluate whether GLS-5300 administered via intramuscular (IM) injection and followed by EP is able to generate protective immunity against MERS CoV and whether there is an immune reactivity follows a pattern of vaccine dose response. Injections will be given in the deltoid or lateral quadriceps muscle followed immediately by EP with the CELLECTRA®-5P device.

Evaluation of IM administration of GLS-5300:
Participants (n=25 per group) will be administered GLS-5300 at one of three dose levels: 0.67 mg, 2 mg, or 6 mg DNA/dose. These doses will be administered as 1 ml IM injections followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations occurring at 0, 4 and 12 weeks (0-4-12 week schedule).

Estimated Number of Participants Screened

It is estimated that approximately 225 participants will need to be screened to fill the desired enrollment of 75 participants.

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)". Pain will be assessed at a minimum of 30 minutes post vaccination according to an AE grading scale (Appendix B). 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 will be monitored from the time of informed consent to study discharge by telephone on day 1 post vaccination and again at weeks 8 and 16 and during on-site visits at weeks 1, 2 or 3, 4, and 12, and 3, 6, and 12 months after the final vaccination. Injection Site Reactions will be monitored up to approximately 1 month following the each vaccination.

In the event that a stopping criterion is reached (Section 7.5), the study will not continue until a full discussion has been conducted with the DoD Research Monitor, Medical Monitor, Principal Investigator, and IRB (if applicable).

Immunogenicity assessment: Blood will be obtained for antibody and T-cell responses at baseline and then at weeks 1 and 2 or 3 and 4; at 2 weeks following each vaccination; and at 3, 6, and 12 months following the final vaccination. Serum will be separated and sent for analysis for humoral responses (neutralizing and binding antibody titers) to the laboratory of Dr. Gary Kobinger at the National Microbiology Laboratory in Quebec,Canada. Whole blood will be processed to obtain peripheral blood mononuclear cells (PBMCs) for determination of cell mediated immune responses (CD4 and CD8 T-cell responsiveness to MERS CoV peptides).

Study Population:

Inclusion Criteria:

a. Age 18-50 years; military, civilian, male and female
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 childbearing potential agree to either remain sexually abstinent, 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 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 unable to become pregnant.
    - *All information about the volunteer's medical history and that of his or her sexual partner will be based on self-report. Only the female volunteer's current pregnancy status will be verified with either a urine or serum pregnancy test.*
f. Normal screening ECG or screening ECG with no clinically significant findings;
g. Screening laboratory must be within normal limits or have Grade 0-1 findings (Appendix B);
h. No history of clinically significant immunosuppressive or autoimmune disease.
i. 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 corticosteroids at a dose less than 20 mg/day).
j. Willing to allow storage and future use of samples for MERS CoV related research

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 MERS CoV except if participant is verified to have received placebo;
c. Previous infection with MERS CoV; as assessed by self report and solicited exposure history
d. Administration of any vaccine within 4 weeks of first dose;
e. A BMI greater than or equal to 35;
f. Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose
g. Administration of any blood product within 3 months of first dose;
h. Pregnancy or breast feeding or have plans to become pregnant during the course of the study;
i. History of 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;
j. Positive serologic test for hepatitis C (exception: successful treatment with confirmation of sustained virologic response);
k. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 (CKD Stage II or greater);
l. Baseline screening lab(s) with Grade 2 or higher abnormality (Appendix B);
m. Chronic liver disease or cirrhosis;
n. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;
o. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or corticosteroids at a dose less than 20 mg/day);
p. Current or anticipated treatment with TNF-α inhibitors, e.g. infliximab, adalimumab, etanercept;
q. Prior major surgery or any radiation therapy within 4 weeks of group assignment;
r. Any pre-excitation syndromes, e.g., Wolff-Parkinson-White syndrome;
s. Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator (AICD);
t. Metal implants within 20 cm of the planned site(s) of injection;
u. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition at the planned site(s) of injection.
v. Prisoner or participants who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness;
w. 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

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.

y. Tattoos covering the injection site area

Table S2. Schedule of Events

Tests and Observations	Screen	Day0	Day1	Wk1 (±2d)	Wk2 (±3d)	Wk3 (±3d)	Wk4 (±5d)	Wk6 (±5d)	Wk8 (±5d)	Wk12 (±5d)	Wk14 (±5d)	Wk16 (±5d)	Wk24 (±10d)	Wk36 (±10d)	Wk60 (±10d)
	Clinical Assessments														
Consent	X														
Med history	X	X[a]													
Demographics	X														
Medications [b]	X	X		X	X [h]	X [h]	X	X		X	X		X	X	X
Phys Exam [c]	X	X		X	X [h]	X [h]	X	X		X	X		X	X	X
Vital signs [c]	X	X		X	X [h]	X [h]	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					
Immunology		X [g]		X[g1]	X[h,g2-3]	X [h,g2-3]	X[g4]	X [g]		X [g]	X [g]		X [g]	X [g]	X [g]
Leukapheresis[i]											X		X		
	Study Related Procedures														
Vaccine + EP		X					X			X					
EP Data [j]		X					X			X					
Diary [l]		X					X			X					
AEs [l]		X	X	X	X [h]	X [h]	X	X	X	X	X	X			
Approx Blood Volume	27	71	0	83	71		71	83	0	71	83[i]	0	71[i]	71	71

Approximate Total Blood Volume over entire Study Duration (ie 15 months) 771 ml

[a] If screening (Day -30 to Day -1) is performed within 14 days of Dose 1, then do not repeat medical history
[b] Prior and new concomitant medications will be recorded at all study visits (Day 0 through study discharge)
[c] Full physical examination performed at screening and study discharge 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
[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
[f] Serum pregnancy test at screening and urine pregnancy test at each subsequent vaccination day.
[g] Collect at least 51 mL at screening and weeks 6, 12,14, 24, 36, 60 (6 x 8.5 mL tubes) whole blood in ACD (yellow top) tubes for PBMC isolationand 10 mL serum
[g1] At week 1 the first 6 participants assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will have whole blood collected in ACD tubes for PBMC isolationand 10 mL serum collected. The remainder of the participants assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will only have 10 mL serum collected at this visit.

[g2-3] At weeks 2 & 3 - the next 12 participants assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will have whole blood collected in ACD tubes for PBMC isolation and 10 mL serum collected based on whether the participant has an EVEN PID number (week 2 blood draw only) or an ODD PID number (week 3 blood draw only). The remainder assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will only have 10 mL serum collected these visits.

[g4] At week 4 the last 7 participants assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will have whole blood collected in ACD tubes for PBMC isolation and 10 mL serum collected. The remainder assigned to each dose group (0.67 mg/dose, 2 mg/dose, 6 mg/dose) will only have 10 mL serum collected at this visit.

[h] Week 2 visit for those with EVEN PID#, Week 3 visit for those with ODD PID#

[i] Leukapheresis may be performed for up to 5 participants based on optional enrollment into substudy (see protocol for details). Leukapheresis will substitute for immunology blood draws during these visits for those who opt for this procedure. Approximately 120ml – 150ml of peripheral blood mononuclear cells will be collected at each visit, weeks 14 and 24

[j] Download EP data within 48 hours of dose and transfer to GeneOne LifeScience or its designee

[k] Record post-treatment reactions the evening following a dose and up to 7 days post dose in Participant Reminder Diary

[l] Detail AEs including injection site reactions either during on-site visits or via telephone.

1. INTRODUCTION

1.1 Background and Rationale

1.1.1 MERS CoV Epidemiology and Clinical Illness

In 2012 a participant presented to a hospital in Jeddah, Saudi Arabia with a progressive respiratory illness and renal failure, from whom viral culture yielded a novel coronavirus (**Zaki 2012 NEJM**). Subsequent cases were identified among those living in or travelers to Saudi Arabia and the Arabian Peninsula. The new virus was subsequently renamed as the Middle East respiratory syndrome coronavirus (MERS CoV) and the disease referred to simply as MERS. Genetic sequence analysis of human coronaviruses has divided the coronaviruses into three distinct phylogenetic groups (α, β, and γ). Both MERS CoV and the Severe Acute Respiratory Syndrome coronavirus (SARS CoV) are β coronaviruses; however, SARS CoV maps to subgroup 2b, whereas MERS CoV maps to subgroup 2c (**Agnihothram 2014 JID, Chan 2012 J Infect**).

MERS typically presents as an upper respiratory tract infection. It is not uncommon, however, for the disease to progress to acute respiratory distress syndrome (ARDS) and multi-organ failure (**Arabi 2014 AIM**). Mortality is highest among the elderly and those with comorbid illness, especially those with underlying lung or cardiac disease (**Arabi 2014 AIM, Saad 2014 Int J Infect Dis**).

As of 1 November 2015, more than 1600 laboratory-confirmed MERS cases and 580 MERS related deaths, yielding a mortality rate of approximately 35-40% among confirmed cases and as high as 50-60% among the earliest cases in Saudi Arabia. A recent survey of banked sera from Saudi Arabian patients presenting to the hospital or for outpatient care, including some individuals with significant camel exposure, revealed that 15 of 10,009 samples were positive. From these data, the investigators extrapolated that as many as 44,000 individuals country-wide may be seropositive (**Muller 2015 Lancet Infect Dis**). This suggests that asymptomatic or less severe illness may not be uncommon and that the overall mortality rate may be much lower than reported.

In June 2015 an individual returning to South Korea from a business trip to the Arabian peninsula developed and succumbed to a progressive respiratory illness that was later confirmed to be caused by MERS CoV. Because of delayed diagnosis, coupled with his seeking care at multiple health care facilities, there was consequent widespread transmission resulting in 186 cases and 36 deaths. Although the mortality rate for the Korean outbreak was less than 20%, transmission in the hospital and to family contacts raised alarm for the potential of an even larger outbreak, as transmission in hospital settings has been already common among MERS cases in Saudi Arabia and Europe (**Arabi 2014 Ann Int Med, Guery 2013 Lancet**). Moreover, the MERS CoV epidemic resulted in a significant negative impact to the Korean economy with GDP slowing to 0.3% growth compared to 0.8% the year prior.

1.1.2 Current Treatment

There are no approved therapies or vaccines for MERS CoV infection. Although numerous treatment strategies have been investigated *in vitro* and in animal models, none have progressed to human evaluation as of November 2015. Vaccine concepts in development include a DNA plasmid-S protein prime followed by S1 protein boost (**Wang 2015 Nat Comm**), a micelle expressing the full length post-fusion S trimer, and modified vaccinia Ankara virus and adenovirus expression systems containing the spike (S) protein, as well as the S protein DNA plasmid vaccine to be administered in this clinical trial (**Muthumani 2015 Sci Transl Med**). Multiple small molecule and biologic therapeutic candidates are being assessed that include immunomodulators, polymerase and fusion protein inhibitors, as well as monoclonal antibodies against the S protein.

The development of vaccine candidates for MERS CoV can be informed by the experiences with SARS CoV. However, only two small Phase I SARS CoV vaccine trials were completed. Two additional Phase I trials were withdrawn prior to enrollment. Martin *et al* reported a 10-person study (NCT00099463) of a DNA vaccine expressing the S-protein of SARS CoV. Participants were vaccinated with 4 mg/vaccination dose over a 3-dose series (**Martin 2008 Vaccine**). There were no serious adverse events (SAEs) or Grade 3 or 4 AEs. The most common reaction was mild injection site pain. Neutralizing antibody responses were not detected with a plaque assay, although 8 of 10 participants had detectable neutralizing titers with a lentivirus pseudotype assay. Five individuals had reciprocal titers above 1:40 (range 1:40-1:100) transiently at week 16 that declined to baseline by week 32. ELISpot measurements of T cell responses showed that 4 of 10 achieved CD4 + T cell specific reactions above threshold with two achieving spot counts ≥ 300 versus only 2 who manifested CD8 + T cell responses at any time point, albeit with <150 spots. A second Phase I clinical trial conducted in China (not listed on ClinicalTrials.gov) tested an inactivated SARS CoV virus vaccine administered at two doses without adjuvant (**Lin 2007 Vaccine**). No SAEs were reported. Antibody titers peaked 2 weeks following the second vaccination and declined thereafter. Seroconversion was documented in 100% of the 36 vaccine recipients on day 42. Antibody titers persisted above threshold in all but one recipient at day 56. Two additional Phase I trials of SARS CoV vaccines were closed prior to enrollment. One was to test a S protein subunit vaccine with an aluminum hydroxide adjuvant (NCT01376765). A second consisted of a whole-inactivated SARS virus given with or without aluminum hydroxide adjuvant (NCT00533741).

Thus, only two SARS CoV Phase I vaccine trials were completed, though neither yielded any safety concerns. Notably, the DNA plasmid used in the current vaccine trial also targets the coronavirus S protein that mediates viral entry into target cells. However, this plasmid backbone differs from past DNA vaccines in several important ways. The SARS CoV S protein DNA plasmid vaccine used the Vical VR-1012 expression vector that was modified to contain the human T cell leukemia virus 1 R region for translational enhancement (**Martin 2006 Clin Vaccine Immunol, Martin 2007 Vaccine**). The GLS-5300 to be used in this study is based on the pGX0001 plasmid backbone and does not contain lentiviral components and has been safely used in numerous clinical trials (**MacGregor 1998 JID, Bagarazzi 2012 Sci Trans Med, Morrow 2015 Mol Ther**).

The safety of the GLS-5300 is also be informed from past experience with similar Inovio vaccine candidates that are in, or have completed, human clinical trials. Specific examples include Phase I and 2 trials of INO-3100, the human papilloma virus (HPV) DNA vaccine that incorporates the HPV E6 and E7 proteins of HPV 16 and 18 into a modified pVAX1 backbone and has been administered with or without IL-12 plasmid DNA adjuvant (**Bagarazzi 2012 Sci Trans Med, Trimble 2015 Lancet**). Current studies include those of a VGX-6150 Hepatitis C vaccine in participants with chronic infection (NCT02027116) and the INO-4212 Ebola virus vaccine (NCT02464670) that use the same plasmid backbone but with different antigen inserts. All of these products to date have been well tolerated and did not elicit any SAEs..

1.1.3 Military Relevance

Emerging and re-emerging infectious diseases pose significant threats to military operations, as they tend to have a high case fatality rate, are often unpredictable in their spread, and occur across areas where service members are deployed. These diseases may arise from within the military community, as spill-over from the surrounding civilian populace or during military operations and deployments. Novel infectious agents pose challenges for early detection and prevention strategies, particularly for military personnel who reside in or are deployed to endemic areas.

MERS CoV, specifically, is a growing global concern given its airborne route of transmission and high fatality rate and, therefore, may impact military operations or readiness in the Central and

Pacific Command (CENTCOM, PACOM) areas of responsibility (AOR) where recent outbreaks have occurred (*i.e.* Republic of Korea, Kingdom of Saudi Arabia). The potential for high person-to-person transmissibility and the continued transmission in the CENTCOM AOR underscore the need for the US military to advance the development of effective countermeasures to mitigate the risk of MERS CoV exposure and transmission to US military personnel.

1.1.4 Pre-clinical experience with GLS-5300

The DNA plasmid that is the component of GLS-5300, pGX9101, has been studied as to its immunogenicity in mice, camels, and rhesus macaques and also as part of a challenge model to protect against MERS CoV infection in a non-human primate infection model using rhesus macaques (**Muthumani 2015 Sci Transl Med**).

Following immunization, mice manifested high binding antibody titers (~1:10,000) following two immunizations with pGX9101 and endpoint titers of ~1:50,000 following three immunizations. Neutralizing titers exceeded 1:1,000 following three immunizations. T cell responses in mice against the MERS S protein were broad based with reactive T cells spanning the entire S protein and a magnitude of a cell mediated response as ~2,500 spot forming units per 10^6 PBMCs.

The ability of pGX9101 to induce a protective immune response was also assessed in camels, the likely intermediate host for MERS. Camels immunized with three injections of pGX9101 at 10 mg per injection, spaced 4 weeks apart were found to develop binding antibodies (3 of 3 animals) with 2 or 3 camels generating detectable neutralizing antibodies.

Finally, non-human primates were immunized with pGX9101 at either low dose (0.5 mg/vaccination) or high dose (2 mg/vaccination) for three vaccinations spaced 3 weeks apart. Notably, after a single vaccination, 2 of 4 animals given a low dose and 4 of 4 macaques given high dose vaccine seroconverted with binding antibody titers of ~1:10,000. After two vaccinations, all animals seroconverted and manifested endpoint binding antibody titers of ~1:50,000. Neutralizing antibody titers after three injections were 1:1,000 without distinction between high or low-dose vaccine. Cytotoxic CD8+ responses were broad based across the MERS S protein, with a dominant response corresponding to the receptor binding region. The magnitude of the response after three vaccinations was approximately 800 SFU/10^6 PBMCs. Importantly, not only was the magnitude of the T cell response significant, but there was breadth of response with almost 20% of cells reactive after immunization.

1.1.5 Human experience with DNA plasmids for gene expression

Gene expression from plasmid DNA has been used as an efficient means to express target proteins for vaccine related immune responses and to replace or augment naturally occurring proteins and enzymes. DNA plasmids as part of vaccine trials have been developed for a variety of infectious diseases, with a number having been tested as part of Phase I and/or Phase II clinical trials in humans. The results from the first DNA plasmid-based vaccine trial were published in 1998 against HIV (**MacGregor 1998 JID**) with more than 1200 participants vaccinated (**Jin 2015 Vaccine, Quirk 2014 Open Forum Infect Dis**). Other published Phase I trials of DNA plasmid vaccines include studies evaluating vaccines against Ebola virus (**Martin 2006, Sarwar 2015, Kibuuka 2014**), HPV, HIV, and influenza (**Bagarazzi 2013, Kalams 2012 PLoS ONE, Ledgerwood 2015 PLoS One**). Phase II clinical trial data from the Inovio HPV DNA vaccine is currently in press.

Experience with DNA vaccines using 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 vaccine against the Zaire strain of Ebola virus (NCT02464670) and a therapeutic vaccine against genotype 1 hepatitis C virus (NCT02027116). Prior studies have examined a DNA plasmid based vaccine

against H5N1 Avian influenza (NCT01184976) that also employed a non-integrative plasmid based on the pVAX1 expression system. Each of these has an insert comprising a portion of the viral DNA representing a consensus sequence not found in nature to improve the immune response against the viral target and to enhance the breadth of the reaction across different viral strains. These studies along with additional studies sponsored by Inovio Pharmaceuticals (formerly VGX Pharmaceuticals) are enumerated in the table below. In each case, Phase I and II studies have shown no evidence of significant vaccine-associated toxicity, with the primary adverse event reported as transient injection site reactions.

1.1.6 Administration of similar DNA plasmids by Electroporation (EP)

Electroporation (EP) enhances gene expression of plasmid DNA delivered by the intramuscular (IM) or intradermal (ID) routes of administration. Following IM or ID delivery of a DNA vaccine or therapeutic product, EP facilitates entry of the DNA into the target site: muscle or dermal cells. Following cellular uptake, there is efficient and increased production of the proteins encoded by the DNA expression system. The different EP devices, each with varying electrical parameters and protocols, have been reviewed (**Prud'homme 2006 Curr Gene Ther**). EP has been extensively used in large animal species, such as dogs, pigs, cattle, and NHP, to deliver therapeutic genes that encode for a variety of hormones, cytokines, enzymes or antigens (**Prud'homme 2006 Curr Gene Ther**) activation of both cellular and humoral responses in animal models (**Hirao 2008 Vaccine, Rosati 2008 Vaccine**). Importantly, immune responses for DNA vaccines delivered with EP are far superior to vaccination without EP (**Rosati 2008 Vaccine**). 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 (**Curcio 2008 Cancer Gene Ther, Ugen 2006 Cancer Gene Ther**). The Inovio Pharmaceuticals novel constant current IM EP device (**Prud'homme 2006 Curr Gene Ther**) referred to as the CELLECTRA® 2000 or CELLECTRA® device will be used in this clinical trial.

As of July 31, 2015, more than 650 human subjects have undergone EP with the CELLECTRA® device in more than 15 different studies. More than 1500 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 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 EP with the CELLECTRA® Device

IM+EP Studies	# Participant	# Dose	ID+EP Studies	# Participant	# Dose
CEL-001[1]	10	10	CEL-002[1]	10	10
HPV-001	18	54	FLU-002	22	39
HPV-002	13	13	FLU-101	105	308
HPV-003 active[2]	125	360	FLUPRIME	40	126
HPV-003 placebo[2]	42	124	FLUPRIME[1]	10	20
FLU-001	32	56	EBOV-001	15	30
FLU-001K	30	59			
HIV-001	12	48			
HVTN 080	40	117			
HVTN 080[1]	8	22			
RV262 A	7	14			
RV262 B[3]	42	75			
VGX-6150-01	18	71			
HPV-004	1	4			
HPV-005	12	41			
HPV-006	1	4			
EBOV-001	75	190			

[1] Number of participants who received EP with no DNA.
[2] Participants were randomized 3 active:1 placebo.
[3] Participants were randomized 4 active:1 placebo, all participant counts listed as active until study is unblinded.
[4] Total number of participants does not include the 13 participants in HPV-002 who were initially enrolled in HPV-001.
[5] Includes 42 placebo recipients and corresponding 126 doses in HPV-003 and estimated 9 placebo recipients and corresponding 18 doses in RV262 B (based on 4:1 randomization).
[6] Includes estimated 69 placebo recipients collectively receiving 186 doses as follows: 42 placebo recipients and corresponding 126 doses in HPV-003; 8 placebo recipients and corresponding 22 doses in HVTN 080; estimated 9 placebo recipients and corresponding 18 doses in RV262 B (based on 4:1 randomization); and 10 placebo recipients and corresponding 20 doses in FLUPRIME.

1.2 GLS-5300

GLS-5300 contains a single plasmid, pGX9001, in sterile water for injection (WFI).

Common name: pGX9001

Chemical name: pGX9001 is a circular, double stranded, deoxyribonucleic acid plasmid consisting of 7025 base pairs.

Distinguishing name: This is a eukaryotic expression plasmid containing DNA encoding for the full-length MERS CoV S protein. pGX9001 incorporates a consensus sequence of published MERS CoV clinical isolate strains. The S protein DNA 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

Because human responses to GLS-5300 are unknown, this study will assess safety, tolerability, and immunogenicity. Based on prior experience with treatment of HIV infection, a dose of 2 mg of GLS-5300 corresponds to a vaccine dose of approximately 30 µg/kg. Preclinical studies in rhesus macaques assessed high (2 mg/vaccination) and low (0.5 mg/vaccination) doses of pGX9001. Robust 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 (**Bagarazzi 2012 Sci Transl Med, Trimble 2015 Lancet**). Preliminary analysis of the human response to VGX-6150 for the treatment of Hepatitis C shows minimal immunologic benefit since when the dose is increased from 2 mg to 6 mg, there is only a small increase in immune response. Notably, both the HPV product and VGX-6150 are based on the same expression system used to construct GLS-5300. Assessment of antibody and T-cell responses following each vaccination will determine the effectiveness of vaccination. Follow-up will determine the longevity of immunogenicity.

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. Since the volunteers in this clinical trial are healthy, and this is a first in man study, no direct benefit is expected. The potential side effects of treatment with the investigational products may include discomfort related to the EP technique such as local edema, swelling, or pain. Systemic side effects with vaccines based on the identical backbone have been demonstrated to be generally minimal in more than 650 participants. Since the volunteers in this clinical trial are healthy, no direct benefit is expected. The potential benefit is to determine whether this vaccine will generate protective levels of neutralizing antibodies and cytotoxic T-cells as prophylactic treatment for those at risk for MERS CoV infection.

1.4.1 Risks to the Study Personnel and the Environment

The principal risk for study personnel is exposure in the clinical setting to infectious pathogens from study participants through various contact mechanisms (e.g., needle stick exposure to blood borne pathogens and exposure to respiratory pathogens from those with upper respiratory tract infection). Adherence to good hygiene practices and standard operating procedures (SOPs) for working with infectious agents and universal precautions will reduce the risk of exposure. There are no known risks to the environment other than those associated with the generation of

biohazardous waste attendant to vaccination of humans. All biohazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site SOPs.

1.4.2 Venipuncture

Some discomfort from the needle stick for the blood draw is possible, including swelling or bruising, and there is a very small risk of infection at the site of the needle stick. A few participants may feel light-headed and may develop a rapid heartbeat during blood collection. These symptoms can be stopped by having the participant lie down and/or by stopping the procedure.

1.4.3 Allergic Reaction

As with any investigational new drug (IND) product, there is the potential risk of a serious, or even life-threatening, allergic reaction the vaccine. To mitigate this risk, potential participants with a history of severe allergic reaction of any kind, or significant allergic reaction to a known component of the experimental products, will be excluded from participation. As the vaccine is formulated only in sterile water, the allergic reaction would most likely be due to the DNA vaccine.

In the event of a severe allergic reaction, the CTC is staffed with trained medical personnel and stocked with appropriate medical emergency equipment to provide acute care for conditions such as anaphylaxis. Further, if required, a formal emergency medical response service (fire department), capable of treating and transferring any life-threatening injuries to a higher level of medical care, is available in close proximity to the trial site.

1.4.4 EP

The EP device delivers three brief (less than 1 second each) electrical impulses to the deltoid (or quadriceps) muscle through 5 electrodes. This results in a brief but intense muscle contractions with each pulse and is associated with local pain/discomfort during the period of EP administration. Additional AEs associated with the procedure has in the past included minor, transient cutaneous bleeding at the sites of electrode and injection needle penetration, and mild to moderate injection site soreness/bruising typically lasting for 24 to 72 hours, but in some instances up to 7 days post administration.

On one occasion during vaccination in the early phase of another study with a separate EP device the injection needle came in contact with the volunteer's periosteum which created resistance when the vaccinator attempted to withdraw the device. This has never been reported for the CELLECTRA® EP device. However, to minimize this risk, those volunteers with a body mass index, measured at study baseline, of less than 18 will have a guard used with the device that prevent the electrodes from inserting the full length into the volunteers arm. Additionally, even if the body mass index of the volunteer is greater than 18, the principal investigator or his delegate may still opt use the guard or not vaccinate the volunteer if he or she feels there is not enough muscle mass to accommodate the electrodes.

1.4.5 EP

Pain associated with the EP has been intense but transient and in the experience of this particular device almost all individuals have reported complete disappearance of pain by 5 minutes post EP. Additionally, there is potential for the delivery of excessive electrical energy to the skin and muscle tissue. To prevent this, the device is designed to perform multiple self-monitoring

functions to identify potentially unsafe operating conditions throughout the vaccination process. Any detected abnormality will result in disconnection and prevention of electrical discharge into the subject. There have been no occurrences of excessive energy delivery in any of the nonclinical and clinical studies conducted with the CELLECTRA® 2000 device.

1.4.6 Electrocardiogram

Although the electrocardiogram is safe procedure, a potential harm may come from discovery of a previously known cardiac condition. This information, however, will be kept confidential and only used to refer the participant to appropriate care and treatment.

1.4.7 Testing for Sexually Transmitted Diseases

There is a risk that data collected from participants on results from HIV, Hepatitis B, and Hepatitis C infection could become public and result in social harm. This will be mitigated by following confidentiality procedures as described below.

