Protocol Number: G03-52-01-002

Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects

NCT Number: NCT05348993

Document Date: 07 Jan 2025

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects

Protocol No.:	G03-52-01-002
Test Product:	G03-52-01
Indication:	Botulism
Sponsor:	Resilience Government Services, Inc.
Development Phase:	Phase 2
Sponsor Signatory:	Resilience Government Services, Inc.
Sponsor Medical Lead:	[redacted]
Date of the Protocol:	06 Jan 2025
Version of the Protocol:	5.0

The confidential information in this document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Independent Ethics Committee (IEC) and/or Institutional Review Board (IRB). It is understood that the information will not be disclosed to others without written authorisation from Resilience Government Services (RGS) except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- Department of Defense (DOD) Clinical Terms of Award, as applicable.
- Applicable Laws and Regulations

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SPONSOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States of America (US) federal regulations and ICH guidelines.

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects

PROTOCOL NUMBER: G03-52-01-002

Resilience Government Services, Inc.

[redacted] 07 Jan 2025

Resilience Government Services Medical Lead Date (day/month/year)

SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined below in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects

PROTOCOL NUMBER: G03-52-01-002

Principal Investigator	Date (day/month/year)

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ADA	Anti-Drug Antibody
AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
AV	Atrioventricular
BAT	Botulinum antitoxin
BMI	Body Mass Index
BoNT	Botulinum Neurotoxin
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CK	Creatine kinase
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DIC	Disseminated intravascular coagulation
DOD	Department of Defense
DP	Drug product
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECLA	Electrochemiluminescence Assay

ELISA	Enzyme-Linked Immunosorbent Assay
ER	Emergency room
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FESAP	Federal Experts Advisory Panel
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropic Hormone
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDES	Internet Data Entry System
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IM	Intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IUD	Intrauterine Contraceptive Device
IV	Intravenous
IVIG	Intravenous immunoglobulin

Kg	Kilogram
LFT	Liver function test
mAbs/mAb	Monoclonal Antibodies
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA®	Medical Dictionary for Regulatory Activities
mEq/L	Milliequivalent per Liter
Mg/mg	Milligram/milligram
mg/dl	Milligram per Deciliter
ML	Medical Lead
Ml/mL	Milliliter
MM	Medical Monitor
Mm/mm	Millimeter
mmHg	Millimeters of Mercury
MNA	Battelle Mouse Neutralization Assay
MPV	Mean platelet volume
N	Number
NAC	Neutralizing Antibody Concentration
NIAID	National Institute of Allergy and Infectious Diseases
NLM	National Library of Medicine
NOAEL	No-Observed-Adverse-Effect-Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
OHRP	Office for Human Research Protections
OTC	Over-the-counter
PD	Pharmacodynamic
PE	Physical Examination
PEP	Post-Exposure Prophylaxis
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol

PrEP	Pre-Exposure Prophylaxis
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVSS	Pharmacovigilance Safety System
RBC/HPF	Red Blood Cells per High-Power Field
RDW	Red cell distribution width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Symptom-directed
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TIG	Tetanus immune globulin
TK	Toxicokinetic
TLFs	Tables, Listings, Figures
µg	Microgram
ULN	Upper Limit of Normal
VZIG	Varicella Zoster Immune Globulin
WBC	White Blood Count
WFI	Water for injection

1. PROTOCOL SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Resilience Government Services, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Investigational Product:
G03-52-01</td></tr>
<tr><td>Name of Active Ingredient:
NX01, NX02, NX11, XB10, XB18, and XB23</td></tr>
<tr><td colspan="3">Protocol Number: G03-52-01-002</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects</td></tr>
<tr><td colspan="3">Study Center(s): Approximately 15 sites</td></tr>
<tr><td colspan="3">Phase of Development: Phase 2</td></tr>
<tr><td colspan="3">Study Duration: Approximately 8 months</td></tr>
<tr><td colspan="3">Subject Participation:
Subject’s participation in Cohort 1-3 of the study is approximately 254 days (up to a 14-day screening, 1-hour inpatient stay and 240 days outpatient follow-up)
Subject’s participation in Cohort 4 is approximately 134 days (up to a 14-day screening, 8-hour inpatient stay and 120 days outpatient follow-up)</td></tr>
<tr><td colspan="3">Objectives and Endpoints:</td></tr>
<tr><td colspan="2">Primary Objectives</td><td>Primary Endpoints</td></tr>
<tr><td colspan="2">• To evaluate the safety and tolerability of single or repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects
• Cohorts 1-3
o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90
o To evaluate lot-to-lot variability of the two doses of G03-52-01
• For Cohort 4, demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post dose</td><td>• The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit
• The occurrence of changes from baseline in physical examination (PE), vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit
• For Cohorts 1-3, to evaluate target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90
• For Cohort 4, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 4 and 8 hours post dose</td></tr>
</table>

Secondary Objectives:	Secondary Endpoints:
• Cohorts 1-3 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 120 o To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study • Cohort 4 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 2 hours post dose o To assess pharmacokinetics (PK) at pre-dose through end of study o To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study	• Cohorts 1-3 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 o Descriptive statistics of selected PD and ADA at all-time points tested • Cohort 4 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose o PK analysis at the determined timepoints o Descriptive statistics of determined PD and ADA timepoints
Exploratory Objectives:	Exploratory Endpoints:
• For Cohorts 1-3, to evaluate pharmacokinetic (PK) parameters to ensure ADA evaluation adequate of the two lots	• For Cohorts 1-3, descriptive statistics of selected PK parameters at all time points tested of the two lots

Methodology:

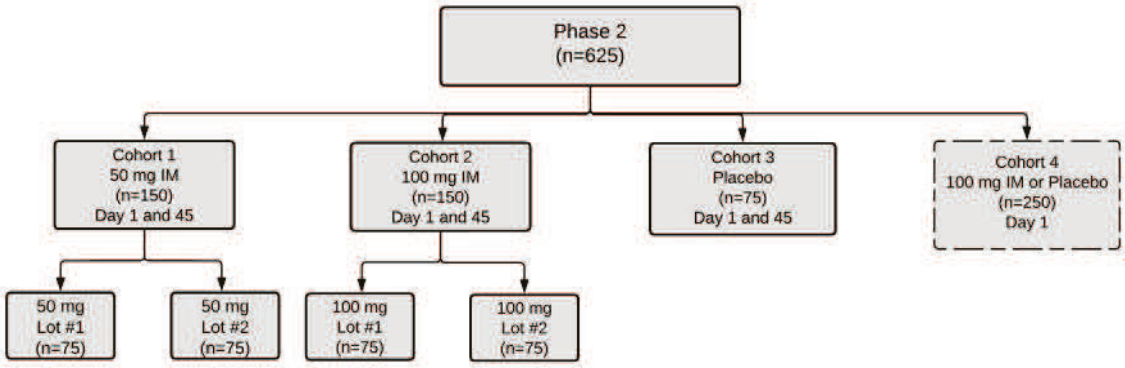
This study is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, PD, and immunogenicity of a repeat dose (50 mg and 100 mg) or single dose (100 mg) of G03-52-01 administered by IM injection(s) in adult subjects.

Approximately 375 subjects will be enrolled in this study. No formal sample size calculations will be performed for this Phase 2 study, as there is no planned formal hypothesis testing, and the target enrollment of 375 subjects was based on previous experiences from studies conducted with similar products. Subjects will be randomized 2:2:1 to the following concurrent cohorts:

- Cohort 1: 50-mg dose of G03-52-01 on Day 1 and repeat 50-mg dose on Day 45 (N=150)
- Cohort 2: 100-mg dose of G03-52-01 on Day 1 and repeat 100-mg dose on Day 45 (N=150)
- Cohort 3: Placebo on Day 1 and placebo on Day 45 (N=75)

Subjects in Cohort 4 will be randomized in a 4:1 to receive a single 100 mg dose of G03-52-01 or Placebo on Day 1 (n=250).

Figure 1: Schematic of Study Design



Subjects who receive 50 mg dose of G03-52-01, 100 mg dose of G03-52-01, or placebo on Day 1 will receive a repeat injection of the same dose on Day 45 for Cohorts 1-3. Within Cohorts 1 and 2, subjects will be randomized 1:1 to Lot 1 or Lot 2 of each respective dose. Subjects in Cohort 4 will be randomized 4:1 to receive G03-52-01 (Lot #C2300157) or Placebo.

The study will include up to 14-day screening period and an approximately 1-hour stay in the clinic after dosing is complete on Day 1 and Day 45 for subjects in Cohorts 1-3 for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240 for Cohorts 1-3.