1.4.8 Leukapheresis

The leukapheresis procedure will be performed at the same study center as all other study procedures (WRAIR CTC, Robert Grant Ave. Silver Spring, MD). American Red Cross personnel will be responsible for performing the procedure, under contract with the WRAIR. Essentially, plasmapheresis will be performed in which approximately 120ml – 150ml of plasma will be removed from the patient over the course of 1.5 – 3 hours with a majority fraction of red blood cells (95% - 97%) being returned to the volunteer. Because the fraction of plasma of primary interest are peripheral blood mononuclear cells, the procedure will referred to as Leukapheresis throughout this protocol. The procedure, (Leukapheresis) will be offered at the weeks 14 and 24 visits. Only a subset of volunteers will be chosen for this optional procedure that will require additional consent. An interim analysis will be conducted in a subset of volunteers (10 per dose group) at the week 6 visit to determine the five highest immune responders (as measured by neutralization antibody titers). The five individuals will then be recruited for the leukapheresis substudy. The next five highest responders will be recruited if the first five decline. Only a subset of participants are being chosen for this procedure so as to make more efficient use of the leukapheresis by focusing on those who will provide the highest yield of potent neutralizing antibodies. Additionally leukocytes are being collected a later time points when antibody affinity has matured sufficiently.

The risks of the leukapheresis procedure include the following:

- blood loss from the inability to return red blood cells during automated plasmapheresis (which may result in the procedure being terminated)
- allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, which may vary in severity from mild to life-threatening
- vascular injury from the needle used in the procedure. These include bruising or hematoma at the venipuncture site which may present with pain, tingling, or paresthesia
- presyncopal/syncopal episodes during volume removal. These include pallor, weakness, lightheadedness, agitation, sweating, nausea, vomiting, hypotension, tachycardia, bradycardia, fainting, and incontinence. These side effects will be closely monitoring during and immediately after the procedure. The normal saline reinfusion performed in conjunction with plasmapheresis will reduce the likelihood of these reactions.
- reactions to the anticoagulant used during plasmapheresis including any of the following: tingling, paresthesia, muscle cramp, tetany, seizure, and metallic taste in the mouth

A recent analysis of apheresis procedures (including plasmapheresis) in the US, estimates the risk of these moderate and severe adverse reactions to be 0.37%. Risk is mitigated by limiting volume of plasma removed, careful screening, modern equipment, and experience personnel. The volunteers will be monitored closely by trained American Red Cross medical personnel during the procedure and will wait at the clinic for 15 minutes after the procedure.

1.4.9 Data Collection

There is a risk that data collected from participants could be unintentionally released to another party, constituting a breach of confidentiality and potentially causing social harm. This risk is also compounded for military personnel who may have information leaked up the chain of command, although military personnel will not be actively recruited for this study. These risks will be mitigated by the universal practice within the research clinic of complete maintenance of confidentiality among study staff, the limited use of participant identifiers on study materials, and the locking of all print materials related to study participants and password protection of electronic documents related to the study.

1.4.10 Unknown Risks

As with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on available information. This would include late effects that have been seen with some vaccines.

Table 1.4: Summary of Reported Adverse Events of SynCon 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 • Keloid scar or hypertrophic 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-5300 administered intramuscularly (IM) followed by EP will be well tolerated and immunogenic.

2.2 Primary Objectives

- Evaluate the safety and tolerability of GLS-5300 when administered by IM injection followed by EP in healthy adult participants.

Primary Safety Endpoints

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

2.3 Secondary Objectives

- Evaluate the cellular and humoral response of GLS-5300 when delivered IM followed by EP
- Evaluate the dose response for cellular and humoral reactivity of GLS-5300 when delivered IM followed by EP

Secondary Immunologic Endpoints

- Quantitative binding antibody titers to the full length MERS CoV Spike (S) glycoprotein
- Qualitative and quantitative levels of neutralizing antibodies against MERS CoV
- Antigen specific cellular immune responses to MERS CoV as determined by:
  - Interferon-gamma (IFN-γ) ELISpot
  - Intracellular cytokine staining (ICS) (cytotoxic T lymphocyte phenotype, lytic granule loading, granzyme B killing of target cells)

2.4 Exploratory Objectives

- Explore whether end point antibody titers to MERS CoV S protein are dose related.
- Explore the time to onset of antibody production and longevity of serologic response
- Explore if increasing dose levels of GLS-5300 more rapidly induce cellular immunity
- Explore the time to onset of T cell responsiveness and longevity of cell mediated immunity
- Evaluate the kinetics of antigen expression in the peripheral blood compartment.
- Evaluate host genetics as a potential predictor of vaccine immune response
- Evaluate additional cellular immune responses
- Neutralizing and non-neutralizing antibody repertoire analysis
- Explore innate immune responses to the MERS CoV S protein.
- Assess cross-neutralization activity against other human coronaviruses.
- Compare ELISA assays for MERS CoV S protein antibodies across laboratories

Exploratory Endpoints

- Comparison of S binding antibody and MERS CoV neutralizing antibody titers
- Kinetics and durability of S binding antibody and MERS CoV neutralizing antibody titers
- Comparison of IFN-γ ELISpot, and ICS responses across different vaccine doses
- Kinetics and durability of IFN-γ ELISpot, and ICS responses across different vaccine doses
- Expression of the full length MERS CoV S protein in the peripheral blood over time.

- Host immune-genotyping as resources are available.
- Epitope mapping of CD4+ and CD8+ T lymphocyte responses
- Immunophenotyping and functional characterization of cellular subsets of interest, including natural killer (NK) cells
- Isolate, express and characterize monoclonal antibodies against the MERS CoV S protein and assess their neutralizing and non-neutralizing functional activity.
- Molecular characterization of study vaccine-elicited antibodies may include, but will not be limited to structural biology analysis, Fc analysis, isotype analysis, epitope mapping.
- Correlation of endpoint antibody binding titers across two different ELISA platforms.

3. STUDY DESIGN

This is a Phase I open-label trial to assess the safety, tolerability, and immunogenicity of GLS-5300 encoding for the S protein of MERS CoV. Eligible participants who consent to participate will be administered GLS-5300 via IM injection followed immediately by EP using the CELLECTRA® 5P Adaptive Constant Current Electroporation device.

3.1 Evaluation of IM Administration of GLS-5300:

Prospective participants who read and sign the informed consent form (ICF) will be screened for eligibility for up to 30 days prior to their first dose. Screening evaluation will consist of a medical history, ECG, and laboratory evaluations. Participants without a history of exclusionary conditions or 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, CPK, will be eligible for participation in the trial. A total of 75 participants divided into 3 groups will be enrolled for this study. It is estimated that approximately 225 participants will need to be screened to fill the desired enrollment of 75 participants.

Group I Participants (n=25) assigned to receive GLS-5300 will be administered 0.67 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Group II Participants (n=25) assigned to receive GLS-5300 will be administered 2 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Group III Participants (n=25) assigned to receive GLS-5300 will be administered 6 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Participants will be enrolled at the lowest dose (Group I) with continuous enrollment through the 1st week of enrollment. At the start of week 2, clinical laboratory data for the first five participants from Group I will be reviewed as part of the safety review. Once safety labs have been reviewed and cleared for the first five participants in Group 1, the second dose level will be opened. The next five participants who have met eligibility criteria will then be enrolled into Group II. Then enrollment for Group I will be completed. Once group 1 has completed enrollment of 25 participants, then Group 2 will be populated sequentially. When the first five participants in Group 2 have reached one week post vaccination then safety labs will be reviewed as above. Once this safety assessment is cleared, then Group III will be opened for enrollment of the next five participants. Then enrollment will be completed for Group 2 and afterwards Group 3.

See Table S1 for a summary of study treatments and schedule of dosing.

Safety assessments: All participants will be monitored for

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

Immunogenicity assessments:

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

- Enrollment (pre 1st dose of vaccine)
- Week 1 and 4 post 1st vaccination
- Week 2 post 1st vaccination (even PID#) or week 3 post 1st vaccination (odd PID#)
- 2 weeks post 2nd and 3rd vaccination
- 3, 6, 12 months after the 3rd vaccination

Leukapheresis

- Leukapheresis in lieu of immunology testing may be performed for up to 5 participants at week 14 and 24, based on enrollment into a dedicated substudy

3.2 Treatment Progression Scheme

This study will utilize a treatment progression scheme to assess and ensure the safety of each dose level of vaccine as follows.

Participants will be contacted by telephone to assess reactions the day following the 1st vaccination to assess whether there are any reported AE's or other reactions. If there are no dose-limiting AE's reported for the first 5 participants enrolled, then enrollment can proceed with the remainder of participants at that dose level.

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. If no Grade 3 or Grade 4 AEs or any Serious Adverse Event (SAE) are noted either with clinical assessments or with safety laboratory assessment for the first 5 participants enrolled at a dose level, then enrollment into the next higher dose level can be opened. Labs will be forwarded for review on a monthly basis thereafter until all participants have completed safety lab draws.

3.3 Safety Monitoring

Safety Monitoring Committee

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the PI, clinic staff, clinical monitor, and DoD Research Monitor. As this study represents the first time GLS-5300 is administered to humans, the investigative team will also establish a Safety Monitoring Committee (SMC) to review safety labs and provide oversight of the safe conduct of the study as an additional measure to address and mitigate any risk.

The SMC will consist of the study PI, the medical monitor and the DoD Research Monitor. Safety reviews will be conducted on a weekly basis either by teleconference or electronically. If there are urgent issues that need to be addressed the SMC will convene ad hoc to address those issues. Enrollment from one dose level to the next will require approval of all review members. A safety

report summarizing the safety data and SMC protocol considerations for the sentinel group of five volunteers at each dose-level (3 safety reports), including laboratory and monitoring data, the timeframe covered, and an assessment about moving forward will be provided to the Vice Chair and Reviewer with the option to refer to the convened IRB.

The SMC will review all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the protocol and provide an unbiased written report of the event. The SMC will also review any withdrawal or discontinuation of study participation of any volunteer and determine if it was product related. The SMC will also pause the study if the pausing rules are met as outlined in Section 7.5 and notify the IRB immediately of this pause. Reports for events determined by either the investigator or entire SMC to be related or unrelated to participation and reports of events resulting in death will be promptly forwarded to the IRBs.

Research Monitor

The research monitor will function as an independent safety advocate for subjects per AR 70-25 and DoD Instruction 3216.02. An independent research monitor is required to review all unanticipated problems involving risk to subjects or others, SAEs, and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor will comment on the outcomes of the event or problem and, in the case of a SAE or death, comment on the relationship to participation in the study. The research monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death will be forwarded to the WRAIR IRB, ORP HRPO, and USAMRMC CSSD PSSB (sponsor safety office) within 48 hours followed by a written report within 10 working days (as per WRAIR SOP UWZ-C-619.02, Safety Reporting for Clinical Trials).

The duties of the research monitor shall be determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions if needed (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official.

The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor’s report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

Data Monitoring

Weekly reports will be generated by a contracted statistical support group. These reports will comprise of the frequencies of SAEs and AESI’s as well as enrollment status (number of volunteers screened, number of volunteer screening failures, and basic laboratory, ECG, and demographic data for each dosing group in the prior week and as compared to entire study period to date. The SMC will review the summarized safety data and other data as appropriate during weekly meetings to

inform decisions as described in section 3.3.1. The SMC will be prepared to review any individual event thought to be of major significance and alert the sponsor, IRB and FDA if there are any safety concerns regarding the continuation of the study.

Statistical support for data monitoring efforts will include generation of data safety reports, maintenance of an archive of electronic copies of the datasets statistical programs used to generate reports, and generating and updating and carrying out statistical analysis plan.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Recruitment of Participants

Healthy adult volunteers, male and female, military and civilian, will be recruited by non-coercive means through WRAIR CTC according to applicable U.S. Army regulations.

Recruitment will be by advertisement in multiple media formats (email, website, social media, newspaper, radio, television) as well as by word of mouth. Recruitment may also include oral presentations and/or distribution of approved recruiting materials at events, meetings, and briefings wherein the desired recruit population might reasonably be expected to attend.

Recruitment may include referrals of potential participants by individual already screened for the study. Participants will be asked to direct interested persons to contact the CTC. Participants will receive $25 for each referred person who then attends a screening session and meets all inclusion and none of the exclusion criteria. Compensation will be independent of the referred person's decision to enroll. Final authority over dispensation of referral compensation will lie with the CTC Director.

All advertisements, both general and specific to this study, will have been reviewed and approved by the WRAIR IRB prior to their use. All recruiting methods will direct the volunteer to contact the CTC via e-mail or phone, or the CTC web site where the same contact information will be given.

Upon calling the recruitment phone number, an IRB approved recruitment script will be used by study personnel to inform potential participants of the details of the study. If the potential participant desires, some basic contact information will be obtained and an appointment for a formal briefing and screening will be made at that time.

Upon contacting the CTC via e-mail, potential participants will be provided an electronic version of the recruitment script to inform them of the details of the study. If the potential participant desires, some basic contact information will be obtained and an appointment for a formal briefing and screening will then be made (via further e-mail or phone conversations).

Volunteers can also be recruited via WRAIR 2038, which is a generic screening protocol managed by the WRAIR CTC. Under this screening protocol, volunteers will undergo a generic screening visit with medical history, exam, vitals, lab tests, along with other potential screening tests. If the volunteer is interested in learning about this clinical trial, they will need to attend a WRAIR 2274 study specific briefing and screening appointment. Then, if the participant remains interested, they will need to sign this study's informed consent form. If the volunteer consents, the screening documentation from WRAIR 2038 can be shared with this study to fulfill the screening requirements, and a copy of said documents can be added to the volunteer's study file for this clinical trial.

If military participants are recruited in formation, then the research monitor who will act as the ombudsman for this study, will be present as an independent party. The ombudsman will be available to help answer any questions from an impartial standpoint. Additionally, no senior NCO or officers will be present during the recruitment brief, as to ensure that there is no undue pressure of influence from the soldier's immediate chain of command.

4.2 Inclusion Criteria

a. Age 18-50 years; military, civilian, male and female.
b. Able to provide consent to participate and having signed an Informed Consent Form.
c. Able and willing to comply with all study procedures.
d. Women of child-bearing potential agree to remain sexually abstinent, 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 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 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;
h. No history of clinically significant immunosuppressive or autoimmune disease.
i. 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 corticosteroids at a dose less than 20 mg/day).
j. Willing to allow storage and future use of samples for MERS CoV related research

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 MERS CoV except if participant is verified to have received placebo;
c. Previous infection with MERS CoV as assessed by self report and solicited exposure history;
d. Administration of any vaccine within 4 weeks of first dose;
e. A BMI greater than or equal to 35;
f. Administration of any monoclonal or polyclonal antibody product within 4 weeks of the first dose;
g. Administration of any blood product within 3 months of first dose;
h. Pregnancy or breast feeding or have plans to become pregnant during the course of the study;
i. History of 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;
j. Positive serologic test for hepatitis C (exception: successful treatment with confirmation of sustained virologic response);
k. Baseline evidence of kidney disease as measured by creatinine greater than 1.5 (CKD Stage II or greater);

l. Baseline screening lab(s) with Grade 2 or higher abnormality;
m. Chronic liver disease or cirrhosis;
n. Immunosuppressive illness including hematologic malignancy, history of solid organ or bone marrow transplantation;
o. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or corticosteroids at a dose less than 20 mg/day);
p. Current or anticipated treatment with TNF-α inhibitors such as infliximab, adalimumab, etanercept;
q. Prior major surgery or any radiation therapy within 4 weeks of group assignment;
r. Any pre-excitation syndromes, e.g., Wolff-Parkinson-White syndrome;
s. Presence of a cardiac pacemaker or automatic implantable cardioverter defibrillator (AICD);
t. Metal implants within 20 cm of the planned site(s) of injection;
u. Presence of keloid scar formation or hypertrophic scar as a clinically significant medical condition at the planned site(s) of injection.
v. Prisoner or participants who are compulsorily detained (involuntary incarceration) for treatment of either a physical or psychiatric illness;
w. 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
x. Tattoos covering the injection site area h
y. 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 – 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.

All data collected up to the time of withdrawal, including any final evaluation and lab results that may be pending at the time of withdrawal will be reported. Likewise, any specimens collected up to the time of withdrawal, including any blood collected for storage and use in future research, will be kept and utilized as outlined in the protocol and consent form. The study termination eCRF will be completed, with the reason for withdrawal specified.

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 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.
- Incarceration: Participation of prisoners is not planned and any volunteer will be suspended from study visits while incarcerated. The IRB will be notified of the period of incarceration. If possible, site teams will coordinate with correctional authorities to ensure that relevant medical information for the safety and care of the patient is communicated promptly.
- Other: The participant was terminated for a reason other than those listed above, such as termination of study by the Sponsor.

5. STUDY TREATMENT

5.1 Investigational Product

GLS-5300, the investigational product to be used in this study contains a DNA plasmid encoding for the S protein of MERS CoV. Each product will be provided at a concentration of approximately 6 mg/ml to be diluted and mixed on site to the needed dose such that a standard 1 ml volume will be administered to all study participants. Because of this the concentration of the final plasmid will vary based on the dosage administered. GLS-5300 is a solution in sterile water for injection (sWFI). Therefore, sWFI will be used for dilution of the biologic products during clinical site formulation. The vaccine product will be shipped from manufacturer at VGXI in Houston Texas on dry ice. The lot number for the vaccine to be used is GLS-5300 15L019.

The IP in this study, GLS-5300, completed FDA review on 17 November 2015, with notification that the protocol had no clinical holds was received and that the clinical trial could proceed. There have been no prior FDA submissions for GLS-5300 either alone or in combination with any other product.

Table 5.1: Investigational Product

GLS-5300	
Recoverable volume per container	0.5 mL minimum
Concentration	6 mg/mL
Container Size and Type	2 mL glass vial

5.2 Packaging and Labeling of GLS-5300

The study products will be supplied in a non-blinded fashion indicating the particular component, GLS-5300. 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. Vial labels text may include the following with minimal recoverable volume as indicated.

Table 5.2: Sample labels for the final drug product components

Biologic Product/ Diluent	Sample Label
GLS-5300	GLS-5300 [6 mg/ml] 0.5 mL/Vial Single Use Vial Lot: GLS-5300.15L019 Date of Manufacture: 19 Aug 15 Final Retest Date 19 Aug 18 Store at or below -15ºC CAUTION New Drug – Limited by Federal Law to Investigational Use GeneOne Life Science, Inc. Rev 000

5.3 Handling of GLS-5300

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 medical 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-5300 will be shipped on dry ice. If there is no dry ice remaining in the frozen shipment container when the shipment is received, the Sponsor must be contacted immediately.

The investigational product 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-5300 must be stored frozen in a freezer (NOT frost-free) at or below -15°C although for long term storage (approximately more than 3 months) it must be stored at -17°C to -23°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-5300

It is the responsibility of the Investigator to ensure that GLS-5300 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. The label should also contain the words "Administer as soon as possible".

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-5300 is supplied in single dose 2 mL vials at a concentration of 6 mg/mL at a volume of 0.5 mL minimum recoverable volume.

GLS-5300 will be combined with sWFI to the required volume and concentration by experienced site personnel for IM administration. Detailed 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. Empty containers should not be returned to GeneOne Life Science, Inc. 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. or designated Study Monitor.

5.9 Use of CELLECTRA® Electroporation Device

The 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® 5P-IM

Number of pulses per treatment = 3
Maximum Current Strength = 0.5 Amperes
Voltage Strength = 1 - 200 Volts
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second
EP needle array length (injection depth) = 12 mm (with array guide in place)
= 18 mm (without array guide)

The **vaccination/electroporation procedure** will be performed by qualified personnel. Any licensed healthcare provider designated to perform the procedure must have the appropriate license to administer vaccinations or parenteral drugs to participants (*e.g.* MD, DO, RN, LPN). Additionally, those administering the vaccination will be trained by the manufacturer in the correct use of the CELLECTRA® 5P-IM electroporation device.
All individuals designated to perform the EP procedure must satisfactorily complete device training from the sponsor or its designee regardless of 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, which may include consent for photography. If consented, injection sites may be photographed in the event of unusual or high-grade injection site reactions at the investigators discretion. (Section 6.5);
- Review and confirm all inclusion/exclusion criteria (Sections 4.2, 4.3);
- Collect demographics, including gender and ethnic origin;
- Obtain complete medical history (including procedures history), present conditions and concomitant illnesses (Section 6.1.5);
- Record concomitant medications/treatments at present and in past 8 weeks;

- Record vital signs including body weight and height, heart rate (HR), blood pressure (BP), respiration rate and oral temperature (Section 6.1.6.3);
- Collect blood for CBC with differential, blood chemistry [Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), glucose, BUN, creatinine, AST, ALT, CPK (Section 6.1.6.6)];
- Collect blood for serologic assessment of HIV, Hepatitis B surface antigen (HBsAg), and Hepatitis C antibody (HCV)
- Serum pregnancy test (Section 6.1.6.6);
- 12 lead ECG (Section 6.1.6.5);
- Physical Exam (Section 6.1.6.2); and
- Determine proposed site of injection(s)

Potential participants will be notified of their eligibility as soon as all lab results are available and an assessment can be made by the investigators. If determined to be eligible, participants will be scheduled for their initial vaccination (Day 0, Visit 1). Regardless of eligibility and enrollment, individuals will be informed at screening and any follow up visits of any significantly abnormal test results in an expeditious manner, via telephone, in person or by written communication. Appropriate counseling will be given regarding necessary medical follow-up. Information on individuals with evidence of reportable infectious diseases (eg, HIV and hepatitis) will be transmitted to the required military and/or civilian public health authorities as applicable. Potential participants will be notified of this possibility during their informed consent process.

6.1.2 Study Evaluations

6.1.2.1 Vaccine Administration Visits (weeks 0, 4, 12)

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 whole blood (at week 4 this will only occur for the final 7 participants assigned to each dose group [i.e. 0.67 mg/dose, 2 mg/dose, 6 mg/dose]) and serum (all participants at all visits regardless of dose group) for immune assessment. If PBMCs are to be shipped to Sponsor for processing, then collection should be planned for Monday thru Friday. Blood must be received in PBMC processing lab within 24 hours of collection. (Shipment of samples to Sponsor on a Friday requires prior approval from the Sponsor and PBMC processing lab)

- **Administer study treatment followed by EP**

The following study evaluations will be performed **post dose**:

- Pain assessment minimum of 30 minutes after EP;
- Injection site reaction assessment a minimum of 30 minutes after vaccination;
- Targeted physical assessment, including vital signs a minimum of 30 minutes after vaccination
- Adverse and Serious adverse event assessment;
- Distribute Participant Reminder Diary;
- Download EP data from device within 48 hours following treatment onto a USB storage device 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 by phone
- Local and systemic injection site review;
- Adverse and Serious adverse event assessment;

6.1.2.3 Visits (Week 1)

The following procedures will be performed during the Safety Visit 1 week after the 1st injection:

- Concomitant medications/treatments;
- Vital signs;
- Targeted physical assessment;
- Local and systemic injection site review;
- Adverse and Serious adverse event assessment;
- Collect blood for safety laboratory assessment (CBC, serum chemistries, CPK)
- Collect whole blood (only first 6 participants assigned to each dose group) and serum (all study participants) for immune assessment as indicated;
- Review Participant Reminder Diary.

6.1.2.4 Visits (Week 2 or 3)

The following procedures will be performed during the Interval Assessment Visits 2 weeks or 3 weeks following the 1st vaccination:

- Participants with an EVEN PID# will be assessed at Week 2 post 1st dose
- Participants with an ODD PID# will be assessed at Week 3 post 1st dose
- Vital signs;
- Targeted physical assessment;
- Concomitant medications/treatments;
- Local and systemic injection site review;
- Adverse and Serious adverse event assessment;
- Collect whole blood (only the 7th through 18th participants in each dose group) and serum (all study participants) for immune assessment as indicated (based on whether the participant is assigned an EVEN or ODD PID as indicated in the first two bullet points of this section).

6.1.2.5 Visits (Weeks 6, 14, 24, 36)

The following procedures will be performed during the Interval Assessment Visits 2 weeks after each injection (weeks 6 and 14) and at 3 and 6 months after the final vaccination (weeks 24 and 36) as below:

- Concomitant medications/treatments;
- Vital signs;
- Targeted physical assessment
- Local and systemic injection site review (only at weeks 6 and 14);
- Adverse and Serious adverse event assessment;
- Collect blood for safety laboratory assessment (CBC, serum chemistries, CPK) (weeks 6 and 14 only)
- Collect whole blood and serum for immune assessment as indicated;
- Leukapheresis in lieu of collection of blood for immune assessment if enrolled (weeks 14 and 24 only)
- Review Participant Reminder Diary (Weeks 6 and 14);

6.1.2.6 Weeks 8 and 16

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;

6.1.2.7 End of Study Visit (Week 60)

The following procedures will be performed 12 months after the end of treatment (week 60 visit):

- Concomitant medications/treatments;
- Vital signs;
- Targeted physical exam;
- Urine Pregnancy test, if applicable;
- Adverse event assessment;
- Collect whole blood and serum for immune assessment.

6.1.2.8 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 the 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.

Any participant who withdraws consent will not have any further data collected after consent has been withdrawn. However, data and samples that were collected prior to a participant's withdrawal of consent will be included in the data analysis, unless otherwise specified by the participant.

6.1.3 Informed Consent and Screening

All potential participants will be given a formal briefing at the WRAIR CTC by an investigator. This briefing, which generally lasts about an hour, will describe the rationale for and key features of the study, the nature and extent of participant participation, inclusion/exclusion criteria, and potential risks and/or benefits to the participant and allow opportunity for potential participants to ask and have addressed any questions or concerns they might have regarding the study. This briefing will involve a combination of standardized presentation materials (*e.g.* briefing slides) and spontaneous interaction between investigator and potential participants. Any standardized materials will have been approved by the WRAIR IRB prior to their use.

Following the formal briefing and prior to undertaking any study procedure, signed informed consent for study participation and use of some collected blood for future research will be obtained from each potential participant in accordance with applicable US Army and federal regulations, utilizing IRB-approved materials. A specific State of Maryland consent for HIV testing and consent for photographs will be obtained at the same time. Participants will also be required to sign a copy of the "Information Sheet Regarding Compensation to Federal Personnel When They Participate

in Research as Human Subjects" to attest that they understand the compensation policies for federal employees as research participants. Potential participants will have the opportunity to ask and have answered any questions they might have about the study prior to giving consent.

The original signed informed consent forms for each participant will be kept on file in a secure location by the investigator. Each potential participant will receive a copy of their signed and dated written informed consent document and any other written information provided to the participants.

After completing informed consent, participants will provide a medical history and undergo physical examination, to include both ECG, and routine standard laboratory screening tests to include: complete blood count (CBC), serum basic metabolic panel (glucose, electrolytes, blood urea nitrogen [BUN], creatinine [Cr], alanine aminotransferase [ALT], aspartate aminotransferase [AST]), , serum pregnancy screen (beta-human chorionic gonadotropin; females only), and viral serologies for hepatitis B and C, HIV, as well as for the viruses under study. Screening history, physical examination, and laboratory findings for all participants will be recorded on appropriate source documents. Participants found to be seropositive for HIV-1 or hepatitis B or C will be counseled and referred to their regular health care provider or public health clinic for further evaluation.