Cohort 4 subjects will have an 8 hour stay at the clinic after dosing for safety, PD, and PK assessment. and safety follow up. Follow-up visits will occur at 24 hours, 72 hours, and on Days 8, 15, 30, 45, 90, and 120.

Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240 for Cohorts 1-3.

Subjects in Cohort 4 will have safety labs drawn at screening and Day 15, 45, and 120.

For Cohorts 1-3, subjects within each dose lot and placebo cohort will be randomized 2:1 to contribute PD or PK samples according to the following schedules:

PD samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. The first 25 subjects randomized for each drug product (DP) lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using MNA at pre-dose and Days 45, 90, and 120.

PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. A total of 25 subjects for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints.

For Cohort 4, PK and PD samples will be tested for the first 30 subjects who receive active drug and complete sample collection at 24 hours. PD samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours and on Days 30, and 45 and 90. PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120.

ADA samples will be tested at pre-dose and Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240 for study subjects in Cohorts 1-3; and at pre-dose and post-dose on Days 90 and 120 for Cohort 4.

An interim Clinical Study Report (CSR) is planned for the first 125 subjects in Cohorts 1-3 through Day 120.

Study Population:

625 healthy male and female subjects between the ages of 18 and 65 years of age

Inclusion Criteria:

1. Informed consent understood and signed prior to screening procedures.

2. Assessed by the Investigator to be a healthy male or healthy, non-pregnant, non-lactating female between the ages of 18 and 65 inclusive on the day of dosing.
3. Able and willing to comply and be available for all protocol procedures and follow-up for the duration of the study.
4. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2.
5. Females of child-bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1 prior to dosing.
    - *A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses) or surgically sterilized via bilateral oophorectomy, or hysterectomy or bilateral tubal ligation.*
6. If the subject is female and of childbearing potential, she agrees to practice abstinence from sexual intercourse with men or use medically effective contraception (methods with a failure rate of < 1% per year when used consistently and correctly) during participation in the study. Acceptable methods include:
    - Hormonal contraception including implants, injections or oral
    - Two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide)
    - Intrauterine device (IUD) or intrauterine system
7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Appendix B will be excluded.
    - *Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once.*
8. The urine drug screen is negative.
    - *For Cohorts 1-3, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication (except for THC) the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria.*
    - *For Cohort 4, If a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication or positive for THC, the PI may enroll the subject if they meet all other inclusion criteria and none of the exclusion criteria.*
9. Breathalyzer test is negative.
10. Available for follow-up for the duration of the study.
11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4, per Investigator discretion.

Exclusion Criteria:

1. History of any uncontrolled or chronic medical conditions that would either interfere with the accurate assessment of the objectives of the study or increase the risk profile of the subject based on Investigator judgement.
    - *Chronic medical conditions include but not limited to diabetes; Asthma requiring use of medication in the year before screening; Autoimmune disorder such as lupus, Wegener's, rheumatoid arthritis, thyroid disease; coronary artery disease; chronic hypertension; history of malignancy except low-grade (squamous and basal cell) skin cancer thought to be cured; chronic renal, hepatic, pulmonary, or endocrine disease (except previous asthma which has required no treatment for the past year).*
2. Known history of severe allergic reaction of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobulins.
    - *Severe allergic reaction is defined as any of the following: anaphylaxis, urticaria, or angioedema.*
3. Known allergic reactions to any of the study product components present in the formulation or in the processing.
4. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds).
5. Clinically significant abnormal electrocardiogram (ECG) at screening.
    - *Clinically significant abnormal ECG results include but not limited to complete left or right bundle branch block; other ventricular conduction block except for incomplete RBB; 2nd degree or 3rd degree atrioventricular (AV) block; sustained ventricular arrhythmia; sustained atrial*

arrhythmia; two Premature Ventricular Contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; or any condition deemed clinically significant by a study investigator.

6. Positive serology results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at screening.
7. Febrile illness with temperature ≥38°C within 7 days of dosing. Subjects with acute febrile illness within 7 days of dosing may be rescreened no earlier than 7 days following resolution of symptoms.
8. Female subjects that are pregnant or breastfeeding or intending to become pregnant within the projected duration of the trial starting from the Screening visit until last visit.
9. Donation of blood or blood product within 56 days of enrollment.
10. Is currently participating or has participated in a study with an investigational product (IP) within 28 days preceding Day 1 (documented receipt of placebo in a previous trial would be permissible for trial eligibility).
11. Plans to enroll in another clinical trial that could interfere with safety assessment of the IP at any time during the study period.
    - *Includes trials that have a study intervention such as a drug, biologic, or device only*
12. Treatment with a monoclonal antibody (mAB) within 3 months of Day 1.
13. Receipt of antibody (e.g., tetanus immune globulin [TIG], varicella zoster immune globulin [VZIG], intravenous immunoglobulin [IVIG], IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given.
14. Reported active drug or alcohol or substance abuse/independence or illicit drug use that, in the opinion of the Investigator, would interfere with adherence to study requirements.
15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4 (PRN use could be allowed with MM approval).
16. Use of any prohibited medication within 28 days prior to study entry or planned use during the study period.
    - *Prohibited medications include immunosuppressive (except nonsteroidal anti-inflammatory drugs [NSAIDs]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents.*
17. Previous exposure to botulinum toxin, receipt of antibodies against botulinum toxin, or previous treatment with equine antitoxin.
18. Any previous injection or any planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.
19. Any illness or condition that in the judgment of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.
20. Is a study site employee, staff, or close relative as defined.
    - *PIs,Sub-Investigators*
    - *Staff who are supervised by the PI or Sub-Investigators*
    - *Member of the team conducting this clinical trial*
    - *Children, spouse, partners, siblings, and parents of site staff*

Test Product, Dose and Mode of Administration:

G03-52-01 DP is a mixture of five human monoclonal immunoglobulin G (IgG)1 antibodies (NX01, NX11, XB10, XB18, and XB23) and one humanized monoclonal IgG1 antibody (NX02) which bind to non-overlapping epitopes on BoNT/A/B.

- Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied for Cohorts 1-3.
- One DP lot (DP Lot #C2300157) for Cohort 4.

Subjects in Cohorts 1-3 will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid muscle on Study Day 1 and Day 45.

Subjects in Cohort 4 will receive a single 100 mg G03-52-01 or equal volume of placebo in the central, thickest portion of the deltoid muscle on Study Day 1.

Placebo Description:

Placebo (0.9% Sodium Chloride Injection, USP) is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection (WFI).

Criteria for Evaluation:

Safety and Tolerability:

Incidence of AEs, SAEs, medically-attended AEs, changes from baseline in PE, vital signs, and clinical safety laboratory values will be evaluated.

Pharmacodynamics:

Neutralizing antibody concentration (NAC) will be measured by MNA for BoNT serotypes A and B.

Pharmacokinetics:

PK parameters will be measured by ELISA or ECLA for each of the mAbs of G03-52-01 and the following parameters will be estimated:

- $AUC_{(0-t)}$: Area under the concentration time curve to the last concentration above the lower limit of quantitation
- Kel: Elimination rate constant
- $AUC_{(0-\infty)}$: Area under the concentration time curve extrapolated to infinity
- $t_{1/2}$: Terminal elimination half-life
- CL: Total clearance
- V_z: Volume of distribution

Immunogenicity:

ADA samples will be tested in all subjects.

Statistical Methods:

Safety and Tolerability:

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). All AEs that occur after the initiation of study medication will be summarized using frequency counts and percentages. Summaries will be presented by dose cohort and control group.

Vital signs, PEs, and clinical laboratory values will be summarized by dose cohort and control group.

Descriptive summary statistics for laboratory data at admission (baseline value) and each applicable post--injection visit, including change from the baseline value, will be calculated. Descriptive summary statistics for vital signs at screening (baseline value) and each applicable post--injection visit, including change from baseline value, will be calculated. Shift tables showing individual subject changes from baseline will be presented for laboratory parameters using toxicity grading scale (Appendix B). Subjects with Graded values of vital sign and laboratory parameters will be identified in listings.

Pharmacodynamics:

PD samples will be tested by MNA for serotypes A and B. The MNA is used to determine the concentration of functional antibodies in a sample capable of neutralizing BoNT (i.e., amount of BoNT/A or BoNT/B toxin neutralization afforded by the combination of antibodies). NAC, as measured by the MNA, is proposed to bridge efficacy between animal models and humans.

- $AUC_{(0-t)}$: Area under the concentration time curve to the last concentration above the lower limit of quantitation
- C_{max}: Maximum observed concentration
- T_{max}: Time of maximum observed concentration

Descriptive summary statistics of BoNT/A or BoNT/B toxin neutralization will be compared between the two dose cohorts.