If deemed appropriate by an investigator, any or all of the screening laboratories may be repeated once as necessary to allow an accurate determination of a potential participant's eligibility if the investigator feels that there may be a reason that the screening laboratories are abnormal due to lab error or normal physiologic variance. Individuals who have minor laboratory abnormalities (considered to be no more than a Grade 1 abnormality using the FDA toxicity scales), that are deemed to be clinically insignificant by the physician investigator, AND do not meet exclusion criteria otherwise defined, may be enrolled in the study.

Participants will be excluded from participation if they fail to meet any of the inclusion or exclusion criteria or have any other finding that in the opinion of an investigator would increase the risk of having an adverse outcome during the trial.

Military participants will also need to submit a signed statement of supervisor's approval.

All participants enrolled in the trial will receive an emergency contact ID card which can be used to contact the PI or AI in the event of an emergency, or to contact study staff for any other needs.

Each participant must meet all inclusion and no exclusion criteria. The PI or designee will make the final decision of the eligibility. Only eligible participants will be given the investigational product. The participant will be informed that a description of this clinical trial will be available on http://www..gov, as required by US law.

If participants are illiterate, administrators of the consent will read the IRB-approved informed consent to the subject in English. The participant can either provide a signature or personal marking (such as a thumb print). The administrators of the consent will then sign and date the form. A copy of the consent form will be filed in the participant's chart and a signed copy will be provided to the participant.

As part of the ICF, participants will be asked to consent to be contacted at a later date for separate enrollment into a possible follow-on trial to determine whether an additional dose of vaccine can boost immune reactivity to 2-5 years post the completion of the initial vaccine series. Participant consent to be contacted for a later trial does not affect participation in the primary protocol nor does

it constitute consent for participation in any potential subsequent trial as a separate consent must be obtained. If they consent and there is a follow-on trial then participants will be contacted using the contact information they have provided during study enrollment, the same contact information that is used to contact participants during phone call visits. Participants will also be asked make every effort to update their contact information should it change.

6.1.4 Participant Identification Number and Group Assignments

Participants will be recruited sequentially and assigned to the three treatment groups based on when they screen. Recruitment will begin for the lowest dose group first and then proceed to the higher dose groups as each group is filled.

Participants will be enrolled sequentially at the lowest dose (Group 1), with continuous enrollment through the first week. At the start of the second week, safety labs will be reviewed for the first five participants from Group 1. Once those safety labs have been cleared, then the second dose level will be opened. The next five participants who meet eligibility criteria and consent to the study will be enrolled into Group 2. Additionally Group 1 enrollment will be completed to a total of 25 participants. When the first five participants in Group 2 have reached one week, safety labs will be reviewed as above. Once the safety assessment has been cleared, then Group 3 will be opened. The next five participants who meet eligibility criteria will be enrolled into Group 3. Then Group 2 enrollment will be completed followed by Group 3.

Each participant who consents will be assigned a unique participant identification designation number (PID#), which identifies the participant for all study-related procedures. Screening numbers are a combination of protocol designation plus a 4-digit subject number starting with 1001. Once assigned, PID numbers cannot be reused for any reason. A copy of the signed and dated consent form will be given to the participant. Information regarding the participant's PID# and screening date will be documented on a screening log.

When a participant has been deemed eligible by criteria listed in protocol Section 4 - Selection and Enrollment of Participants, the clinical site will contact the Sponsor to register the participant and provide the required eligibility information.

6.1.5 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 that occurs after the first vaccination is to be documented as an AE 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.

6.1.6 Safety Assessments

The following participant evaluations for safety will be performed.

6.1.6.1 Participant self-evaluations

Participants will record any post treatment reactions (local and systemic) and enter this information in a 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 ruler (Appendix B). The study staff will review the memory aid; the reported events will be assessed for clinical significance and recorded on the CRFs as appropriate. Although the memory aids may be

collected from participants and the conclusion of that study visit, they do not necessarily have to be collected as they are not diaries to be used 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 reminder diary 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.

6.1.6.2 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 a minimum of 30 minutes after EP, as well as at the follow up visits.

6.1.6.3 Vital Signs

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

6.1.6.4 Weight and Height

Weight (lb) and height (in) will be collected at specified visits.

6.1.6.5 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.

6.1.6.6 Laboratory Evaluations

At screening, Week 1, Week 6, and Week 14 blood samples will be taken to be tested for serum chemistry and hematology. Approximately 771 mL of blood will be drawn from each participant during the entire duration of the study.

<u>Hematology</u>
CBC: White blood cell (WBC) count and differential count, Red blood cell (RBC) count, Hemoglobin, Hematocrit, Platelet count;

<u>Serum Chemistry</u>
Serum electrolytes, blood urea nitrogen (BUN), creatinine (Cr), glucose, ALT, AST, CPK;

<u>Serology (screening only):</u>
Antibody to HIV (human immunodeficiency virus), Hepatitis B surface antigen (HBsAg), and Hepatitis C antibody (HCV Ab);

<u>Pregnancy Test</u>

For female participants of reproductive potential, a serum pregnancy test will be obtained at screening. A negative result for urine β-HCG (test must have a sensitivity of at least 25 mIU/mL) must be available prior to each administration of vaccine. If the β-HCG test is positive indicating that the participant is pregnant prior to completing the prescribed regimen then 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.

6.2 MERS-001 substudy

Participants will be asked to participate in a substudy for which leukapheresis may be performed at selected time points in lieu of collection of blood for immune analysis. Participants will be asked to provide consent for this trial; participation and consent does not affect participation in the main study. Up to 5 participants may be selected for participation. Leukapheresis will be performed as per WRAIR protocol in lieu of collection of blood for immune assessment at weeks 14 and 24. This procedure will take approximately 1-3 hours for each participant.

Participants will be asked to participate in the substudy based on an interim analysis which will be conducted in a subset of volunteers (10 per dose group) at the week 6 visit to determine the five highest immune responders (as measured by neutralization antibody titers). The five individuals will then be recruited for the leukapheresis substudy. The next five highest responders will be recruited if the first five decline.

6.3 Injection of Investigational Product followed by Electroporation

A total of 3 cohorts of participants will receive a 3-vaccination series.

- Group 1 (n=25) will receive 0.67mg GLS-5300 given by IM injection followed by EP with CELLECTRA®-5P
- Group 2 (n=25) will receive 2mg GLS-5300 given by IM injection followed by EP with CELLECTRA®-5P
- Group 3 (n=25) will receive 6 mg GLS-5300 given by IM injection followed by EP with CELLECTRA®-5P

Vaccinations will be delivered IM into the deltoid followed immediately by EP. If the deltoid is not a suitable location, the IM injection should be in the lateral quadriceps 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 the data file that is created should be sent to the Sponsor (GeneOne Life Science, Inc.) or designee by email.

Management of anxiety and pain due to EP procedure

Participants will be offered an analgesic (e.g. ibuprofen, acetaminophen, and EMLA cream) before and/or after injection/EP.

Participants who are allergic to or have contraindications 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.

Laboratory AEs will be assessed and graded. See Section 7.1.8 for details.

6.5 Assessment of Clinical Adverse Events

The injection site will be assessed by study personnel prior to and within a minimum of 30 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). They will also be advised to record local and systemic events for 6 days after vaccination in a Post Vaccination Diary (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 CRF.

6.6 Assessment of Injection Site Reactions

The Study Treatment procedure consists of insertion of the CELLECTRA® electroporation array needles (electrodes) through the skin and into the underlying muscle, and intramuscular of the study drug(s) 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, and 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. 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.)
- 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

6.7 Immunogenicity Assessments

6.7.1 Research Laboratory Assays

Currently, the correlate of immunity for MERS CoV is not entirely defined. It is clear that most neutralizing antibodies are directed against the surface Spike glycoprotein with particular immunologic focus at the receptor-binding domain in the S1 subunit. However, additional targets of humoral and cellular immunity are still to be defined. Thus immunogenicity assessments will not only measure known correlates (S neutralizing antibodies) but evaluate other potential mechanisms of immune response as well.

All blood specimens will be collected at the WRAIR CTC and processed by the US Military HIV Research Program (MHRP) in the laboratories of Dr. Mark Manak and Dr. Sheila Peel. Specimens for analysis of primary and secondary immunologic endpoints will be shipped to a specimen repository at the ACTG laboratory at the University of Pennsylvania. Additional specimens for exploratory endpoints will be retained at the MHRP. Specimens at the University of Pennsylvania

will be sent in batched shipments to the laboratory of Dr. Gary Kobinger, in Quebec, Canada where they will undergo analysis for primary and secondary endpoints. A division of labor for the laboratory assays is provided in the table below. All specimens for primary and secondary analysis will be destroyed after these analyses have been completed. Specimens for exploratory endpoint analysis will be retained at the MHRP indefinitely.

Dr. Gordon Joyce, Dr. Shelly Krebsand their laboratories will be isolating and characterizing monoclonal antibodies from vaccinees who had high virus neutralizing and antigen binding antibody responses. They will also screen serum from vaccinees to in competition binding studies to better characterize the epitopes to which vaccine-elicited antibodies are directed against. Dr. Joyce's and Dr. Krebs's laboratorieswill carry out structural studies on isolated antibodies to resolve, at an atomic scale, the antigen-antibody complexes and how their structural relationship correlates to functional responses.

Table 6.8 Primary and Secondary Immunology Assays

Assay	**ELISA**	**Neutralization**	**ELISpot**	**ICS**
Specimen	Frozen Serum	Frozen Serum	Frozen Cells	Frozen Cells
Measure	Binding antibody to vaccine antigens	Neutralizing activity against MERS CoV	Measures cytokine secretion after stimulation with Ag and T-cell epitope mapping	Phenotyping T cells and characterize the cytokines elicited by the vaccine
Collection Lab	WRAIR CTC	WRAIR CTC	WRAIR CTC	WRAIR CTC
Processing Lab	MHRP	MHRP	MHRP	MHRP
Storage Lab	UPENN	UPENN	UPENN	UPENN
Analysis Lab	Laval Institute-University of Quebec Wistar Institute	Laval Institute-University of Quebec	Wistar Institute	Wistar Institute

6.7.2 ELISA

Antibody Responses A standardized binding ELISA will be performed at the laboratory of Dr. Gary Kobinger to measure the anti-MERS S protein binding antibody responses. Briefly, 96-well enzyme immunoassay plates will be coated with purified recombinant human betacoronavirus spike protein from MERS CoV strain 2c EMC/2012 (Clade A) (Sino Biological, Inc.). 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 of a sample meets the above criteria.

A second ELISA platform will be used as a comparator on volunteer serum and will be performed in the laboratory of David Weiner at the Wistar Institute. Briefly, plates are coated with 1ug/ml of full length MERS spike protein. After blocking and washing, pre- and post-immunization sera from each individual is diluted to a single dilution and incubated at 37^{o}C for 1hr. Positive controls

consisting of vaccinated non-human primate sera and a negative control are included in each run and each sample is run in triplicate. After washing, an HRP-conjugated anti-human-IgG secondary antibody are incubated at room temperature for 1hr. After washing, signal is developed with SigmaFast OPD substrate, then stopped with 1N H_2SO_4. OD450 values are read on a Synergy 2 microplate reader. Positive post-immunization samples will be identified as those with an OD450 above the corresponding cut-off value determined from seronegative samples, and must be at least 2.5 SD above the OD450 of pre-immunization baseline samples and 2.5 SD above the background control wells. The cut-off value is set as the upper 95% confidence interval of the OD450 of pooled seronegative sera.

The serum samples tested on the above ELISA platform at the Wistar Insitute will also be evaluated for quantitative endpoint binding titers. In brief, OD450 values are read on a Synergy 2 microplate reader. An endpoint dilution for each individual is identified as the reciprocal of the highest dilution where the OD450 is above the corresponding cut-off value determined from seronegative samples, and must be at least 2.5 SD above the OD450 of pre-immunization baseline samples and 2.5 SD above the background control wells.

All samples tested by ELISA at the Wistar Institute will also be evaluated qualitatively for MERS CoV S protein binding by Western Blot. Positive post-immunization samples are identified by the presence of an antigen specific band of the expected 160 kDa size.

6.7.3 Neutralizing Antibodies

Neutralizing antibodies against MERS CoV will be performed in the laboratory of Dr. Gary Kobinger as previously described to determine TCID50 (**Muthumanni 2015 Sci Trans Med**). Sera from immunized participants will be mixed with 100 infectious particles MERS CoV EMC/2012 and overlaid onto a monolayer of Vero cells. The titer of neutralizing antibody is reported as the reciprocal of the highest dilution for which less than 50% of the cells show cytopathic effects. Pseudovirus assays will be used to determine the breadth of response as described previously (**Muthumanni 2015 Sci Transl Med**)

6.7.4 ELISpot

The number of antigen-specific IFN-γ secreting spot forming units (SFU) will be determined in the laboratory of Dr. David Weiner by IFN-γ ELISpot assays in response to stimulation with MERS CoV peptides using 15-mer peptides overlapping by 11 amino acids spanning the entire S protein (GenScript) as described (**Muthumanni 2015 Science**). Briefly, PBMCs will be thawed and plated at 200,000 cells/well. Cells will be incubated with MERS CoV peptides, incubated overnight, and IFN-γ release detected using standard procedures. The average number of SFU counted in media control wells will be subtracted from the average in individual MERS CoV peptide wells and then adjusted to $1x10^6$ PBMCs for each MERS CoV peptide pool.

6.7.5 Flow Cytometry

Flow cytometric assays will include an examination of the influence of vaccination on the ability of participant T cells to exhibit phenotypic markers associated with cytolytic potential after short-term stimulation by MERS CoV (hereafter referred to as “CTL Phenotyping”), the ability of participant 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 participant 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 participant samples are present.

(i) The assay for CTL Phenotyping will employ a 6-hour *in vitro* stimulation of unfractionated participant PBMCs using peptides spanning the S glycoprotein as described above along with a positive control (Staphylococcal enterotoxin B or a combination of phorbol 12-myristate 13-acetate and Ionomycin). The CTL Phenotyping assay will examine the following external cellular markers: CD3, CD4, CD8 (T-cell identification); CD45RO, CCR7 (memory subset identification); CD107a (marker of lytic degranulation). The CTL Phenotyping assay will additionally analyze the following intracellular markers: interferon gamma (IFN-γ, Th1 biasing cytokine), tumor necrosis factor alpha (TNF-α), Granzyme A, Granzyme B, and perforin (proteins involved in lytic degranulation and cytotoxic potential). The markers evaluated in this assay may change as new relevant data become available.

(ii) The Lytic Granule Loading assay will employ a 120-hour *in vitro* stimulation of unfractionated participant PMBCs using peptides spanning the MERS S protein, an irrelevant peptide control (OVA), and a positive control (concanavalin A). The Lytic Granule Loading assay will examine the following external cellular markers: CD3, CD4, CD8 (T cell identification); and CD137 (also known as 41BB, marker of T cell activation). The Lytic Granule Loading assay will additionally analyze the following intracellular markers: Granzyme A, Granzyme B, Granulysin, and Perforin (proteins involved in cytotoxic potential). The markers evaluated in this assay may change as new relevant data become available.

(iii) The Killing assay will employ 120-hour *in vitro* stimulation of unfractionated PBMC using peptides spanning the MERS S protein. Stimulated whole PBMC or $CD8^+$ T-cells isolated after 120-hours will be co-incubated for 60 minutes with target cells that have received a stain that differentiates them from participant PBMC/$CD8^+$ T-cells and have additionally been pulsed with a reagent which is activated upon cleavage of terminal caspases. Target cells are identified using a stain and analyzed for the presence of cleaved caspase activity in targets as a measure of functional cytolytic degranulation and killing. Employment of this assay may change pending readouts from the Lytic Granule Loading assay. The markers evaluated in this assay may change as new relevant data become available.

6.7.6 Leukapheresis

Leukapheresis provides a mechanism for collecting large numbers of leukocytes for better characterization of host immunity without drawing off other essential fractions of participants' blood (*i.e.* red blood cells, clotting factors). Leukapheresis is essentially a special type of plasmapheresis in which the component of plasma that are being drawn off from the blood for processing and storage are white blood cells with single nuclei circulating in the peripheral blood (peripheral blood mononuclear cells). Because these collected cells of interest are leukocytes, the procedure is termed leukapheresis. The purpose of collecting additional leukocytes is to better understand T and B cell immunity, through phenotyping DNA and RNA sequencing and transcriptomics, and array analysis, in response to vaccination. This additional analysis would be limited by small volume blood draws.

At the week 14 and 24 visits, in lieu of peripheral blood phlebotomy, a subset of volunteers (5) will have the option of undergoing apheresis to collect plasma and PBMCs and plasma. Leukocytes

and plasma will be obtained using automated apheresis techniques conducted by a qualified apheresis nurse/technician. During apheresis, whole blood is withdrawn through a catheter placed in an antecubital vein and channeled into a cell separator where cellular and plasma fractions are separated by centrifugation. The component to be harvested (*i.e.* leukocytes) will be directed into a collection bag while the erythrocytes, platelets, and plasma components not of interest (e.g. immunoglobulins, clotting factors, albumin) are returned to the donor. The return is accomplished through a second needle placed at another site, usually in the other antecubital vein. Approximately 120-150ml of peripheral blood mononuclear cells will be targeted for collection. Approximately 50 mL of red blood cell volume may be lost as residual loss in the machine during the procedure. Those volunteers who undergo leukapheresis will be exempted from the storage and additional testing blood draw scheduled at the same visit. Leukapheresis will not be performed on participants with platelet counts <150,000 or with hemoglobin < 12.0 mg/dL.

6.7.7 Antibody Characterization

As part of potential exploratory objectives, B lymphocytes specific for epitopes on the MERS CoV spike protein will be sorted by flow cytometry. Neutralizing and non-neutralizing antibodies will be screened and expressed. Resolution of antibody structures in complex with the S protein may be resolved. Non-neutralizing antibody functional assays may include antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), antibody-dependent cell-mediated viral inhibition (ADCVI), and viral capture.

6.7.8 Host Genetics

Host immune-genotyping will be performed as resources are made available. Investigators will perform targeted analyses of genetic polymorphisms within host genes that may influence immune response to vaccination. Targeted genes involved in humoral and cell-mediated immune responses will include Fcγ receptors, capable of binding diverse immunoglobulin isotypes; and the alleles comprising Class I HLA-A, -B, and -C loci, respectively. HLA typing procedures that will be used in this study have yet to be validated for clinical use but represent essential research tools for the analyses of adaptive immune responses to vaccination. HLA typing data will be unlinked from personal identifiers, and reported in aggregate for the populations studied.

6.8 Future Use of Specimens

Biological samples such as serum, plasma, PBMCs, whole blood, will be stored in a quality-controlled environment. Transport and storage of these biological samples will be handled according to GLP standards. Any future use of these biological samples that are not specified in the protocol will require additional IRB review and approval. Future use will be for any type of research. Biological samples such as serum, plasma, PBMCs, whole blood, remaining after all assays described in this protocol have been completed will be bar coded and archived using electronic specimen storage and tracking system. PBMCs will be stored at -125C or lower and plasma/sera will be stored at -70C or lower. Samples will be archived in the MHRP Specimen Processing Lab and Repository (SPL) in Rockville, Maryland and the University of Pennsylvania Specimen Processing Laboratory in Philadelphia Pennsylvania indefinitely. The Principal Investigator and the Sponsor and authorized regulatory bodies may have access to the data regarding the archived specimens.

Participants will not be considered eligible to participate unless they consent to have their specimens stored for future use. Although the results of this research, including donated specimens, may be patentable or have commercial value, Participants will have no legal or financial interest in any commercial development resulting from the research

6.9 Downloading of EP Data from CELLECTRA® Device

Within 48 hours following each Study Treatment, data will be downloaded from the EP device onto a USB Storage Device and the device forwarded by Courier or Express mail to the Sponsor (GeneOne Life Science, Inc.) or designee by email. Instructions on how to download the data and Sponsor contact information will be provided under a separate cover. Training will also be provided. Data contained in the download will be coded and unidentifiable. Data from the EP device will be downloaded to monitor and assess the function and any errors that may occur during use. Information will include impedance measurements and voltages generated and will be used for quality control and improvement of the device.

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 case report forms (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 had received polyclonal or monoclonal antibodies within 4 weeks of the first dose or 2 weeks before a subsequent dose of investigational product.

Participants must not receive a course of systemic corticosteroids (≥20 mg/day of prednisone or equivalent for 5 days) within 2 weeks before or after any dose of investigational product.

7. EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 Safety Parameters

The safety of GLS-5300 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 Clinical Investigator's Brochure (CIB) 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 7.1.9 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 off study drug period will be recorded as an AE

Unrelated AEs 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
- 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 in participant 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. Evaluation in a non-admitted status such as overnight or overday observation, emergency department or urgent care setting, or in an office setting 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 in participant hospitalization, or the development of drug dependency or drug abuse; development of malignancies;
- 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 out-patient 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 9.7.2.

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 Unanticipated Adverse Device Events

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

Reports of UADEs will be sent to the Sponsor within 10 working days of becoming aware of the event. UADEs will be reported to the WRAIR IRB as expedited reports, as noted in Section 7.4, below.

7.1.6 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.

7.1.7 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-5300), and the investigational CELLECTRA® device. An AE may also be assessed as not related to the investigational product. The Principal Investigator, with the assistance of the DoD Research Monitor as needed, 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.

Relationship to Investigational Product

The investigator must assign a relationship of each AE to the receipt of the investigational product. The investigator will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to receipt of the investigational product, and identification of possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by investigators to assess the relationship of an AE to study product administration. ONLY A PHYSICIAN CAN MAKE THIS DETERMINATION.

Not related: No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.

Unlikely: Likely unrelated to the investigational product. Likely to be related to factors other than investigational product, but cannot be ruled out with certainty.

Possible: An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology such as the subject's clinical status or underlying factors including other therapy.

Probable: There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the subject's clinical state or factors including other therapy.

Definite: An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

7.1.8 Abnormal Evaluation or Laboratory Value

Laboratory, physical exam, or EKG abnormalities are usually not recorded as AEs or SAEs. However, clinical, EKG or 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 7.1.6. If abnormalities are deemed by the principal investigator to not be clinically significant and stable then they will not be followed thereafter.

7.1.9 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-5300. The principal investigator will report this event to the study team and medical monitor, or its designee, and to the IRB. Site 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. Data and samples that were collected prior to a participant's withdrawal of consent will be included in the data analysis, unless otherwise specified by the participant. 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 until 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.

7.1.10 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 a minimum of 30 minutes after injection of GLS-5300 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 Reminder Diary. 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, during this 7 day period after each injection/EP procedure.

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 and DoD safety monitor will be responsible locally for safety..

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.

7.4 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
- Unexpected adverse device events: all

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.

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

7.5 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 DoD Research Monitor or Principal Investigator and the IRB/EC (if applicable):

- Three or more participants (per dose level) 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; This does not include participants who discontinue due to pain related to the EP Procedure.
- Any participant experiences an SAE (e.g., 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 assessed as related to Study Treatment.

Relatedness to Study Treatment will be considered Possibly, Probably, or Definitely, as determined by the PI.

*Immediate pain from IP will not be considered stopping criteria

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. DATA AND STATISTICAL CONSIDERATIONS

8.1 Data Management and Statistical Analysis

Data management will be carried out by WRAIR or one of its representatives. Data collection will be conducted on tablets or computers with daily upload to a central database. Access to the data collection software is limited by individual username and password. Data is stored in encrypted fashion on the local computer. After the data is uploaded to the central database it is deleted from the local tablet or computer.

Data obtained in the conduct of this study are housed in a secure database maintained by the WRAIR and/or its representative. All research data will be entered in a secure database with standardized quality assurance review procedures in accordance with Good Clinical Practices (GCP). Data will be entered into and maintained in a password-protected database. Data are accessible only to clinical, data management, Sponsor and information technology staff authorized to work on the protocol. The database will be located at the WRAIR CTC and/or its representative and protected by a firewall.

This data does not contain participant names or Social Security or other national identification number, but is referenced only by the study specific identification code. All subjects consented will be assigned a 7-digit participant identification number (PID). The first three digits are the protocol number (2274), followed by a 3-digit number which, will be assigned sequentially.

Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. However, ethical considerations or other events may result in the failure to obtain and record certain data, or to record data at the times specified. If this occurs, the events and, the reasons for the event must be clearly documented on the case report form for deviations and reported as described above.

Analysis files are created on a periodic basis and made available to the Principal Investigators, Associate Investigators (AIs) and Medical Monitor at the direction of the Principal Investigator. Other collaborators may be given access to these analysis files, or data gathered from them, at the direction of the Principal Investigator. Data may be made available as a listing, external file, or through a query program.

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

Analysis populations will include:

Per-protocol (PP) analysis to comprise participants who receive all vaccine doses, have no protocol deviations as defined below, and have primary endpoint data available. Participants in this sample will be grouped to treatment arms as assigned.

The modified intention to treat (mITT) analysis includes all participants who receive at least one Study Treatment. Participants in this ample will be grouped to treatment arms as assigned. 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 and for whom post-dose safety data are available. 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: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, stratified by treatment arm.

All data from enrolled participants will be analyzed according to the initial assignment regardless of how many vaccinations they received. The analysis is a modified intent-to-treat analysis in that individuals who are screened but not enrolled do not contribute data and hence are excluded.

8.3 Safety Analysis

8.3.1 Adverse events

All solicited and unsolicited AEs will be summarized by frequency per treatment arm. 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. Percentages, along with associated 95% Clopper-Pearson confidence intervals, will be based on the number of participants who were treated. 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.

The main summary of safety data will be based on events occurring within 28 days of administration of Study Treatment (as specified in Section 9.6.1).

8.3.2 Laboratory Data and Vital Signs

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. Proportions of responders will be presented with their corresponding 95% CI estimates, based on Clopper-Pearson methodology. Continuous variables (e.g., neutralizing and binding antibody titer) will be analyzed by assay within treatment arm with mean values and corresponding 95% CI estimates, based on t distributions.

8.5 Sample Size

No formal power analysis is applicable to this study, as descriptive statistics will be used to summarize the data.

With 25 participants per treatment arm, the study provides 95% confidence that the true incidence of SAEs is <20% if no SAEs are observed in the treatment arm. Overall, with 75 treated participants, the study provides 95% confidence that the true incidence of SAEs is <5%, if no SAEs are observed.