Pharmacokinetics:

PK parameters will be estimated for each of the six mAbs separately using noncompartmental methods in WinNonlin or a similar software package. Parameters will be estimated by dose cohort. Summary statistics will include the mean, median, coefficient of variation, and range. When evaluable, estimate PK will include:

- $AUC_{(0-t)}$: Area under the concentration time curve to the last concentration above the lower limit of quantitation
- Kel: Elimination rate constant
- $AUC_{(0-\infty)}$: Area under the concentration time curve extrapolated to infinity
- $t_{1/2}$: Terminal elimination half-life
- CL: Total clearance
- V_z: Volume of distribution

Descriptive summary statistics of the PK parameters will be compared between the two dose cohorts.

Immunogenicity:

Immunogenicity will be evaluated by the incidence of ADA and antibody titers. The presence of ADA will be evaluated over the course of the post-injection period. Descriptive summary statistics of antibody titers will be compared between the 3 cohorts.

Date of the Protocol: 12 Apr 2024

2. GENERAL INFORMATION

A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects.

Protocol No.:	G03-52-01-002
Sponsor:	Resilience Government Services, Inc. 13200 NW Nano Court Alachua, FL 32615, USA
Clinical Research Organization:	ICON GPHS [redacted]
ICON Medical Monitor:	[redacted] ICON Clinical Research LLC [redacted]
Resilience Government Services Medical Lead:	[redacted]
Contract Research Organization (CRO) Safety and Pharmacovigilance Contractor:	ICON Pharmacovigilance & Safety Services [redacted]
Central Laboratory for Safety Testing (Cohorts 1-3):	[redacted]
Back up Laboratory for Safety Testing (Cohorts 1-3):	[redacted]
Central Laboratory for Safety Testing (Cohort 4):	ICON Laboratory Services [redacted]
Research Laboratory for PK and ADA Samples:	[redacted]

Research Laboratory for MNA Samples:	[redacted]

3. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1. Background Information

3.1.1. Introduction

Botulism is caused by absorption of Botulinum Neurotoxin (BoNT) into the blood stream following oral ingestion (food-borne botulism), through the growth of *C. botulinum* in the gastrointestinal tract (infant botulism), in wounds contaminated by the organism (wound botulism), or through inhalation (inhalation botulism).[1] There are 7 BoNT serotypes (A-G)[2] which differ by 35-68% at the amino acid level. Recent data has been published identifying a BoNT/H serotype that appears to be a hybrid of A and F serotype.[3] Three of the BoNT serotypes (A, B, E) cause up to 99% of the cases of human botulism.[4, 5]

Botulism is characterized by prolonged paralysis, which is either immediately fatal or requires prolonged hospitalization in an Intensive Care Unit and mechanical ventilation. The onset and severity of symptoms depends on the amount of toxin absorbed. Onset of symptoms typically occurs 12-72 hours after ingestion, with a range of up to 8 days. Recovery from the paralysis does not occur until new nerve growth occurs. Mechanical ventilator support is commonly needed for 2 to 8 weeks, with some patients requiring support for up to 7 months.[6, 7]

The development of approaches to treat or prevent biothreat botulism has been designated a high priority area by the National Institute of Allergy and Infectious Diseases (NIAID) [see NIAID Biodefense Research Agenda for the Centers for Disease Control and Prevention (CDC) Category A Agents].[8] In June 2011, the Federal Experts Advisory Panel (FESAP) published recommendations concerning the Select Agent Program to address the requirements of Executive Order 13546, "Optimizing the Security of Biological Select Agents and Toxins in the United States", published in the Federal Register on July 8th, 2010; the recommendations of the FESAP classified Botulinum toxins as "Tier 1" agents.

3.1.2. Currently Available Treatments

Equine antitoxin and human botulism immune globulin are currently used to treat adult [9, 10] and infant botulism,[11] respectively. Traditional antitoxins are not readily renewable resources, requiring animal or human immunization, plasmapheresis or bleeding, and serum processing for each lot. Moreover, each lot produced will vary in antibody composition, potency, dosing, and possibly safety profile. Human botulism immune globulin is produced by plasmapheresing laboratory personnel who have been immunized because they are at risk of exposure to BoNT.[11] Although human botulism immune globulin has been shown to be both safe and effective for treating infant botulism, scaling of this product for the biothreat drug repository is not feasible.[11] Moreover, the pentavalent toxoid used to produce botulism immune globulin is no longer available,[12] raising questions concerning the ability to continue to make this product.

With the previous generation of equine antitoxin there was a 9% incidence of acute or delayed hypersensitivity reactions, including serum sickness (3.7%) and anaphylactic shock (1.9%).[9] The observed side effects are attributable to the residual content of the equine Fc region. The current generation heptavalent botulinum antitoxin (BAT) also is produced from horses, but is more thoroughly digested to yield largely Fab and Fab'$_2$ to theoretically reduce the incidence of

hypersensitivity reactions.[13] BAT has a very short serum half-life (8-34 hours depending on serotype) and as a result, an approximately 2% incidence of recurrence of botulism occurs after treatment, a phenomenon called BoNT reintoxication.[14] BAT has an approximately 1% incidence of anaphylaxis, as reported at the 2011 Interagency Botulism Coordinating Committee Meeting by CDC. Rapid deployment of equine antitoxin also is complicated by the inability to use it prophylactically and the need to dilute the product 10-fold and infuse intravenously (IV) slowly over hours. Finally, the potency of equine antitoxins, such as BAT, can vary significantly for sub-serotypes where there is significant sequence difference between the immunizing sub-serotype and other sub-serotypes.

3.1.3. G03-52-01 Development

G03-52-01 drug product (DP) is being investigated for pre-exposure and post-exposure prophylaxis of botulism from BoNT/A and/or BoNT/B in adults. G03-52-01 is a mixture of five human immunoglobulin G (IgG)1 antibodies and one humanized IgG1 antibody each with distinct specificities that are individually expressed in a Chinese hamster ovary (CHO) cell line. Each of the drug substance antibodies (anti-BoNT/A NX01, NX02, NX11 and anti-BoNT/B XB10, XB18, XB23) used in the manufacture of G03-52-01 binds non-overlapping regions on BoNT/A or BoNT/B. While each of the monoclonal antibodies (mAbs) binds to a distinct epitope on BoNT/A or BoNT/B, none was able to sufficiently neutralize BoNT when tested alone *in vivo*. The *in vivo* studies showed that the highest levels of mAb potency were dependent on the presence of three antibodies.[15] The protective capacity of G03-52-01 to neutralize toxicity caused by BoNT/A and BoNT/B has been verified in mice and in guinea pigs.

As these DPs are directed at foreign targets not expressed in animals or humans and based on the observed lack of cross-reactivity of G03-52-01 in healthy human and animal tissue, the focus of the nonclinical safety evaluation of G03-52-01 was to assess potential off-target toxicity and to identify any untoward effects due to administration of either DP.

A Good Laboratory Practice (GLP) 12-week repeat dose toxicity study was performed to evaluate the safety of G03-52-01 in rats when administered by intramuscular (IM) injection once weekly for three injections and to evaluate toxicity and reversibility of effects after a two-month recovery period. The study consisted of four Main Study/Recovery dose groups (15 rats/sex/group) and four Toxicokinetic (TK) dose groups (12 rats/sex/group) Experimental endpoints included moribundity/mortality; physical examinations (PEs), injection site (Draize) reactogenicity scoring; body weights; food consumption; body temperature measurements; clinical pathology parameters (clinical chemistry, hematology, and coagulation); serum drug levels/TKs; organ weights; gross pathology at necropsy; and microscopic pathology. IM treatment at doses of 10, 50, or 100 mg/kg of G03-52-01 against BoNTs A and B did not result in any treatment-related, toxicologically significant, or adverse findings following three injections on Study Days 1, 8, and 15. Therefore, the No Observed Adverse Effect Level (NOAEL) was 100 mg/kg for this study.

The safety and pharmacokinetics (PK) of G03-52-01 were evaluated in a Phase 1 clinical study of a single IM injection of G03-52-01 conducted by Resilience Government Services (RGS). There were no safety concerns with the administration of the DP. All subjects in Cohorts 1-3 of the Phase 2 clinical study completed their last subject visit. All available safety data was reviewed by the DSMB and no safety concerns were identified.

3.2. Rationale For Use of G03-52-01

BoNTs considered the most potent biologic toxins known and are classified as a Category A biothreat with BoNT/A most likely to be used in this scenario. Military biological warfare can weaponize, produce, and disperse aerosols of manufactured purified botulinum toxins with the intent of inhalational exposures.[4] The lethal doses for purified crystalline botulinum toxin type A for a 154-lb (70-kg) man are estimated to be 70 µg when introduced orally and 0.80–0.90 µg when inhaled.[16, 17, 18] Considering the increase in medicinal use, legalized and illicit manufacturing, and limited availability for prophylaxis and treatment options, the serious threat for protecting at-risk military personnel remains.