8.6 Missing Values

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

8.7 Interim analyses

An interim analysis will be carried out prior to the database lock but on monitored data according to a formal statistical analysis plan being developed by the Principal Investigator and the data

management and analysis team. In brief, this interim analysis will be carried out on all enrolled study participants and focus primarily on safety, reactogenicity, and immunogenicity data. The primary analysis will evaluate baseline demographics and adverse event outcomes in aggregate and across the three different dose groups. Both reactogenicity and longer term adverse event endpoints will be compared across groups. The primary immunogenicity endpoint to be evaluated will be a comparison, across the three dose groups, of endpoint antibody binding titers to the Spike protein and virus neutralization antibody titers at the Week 14 visit. In the interim analysis, there will also be comparisons carried out on neutralizing and binding antibody titer curves across all time points up to Week 14. Cellular immunologic outcomes will be assessed in the final analysis. No individual data will be released and these analyses will not impact the course of this study, though they may be published or used in the planning of future studies. Safety analyses may include enrollment and demographic information, medical history, concomitant medications, physical assessments, protocol adherence, clinical laboratory values, and solicited and unsolicited adverse events.

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 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 Medical Care for Research-Related Injury

All non-exempt research involving human subjects shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a participant is injured because of participation in this research and is a DoD healthcare beneficiary (eg, active duty in the military, military spouse or dependent), the participant is entitled to medical care for that injury within the DoD healthcare system, as long as the participant remains a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at military hospitals or clinics.

If a participant is injured because of participation in this research and is not a DoD healthcare beneficiary, the participant entitled to medical care for that injury at an military hospital or clinic; medical care charges for care at an military hospital or clinic will be waived. It cannot be determined in advance which military hospital or clinic will provide care. If the participant obtains care for research-related injuries outside of a military hospital or clinic, the participant or the participant's insurance will be responsible for medical expenses.

For all participants: Transportation to and from DoD hospitals or clinics will not be provided, except in emergencies or situations where a non-DoD health care beneficiary requires a military escort for access to said hospitals or clinics. No reimbursement is available if the participant incurs medical expenses to treat research-related injuries. No compensation is available for research-related injuries. The participant is not waiving any legal rights. The participant should contact the PI if the participant believes he or she has sustained a research-related injury. The participant should contact the PI for any questions.

9.3 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. The following clinical site monitoring tasks will be performed at all site.

9.4 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).

9.5 Records Retention

It is the Sponsor's responsibility to retain study essential documents 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.

9.6 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. Records for all clinical participants in this trial will be monitored. The following clinical site monitoring tasks will be performed at all site:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure compliance with all applicable requirements
- All clinical site monitoring visits will be documented
- Periodic site visits will be performed throughout the study
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
- Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB/EC policies
- Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor
- Remind the Investigator as necessary of the obligation to immediately report all serious adverse events (SAE) and provide subsequent follow-up report of the final outcome to the IRB/EC
- Inspect all Case Report Form (CRF) pages for completeness, logic, and internal consistency throughout the study
- Assure that the study facilities continue to be acceptable
- Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed
- Assure that test article accountability and reconciliation records are complete and accurate

- Assure that all participant specimens are being stored and forwarded properly for testing

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, representatives of the Department of Defense, 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.

9.7 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).

9.7.1 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 28 day period following each administration of Study Treatment. See next section for SAEs. All Adverse Events will be summarized at the time of continuing review.

9.7.2 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 WRAIR IRB per standard operating procedures within 24 hours.

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 7.1.7 (Serious Unexpected Suspected 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.

SAE TELEPHONE AND CONTACT INFORMATION:

MEDICAL MONITOR:	Joel Maslow, MD PhD MBA	MAILING ADDRESS:

PHONE:	(484) 965-9146	GeneOne Life Science, Inc.
SAFETY PHONE:	(215) 703-5843	1040 DeKalb Pike
FACSIMILE:	(484) 965-9146	Suite 200
EMAIL:	error@GeneOneLS-US.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 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). Additionally, reporting of all deaths will occur in real-time.

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.

9.7.3 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 9.7.2, should the Investigator become aware of an SAE (assessed as related to the investigational product following the guidelines in Section 7.1.7) that occurs within 28 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.

9.7.4 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 D must be completed and emailed to the Sponsor at error@GeneOneLS-US.com, and Inovio Pharmaceuticals at EPerror@inovio.com.

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.

9.10 Protocol Deviations

A protocol deviation is defined as an isolated occurrence involving a procedure that did not follow the study protocol. The timeline for reporting protocol deviations to the Division of Human Subjects Protection/ WRAIR IRB is determined by the categorization of the deviation: (1) emergent/significant or (2) non-emergent/minor. Unanticipated problems should be reported in the appropriate timeframe according to the seriousness of the event as a significant deviation or a minor deviation.

Emergent/significant deviations are departures from protocol that have a significant impact on the welfare or safety of a volunteer or on the integrity of the study data. Examples: providing the wrong lab result to a volunteer or failure to obtain a scheduled blood draw for multiple participants. Changes in protocol procedures may be initiated without prior IRB/ethical review committee approval,only in cases where the change (s) is /are necessary to eliminate an immediate apparent hazard.

Non-emergent/minor deviations are routine departures that typically involve a volunteer's failure to comply with the protocol. Examples include missing scheduled visits and failing to complete a required questionnaire. Minor deviations will be reported to the sponsor and the Division of

Human Subjects Protection/IRB in a summary report with the annual continuing review report. A cumulative deviation report will be submitted to the HSPB/WRAIR IRB with each protocol continuing review report or with the closeout report, whichever comes first.

All major protocol deviations that adversely affect the safety or rights of a participant or scientific integrity of the study, will be reported to the WRAIR HSPB within 48 hours and a written report should be submitted within 10 working days. The contact information for the WRAIR HSPB is as follows:

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940
Fax: 301-319-9961
E-mail: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

All protocol deviations occurring within the reporting period should be summarized in the continuing review reports that are submitted to the WRAIR HSPB.

10. Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, SSPs, SOPs, recruitment materials, etc) must be reviewed and approved prior to implementation. Any protocol amendment will be agreed upon and approved by the sponsor's representative prior to submission to the WRAIR IRB and prior to implementation of said change or modification. The informed consent document must be revised to concur with any amendment as appropriate and must be reviewed and approved with the amendment. Any subject already enrolled in the study will be informed about the revision and asked to sign the revised informed consent document if the modification directly affects the individual's participation in the study. A copy of the revised, signed, and dated informed consent document will be given to the subject. All original versions of the informed consent document will be retained in the protocol regulatory file.

Any modification that could potentially increase risk to subjects must be submitted to the ORP HRPO and the FDA for approval prior to implementation. Documentation that the WRAIR IRB reviewed and approved the modifications also will be submitted.

11. Volunteer Registry Data Sheets

It is the policy of the USAMRMC that data sheets are to be completed for all participants participating in research (Form 60-R, Volunteer Registry Data Sheet). The data sheets will be entered into this Command's Volunteer Registry Database. The information to be entered into this confidential data base includes the participant's name, address, and Social Security Number; study title; and dates of participation. The intent of this data base is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure research participants are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. The Volunteer Registry Database is a separate entity and is not linked to the study database.

12. 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).

All data collected during this study will be used to support this IND. All data may be published in the open medical or military literature with the identity of the participants protected. Anyone desiring to publish or present data obtained during the conduct of the study will conform to WRAIR, USAMRIID, and GeneOne Life Science Inc. policies and then forward the publication for review to the Commander, WRAIR or designee and usarmy.detrick.medcom-usamrmc.list.clearances@mail.mil prior to submission.

13. 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 Gonadotropin

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
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
PCR	Polymerase Chain Reaction
PBMC	Peripheral Blood Mononuclear Cells
S protein	MERS Spike protein
SARS	Severe Acute Respiratory Syndrome
SAE	Serious Adverse Event
PID	Participant Identification Number
SynCon®	Synthetic consensus
ULN	Upper Limit of Normal
WFI	Water for Injection
WOCBP	Women of Childbearing Potential
ZEBOV	Zaire Ebola virus

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15. APPENDICES

Appendix A: Participant Memory Aid

Appendix B: Toxicity Grading Scale

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

Appendix C: Collection and Shipping of Immunologic Samples

Serum and Whole Blood

1. **Specifics as to timing and amounts of serum and whole blood required at each blood draw is included in the Laboratory Manual**

2. **Shipping specifications are included the Laboratory Manual**

3. **Serum and whole blood not used for above analyses to be shipped overnight to:**

Lab Mailing
Department of Medicine
Division of Infectious Diseases
Specimen Processing Laboratory
3510 Hamilton Walk
319 Johnson Pavillion
Philadelphia, PA 19104-6073
Telephone: (215) 349-8092

The following information must be included on the label for each of the immunologic samples drawn to allow accurate processing and analysis of samples:

Study Number
Participant ID
ParticipantVisit name/time point
Visit Date

Appendix D: Reporting of Device Related Complaints

CELLECTRA® Error Reporting Form

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

Protocol#_____ **Site#** _____ **Subject ID** _____ **Week#**_____ **Visit Date**_____

DEVICE INFORMATION

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:
_____

Type and Location of Treatment/EP: ☐ **IM** ☐ **ID**
☐**R**ight Arm ☐**L**eft Arm
☐**L**eft Quadriceps ☐**R**ight Quadriceps
☐ Other Location, specify:_____

IM-5P ONLY, was the EP Guide used? ☐ YES ☐ NO

IM-5P ONLY: If EP Guide was used, please provide reason and include subject'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
☐ **IM-5P ONLY**: 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: _____ **Total # of attempts:** _____

<u>Impedance Test Error (IM-5P Only)</u>
Was the array fully inserted in subject's arm? ☐ YES ☐ NO
Were all attempts performed on the same day? ☐ YES ☐ NO
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 subject's arm? ☐ YES ☐ NO

Was the array inserted perpendicular to the subject's arm? ☐ 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.

Please provide any additional information below (continue on back if necessary):

Version 26Mar2015

Appendix E RESEARCH MONITOR

Research Monitor:
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Infectious Diseases Division Uniformed Services University of the Health Sciences Room A3060
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Fax: 301 295 3557

Alternate Research Monitor:
Marvin Joel Sklar LCDR, MC, USN
IDD/VRDD
Naval Medical Research Center
(301)319-7478
Marvin.j.sklar.mil@mail.mil

Research Monitor:

The Research monitor will function as an independent safety advocate for participants per AR70-25 and DoD Instruction 3216.02.

The Research Monitor is required to review all unanticipated problems involving risks to participants or others, serious adverse event (SAE) reports, and all participant deaths. The Research Monitor will provide an unbiased written report of all unanticipated problems involving risks to participants or others, and related SAEs and deaths, within 10 working days to the WRAIR IRB by email (Usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil), or by mail at the following address: Walter Reed Army Institute of Research, ATTN: Human Subjects Protection Branch, 503 Robert Grant Ave, Silver Spring, MD 20910. In addition to submission of the DOD Research Monitor reports to the WRAIR IRB, a copy of the same report will be sent to the Sponsor team. All Research Monitor reports for unrelated SAEs and deaths should be kept with the corresponding SAE reports at the study site. The WRAIR HSPB will submit copies of these reports to the USAMRMC ORP HRPO as per SOP UWZ-C-636. The DoD Research Monitor at a minimum must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The Monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. The DoD Research Monitor should review all initial reports for SAEs, unanticipated problems involving risks to participants or others, and all participant deaths in a timely manner, and provide their own independent report.

Appendix F WRAIR Reporting Requirements

Unanticipated Problems Involving Risks To Participants Or Others

Unanticipated problems involving risks to participants or others encompass a broader category of events than SAEs and may include issues such as problems with loss of control of participant data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (e.g., program personnel) must also be reported.

Unanticipated problems involving risks to participants or others are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigators brochure or informed consent document; and (b) the characteristics of the participant population;
- Related or possibly related to a participant's participation in the study; and
- Suggests that the study places participants or others at a greater risk of harm than was previously known or recognized.

Unanticipated problems involving risk to participants or others, should be promptly reported (48 hours) by telephone, email, or fax to the WRAIR HSPB. A complete written report should follow the initial notification within 10 working days. All unanticipated problems occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR HSPB. The contact information for the WRAIR HSPB is as follows:

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940
Fax: 301-319-9961
E-mail: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

Serious Adverse Events

All related serious adverse events (SAEs) and deaths should be reported to the WRAIR HSPB within 48 hours by telephone, email, or fax. A complete written report should follow the initial notification within 10 working days. All SAEs occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR HSPB. The contact information for the WRAIR HSPB is as follows:

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940
Fax: 301-319-9961
E-mail: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

Protocol Modifications/Amendments

All amendments/modifications to the protocol and supporting documents (informed consent, SSPs, SOPs, recruitment materials, etc.) must be reviewed by the WRAIR HSPB and a WRAIR Commander Authorization Approval issued prior to WRAIR participation on the amended/modified protocol.

Continuing Reviews and Closeout Report

The WRAIR Point of Contact will be responsible for preparing and submitting continuing review reports as per UWZ-C-618 and a closeout report as per WRAIR Policy 12-2. The WRAIR HSPB will review and acknowledge the reports in order for WRAIR personnel to continue their participation on the study. Once all study activities have been completed, to include data analysis, a closeout report will need to be submitted to the WRAIR HSPB to close the study.

Pending Inspections/Issuance of Reports

The knowledge of any pending compliance inspection/visit by the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the WRAIR HSPB.

APPENDIX G: Research Team Roles, Responsibilities and Study Team Listing

Principal Investigator

- Complies with protocol and all Federal and local regulations and policies and has ultimate responsibility for the conduct of the study and submission of the study report.
- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Supervises sub-investigators and protocol nurse coordinator
- Trains study staff
- Screens individuals and reviews all of the screening tests to determine eligibility of person to participate in the study. Investigator or designee makes final eligibility decision.
- Permits auditing, institutional monitoring (US Army Medical Materiel Development Activity), and inspection by the US Food and Drug Administration
- Assures adequate resources, time, and participant population to meet study requirements
- Provides medical care for adverse events
- Documents protocol deviations
- Reports all serious adverse events to the regulatory bodies (i.e., WRAIR IRB or UMB HRPP) and sponsor's representative (US Army Medical Materiel Development Activity)
- Delegates investigational product accountability and administration
- Evaluates AEs for diagnosis, relationship, and severity. Ensures documentation and safety reporting
- Ensures that he/she has sufficient time to conduct and complete the study
- Ensures he/she has adequate staff and appropriate facilities that are available for the duration of the study and to ensure that other studies do not divert essential participants or facilities away from the study at hand
- Submits an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and, where required, to relevant authorities
- Acquires the normal ranges for laboratory tests performed locally and, if required by local regulations, obtains the laboratory licenses or certifications
- Informs the IRB of any non-protocol specified laboratory testing that may occur on stored serum samples left over after protocol specified laboratory testing is completed (e.g., clinical tests performed in the evaluation of a participant's medical problem or additional specific immunologic evaluations as they become available)

- Prepares and maintains adequate case histories designed to record observations and other data pertinent to the study
- Conducts the study in compliance with the protocol and any amendments
- Cooperates with representatives of USAMMDA in monitoring the study and in resolution of queries about the data

Associate Investigators

- Complies with GCP and Belmont Principles
- Qualified by training, education and experience
- Assists principal investigator in conduct of study
- Assists in supervising study staff
- Reviews all of the screening tests to determine eligibility of individual to participate in the study. Investigator or designee makes final eligibility decision.
- Evaluates adverse events
- Screens individuals for protocol participation (physical examination and medical history)

Study Coordinator(s)

- Complies with GCP and Belmont Principles
- Qualified by training, education and experience, and holds a current, unrestricted nursing license
- Investigational vaccine accountability delegated to licensed nursing personnel. Reviews all of the screening tests
- Schedules follow-up appointments
- Collects information on adverse events
- Accurate and timely completion of case report forms
- Trains staff on protocols/protocol changes
- Documents protocol deviations.
- Stores IND product in temperature controlled and monitored units
- Signs out IND product to the investigational product preparer
- Verifies and records administration of investigational products to study participants

Other Study Staff

- Complies with GCP and Belmont Principles
- Qualified through training, education, and experience
- Recruits study participants with IRB approved materials
- Collects pre- and post-vaccination vital signs

- Contacts study participants to collect adverse event data
- Schedules follow-up appointments
- Follows-up on non-compliant study participants
- Ensures efficient clinic flow
- Performs participant specific training

Study Administrative Support

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Maintains essential clinical trial documents
- Hosts visits of auditors, monitors and inspectors
- Coordinates routing of all protocol activity
- Maintains and updates all study staff curriculum vitae and GCPs training certificates

IND Product Support

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Assists with vaccine accountability, storage and vial destruction
- Issues vaccine to clinic

Research Monitor/Ombudsman

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Acts as safety advocate for study participants
- Reviews all severe adverse events, serious adverse events, protocol violations, and annual reports
    - May perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis)
    - May discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research
    - Have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report

- Acts as an independent party and can be available to help answer any questions from an impartial standpoint

Data Manager

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Ensures the accuracy, quality, and integrity of the data
- Performs MedDRA and WHO coding
- Reviews electronic case report forms (eCRF) for consistency and clarity, generates and resolves data queries and provides analysis and feedback to PIs, protocol nurse coordinators, and protocol team
- Runs discrepancy report and quality control check reports and distributes to the protocol nurse coordinator to review for data accuracy against the eCRF
- Oversees the data entry process for the study
- Manages and maintains the database

Statistician

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Statistically analyzes the verified data according to the protocol, statistical analysis plan and any amendments in place
- Provides documentation of statistical findings to the principal investigator for incorporation into required reports

Clinical Monitors

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience
- Reviews study procedures, staff training and study documentation to ensure safety and accuracy in accordance with internal procedures

Regulated Studies Laboratory Staff and Research Investigators

- Complies with GCP, Good Laboratory Practices and Belmont Principles
- Qualified through training, education and experience
- Analyzes study participants sera for immune response to vaccines

Clinical Laboratory Staff

- Complies with GCP and Belmont Principles
- Qualified through training, education and experience

- Performs all phlebotomy for the study
- Processes biochemistry, hematology, urinalysis, hepatitis panel, human immunodeficiency virus, and β-hCG samples on study participants
- Performs urine pregnancy test

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Appendix H Compensation for Participation:

Participants will receive financial compensation at each visit for the time and effort involved in participating in this study. They will be compensated as follows:

- $25 for the screening visit (1 visit)
- $25 for the follow up phone calls (3)
- $300 per vaccination (3) plus $130 per scheduled Follow Up study visit (6)
- $220 bonus for completing all injections and scheduled visits through Week 60
- $150 for completing the last scheduled study visit
- If chosen for leukapheresis compensation for those visits will be $350 for those visits in addition to the $130 follow up

By regulation, active duty personnel and federal employees can be compensated only for visits in which blood draws occur, and then only $50 per visit, unless the visits occur during off-duty hours or when they are on leave. If the volunteer is off-duty or on leave, he or she will be paid the same as non-military/non-federal personnel.

The total amount of compensation may vary depending on the number of visits completed. Civilian (non-Federal employee) volunteers who undergo injection may receive approximately $2,000 in compensation. Participants who are on active duty or federal employees who are part of a vaccine group are expected to receive approximately $425 in compensation, unless they are on approved leave or participating outside of normal duty hours.

Clinical Study Documents

WRAIR-2274 Statistical Analysis Plan (135 pages)

GLS5300-MERS_WR
AIR2274_Statistical A

STATISTICAL ANALYSIS PLAN

for

Protocol: WRAIR #2274

Study Title:

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Version 1.0

DATE: 07 June 2017

Prepared and distributed by:
The Emmes Corporation
Rockville, Maryland USA

Study Title

Protocol Number Code:	Protocol: WRAIR #2274
Development Phase:	Phase I
Products:	GLS-5300
Form/Route:	GLS-5300 administered by intramuscular (IM) injection followed by electroporation (EP)
Indication Studied:	
Sponsor:	GeneOne Life Science, Inc. 1040 DeKalb Pike, Suite 200 Blue Bell, PA 19422
Principal Investigator:	Kayvon Modjarrad, MD, PhD
Medical Monitor:	Joel Maslow, MD PhD MBA FACP
Biostatistician:	Jeanine May, PhD
Clinical Trial Initiation Date:	16FEB2016
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	07JUN2017
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

SIGNATURE PAGE

SPONSOR: GeneOne Life Science Inc.

STUDY TITLE: Phase I, open-label, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5300, administered IM and followed by electroporation in healthy volunteers

PROTOCOL NUMBER: WRAIR #2274

Principal Investigator: Kayvon Modjarrad, MD, PhD

Signed: _____ Date: 15 June 2017

The Emmes Corporation: Jeanine May, PhD

Signed: Jeanine May Date: 16 JUNE 2017

Title: Statistician

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APPENDIX I - TABLE MOCK-UPS - *See separate document*

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APPENDIX III - DATA LISTING MOCK-UPS - *See separate document*

List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AICD	Automatic Implantable Cardioverter Defibrillator
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CPK	Creatine Phosphokinase
CoV	Coronavirus
Cr	Creatinine
CRF	Case Report Forms
CRO	Clinical Research Organization
CSR	Clinical Study Report
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Intracellular cytokine staining
IM	Intramuscular
IND	Investigational New Drug Application
INF-γ	Interferon Gamma
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MERS	Middle East respiratory syndrome
MERS CoV	Middle East respiratory syndrome Coronavirus

LIST OF ABBREVIATIONS *(continued)*

mITT	Modified Intention-to-treat
PBMC	Peripheral Blood Mononuclear Cells
S protein	MERS Spike protein
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SAE	Serious Adverse Event
SFU	Spot Forming Units
PID	Participant Identification Number
PP	Per Protocol

1 PREFACE

The Statistical Analysis Plan (SAP) for "Phase I, open-label, dose-ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5300, administered intramuscularly (IM) and followed by electroporation (EP) in healthy volunteers" describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for immunogenicity and safety outcomes, and (4) a list of proposed tables and figures. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments

2 INTRODUCTION

This is a Phase I open-label dose ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5300. GLS-5300 contains plasmid pGX9101 that encodes for a consensus sequence of the spike (S) protein of the Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV). Currently there are no approved treatments or prophylactic vaccines for MERS CoV, although a number of products are poised to be advanced into human trials.

Based on prior experience with treatment of HIV infection, a dose of 2 mg of GLS-5300 corresponds to a vaccine dose of approximately 30 µg/kg. Preclinical studies in rhesus macaques assessed high (2 mg/vaccination) and low (0.5 mg/vaccination) doses of pGX9001. Robust 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 (**Bagarazzi 2012 Sci Transl Med, Trimble 2015 Lancet**). Preliminary analysis of the human response to VGX-6150 for the treatment of Hepatitis C shows minimal immunologic benefit since when the dose is increased from 2 mg to 6 mg, there is only a small increase in immune response. Notably, both the HPV product and VGX-6150 are based on the same expression system used to construct GLS-5300. Assessment of antibody and

T-cell responses following each vaccination will determine the effectiveness of vaccination. Follow-up will determine the longevity of immunogenicity.

2.1 Purpose of the Analyses

These analyses will assess the safety, tolerability, and immunogenicity of GLS-5300 and will be included in the clinical study report. Note, not all analyses for endpoints included in the protocol are detailed in this plan. See Section 8.2 for details regarding which exploratory endpoint analyses are included in this SAP. Furthermore, the interim safety monitoring assessment which is required before enrollment to the next dose level that is conducted throughout the study is not included in this SAP. In addition, the analysis for the leukapheresis substudy is also not included in this SAP. The interim analyses assessing safety and immunogenicity up to the Week 14 visit is also included in this SAP.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

Primary Objectives

- Evaluate the safety and tolerability of GLS-5300 when administered by IM injection followed by EP in healthy adult participants

Secondary Objectives

- Evaluate the cellular and humoral response of GLS-5300 when delivered IM followed by EP
- Evaluate the dose response for cellular and humoral reactivity of GLS-5300 when delivered IM followed by EP

Exploratory Objectives

- Explore whether end point antibody titers to MERS CoV S protein are dose related
- Explore the time to onset of antibody production and longevity of serologic response
- Explore if increasing dose levels of GLS-5300 more rapidly induce cellular immunity
- Explore the time to onset of T cell responsiveness and longevity of cell mediated immunity
- Evaluate the kinetics of antigen expression in the peripheral blood compartment
- Evaluate host genetics as a potential predictor of vaccine immune response
- Evaluate additional cellular immune responses
- Neutralizing and non-neutralizing antibody repertoire analysis
- Explore innate immune responses to the MERS CoV S protein
- Assess cross-neutralization activity against other human coronaviruses

3.2 Endpoints

Primary Safety Endpoints

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

Secondary Immunologic Endpoints

- Quantitative binding antibody titers to the full length MERS CoV Spike (S) glycoprotein
- Qualitative and quantitative levels of neutralizing antibodies against MERS CoV
- Antigen specific cellular immune responses to MERS CoV as determined by:
  - Interferon-gamma (IFN-γ) ELISpot
  - Intracellular cytokine staining (ICS) (cytotoxic T lymphocyte phenotype, lytic granule loading, granzyme B killing of target cells)

Exploratory Endpoints

- Comparison of S binding antibody and MERS CoV neutralizing antibody titers
- Kinetics and durability of S binding antibody and MERS CoV neutralizing antibody titers
- Comparison of IFN-γ ELISpot, and ICS responses across different vaccine doses
- Kinetics and durability of IFN-γ ELISpot, and ICS responses across different vaccine doses
- Expression of the full length MERS CoV S protein in the peripheral blood over time
- Host immune-genotyping as resources are available
- Epitope mapping of CD4+ and CD8+ T lymphocyte responses
- Immunophenotyping and functional characterization of cellular subsets of interest, including natural killer (NK) cells
- Isolate, express and characterize monoclonal antibodies against the MERS CoV S protein and assess their neutralizing and non-neutralizing functional activity

3.3 Study Definitions and Derived Variables

The Study Treatment procedure consists of insertion of the CELLECTRA® electroporation array needles (electrodes) through the skin and into the underlying muscle, and intramuscular of the study vaccine followed by delivery of the electroporation pulses. This procedure is broadly described as administration because it involves more than the injection of a drug. For purposes of defining the analysis populations and compliance measures, treatment administration for this protocol includes both the vaccine dose (IM injection) as well as the following EP administration. A successful treatment administration requires that the vaccine dose and the EP were administered successfully.

Immunologic Endpoints:

The endpoint pertaining to the quantitative binding antibody titers to the MERS CoV Spike (S) glycoprotein includes the ELISA antibody responses. ELISA antibody response results will be presented as end-point titer. The positive response for the ELISA antibody response will be defined using a specific threshold. Titer responses greater than X dilution will be defined as having a positive response. The lowest dilution (1:100) to be tested will be used as the lower limit of detection. Observations below the lower limit of detection will be imputed to 1/2 the lowest observable value (i.e. 50).

The endpoint pertaining to the qualitative and quantitative levels of neutralizing antibodies against MERS CoV will be defined using the titer of the neutralizing antibody which will be reported as the reciprocal of the highest dilution for which less than 50% of the cells show cytopathic effects. The lowest dilution (1:10) to be tested will be used as the lower limit of detection. Observations below the lower limit of detection will be imputed to 1/2 the lowest observable value (i.e., 5). The positive response for the neutralizing antibody titer will be defined using a specific threshold. Neutralizing antibody titer responses greater than X dilution will be defined as having a positive response.

One of the endpoints pertaining to the antigen-specific cellular immune responses to MERS CoV is determined by the interferon-gamma (IFN-γ) ELISpot. The IFN-γ ELISpot will be derived by subtracting the average number of spot forming units (SFU) counted in media control wells and the average in individual MERS CoV peptide wells and then adjusted to $1x10^6$ PBMCs for each MERS CoV peptide pool. To obtain these values, PBMCs will be thawed and plated at 200,000 cells/well. Cells will be incubated with MERS CoV peptides, incubated overnight, and IFN-γ release detected using standard procedures. If the media control wells value is greater than the MERS CoV peptide wells value, an imputed value of half of the smallest positive adjusted value is used for the analysis. For values of the MERS CoV peptide wells that are tabulated as too numerous to count (TNTC), the largest MERS CoV peptide well value is imputed.

The other endpoint pertaining to the antigen-specific cellular immune responses to MERS CoV is determined by the ICS (cytotoxic T lymphocyte phenotype, lytic granule loading, granzyme B killing of target cells).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase I open-label dose ranging study to evaluate the safety, tolerability, and immunogenicity of GLS-5300. GLS-5300 contains plasmid pGX9101 that encodes for a consensus sequence of the spike (S) protein of the Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV). Currently there are no approved treatments or prophylactic vaccines for MERS CoV, although a number of products are poised to be advanced into human trials.

This clinical trial will evaluate whether GLS-5300 administered via intramuscular (IM) injection and followed by electroporation (EP is able to generate protective immunity against MERS CoV and whether

there is an immune reactivity follows a pattern of vaccine dose response. Injections will be given in the deltoid or lateral quadriceps muscle followed immediately by EP with the CELLECTRA®-5P device.

Healthy adult volunteers, male and female, military and civilian, will be recruited by non-coercive means through WRAIR CTC according to applicable U.S. Army regulations. A total of 75 participants aged 18 to 50 divided into 3 groups will be enrolled for this study and followed for 60 weeks.

> Group I Participants (n=25) assigned to receive GLS-5300 will be administered 0.67 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.
>
> Group II Participants (n=25) assigned to receive GLS-5300 will be administered 2 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.
>
> Group III Participants (n=25) assigned to receive GLS-5300 will be administered 6 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Participants will be enrolled at the lowest dose (Group I) with continuous enrollment through the 1st week of enrollment. At the start of week 2, clinical laboratory data for the first five participants from Group I will be reviewed as part of the safety review. Once safety labs have been reviewed and cleared for the first five participants in Group 1, the second dose level will be opened. The next five participants who have met eligibility criteria will then be enrolled into Group II. Then enrollment for Group I will be completed. Once group 1 has completed enrollment of 25 participants, then Group 2 will be populated sequentially. When the first five participants in Group 2 have reached one week post vaccination then safety labs will be reviewed as above. Once this safety assessment is cleared, then Group III will be opened for enrollment of the next five participants. Then enrollment will be completed for Group 2 and afterwards Group 3.

Review of safety labs will be conducted by a safety monitoring committee consisting of the study PI, medical monitor and the DoD Research Monitor. Safety reviews can be by teleconference or electronically such as email. Enrollment to the next dose level will require approval of all review members. The IRB will be provided a summary statement of each safety review.

Safety assessments: All participants will be monitored for

- Local and systemic adverse events (AE's) at each study visit.
- Laboratory related AE's following the first, second, and third vaccination.
- Injection site reactions for up to one month following each vaccination.

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

- Enrollment (pre 1st dose of vaccine)
- Week 1 Week 2 or week 3 post 1st vaccination)

- Week 4 post 1st vaccination
- Weeks 6, 12, and 14 (to include time points that correspond to 2 weeks post 2nd and 3rd vaccination)
- 3, 6, 12 months after the 3rd vaccination

4.2 Selection of Study Population

Inclusion Criteria

a. Age 18-50 years; military, civilian, male and female.

b. Able to provide consent to participate and having signed an Informed Consent Form.

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

d. Women of child-bearing potential agree to remain sexually abstinent, 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 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 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;

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

i. 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 corticosteroids at a dose less than 20 mg/day).

j. Willing to allow storage and future use of samples for MERS CoV related research

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 MERS CoV except if participant is verified to have received placebo;

c. Previous infection with MERS CoV as assessed by self report and solicited exposure history;

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

e. A BMI greater than or equal to 35;

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

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

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

i. History of 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;

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

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

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

m. Chronic liver disease or cirrhosis;

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

o. Current or anticipated concomitant immunosuppressive therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or corticosteroids at a dose less than 20 mg/day);

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

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

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

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

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

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

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

w. 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

x. Tattoos covering the injection site area

y. 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.

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. The investigator will make every effort to have all scheduled immune assessment blood samples collected. Unless a participant refuses to continue participation, all follow-up visits and procedures should be completed as indicated, following the last dose whether or not the participant has completed all doses.

All data collected up to the time of withdrawal, including any final evaluation and lab results that may be pending at the time of withdrawal will be reported. Likewise, any specimens collected up to the time of withdrawal, including any blood collected for storage and use in future research, will be kept and utilized as outlined in the protocol and consent form. The study termination eCRF will be completed, with the reason for withdrawal specified.

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 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.

Incarceration: Participation of prisoners is not planned and any volunteer will be suspended from study visits while incarcerated. The IRB will be notified of the period of incarceration. If possible, site teams will coordinate with correctional authorities to ensure that relevant medical information for the safety and care of the patient is communicated promptly.

Other: The participant was terminated for a reason other than those listed above, such as termination of study by the Sponsor.

4.3 Treatments

GLS-5300, the investigational product to be used in this study contains a DNA plasmid encoding for the S protein of MERS CoV. Each product will be provided at a concentration of approximately 6 mg/ml to be diluted and mixed on site to the needed dose such that a standard 1 ml volume will be administered to all study participants. Because of this the concentration of the final plasmid will vary based on the dosage administered. GLS-5300 is a solution in sterile water for injection (sWFI). Therefore, sWFI will be used for dilution of the biologic products during clinical site formulation. The vaccine product will be shipped from manufacturer at VGXI in Houston, Texas on dry ice. The lot number for the vaccine to be used is GLS-5300 15L019.

A total of 75 participants divided into 3 groups will be enrolled for this study. It is estimated that approximately 225 participants will need to be screened to fill the desired enrollment of 75 participants.

Group I Participants (n=25) assigned to receive GLS-5300 will be administered 0.67 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Group II Participants (n=25) assigned to receive GLS-5300 will be administered 2 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

Group III Participants (n=25) assigned to receive GLS-5300 will be administered 6 mg DNA/dose given as a 1 ml IM injection followed by EP with the CELLECTRA®-5P device. Participants will receive a 3-dose series with immunizations at 0, 4 and 12 weeks.

4.3.1 Method of Assigning Subjects to Treatment Groups (Randomization)

Participants will be enrolled at the lowest dose (Group I) with continuous enrollment through the 1st week of enrollment. At the start of week 2, clinical laboratory data for the first five participants from Group I will be reviewed as part of the safety review. Once safety labs have been reviewed and cleared for the first five participants in Group 1, the second dose level will be opened. The next five participants who have met eligibility criteria will then be enrolled into Group II. Then enrollment for Group I will be completed. Once group 1 has completed enrollment of 25 participants, then Group 2 will be populated sequentially. When the first five participants in Group 2 have reached one week post vaccination then safety labs will be reviewed as above. Once this safety assessment is cleared, then Group III will be opened for enrollment of the next five participants. Then enrollment will be completed for Group 2 and afterwards Group 3.

4.4 Immunogenicity and Safety Variables

Safety Assessments:

Participant self-evaluations are used to record any post treatment reactions (local and systemic). Participants enter the information in a post-vaccination memory aid on the evening of each dose and for 7 days post each dose. Any memory aid entry determined to meet the criteria for a Grade 1 or higher adverse event will be documented as an adverse event.

Additional safety assessments include unsolicited adverse events and laboratory safety assessments. Unsolicited adverse events will be collected for the duration of the study. Details for these events will be collected either during on-site visits or via telephone. Laboratory safety assessments are collected at Screening, Week 1, Week 6 and Week 14. If a laboratory safety assessment is clinically significant, then an adverse event will be entered.

Immunologic Assessments:

Currently, the correlate of immunity for MERS CoV is not defined. It is clear that most neutralizing antibodies are directed against the surface Spike glycoprotein with particular immunologic focus at the receptor-binding domain in the S1 subunit. However, additional targets of humoral and cellular immunity are still to be defined. Thus immunogenicity assessments will not only measure known correlates (S neutralizing antibodies) but evaluate other potential mechanisms of immune response as well.

All blood specimens will be collected at the WRAIR CTC and processed by the US Military HIV Research Program (MHRP) in the laboratories of Dr. Mark Manak and Dr. Sheila Peel. Specimens for analysis of primary and secondary immunologic endpoints will be shipped to a specimen repository at the ACTG laboratory at the University of Pennsylvania. Additional specimens for exploratory endpoints will be retained at the MHRP. Serum specimens at the University of Pennsylvania will be sent in batched shipments to the laboratory of Dr. Gary Kobinger at the National Microbiology Laboratory (NML) in Winnipeg, Canada where they will undergo ELISA and Neutralization analysis for secondary immunogenicity endpoints. PBMC specimens at the University of Pennsylvania will be sent in batched shipments to the laboratory of Dr. David Weiner at the Wistar Institute in Philadelphia, PA, USA where they will undergo ELISpot and ICS analysis for secondary immunogenicity endpoints. A division of labor for the laboratory assays is provided in the table below. Specimens for exploratory endpoint analysis will be retained at the UPENN or MHRP repositories for a period of 10 years.

Table 4.4.2 Primary and Secondary Immunology Assays

Assay	**ELISA**	**Neutralization**	**ELISpot**	**ICS**
Specimen	Frozen Serum	Frozen Serum	Frozen Cells	Frozen Cells
Measure	Binding antibody to vaccine antigens	Neutralizing activity against MERS CoV	Measures cytokine secretion after stimulation with Ag and T-cell epitope mapping	Phenotyping T cells and characterize the cytokines elicited by the vaccine
Collection Lab	WRAIR CTC	WRAIR CTC	WRAIR CTC	WRAIR CTC
Processing Lab	MHRP	MHRP	MHRP	MHRP
Storage Lab	UPENN	UPENN	UPENN	UPENN
Analysis Lab	NML	NML	WISTAR	WISTAR

Whole blood in ACD (yellow top) tubes for PBMC isolation and serum will be collected on all participants at Baseline (Day 0), and Weeks 1, 2 or 3, 4, 6, 12, 14, 24, 36, and 60.

5 SAMPLE SIZE CONSIDERATIONS

No formal power analysis is applicable to this study, as descriptive statistics will be used to summarize the data. With 25 participants per treatment arm, the study provides 95% confidence that the true incidence of SAEs is <20% if no SAEs are observed in the treatment arm. Overall, with 75 treated participants, the study provides 95% confidence that the true incidence of SAEs is <5%, if no SAEs are observed.

6 GENERAL STATISTICAL CONSIDERATIONS

6.1 General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by dose level and subject, and when appropriate by visit number

within subject. All summary tables will be structured with a column for each dose level in the order (Group 1, 2, 3) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2 Timing of Analyses

The interim analyses will be performed after the immunology assays for samples up to the Week 14 visits are completed. The final analysis described in this SAP will be performed after the main immunology assays are completed. The main immunology assays are defined in Section 4.4.

6.3 Analysis Populations

A tabular listing of all subjects, visits, and observations excluded from the various analysis populations will be provided in the CSR (Appendix 16.2.3).

6.3.1 Modified Intention-to-Treat (mITT) Population

The modified intention to treat (mITT) analysis includes all participants who receive at least one study treatment administration (IM injection with EP). Participants in this sample will be grouped based dose assigned. Analyses on the mITT sample will be considered supportive of the corresponding PP analyses.

6.3.2 Per Protocol (PP) Population

Per-protocol (PP) analysis to comprise participants who receive all treatment administrations, have no major protocol deviations, and have primary endpoint data available. A participant will be defined as having primary endpoint data available if they have not terminated from the protocol earlier than the active treatment administration period. The active treatment administration period will be defined as prior to Week 14 as this would ensure participants did not terminate prior to the third treatment administration. Participants in this sample will be grouped for purposes of the tables, figures and listings based on dose assigned.

6.3.3 Safety Population

The safety analysis set includes all participants who receive at least one study treatment and for whom post-dose safety data are available. A participant will be considered to have post-dose safety data available if he/she attends at least one post treatment study visit. Participants will be analyzed according to the dose of GLS-5300 they received.

6.4 Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5 Missing Data

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

6.6 Interim Analyses and Data Monitoring

An interim analysis of immunogenicity data will take place after week 14 visits have been completed. This will not be used to make any decisions concerning the conduct of the trial. Since this early look at the data is not intended to impact the conduct of the trial, alpha-spending adjustments are not needed to control the overall Type I error. Tables, figures and listings included in the interim analyses are indicated with an A superscript in the Appendix and will only include data up to and including the Week 14 visit.

6.7 Multiple Comparisons/Multiplicity

In general, descriptive statistics will be used to summarize the data pertaining to the non-immunological endpoints with the exception of some of the safety data being analyzed using Fisher's exact tests and t-tests as noted in Section 9. Immunological endpoints will be analyzed as denoted in Section 8. No adjustments for multiple testing are planned.

7 STUDY SUBJECTS

7.1 Subject Disposition

Table 14.1.1 (Appendix I), will present a summary of the reasons that subjects were screened but not enrolled. The composition of analysis populations, including reasons for subject exclusion, by group, is presented in Table 14.1.2 (Appendix I).

The disposition of subjects in the study will be tabulated by group (Table 14.1.3, Appendix I). The table shows the total number of subjects screened, enrolled, receiving at least 1 dose, receiving at least 2 doses, discontinued dosing and the number completing the study. A listing of subjects who discontinued dosing and the reason will be included in Listing 16.2.1 (Appendix III).

A flowchart showing the disposition of study subjects, adapted from the Consort Statement will be included (Figure 14.1.1, Appendix II). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by group.

7.2 Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 14.1.4). All subject-specific protocol deviations and non subject-specific protocol deviations will be included in Appendix III as data listings (Listings 16.2.2.1 and 16.2.2.2, respectively).

Subjects excluded from the analysis populations and reasons are provided in Listing 16.2.3.

8 IMMUNOGENICITY EVALUATION

All immunogenicity variables will be listed by group, subject and visit. Data will be summarized by group.

The primary objective and endpoints are summarized in Section 9 since they pertain to the safety and tolerability of GLS-5300.

8.1 Secondary Endpoint Analyses

The secondary objectives of the study include evaluating the cellular and humoral response of GLS-5300 when delivered IM followed by EP as well as evaluating the dose response for cellular and humoral reactivity of GLS-5300 when delivered IM followed by EP.

Immunologic Endpoint: ELISA

Tables 14.2.1.1 and 14.2.1.4 summarize the geometric mean of the ELISA titer response with 95% confidence intervals by study day and group for the mITT and the PP populations respectively. Tables 14.2.1.2 and 14.2.1.5 summarize the proportions of positive response with 95% confidence intervals by study day and group for the mITT and the PP populations respectively. Table 14.2.1.3 displays p-values from Fisher's exact tests comparing proportions of positive response between treatment group at multiple time points.

Listing 16.2.6.1 includes the individual immunogenicity titer response data which includes the ELISA and neutralizing antibody titer responses. Figure 14.2.1.1 illustrates the reverse cumulative distribution (Reed, Meade and Steinhoff, 1995) of ELISA by study day and group and will be used to evaluate the dose response. In addition, Figure 14.2.1.2 displays the ELISA geometric mean with 95% confidence intervals over time by group.

To compare the ELISA titer responses across the three groups by study day to determine whether the responses differ by dose will be analyzed using the Kruskal-Wallis test. This test is a non-parametric test and is an extension to more than two groups of the Wilcoxon rank sum test for two groups. Since sample sizes are not large enough to assume asymptotic normality and the analyses endpoints are likely skewed (titer responses), non-parametric tests are employed as they do not require distributional assumptions. The null hypothesis of the Kruskal-Wallis test is that the three different dose groups have the same distribution of the ELISA responses for a particular study visit. If a significant difference is determined using the Kruskal-Wallis test, pairwise comparisons will be evaluated.

Immunologic Endpoint: Neutralizing antibodies

Table 14.2.2.1 summarizes the geometric mean of the neutralizing antibody (NT50) response with 95% confidence intervals by study day and group for the mITT population. Table 14.2.2.2 summarizes the NT50 positive response with 95% confidence intervals by study day and group for the mITT population. Figure 14.2.2.1 illustrates the reverse cumulative distribution of NT50 by study day and group and will be used to evaluate the dose response. In addition, Figure 14.2.2.2 displays the NT50 geometric mean with

95% confidence intervals over time by group. Tables 14.2.2.3 and 14.2.2.4 summarize the results for the PP population.

Identical statistical analyses to compare the neutralizing antibody titer response across the three groups by study day as noted for the ELISA endpoint will be used.

Immunologic Endpoint: IFN-γ ELISpot

Figure 14.2.3 summarizes the distributions of the IFN-γ ELISpot via box plots by group and study day. Tables 14.2.3.1 and 14.2.3.2 summarize the distributions if IFN-γ values by group and study day, reported in Spot Forming Units per million cells (SFU/10^6 cells), for the mITT population. Tables 14.2.3.3 and 14.2.3.4 present analogous summaries for the PP population. Results of t-tests comparing mean IFN-γ values between groups are displayed in table 14.2.3.5.

Immunologic Endpoint: ICS Figure 14.2.4 displays the ICS geometric mean by group (with 95% confidence intervals) over time. Figure 14.2.5 summarizes the distributions of the ICS via box plots by group and study day. Results of t-tests comparing mean ICS values between groups are displayed in table 14.2.3.6.

8.2 Exploratory Endpoint Analyses

As described above, immunological endpoints will be summarized graphically to display trends over time for different dose groups. Comparison of these trends will allow for qualitative assessment of exploratory endpoints, including:

- Comparison of S binding antibody and MERS CoV neutralizing antibody titers
- Kinetics and durability of S binding antibody and MERS CoV neutralizing antibody titers
- Comparison of IFN-γ ELISpot, and ICS responses across different vaccine doses
- Kinetics and durability of IFN-γ ELISpot, and ICS responses across different vaccine doses

9 SAFETY EVALUATION

The primary objective of the study is to evaluate the safety and tolerability of GLS-5300 when administered by IM injection followed by EP in healthy adult participants. Safety assessments including the primary safety endpoints are defined in the following subsections. All safety outcomes will be assessed by dose group ordered from lowest to highest (0.67 mg/dose, 2 mg/dose, 6 mg/dose) and overall which includes all dose groups.

9.1 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: mean standard deviation, minimum, median, and maximum values for continuous variables, and percentages for categorical variables, stratified by treatment group.

The analysis is a modified intent-to-treat analysis in that individuals who are screened but not enrolled do not contribute data and hence are excluded.

Summaries of age, baseline temperature, baseline respiration rate, baseline blood pressure, baseline heart rate, gender, ethnicity, and race will be presented by group (Tables 14.1.5.1-14.1.5.2, Appendix I). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual subject listings (Appendix III) will be presented for all demographics (Listing 16.2.4.1); pre-existing medical conditions (Listing 16.2.4.2); vital signs and oral temperature (Listing 16.2.9.1); and concomitant medications (Listing 16.2.10).

9.1.1 Concurrent Illnesses and Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA coded using MedDRA dictionary version 18.1 or higher. Summaries of subjects' pre-existing medical conditions will be presented by group (Table 14.1.6, Appendix I).

Individual subject listings will be presented for all medical conditions (Listing 16.2.4.2, Appendix III).

9.2 Measurements of Treatment Compliance

All subjects were to receive three treatment administrations in the clinic. The number of treatment administrations to subjects will be presented by treatment group site as part of the subject disposition table (Table 14.1.3, Appendix I). In addition, the listing of treatment administration compliance data is provided in Listing 16.2.5, Appendix III, including whether reflux/leakage occurred at the injection site during administration.

9.3 Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total number of subjects. All adverse events reported will be included in the summaries and analyses.

9.3.1 Solicited Events and Symptoms

One of the primary endpoints of interest is the administration (injection) site reactions. These local solicited events pertaining to administration (injection) site reactions include tenderness, pruritus, erythema, induration/swelling and bruising. The systemic solicited events include fever, malaise/fatigue, myalgia, headache, arthalgia and nausea. Both local and systemic events are recorded in the tables summarized.

The proportion of subjects reporting at least one solicited adverse event will be summarized for each solicited adverse event, any systemic symptom, any local symptom, and any symptoms. The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) will be presented and a Fisher's exact test will be performed to test for the difference in the proportion of subjects reporting a solicited adverse event (Table 14.3.1.1, Appendix I). Table 14.3.1.2 summarizes the number and percentage of subjects experiencing solicited events by symptom, maximum severity, dose and group.

Solicited adverse events by subject will be presented in Listing 16.2.7.1, Appendix III.

9.3.2 Unsolicited Adverse Events

Unsolicited AEs will be summarized for the 28 day period following each administration of Study Treatment. The proportion of subjects reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each vaccination and over all vaccinations. Denominators for percentages are the number of subjects who received the vaccination being summarized. A 95% CI will be presented along with a Fisher's exact test comparing the treatment groups and testing the difference in the proportion of subjects reporting an unsolicited adverse event for each MedDRA system organ class and preferred term.

Adverse events by subject will be presented in Listing 16.2.7.2, Appendix III.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, dose and group:

- Subject level summary (Tables 14.3.1.3, Appendix I)
- Subject level summary of severity and relationship to study product (Tables 14.3.1.4, Appendix I);
- Subject listing of non-serious adverse events of moderate or greater severity (Table 14.3.2.2, Appendix I);

The frequency and incidence of non-serious adverse events are displayed in bar charts by severity and MedDRA system organ class for each group (Figure 14.3.1.1 and 14.3.1.2, Appendix II, respectively). The overall frequency and incidence of adverse events by severity and group is displayed in Figures 14.3.1.3 and 14.3.1.4 respectively. The frequency and incidence of non-serious adverse events are displayed in bar charts by relationship to treatment and MedDRA system organ class for each group (Figure 14.3.1.5 and 14.3.1.6, Appendix II, respectively). The overall frequency and incidence of adverse events by relationship to treatment and group is displayed in Figures 14.3.1.7 and 14.3.1.8 respectively.

9.4 Deaths, Serious Adverse Events and other Significant 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.

The following listings will be presented including Subject ID, Age (years) Adverse Event Description, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (Table 14.3.2.1, Appendix I);
- Non-Serious, Unsolicited, Moderate or Severe Adverse Events (Table 14.3.2.2, Appendix I)

9.5 Pregnancies

For any subjects in the Safety population who became pregnant or pregnancy in the partner of a male participant exposed to study treatment during the study, every attempt was made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A listing of pregnancies and outcomes will be presented (Listing 16.2.11, Appendix III).

9.6 Clinical Laboratory Evaluations

Descriptive statistics including mean, standard deviation, median, minimum and maximum values by study day, for each laboratory parameter, will be summarized in Table 14.3.4.1, Appendix I. Changes in laboratory values will be presented in Figure 14.4, Appendix II.

Listings 16.2.8.1-16.2.8.2 presented in Appendix III will provide a complete listing of individual clinical laboratory results for Hematology and Chemistry respectively.

9.7 Vital Signs and Physical Evaluations

Vital sign measurements including oral temperature, respiration rate, blood pressure and heart rate will be measured at specified visits. Baseline vital signs are summarized in Table 14.1.5.2, Appendix I. A complete listing of the vital sign data is found in Listing 16.2.9.1, Appendix III.

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. Physical exam findings are listed in Appendix III, Listing 16.2.9.2.

9.8 Concomitant Medications

All medications taken or medical procedures performed within 8 weeks prior to enrollment and during the study must be recorded on the case report forms. A by-subject listing of concomitant medication use will be presented in Listing 16.2.10, Appendix III.

9.9 Other Safety Measures

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.

10 REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as "> 0.999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values < 1% will be presented as "<1". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

11 TECHNICAL DETAILS

SAS version 9.3 or above will be used to generate all tables, figures and listings.

12 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The protocol references summarizing the current medications/treatments via descriptive statistics. Rather than descriptive statistics, current medications will be summarized via a line listing.

13 REFERENCES

1. Bagarazzi ML, Yan J, Morrow MP, et al. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Sci Transl Med. 2012 Oct 10;4(155):155ra138.
2. Reed GF, Meade BD, Steinhoff MC. The reverse cumulative distribution plot: a graphic method for exploratory analysis of antibody data. Pediatrics. 1995 Sep;96(3 Pt 2) 600-603. PMID: 7659485.

14 LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices I, II, and III.

Statistical Analysis Plan

Appendix I:

Table Mock-Ups

for

Protocol: WRAIR #2274

Study Title:

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Version 1.0

Prepared and distributed by:
The Emmes Corporation
Rockville, Maryland

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Post Dose 2: Systemic Symptom 37

Post Dose 2: Local Symptom 39

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SECTION 14.1: DEMOGRAPHIC DATA

TABLE 14.1.1:
Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	Number of Times Item Marked Ineligible*
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Any inclusion criterion	x
	[inclusion criterion 1]	x
	[inclusion criterion 2]	x
	[inclusion criterion 3]	x
Exclusion	Any exclusion criterion	x
	[exclusion criterion 1]	x
	[exclusion criterion 2]	x
	[exclusion criterion 3]	x

*More than one criterion may be marked per subject.

TABLE 14.1.2:
Analysis Populations by Group

Analysis Populations	Reason Subjects Excluded	Group 1: 0.67 mg/dose (N=X)		Group II: 2 mg/dose (N=X)		Group III: 6 mg/dose (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Modified Intention-to-Treat (mITT) Population	Any Reason	x	x.x	x	x.x	x	x.x	x	x.x
	Did not receive at least one treatment administration								
Per Protocol (PP) Population	Any Reason								
	Did not receive all vaccine doses								
	Had a protocol deviation								
	No primary endpoint data available								
Safety Population	Any Reason								
	Did not receive at least one dose of study treatment								
	No post-dose safety data are available								

N= Number of subjects in the mITT population

TABLE 14.1.3:
Subject Disposition by Group

	Group I: 0.67 mg/dose (N=X)		**Group II: 2 mg/dose (N=X)**		**Group III: 6 mg/dose (N=X)**		**All Subjects (N=X)**	
Subject Disposition	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Screened	--	--	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100	x	100
Received at least one treatment administration	x	x.x	x	x.x	x	x.x	x	x.x
Received at least two treatment administrations	x	x.x	x	x.x	x	x.x	x	x.x
Discontinued Dosing[a]	x	x.x	x	x.x	x	x.x	x	x.x
Received All Scheduled Treatment Administrations	x	x.x	x	x.x	x	x.x	x	x.x
Completed Follow-up (Study Week 60)								
Completed Per Protocol[b]								

N= Number of subjects in the Safety population

[a]Refer to Listing 16.2.1 for reasons subjects discontinued treatment early.

[b]Refer to Listing 16.2.3 for reasons subjects are excluded from the analysis population.