Two polyclonal antisera-based products are available for the treatment of botulism, BAT® and BabyBIG®. The BAT and BabyBIG polyclonal antisera to treat botulism are made by hyper immunizing either horses or human volunteers, respectively. Equine and human polyclonal antisera are not easily produced or scaled up, carry infectious agent risks, and differ from lot-to-lot production. The development of mAbs represents an alternative that can be produced at larger scale and with high quality

Based on nonclinical and clinical experience with other anti-BoNT mAbs, use of G03-52-01 for the prophylaxis and treatment of inhalation botulism from serotypes A and B in adults may provide the following advantages over the equine antitoxins:

- An improved safety profile:
  - Substantially decreased anaphylaxis and no risk of serum sickness
  - G03-52-01 is directed at foreign targets not expressed in animals or humans
  - Toxicity studies demonstrated a lack of cross-reactivity of G03-52-01 in healthy human tissue
- A longer half-life
- The ability to administer repeated doses for prevention and therapy
- The ability to use small doses via IV and IM administration (permitting flexible administration scenarios, including self-administration)
- The ability to easily and consistently manufacture a large number of doses in sufficient quantities for stockpiling

The Phase 1 clinical trial evaluated the safety and tolerability of a single IM injection of G03-52-01 administered to healthy adults. Sentinel dosing occurred within each cohort as described in the full protocol (G03-52-001.001). The starting dose in the clinical trial was 10 mg, which was escalated to 25 mg, 50 mg, and 100 mg with no safety concerns identified. G03-52-01 was safe and well tolerated in all subjects who participated in the Phase 1 study and in the Phase 2 study to date.

The nonclinical Investigational New Drug (IND)-enabling toxicology studies were designed to support this clinical design, including the dose levels and IM route of administration. Based on the potency of the G03-52-01 lots manufactured to date, the doses evaluated are anticipated to support PK analyses with serum drug concentrations in the range for pre-exposure and post-exposure prophylaxis of botulism from BoNT/A and BoNT/B.

3.3. Potential Risks and Benefits

3.3.1. Potential Risks

The potential risks to the subjects due to participation in the study are those related to venipuncture, the IM injection and the administration of G03-52-01.

Venipuncture

Venipuncture causes transient discomfort and may cause fainting. Bruising at the site of the venipuncture may occur but can be prevented or lessened by applying pressure for several minutes. Infection at the site is possible but highly unlikely as aseptic technique must be employed.

IM Injection

An IM injection may cause some discomfort at the injection site. Other risks may include pain, redness, swelling, or warmth at the injection site. These risks are minimal.

G03-52-01

No safety concerns or risks associated with G03-52-01 were indicated during a Phase 1 study.

Risk Factors Associated with Monoclonal Antibodies

Injections of mAbs may be associated with injection reactions including anaphylaxis/anaphylactoid type reaction, especially during a first exposure, and when administered rapidly. Fever, chills and rigors, typically occurring within the first two hours following injection, characterize these reactions. Other symptoms sometimes associated with injection reactions include nausea, vomiting, rash, pruritus, bronchospasm or other acute pulmonary response, angioedema, hypotension, hypertension, cardiac arrhythmias, dizziness, dyspnea, headache, and malaise.

Risk of Immunogenicity

Antibodies directed against G03-52-01 may develop following injection. This will be assessed by taking blood samples at selected visits throughout the study. G03-52-01 is a fully humanized mAb which based on experience with other humanized or chimeric mAbs, reduces the immunogenic potential.

3.3.2. Known Potential Benefits

This trial has no benefit for the subjects participating in the trial. The knowledge gained in this trial may help society, especially those exposed to, or at risk of being exposed to, the toxins of botulism.