TABLE 14.1.4:
Distribution of Protocol Deviations by Category, Type, and Group

Category	Deviation Type	Group I: 0.67 mg/dose (N=X)		Group II: 2 mg/dose (N=X)		Group III: 6 mg/dose (N=X)		All Subjects (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Eligibility/enrollment	Any type								
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x
	Met exclusion criterion								
	ICF not signed prior to study procedures								
	Other								
Treatment administration schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Missed treatment administration								
	Delayed treatment administration								
	Other								
Follow-up visit schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Other								

TABLE 14.1.4: Distribution of Protocol Deviations by Category, Type, and Group *(continued)*

Category	Deviation Type	Group I: 0.67 mg/dose (N=X)		Group II: 2 mg/dose (N=X)		Group III: 6 mg/dose (N=X)		All Subjects (N=X)	
		# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Protocol procedure/assessment	Any type								
	Incorrect version of ICF signed								
	Blood not collected								
	Other specimen not collected								
	Too few aliquots obtained								
	Specimen result not obtained								
	Required procedure not conducted								
	Required procedure done incorrectly								
	Study product temperature excursion								
	Specimen temperature excursion								
	Other								
Treatment administration	Any type								
	Required procedure done incorrectly								
	Study product temperature excursion								
	Other								

N=Number of subjects in the mITT population

TABLE 14.1.5.1[A]:
Summary of Categorical Demographic and Baseline Characteristics by Group

Variable	Characteristic	Group I: 0.67 mg/dose (N=X)		Group II: 2 mg/dose (N=X)		Group III: 6 mg/dose (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Sex	Male	x	x.x	x	x.x	x	x.x	x	x.x
	Female								
Ethnicity	Not Hispanic or Latino	x	x.x	x	x.x	x	x.x	x	x.x
	Hispanic or Latino								
	Not Reported								
	Unknown								
Race	American Indian or Alaska Native	x	x.x	x	x.x	x	x.x	x	x.x
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Black or African American								
	White								
	Multi-Racial								
	Unknown								

N=Number of subjects in the mITT population

TABLE 14.1.5.2[A]:
Summary of Continuous Demographic and Baseline Characteristic by Group

Variable1	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Age (years)	Mean	x.x	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x	x.x
	Median	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x
	Maximum	x	x	x	x
Baseline Temperature (°C)	Mean				
	Standard Deviation				
	Median				
	Minimum				
	Maximum				
Baseline Respiration Rate (breaths/min)	Mean				
	Standard Deviation				
	Median				
	Minimum				
	Maximum				
Baseline Systolic Blood Pressure (mmHg)	Mean				
	Standard Deviation				
	Median				
	Minimum				
	Maximum				

1 The interim analyses will not include the baseline vital signs.

TABLE 14.1.5.2[A]: Summary of Continuous Demographic and Baseline Characteristic by Group
(continued)

Baseline Diastolic Blood Pressure (mmHg)	Mean				
	Standard Deviation				
	Median				
	Minimum				
	Maximum				
Baseline Pulse (beats/min)	Mean				
	Standard Deviation				
	Median				
	Minimum				
	Maximum				

N=Number of subjects in the mITT population

TABLE 14.1.6:
Summary of Subjects with Pre-Existing Medical Conditions by MedDRA® System Organ Class and Group

	Group I: 0.67 mg/dose (N=X)		Group II: 2 mg/dose (N=X)		Group III: 6 mg/dose (N=X)		All Subjects (N=X)	
MedDRA® System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]								
[SOC 2]								

N= Number of subjects in the Safety population; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

SECTION 14.2: IMMUNOGENICITY DATA

TABLE 14.2.1.1[A]:
ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, mITT population

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Day 0	N	x	x	x	x
	GMT	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Week 1	N				
	GMT				
	95% CI				
Week 2	N				
	GMT				
	95% CI				
Week 3	N				
	GMT				
	95% CI				
Week 4	N				
	GMT				
	95% CI				
Week 6	N				
	GMT				
	95% CI				
Week 12	N				
	GMT				
	95% CI				
Week 14	N				
	GMT				
	95% CI				
Week 24	N				
	GMT				
	95% CI				

TABLE 14.2.1.1[A]: ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, mITT population *(continued)*

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Week 36	N				
	GMT				
	95% CI				
Week 60	N				
	GMT				
	95% CI				

N= Number of subjects in the mITT population

TABLE 14.2.1.2:
ELISA Positive Response Results by Study Day and Group, mITT Population

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Day 0	N	x	x	x	x
	Positive Response	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Week 1	N				
	Positive Response				
	95% CI				
Week 2	N				
	Positive Response				
	95% CI				
Week 3	N				
	Positive Response				
	95% CI				
Week 4	N				
	Positive Response				
	95% CI				
Week 6	N				
	Positive Response				
	95% CI				
Week 12	N				
	Positive Response				
	95% CI				
Week 14	N				
	Positive Response				
	95% CI				
Week 24	N				
	Positive Response				
	95% CI				

TABLE 14.2.1.2: ELISA Positive Response Results by Study Day and Group, mITT Population
(continued)

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Week 36	N				
	Positive Response				
	95% CI				
Week 60	N				
	Positive Response				
	95% CI				

N= Number of subjects in the mITT population

TABLE 14.2.1.3:
P-values for Fisher's Exact Tests Comparing ELISA Positive Response between Groups for each Study Day, mITT Population

	N = number of observations for each time point per group			Fisher's Exact Test Results		
Time Point	**Group I (0.67 mg/dose)**	**Group II (2 mg/dose)**	**Group III (6 mg/dose)**	**Group I vs. Group II**	**Group II vs. Group III**	**Group I vs. Group III**
Day 0	N	N	N	p	p	p
Week 1						
Week 2/3						
Week 3						
Week 4						
Week 6						
Week 12						
Week 14						
Week 24						
Week 36						
Week 60						

N= Number of subjects in the mITT population

TABLE 14.2.1.4:
ELISA Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, PP population

Same format as Table 14.2.1.1

TABLE 14.2.1.5:
ELISA Positive Response Results by Study Day and Group, PP Population

Same format as Table 14.2.1.2

TABLE 14.2.2.1[A]:
Neutralizing Antibody (NT50) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, mITT population

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Day 0	N	x	x	x	x
	GMT	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Week 1	N				
	GMT				
	95% CI				
Week 2	N				
	GMT				
	95% CI				
Week 3	N				
	GMT				
	95% CI				
Week 4	N				
	GMT				
	95% CI				
Week 6	N				
	GMT				
	95% CI				
Week 12	N				
	GMT				
	95% CI				
Week 14	N				
	GMT				
	95% CI				
Week 24	N				
	GMT				
	95% CI				

TABLE 14.2.2.1[A]:
Neutralizing Antibody (NT50) Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, mITT population *(continued)*

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Week 36	N				
	GMT				
	95% CI				
Week 60	N				
	GMT				
	95% CI				

N= Number of subjects in the mITT population

TABLE 14.2.2.2:
Neutralizing Antibody (NT50) Positive Response[a] Results by Study Day and Group, mITT Population

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Day 0	N	x	x	x	x
	Positive Response	x.x	x.x	x.x	x.x
	95% CI	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Week 1	N				
	Positive Response				
	95% CI				
Week 2	N				
	Positive Response				
	95% CI				
Week 3	N				
	Positive Response				
	95% CI				
Week 4	N				
	Positive Response				
	95% CI				
Week 6	N				
	Positive Response				
	95% CI				
Week 12	N				
	Positive Response				
	95% CI				
Week 14	N				
	Positive Response				
	95% CI				
Week 24	N				
	Positive Response				
	95% CI				

TABLE 14.2.2.2: Neutralizing Antibody (NT50) Positive Response[a] Results by Study Day and Group, mITT Population *(continued)*

Time Point	Statistic	Group I: 0.67 mg/dose (N=X)	Group II: 2 mg/dose (N=X)	Group III: 6 mg/dose (N=X)	All Subjects (N=X)
Week 36	N				
	Positive Response				
	95% CI				
Week 60	N				
	Positive Response				
	95% CI				

N= Number of subjects in the mITT population

[a] Positive response represents the percentage of subjects with an IC50 value more than a specified threshold.

TABLE 14.2.2.3:
Neutralizing Antibody (NT50)Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Study Day and Group, PP population

Same format as Table 14.2.2.1

TABLE 14.2.2.4:
Neutralizing Antibody (NT50)Positive Response Results by Study Day and Group, PP Population

Same format as Table 14.2.2.2

TABLE 14.2.3.1:
Summary of IFN-γ ELISpot Results (SFU/1,000,000 cells per well) by Group, mITT population

	Group I: 0.67 mg/dose (N=X)				Group II: 2 mg/dose (N=X)				Group III: 6 mg/dose (N=X)				All Subjects (N=X)			
Time Point	**N**	**Mean (SD)**	**Median (Min, Max)**	**(Q1, Q3)**	**N**	**Mean (SD)**	**Median (Min, Max)**	**(Q1, Q3)**	**N**	**Mean (SD)**	**Median (Min, Max)**	**(Q1, Q3)**	**N**	**Mean (SD)**	**Median (Min, Max)**	**(Q1, Q3)**
Day 0	x	x.x (x.xx)	x.x (x.x, x.x)	(x.x, x.x)	x	x.x (x.xx)	x.x (x.x, x.x)	(x.x, x.x)	x	x.x (x.xx)	x.x (x.x, x.x)	(x.x, x.x)	x	x.x (x.xx)	x.x (x.x, x.x)	(x.x, x.x)
Week 1																
Week 2																
Week 3																
Week 4																
Week 6																
Week 12																
Week 14																
Week 24																
Week 36																
Week 60																

TABLE 14.2.3.2:
Summary of IFN-γ ELISpot Results (1,000,000 cells per well) by Group, PP population

Same format as Table 14.2.3.1

NOTE: ***The following table will be repeated seven times: once for each of the six separate S-protein based peptide pools and once for the result that is the sum of the six pools combined***.

TABLE 14.2.3.3:
T-test Results Comparing IFN-γ Means between Groups for each Study Day, mITT Population

	X=Mean IFN-γ value N = number of observations for each time point per group			T-Test Results: t-statistic (p-value)		
Time Point	**Group I (0.67 mg/dose)**	**Group II (2 mg/dose)**	**Group III (6 mg/dose)**	**Group I vs. Group II**	**Group II vs. Group III**	**Group I vs. Group III**
Day 0	x (N)	x (N)	x (N)	t (p)	t (p)	t (p)
Week 1						
Week 2						
Week 3						
Week 4						
Week 6						
Week 12						
Week 14						
Week 24						
Week 36						
Week 60						

TABLE 14.2.3.4:
T-test Results Comparing ICS Means between Groups for each Study Day, mITT Population

Same format as Table 14.2.3.3

SECTION 14.3: SAFETY DATA

TABLE 14.3.1.1[A]:
Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Group

Post Dose 1

	Post Dose 1								
	Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
Symptom	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Systemic Symptom									
Fever									
Malaise/Fatigue									
Myalgia									
Headache									
Arthalgia									
Nausea									
Any Local Symptom									
Pain									
Tenderness									
Pruritus									
Erythema									
Induration/Swelling									
Bruising									

N=Number of subjects in the Safety population

TABLE 14.3.1.1: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Group *(continued)*

Post Dose 2

	Post Dose 2								
	Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Systemic Symptom									
Fever									
Malaise/Fatigue									
Myalgia									
Headache									
Arthalgia									
Nausea									
Any Local Symptom									
Pain									
Tenderness									
Pruritus									
Erythema									
Induration/Swelling									
Bruising									

N=Number of subjects in the Safety population

TABLE 14.3.1.1: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Group *(continued)*

Post Dose 3

	Post Dose 3								
	Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Systemic Symptom									
Fever									
Malaise/Fatigue									
Myalgia									
Headache									
Arthalgia									
Nausea									
Any Local Symptom									
Pain									
Tenderness									
Pruritus									
Erythema									
Induration/Swelling									
Bruising									

N=Number of subjects in the Safety population

TABLE 14.3.1.1: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Group *(continued)*

Post Any Dose (Overall)[A]

	Post Any Dose								
	Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
Symptom	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Systemic Symptom									
Fever									
Malaise/Fatigue									
Myalgia									
Headache									
Arthalgia									
Nausea									
Any Local Symptom									
Pain									
Tenderness									
Pruritus									
Erythema									
Induration/Swelling									
Bruising									

N=Number of subjects in the Safety population

TABLE 14.3.1.2:
Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group

Post Dose 1: Any Symptom

Symptom	Severity	Post Dose 1								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 1: Systemic Symptom

Symptom	Severity	Post Dose 1								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Systemic Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									
Fever	Mild									
	Moderate									
	Severe									
	Not Reported									
Malaise/Fatigue	Mild									
	Moderate									
	Severe									
	Not Reported									
Myalgia	Mild									
	Moderate									
	Severe									
	Not Reported									
Headache	Mild									
	Moderate									
	Severe									
	Not Reported									
Arthalgia	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Dose 1								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Nausea	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 1: Local Symptom

Symptom	Severity	Post Dose 1								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Local Symptom	Mild									
	Moderate									
	Severe									
	Not Reported									
Pain	Mild									
	Moderate									
	Severe									
	Not Reported									
Tenderness	Mild									
	Moderate									
	Severe									
	Not Reported									
Pruritus	Mild									
	Moderate									
	Severe									
	Not Reported									
Erythema	Mild									
	Moderate									
	Severe									
	Not Reported									
Induration/Swelling	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Dose 1								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Bruising	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 2: Any Symptom

Symptom	Severity	Post Dose 2								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 2: Systemic Symptom

Symptom	Severity	Post Dose 2								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Systemic Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									
Fever	Mild									
	Moderate									
	Severe									
	Not Reported									
Malaise/Fatigue	Mild									
	Moderate									
	Severe									
	Not Reported									
Myalgia	Mild									
	Moderate									
	Severe									
	Not Reported									
Headache	Mild									
	Moderate									
	Severe									
	Not Reported									
Arthalgia	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Dose 2								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Nausea	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 2: Local Symptom

Symptom	Severity	Post Dose 2								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Local Symptom	Mild									
	Moderate									
	Severe									
	Not Reported									
Pain	Mild									
	Moderate									
	Severe									
	Not Reported									
Tenderness	Mild									
	Moderate									
	Severe									
	Not Reported									
Pruritus	Mild									
	Moderate									
	Severe									
	Not Reported									
Erythema	Mild									
	Moderate									
	Severe									
	Not Reported									
Induration/Swelling	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

		Post Dose 2								
		Group I: 0.67 mg/dose (N=X)			**Group II: 2 mg/dose (N=X)**			**Group III: 6 mg/dose (N=X)**		
Symptom	**Severity**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Bruising	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 3: Any Symptom

Symptom	Severity	Post Dose 3								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 3: Systemic Symptom

Symptom	Severity	Post Dose 3								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Systemic Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									
Fever	Mild									
	Moderate									
	Severe									
	Not Reported									
Malaise/Fatigue	Mild									
	Moderate									
	Severe									
	Not Reported									
Myalgia	Mild									
	Moderate									
	Severe									
	Not Reported									
Headache	Mild									
	Moderate									
	Severe									
	Not Reported									
Arthalgia	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Dose 3								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Nausea	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Dose 3: Local Symptom

Symptom	Severity	Post Dose 3								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Local Symptom	Mild									
	Moderate									
	Severe									
	Not Reported									
Pain	Mild									
	Moderate									
	Severe									
	Not Reported									
Tenderness	Mild									
	Moderate									
	Severe									
	Not Reported									
Pruritus	Mild									
	Moderate									
	Severe									
	Not Reported									
Erythema	Mild									
	Moderate									
	Severe									
	Not Reported									
Induration/Swelling	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Dose 3								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Bruising	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Any Dose: Any Symptom

Symptom	Severity	Post Any Dose								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Any Dose: Systemic Symptom

Symptom	Severity	Post Any Dose								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Systemic Symptom	Mild	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	Moderate									
	Severe									
	Not Reported									
Fever	Mild									
	Moderate									
	Severe									
	Not Reported									
Malaise/Fatigue	Mild									
	Moderate									
	Severe									
	Not Reported									
Myalgia	Mild									
	Moderate									
	Severe									
	Not Reported									
Headache	Mild									
	Moderate									
	Severe									
	Not Reported									
Arthalgia	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Any Dose								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Nausea	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Post Any Dose: Local Symptom

Symptom	Severity	Post Any Dose								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Local Symptom	Mild									
	Moderate									
	Severe									
	Not Reported									
Pain	Mild									
	Moderate									
	Severe									
	Not Reported									
Tenderness	Mild									
	Moderate									
	Severe									
	Not Reported									
Pruritus	Mild									
	Moderate									
	Severe									
	Not Reported									
Erythema	Mild									
	Moderate									
	Severe									
	Not Reported									
Induration/Swelling	Mild									
	Moderate									
	Severe									
	Not Reported									

TABLE 14.3.1.2: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Group *(continued)*

Symptom	Severity	Post Any Dose								
		Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Bruising	Mild									
	Moderate									
	Severe									
	Not Reported									

N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

TABLE 14.3.1.3[A]:
Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Group

MedDRA® System Organ Class	MedDRA® Preferred Term	Group I: 0.67 mg/dose (N=X)			Group II: 2 mg/dose (N=X)			Group III: 6 mg/dose (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any SOC	Any PT	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = number of subjects in the Safety Analysis Population who received the specified dose. This table presents number and percentage of subjects. A subject is only counted once per PT/time point.

TABLE 14.3.1.4:
Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Group

Group I: 0.67 mg/dose (N=X)

		Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
MedDRA® System Organ Class	MedDRA® Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.

[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.

[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

TABLE 14.3.1.4: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Group *(continued)*

Group II: 2 mg/dose (N=X)

		Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
MedDRA® System Organ Class	**MedDRA® Preferred Term**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.

[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.

[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

TABLE 14.3.1.4: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Group *(continued)*

Group III: 6 mg/dose (N=X)

MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.

[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.

[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

TABLE 14.3.1.4: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Group *(continued)*

All Subjects (N=X)

		Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
MedDRA® System Organ Class	**MedDRA® Preferred Term**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	Any PT	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.

[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.

[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

TABLE 14.3.2.1:
Listing of Serious Adverse Events

Part 1

Subject ID	Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	# of Days Post Dose the Event Became Serious	Duration (Days)	Reason Reported as an SAE	Severity

Part 2

Subject ID	Adverse Event	Relationship to Study Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

TABLE 14.3.2.2:
Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Part 1

Subject ID	Group	AE Number	Adverse Event	Associated with Dose #	# of Days Post Associated Dose	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternate Etiology

Part 2

Subject ID	Adverse Event	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

SECTION 14.3.3: NARRATIVES OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

(Not included in SAP. This is a placeholder for the CSR)

TABLE 14.3.4.1:
Laboratory Summary Statistics by Parameter, Study Day, and Group

Chemistry Results: ALT (U/L)

Time Point	Group	N	Mean	Standard Deviation	Median	Min, Max
Screening	0.67 mg/dose	x	xx.x	xx.x	xx.x	xx.x, xx.x
	2 mg/dose					
	6 mg/dose					
Week 1	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					
Week 1, Change from Screening	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					
Week 6	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					
Week 6, Change from Screening	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					
Week 14	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					
Week 14, Change from Screening	0.67 mg/dose					
	2 mg/dose					
	6 mg/dose					

N= Number of subjects in the Safety population

TABLE 14.3.4.1: Laboratory Summary Statistics by Parameter, Study Day, and Group *(continued)*

Chemistry Results: AST (U/L)

Same format as table for ALT with the same number of significant digits

Chemistry Results: Creatinine (mg/dL)

Same format as table for ALT with values captured with the following significant digits: x.xx

Chemistry Results: Sodium (mmol/L)

Same format as table for ALT with values captured with the following significant digits: xxx

Chemistry Results: Glucose (mg/dL)

Same format as table for ALT with values captured with the following significant digits: xxx

Chemistry Results: Bicarbonate (mmol/L)

Same format as table for ALT with values captured with the following significant digits: xx

Chemistry Results: Blood Urea Nitrogen (mg/dL)

Same format as table for ALT with values captured with the following significant digits: xx

Chemistry Results: Creatine Kinase (IU/L)

Same format as table for ALT with values captured with the following significant digits: xxx

Chemistry Results: Chloride (mmol/L)

Same format as table for ALT with values captured with the following significant digits: xxx

Chemistry Results: Potassium (mmol/L)

Same format as table for ALT with values captured with the following significant digits: x.x

Hematology Results: Hemoglobin (g/dL)

Same format as table for ALT with values captured with the following significant digits: xx.x

Hematology Results: Platelets (10^9/L)

Same format as table for ALT with values captured with the following significant digits: xxx

Hematology Results: WBC (10^9/L)

Same format as table for ALT with values captured with the following significant digits: x.x

Hematology Results: Neutrophils (cells/μL)

Same format as table for ALT with values captured with the following significant digits: xxxx

TABLE 14.3.4.1: Laboratory Summary Statistics by Parameter, Study Day, and Group *(continued)*

Hematology Results: Eosinophils (cells/μL)

Same format as table for ALT with values captured with the following significant digits: xxx

Hematology Results: Lymphocytes (cells/μL)

Same format as table for ALT with values captured with the following significant digits: xxxx

Hematology Results: Erythrocytes (10^{12}/L)

Same format as table for ALT with values captured with the following significant digits: x.xx

Hematology Results: Monocytes (cells/μL)

Same format as table for ALT with values captured with the following significant digits: xx

Statistical Analysis Plan

Appendix II:

Figure Mock-Ups

for

Protocol: WRAIR #2274

Study Title:

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Version 1.0

Prepared and Distributed by:
The Emmes Corporation
Rockville, Maryland

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Group II: 2 mg/dose (N=X) 8

Group III: 6 mg/dose (N=X) 8

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Group II: 2 mg/dose (N=X) 9

Group III: 6 mg/dose (N=X) 9

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Group I: 0.67 mg/dose (N=X) 13

Group II: 2 mg/dose (N=X) 13

Group III: 6 mg/dose (N=X) 13

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FIGURE 14.1.1:
CONSORT Flow Diagram

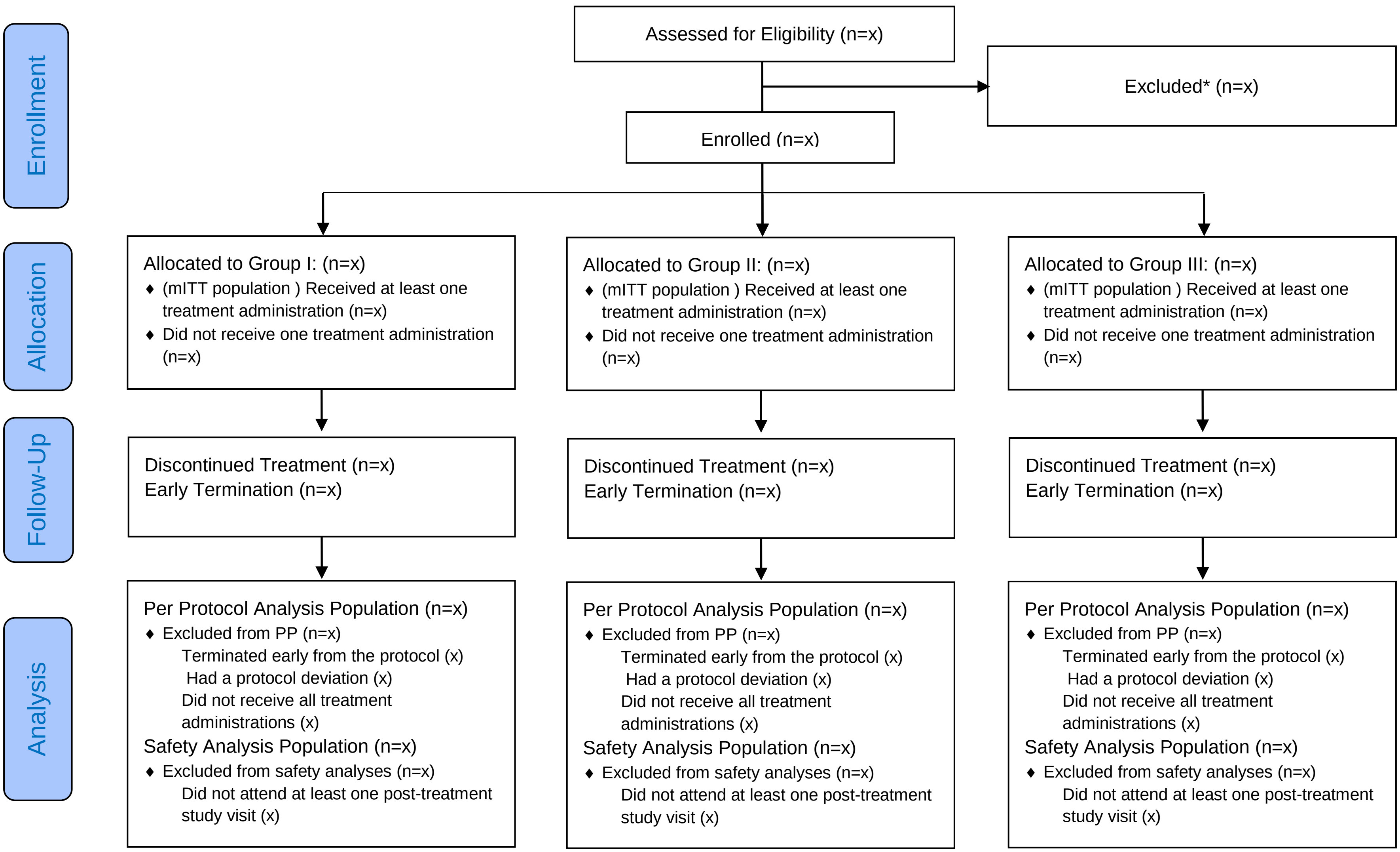
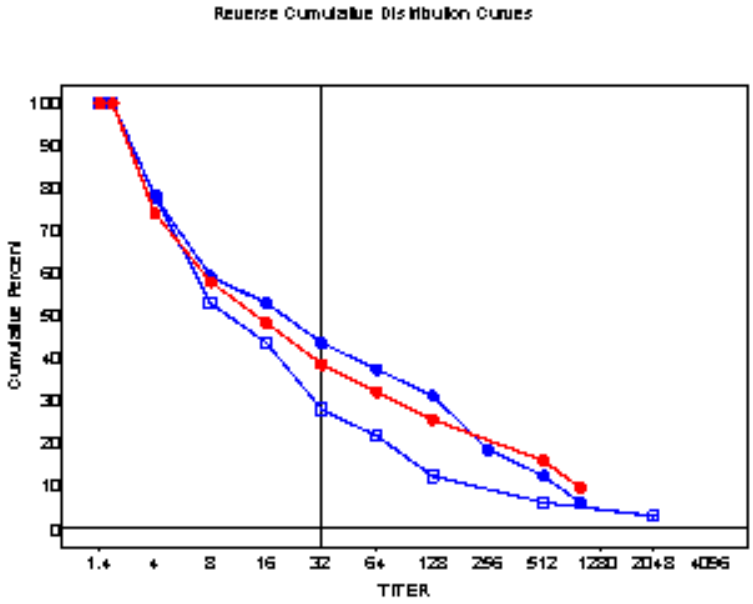


FIGURE 14.2.1.1[A]:
Reverse Cumulative Distribution of ELISA by Study Day and Group

Example figures provided.