4. OBJECTIVES

4.1. Study Objectives

Primary Objective:

- To evaluate the safety and tolerability of single or repeat IM administration of G03-52-01 in health adult subjects
- For Cohorts 1-3
  - Demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90
  - To evaluate lot-to-lot variability of two doses of G03-52-01
- For Cohort 4, demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post dose

Secondary Objective:

- Cohorts 1-3
  - Demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120
  - To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study
- Cohort 4
  - Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 2 hours post dose
  - To assess pharmacokinetics (PK) at pre-dose through end of study
  - To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study

Exploratory Objectives:

- For Cohorts 1-3, to evaluate PK parameters to ensure ADA evaluation adequate of the two lots

4.2. Study Outcome Measures

4.2.1. Primary Endpoints

- The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit
- The occurrence of changes from baseline in PE, vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit

- For Cohorts 1-3, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90
- For Cohort 4, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 4 and 8 hours post dose

4.2.2. Secondary Endpoints

- Cohorts 1-3
  - To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120
  - Descriptive statistics of selected PD and ADA at all timepoints tested
- Cohort 4
  - To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose
  - PK analysis at the determined timepoints
  - Descriptive statistics of determined PD and ADA timepoints

4.2.3. Exploratory Endpoints

- For Cohorts 1-3, descriptive statistics of selected PK parameters at all time points tested of the two lots

5. INVESTIGATIONAL PLAN

5.1. Study Design

This is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, pharmacodynamics (PD), and immunogenicity of a single dose (100 mg) and a repeat dose (50 mg and 100 mg) of G03-52-01 administered by IM injection(s) in adult subjects (Appendix C).

Approximately 625 subjects will be enrolled in this study to receive active product or placebo on Day 1 or Day 1 and Day 45, and will be randomized to the following concurrent cohorts:

- Cohort 1 (N=150, 75 lot #1, 75 lot #2): 50-mg dose
- Cohort 2 (N=150, 75 lot#1, 75 lot#2): 100-mg dose
- Cohort 3 (N=75): Placebo
- Cohort 4 (N=250): 100 mg dose or Placebo

The study will include up to 14-day screening period and an approximately 1-hour stay for Cohorts 1-3 and 8 hours stay for Cohort 4 in the clinic after dosing is complete for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur at 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240 for Cohorts 1-3. For Cohort 4, follow-up visits will occur 24 hours, 72 hours, and on Days 8, 15, 30, 45, 90, and 120.

Safety Analysis

Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240 for Cohort 1-3. Subjects in Cohort 4 will have safety labs drawn at screening and on Day 15, 45, and 120.

PD Analysis

PD samples will be collected for all subjects. Analysis will be completed by the Battelle Mouse Neutralization Assay (MNA) for Serotypes A and B.

Samples for subjects in Cohorts 1-3 will be tested at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using MNA at pre-dose and Days 45, 90, and 120.

All subjects in Cohort 4 will have samples collected at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours and on Days 30, 45, and 90. Samples will be analyzed for the first 30 subjects in Cohort 4, who receive active drug and complete the sample collection at 24 hours. See Figure 2 and Figure 3.

PK Analysis

PK samples will be collected for all subjects. Analysis will be completed by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA).

Samples for subjects in Cohorts 1-3 will be tested at pre-dose, 24 hours and 72 hours post-dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints.

All subjects in Cohort 4 will have samples collected at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120. Samples will be analyzed for the first 30 subjects in Cohort 4, who receive active drug and complete sample collection at 24 hours. See Figure 2 and Figure 3.

ADA Analysis

ADA will be evaluated by ECLA at pre-dose and on Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240 for study subjects in Cohorts 1-3; and at pre-dose and post dose on Days 90 and 120 for subjects in Cohort 4. See Figure 2 and Figure 3.

Figure 2: Cohort 4 Assessments

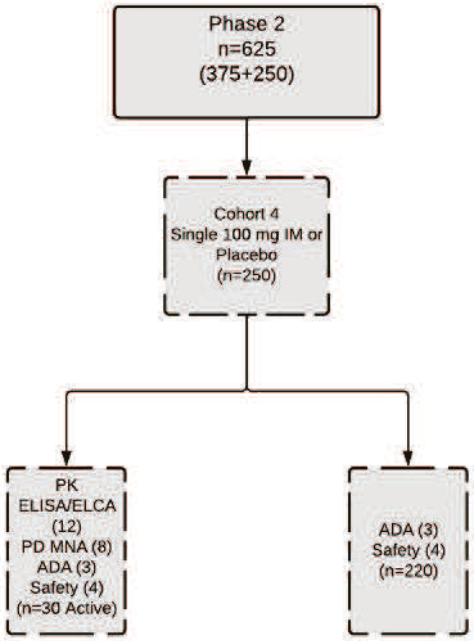