The x-axis will be scaled to the appropriate titer dilution rates. Separate plots will be provided for each Study Day (Day 0, Week 1, Week 2, Week 3, Week 4, Week 6, Week 12, Week 14, Week 24, Week 36 and Week 60). Each line on the figure will represent one of the three dose groups.



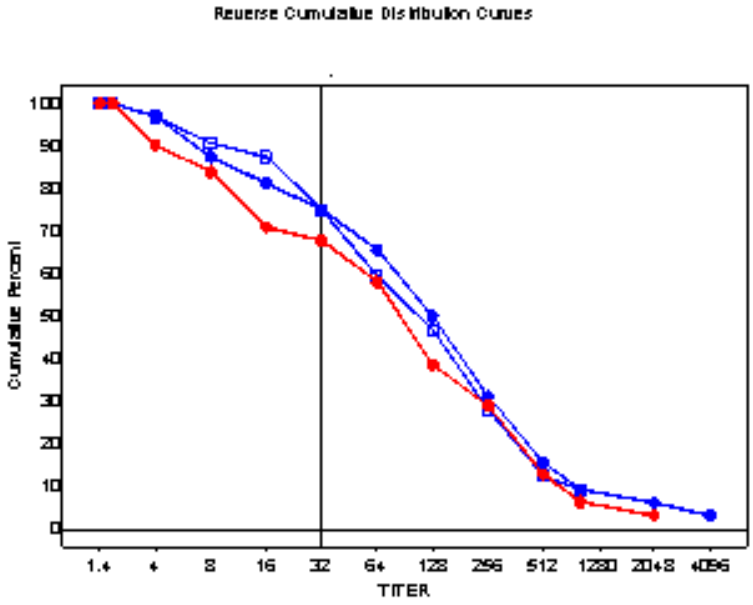
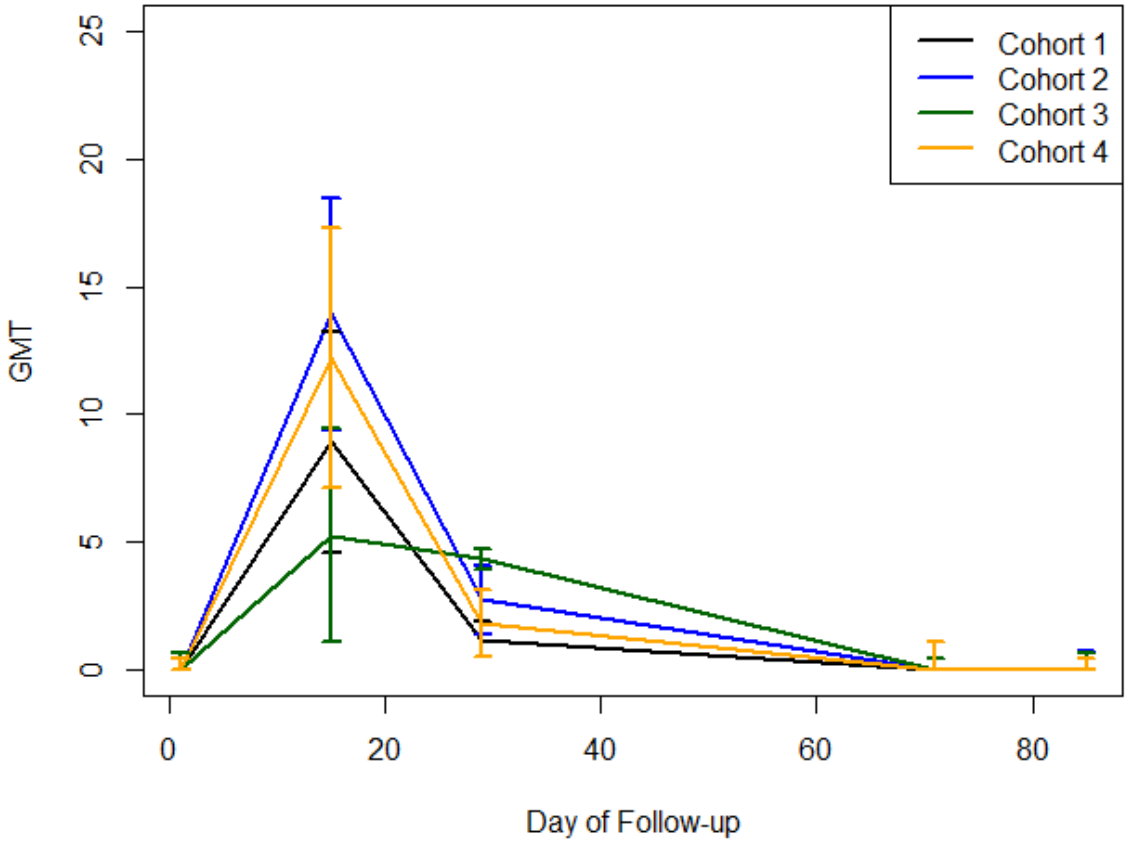


FIGURE 14.2.1.2[A]:
ELISA Geometric Mean (95% Confidence Interval) Over Time by Group

Example figures provided.



The x-axis will be scaled to the appropriate day of follow-up relative to the first treatment administration. The y-axis will be scaled to the geometric mean titer response and the confidence intervals will be displayed for each group for each different study day assessed. Each line on the figure will represent one of the three dose groups.

FIGURE 14.2.2.1[A]:
Reverse Cumulative Distribution of Neutralizing Antibody (NT50) by Study Day and Group

Example figures provided in Figure 14.2.1.1.

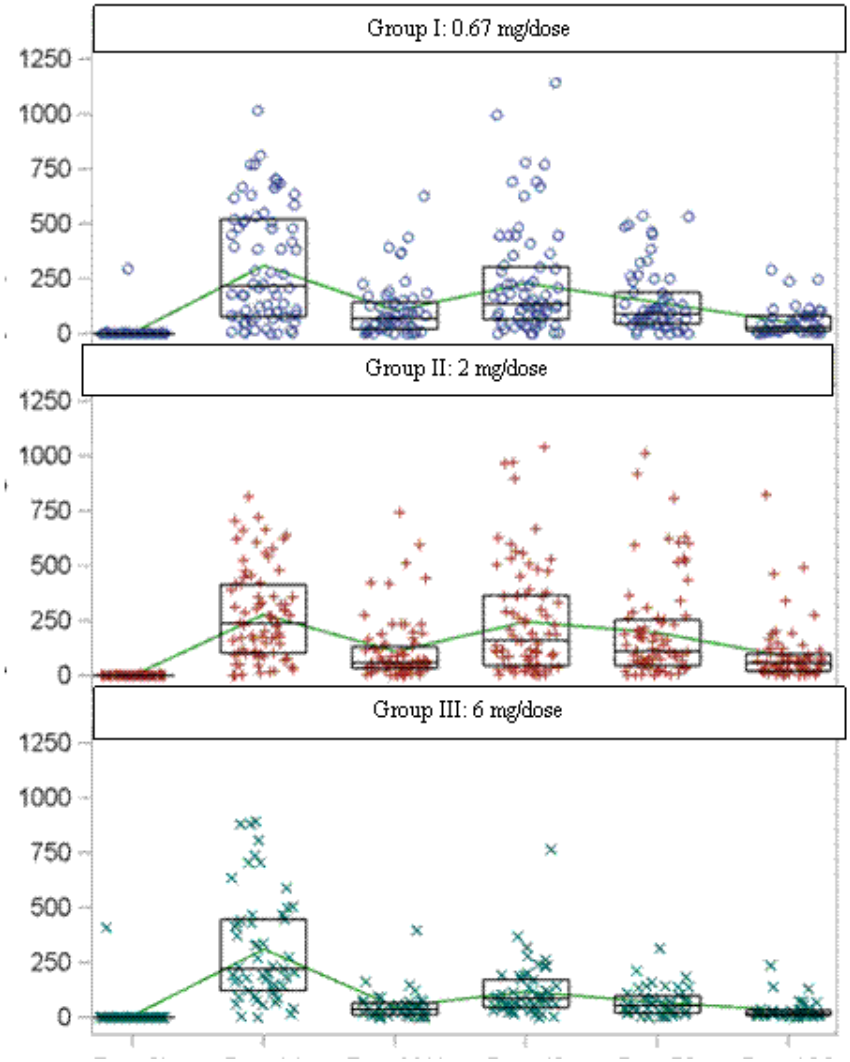
The x-axis will be scaled to the appropriate titer dilution rates. Separate plots will be provided for each Study Day (Day 0, Week 1, Week 2, Week 3, Week 4, Week 6, Week 12, Week 14, Week 24, Week 36 and Week 60). Each line on the figure will represent the three dose groups.

FIGURE 14.2.2.2[A]:
Neutralizing Antibody (NT50) Geometric Mean (95% Confidence Interval) Over Time by Group

Example figures provided in Figure 14.2.1.2.

NOTE:	*The following figure will be repeated seven times: once for each of the* six *separate S-protein based peptide pools and once for the result that is the sum of the* six *pools combined.*

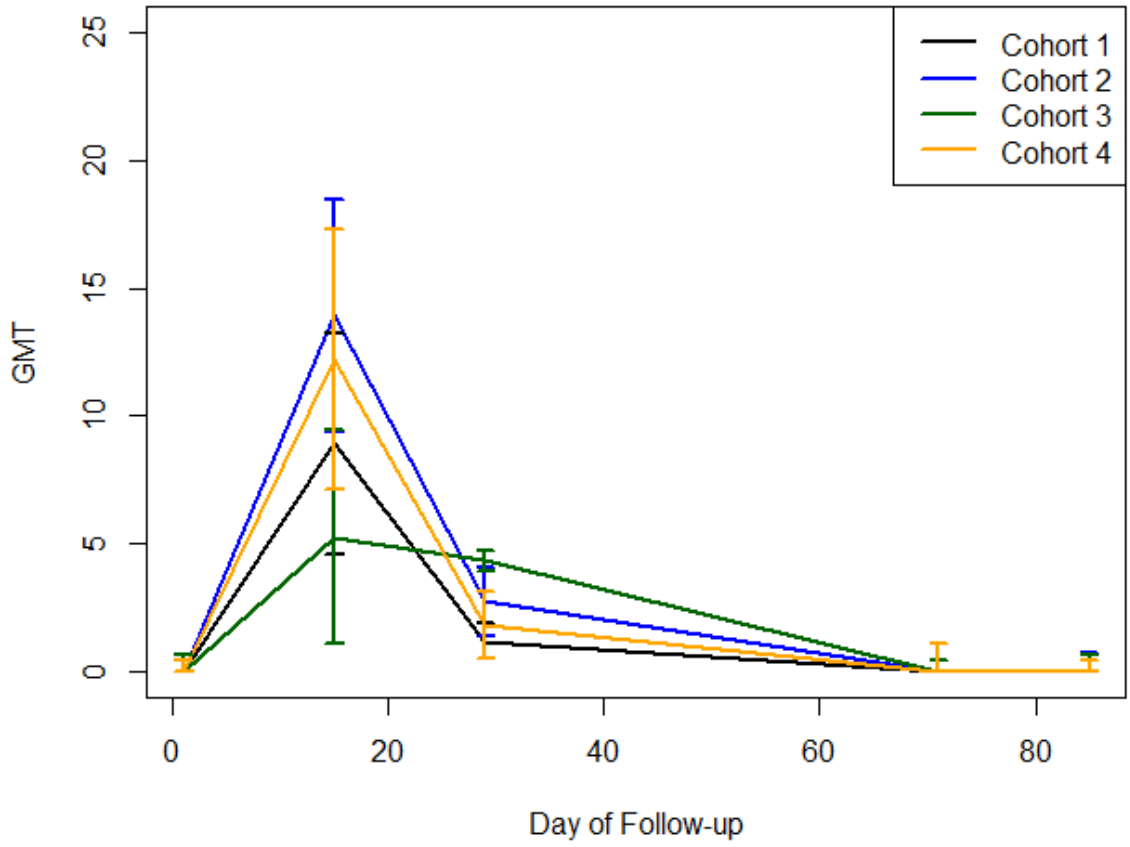
FIGURE 14.2.3:
Boxplots of IFN-γ ELISpot Results (Spot Forming Units per million cells), Background Subtracted by Group



The x-axis will define the timepoints where the ELISpot assay results are obtained. The y-axis will be labeled as the number of spot forming units (SFU) for the adjusted ELISpot endpoint.

FIGURE 14.2.4: ICS Geometric Mean (95% Confidence Interval) Over Time by Group

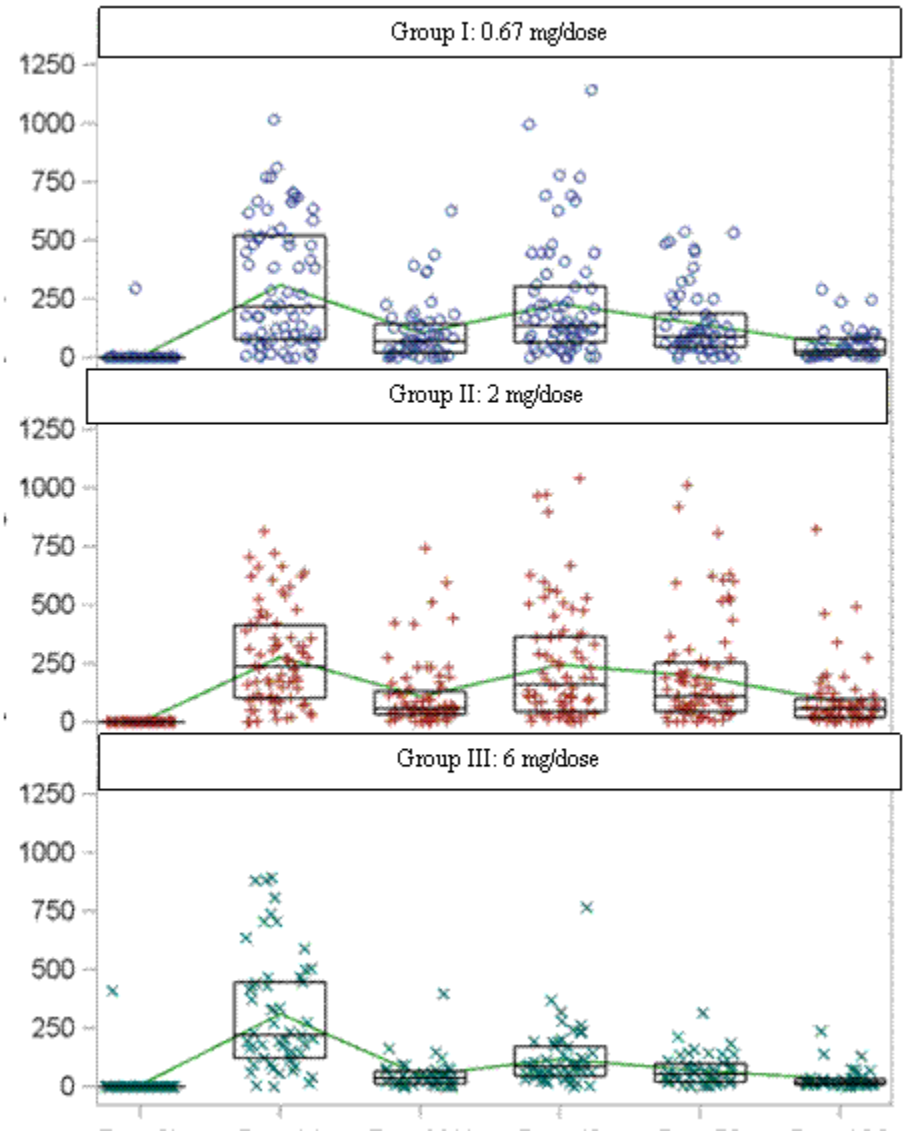
Example figures provided.



The x-axis will define the timepoints where the ICS assay results are obtained.

NOTE: Figures 14.2.4 and 14.2.5 will be repeated for each cytokine under evaluation.

FIGURE 14.2.5: Box Plots of ICS Results Over Time by Group (% of cells expressing the cytokine under evaluation)

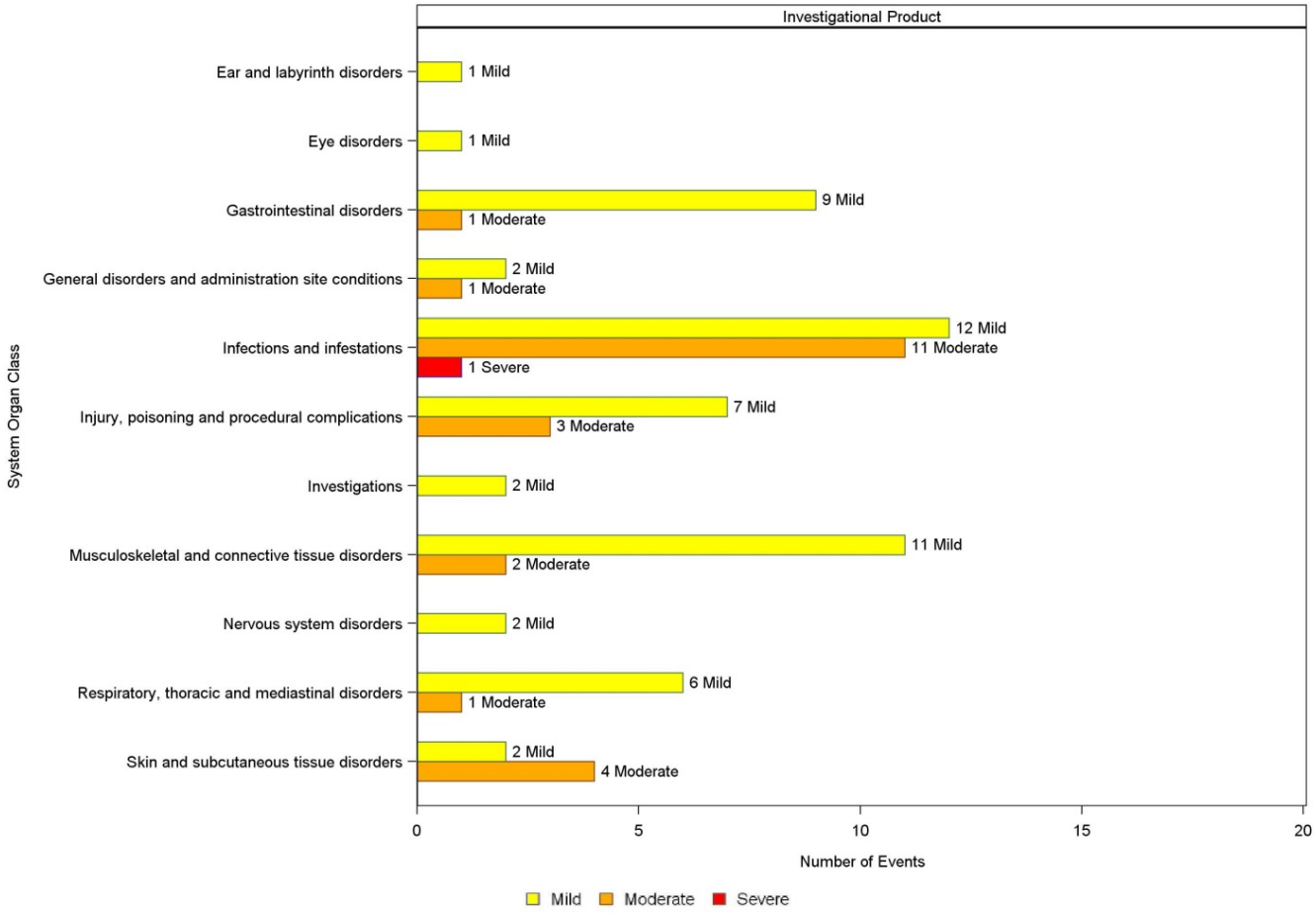


The x-axis will define the time points where the ICS assay results are obtained. The y-axis will be labeled as the proportion of cells expressing the cytokine under evaluation.

FIGURE 14.3.1.1:
Frequency of Adverse Events by MedDRA® System Organ Class and Severity

Group I: 0.67 mg/dose (N=X)

Sample Figure provided. Figure will be generated for each Group.



Group II: 2 mg/dose (N=X)

See sample figure above.

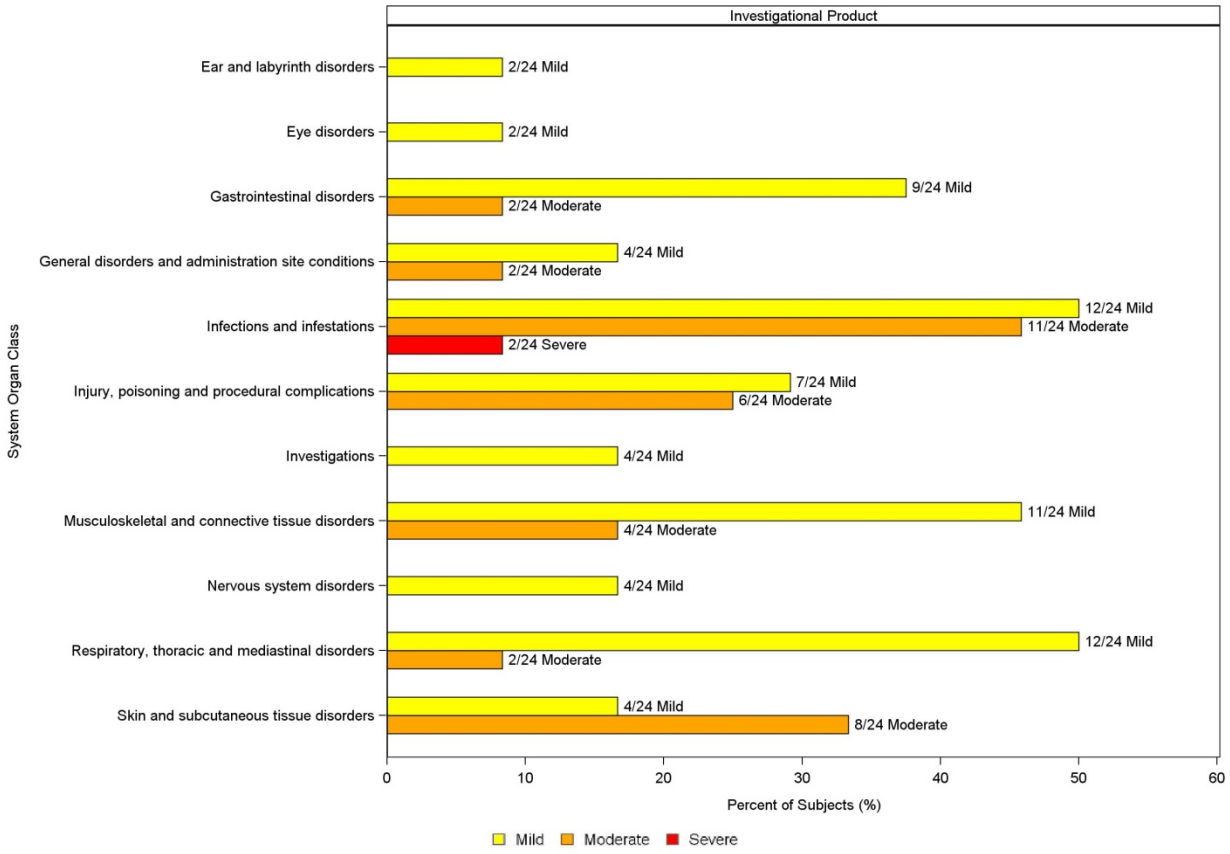
Group III: 6 mg/dose (N=X)

See sample figure above.

FIGURE 14.3.1.2:
Incidence of Adverse Events by MedDRA® System Organ Class and Severity

Group I: 0.67 mg/dose (N=X)

Sample Figure provided. Figure will be generated for each Group.



Group II: 2 mg/dose (N=X)

See sample figure above.

Group III: 6 mg/dose (N=X)

See sample figure above.

FIGURE 14.3.1.3:
Frequency of Adverse Events by Severity

Sample Figure provided. Figure will include four sets of bar graphs (Group I, Group II, Group III and All Subjects) rather than defining Investigational product and control.

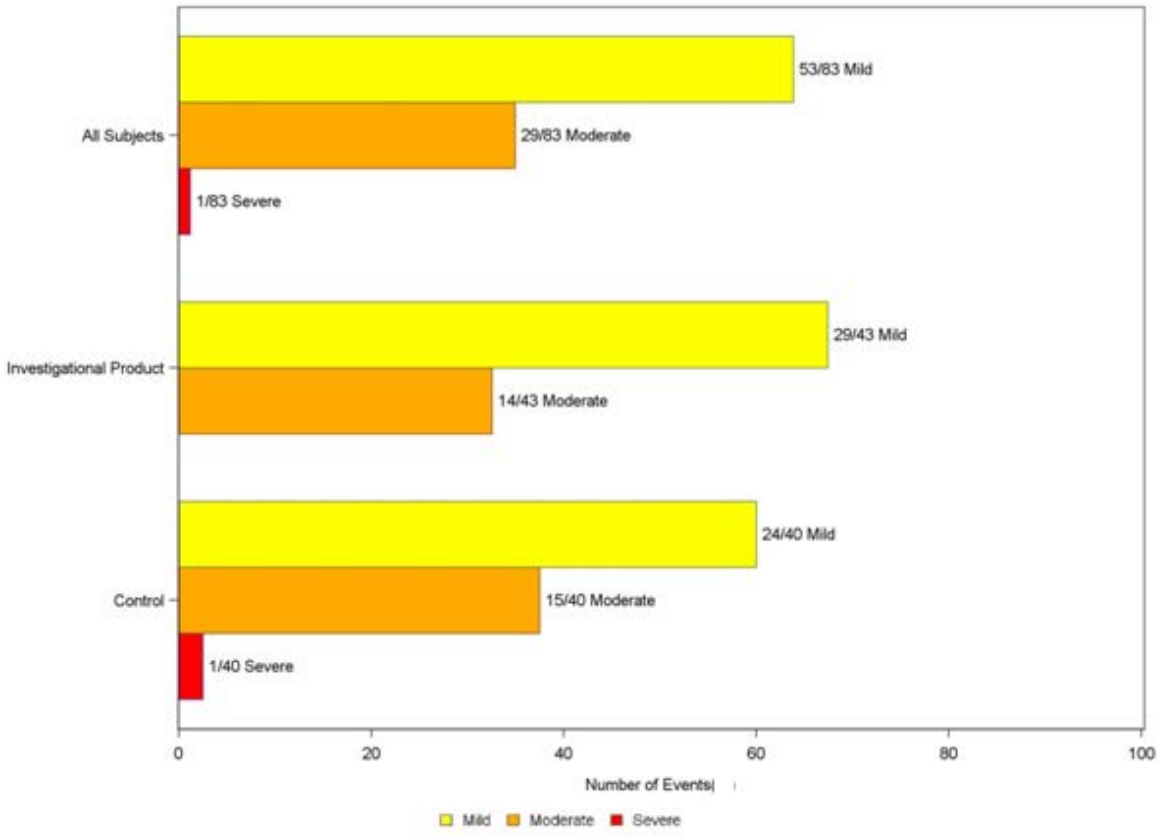


FIGURE 14.3.1.4:
Incidence of Adverse Events by Severity

Sample Figure provided. Figure will include four sets of bar graphs (Group I, Group II, Group III and All Subjects) rather than defining Investigational product and control.

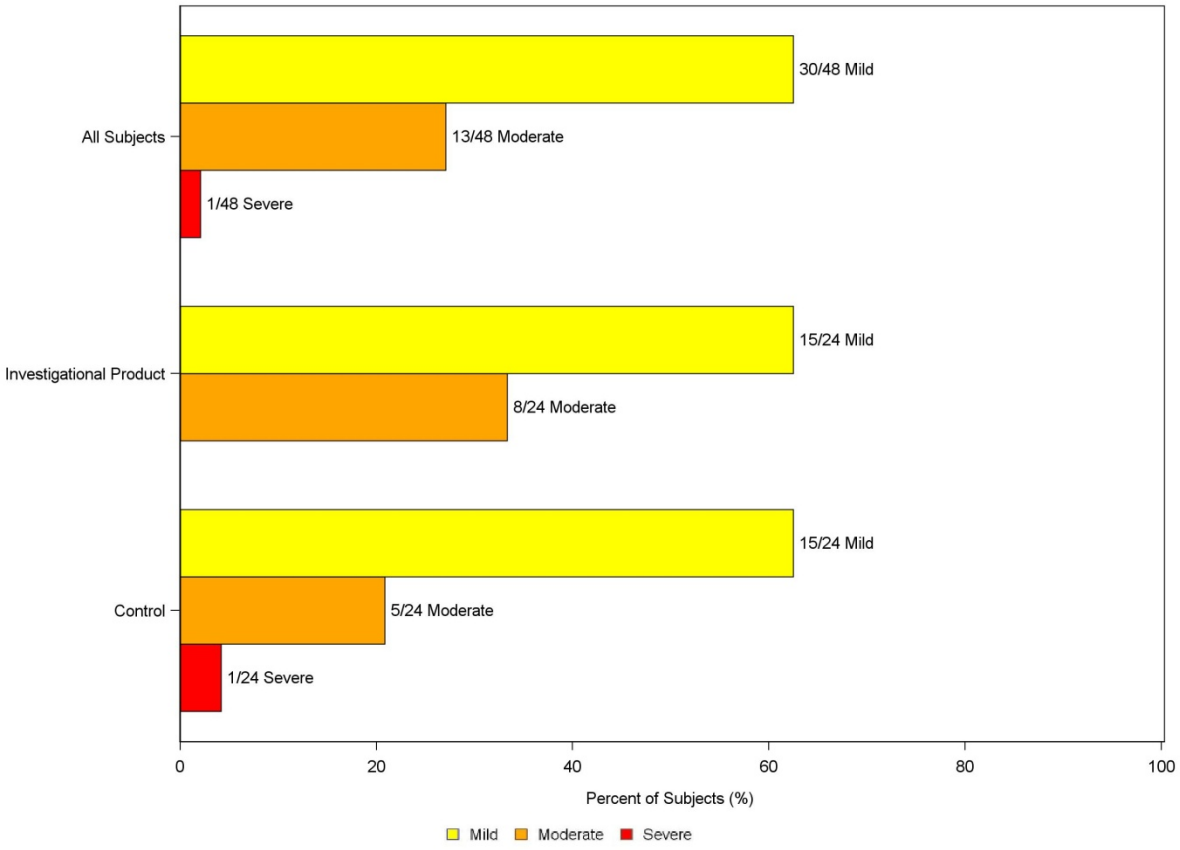
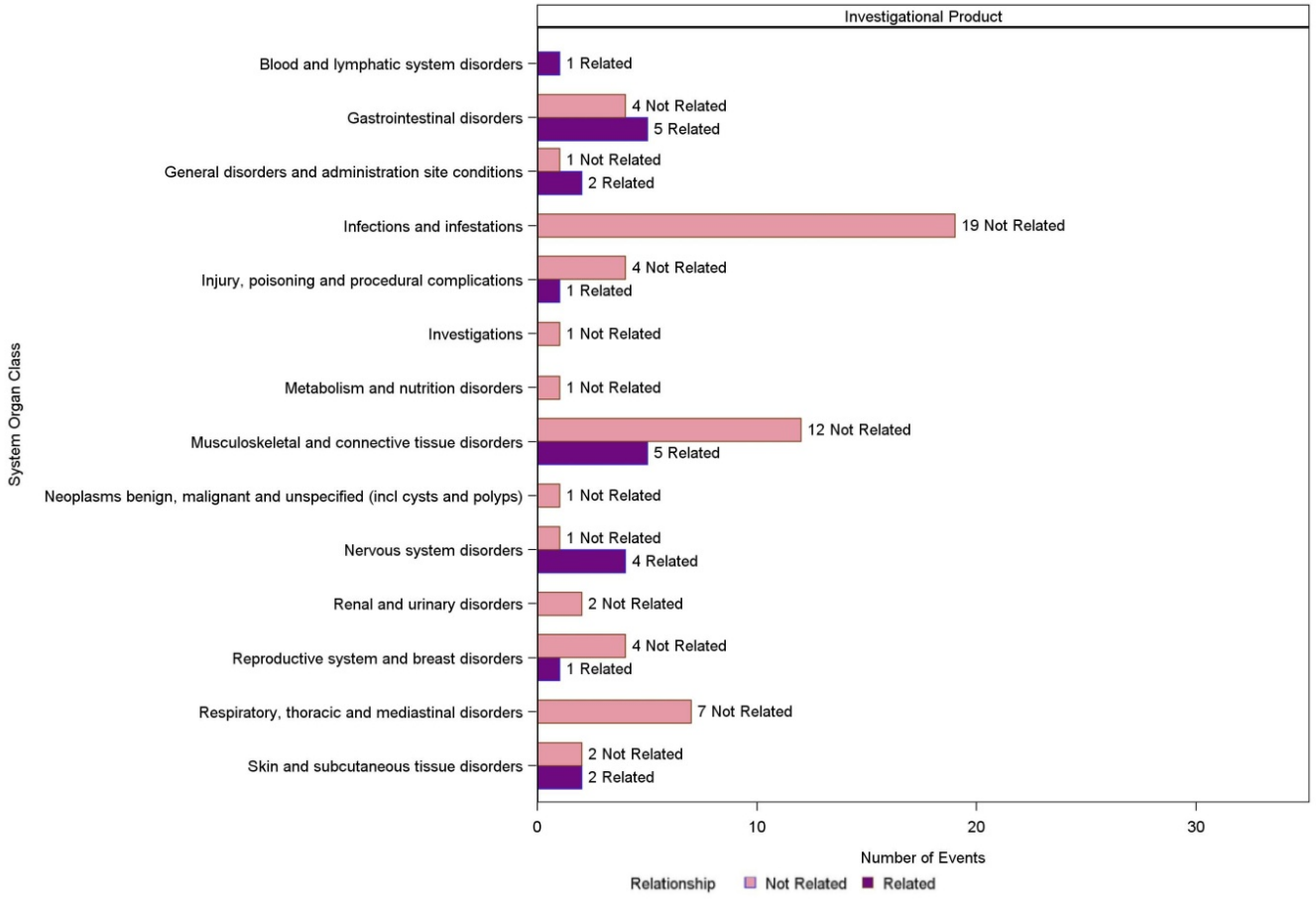


FIGURE 14.3.1.5:
Frequency of Adverse Events by MedDRA® System Organ Class and Relationship to Treatment

Group I: 0.67 mg/dose (N=X)

Sample Figure provided.



Group II: 2 mg/dose (N=X)

See sample figure above.

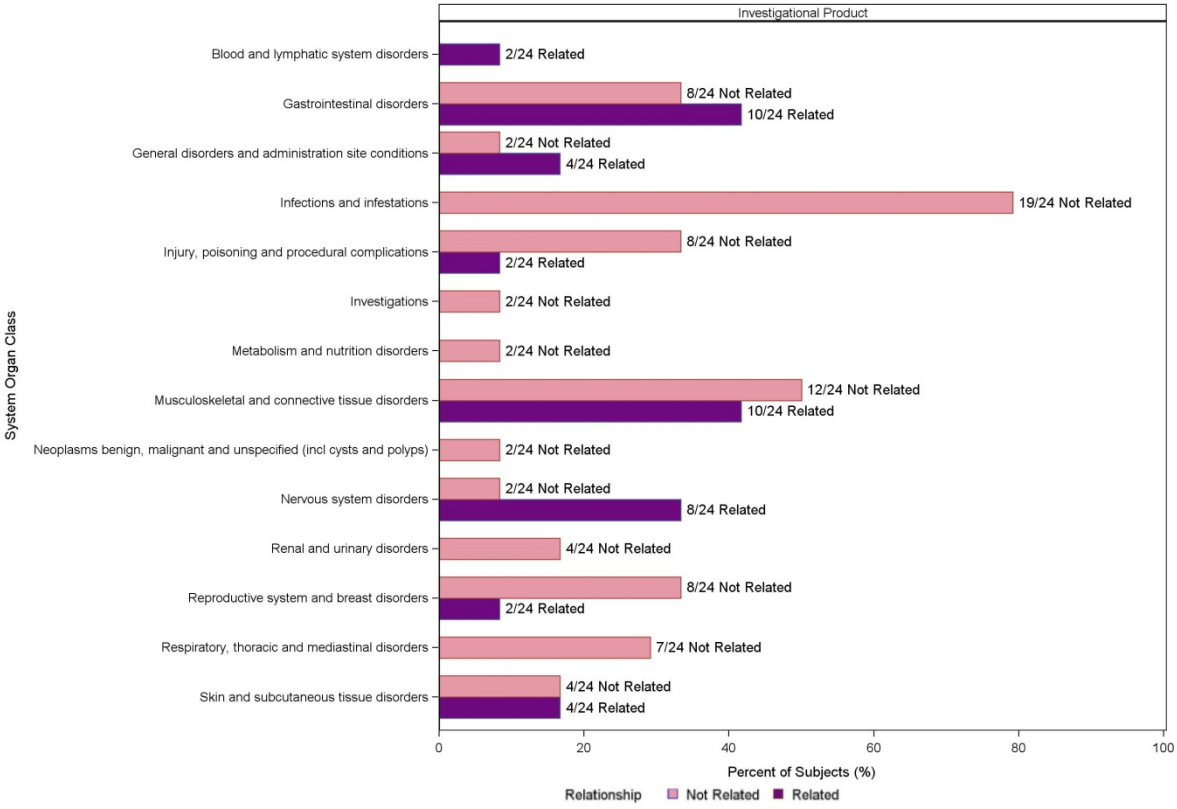
Group III: 6 mg/dose (N=X)

See sample figure above.

FIGURE 14.3.1.6:
Incidence of Adverse Events by MedDRA® System Organ Class and Relationship to Treatment

Group I: 0.67 mg/dose (N=X)

Sample Figure provided.



Group II: 2 mg/dose (N=X)

See sample figure above.

Group III: 6 mg/dose (N=X)

See sample figure above.

FIGURE 14.3.1.7:
Frequency of Adverse Events by Relationship to Treatment

Sample Figure provided. Figure will include four sets of bar graphs (Group I, Group II, Group III and All Subjects) rather than defining Investigational product and control.

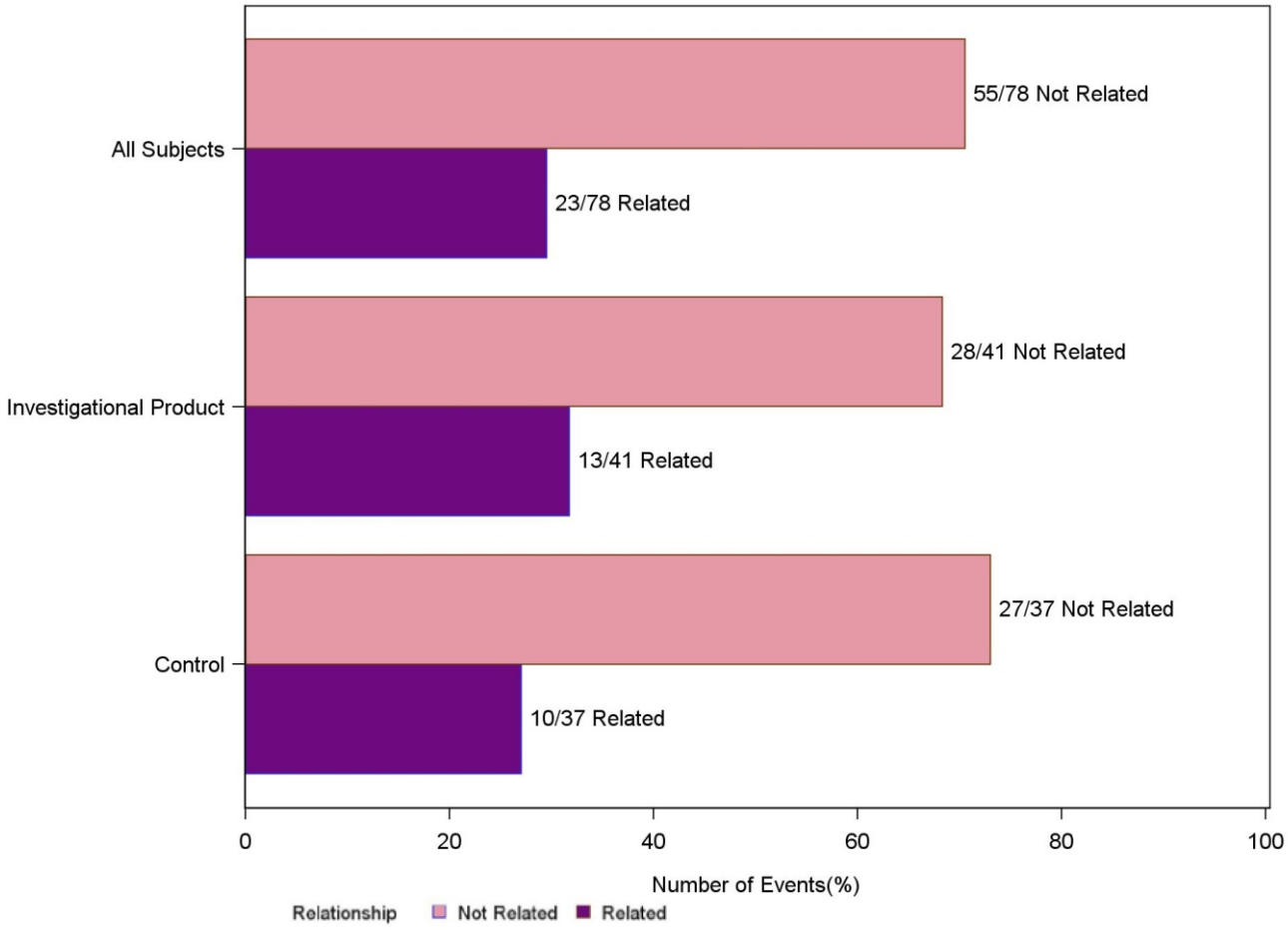


FIGURE 14.3.1.8:
Incidence of Adverse Events by Relationship to Treatment

Sample Figure provided. Figure will include four sets of bar graphs (Group I, Group II, Group III and All Subjects) rather than defining Investigational product and control.

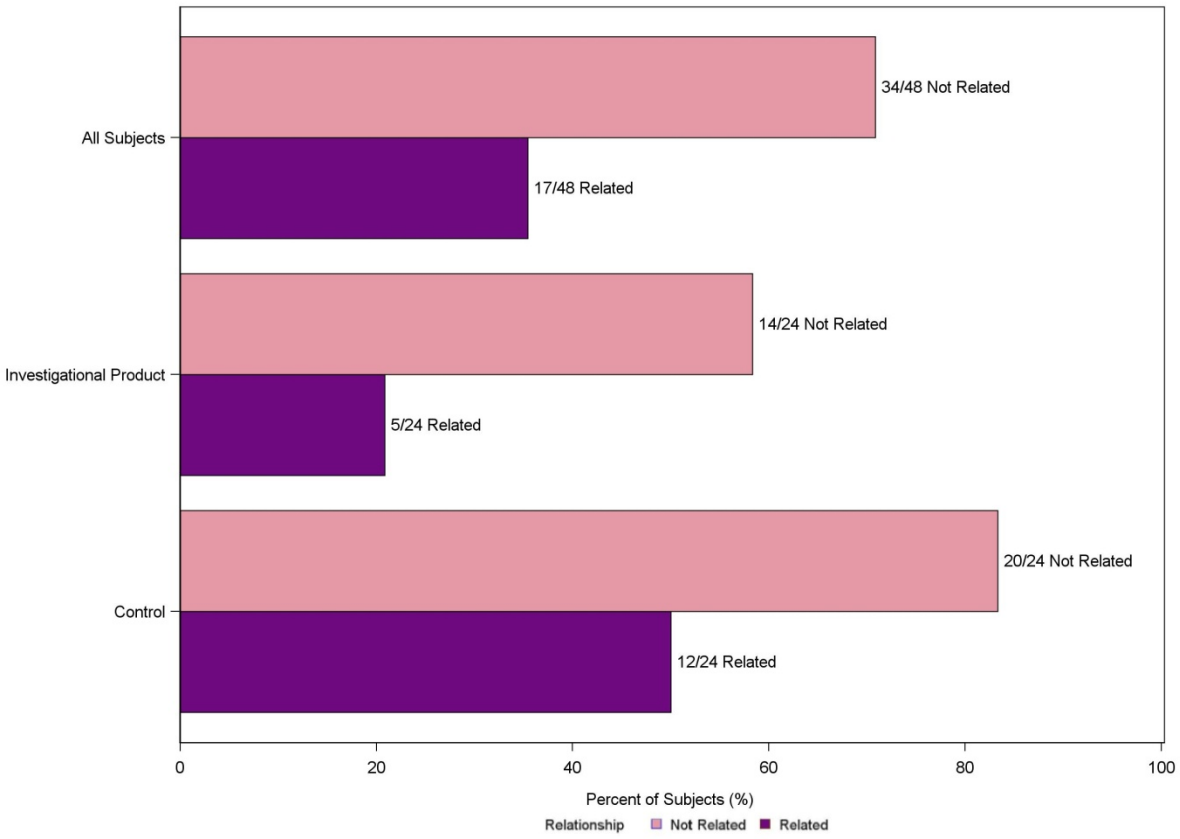
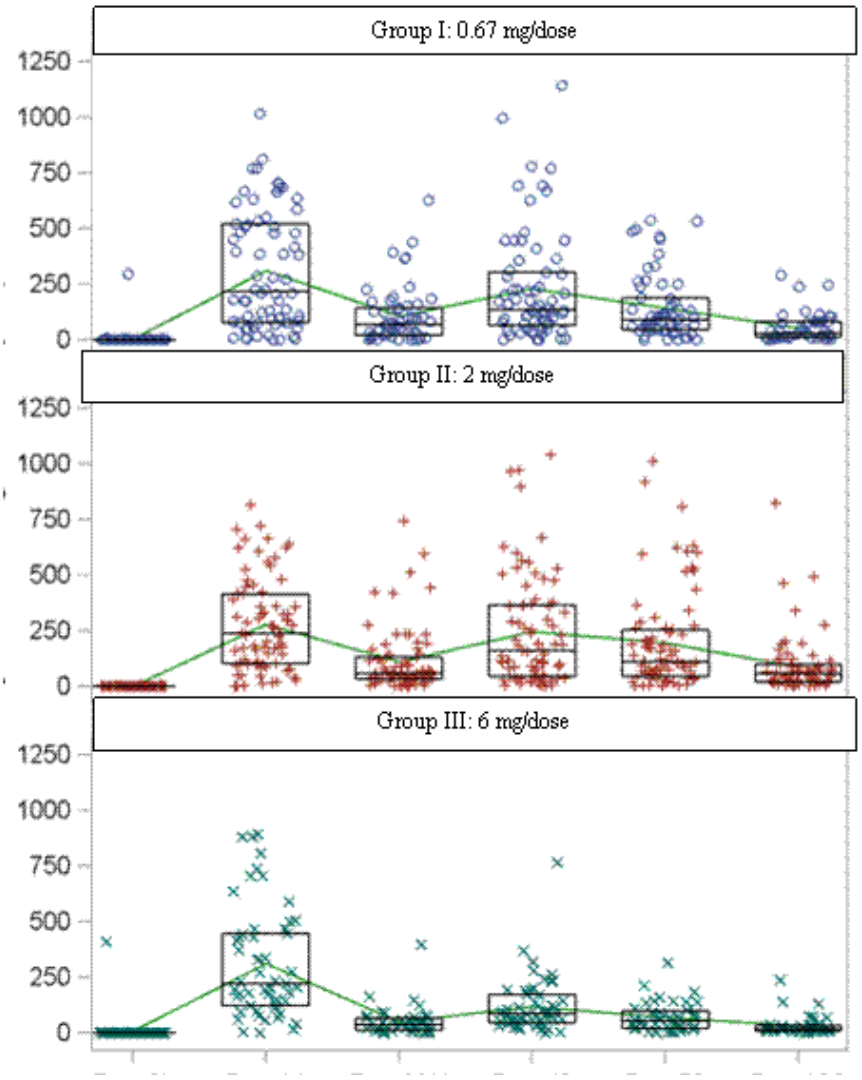


FIGURE 14.3.4:
Laboratory Results by Scheduled Visits: Mean Changes from Screening by Laboratory Parameter, and Group

Sample figure provided below. This paneled figure will be presented for each of the laboratory results collected in the study.

Laboratory safety assessments are collected at Screening, Week 1, Week 6 and Week 14; therefore, only three sets of box plots summarizing the changes from screening will be evaluated for each Group. The x-axis on the figure will be defined as the visit date that the change is measured by (i.e. The x-axis tick mark for the Week 1 change from screening will indicate Week 1). The y-axis of the plot will contain the laboratory result title being summarized and corresponding units of measure. The green lines in the plot connect the median change from screening at each of the timepoints for each Group.



Statistical Analysis Plan

Appendix III:

Listing Mock-Ups

for

Protocol: WRAIR #2274

Study Title:

PHASE I, OPEN-LABEL, DOSE RANGING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF GLS-5300, ADMINISTERED IM FOLLOWED BY ELECTROPORATION IN HEALTHY VOLUNTEERS

Version 1.0

Prepared and distributed by:
The Emmes Corporation
Rockville, Maryland

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LISTING 16.2.1:
Discontinuation of Treatment Subjects

Subject ID	Group	Reason for Treatment Discontinuation	Study Day

LISTING 16.2.2.1:
Subject-Specific Protocol Deviations

Subject ID	Treatment Group	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

LISTING 16.2.2.2:
Non-Subject-Specific Protocol Deviations

Site	Deviation	Start Date	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

LISTING 16.2.3:
Subjects Excluded from Analysis Populations

Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

LISTING 16.2.4.1:
Demographics Data

Subject ID	Group	Sex	Age at Enrollment (years)	Ethnicity	Race

LISTING 16.2.4.2:
Pre-Existing Medical Conditions

Subject ID	Group	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA® System Organ Class	MedDRA® Preferred Term

LISTING 16.2.5:
Treatment Administration Compliance Data

Subject ID	Group	GLS-5300 Dose(s) Missed/Unsuccessful	Electroporation Missed/Unsuccessful	Reflux/leakage at the Injection Site during Administration
		[e.g., Day 0, Week 4, Week 12]	[e.g., Day 0, Week 4, Week 12]	

LISTING 16.2.6.1:
Individual Immunogenicity Titer Response Data

Subject ID	Group	Planned Time Point	Actual Study Day	ELISA Titer	Neutralizing Antibody Titer

LISTING 16.2.6.2:
Individual IFN-γ secreting spot forming units (SFU) ELISpot Response Data

Subject ID	Group	Planned Time Point	Actual Study Day	Average Number of SFUs counted in the Media Control Wells (SFU)	Average Number of SFUs counted in the MERS CoV peptide wells (SFU)

LISTING 16.2.6.3:
Individual Flow Cytometry Response Data

Data listings will summarize the data provided.

LISTING 16.2.7.1:
Solicited Events - Systemic Symptoms[a]

Subject ID	Group	Dose Day	Solicited Systemic Symptom	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternate Etiology

[a] Potential Solicited Systemic Reactions include: Fever, Malaise/Fatigue, Myalgia, Headache, Arthralgia, and Nausea.

LISTING 16.2.7.1:
Solicited Events - Injection/Administration Site Reaction[a] Symptoms

Subject ID	Group	Dose Day	Injection/ Administration Site Reaction Symptom	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternate Etiology

[a] Potential Solicited Injection/Administration Site Reactions include: Pain, Tenderness, Pruritus, Erythema, Induration/Swelling and Bruising.

LISTING 16.2.7.2:
Unsolicited Adverse Events

Part 1

Subject ID	Group	AE Number	Adverse Event	Duration (Days)	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternate Etiology

Part 2

Subject ID	Adverse Event	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	Comments

Note: For additional details about SAEs, see Table 14.3.2.1.

LISTING 16.2.8.1:
Clinical Laboratory Results – Hematology

Subject ID	Group	Sex	Age (years)	Planned Time Point	Actual Study Day	Hemoglobin (g/dL)	Platelets (10^9/L)	WBC (10^9/L)	Neutrophils (cells/μL)	Eosinophils (cells/μL)	Lymphocytes (cells/μL)	Erythrocytes (10^{12}/L)	Monocytes (cells/μL)	Basophils (cells/μL)	Hematocrit (%)

LISTING 16.2.8.2:
Clinical Laboratory Results – Chemistry

Subject ID	Group	Sex	Age (years)	Planned Time Point	Actual Study Day	ALT (SGPT) (U/L)	AST (SGOT) (U/L)	Creatinine (mg/dL)	Sodium (mmol/L)	Glucose (mg/dL)	Bicarbonate (mmol/L)	Blood Urea Nitrogen (mg/dL)	Creatine Kinase (IU/L)	Chloride (mmol/L)	Potassium (mmol/L)

LISTING 16.2.9.1:
Vital Signs

Subject ID	Group	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

LISTING 16.2.9.2:
Physical Exam Findings

Subject ID	Group	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Number)

LISTING 16.2.10:
Concomitant Medications

Subject ID	Group	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Number)	Taken for a condition on Medical History? (MH Number)

LISTING 16.2.11.1:
Pregnancy Reports - Maternal Information

Subject ID	Group	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

LISTING 16.2.11.2:
Pregnancy Reports - Gravida and Para

			Live Births												
Subject ID	**Pregnancy Number**	**Gravida**	**Extremely Preterm Births**	**Very Preterm Births**	**Early Preterm Births**	**Late Preterm Births**	**Early Term Births**	**Full Term Births**	**Late Term Births**	**Post Term Births**	**Still Births**	**Spontaneous Abortion/ Miscarriage**	**Elective Abortions**	**Therapeutic Abortions**	**Major Congenital Anomaly with Previous Pregnancy?**

Note: Gravida includes the current pregnancy, para events do not.

LISTING 16.2.11.3:
Pregnancy Reports - Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

LISTING 16.2.11.4:
Pregnancy Reports - Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

LISTING 16.2.11.5:
Pregnancy Reports - Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion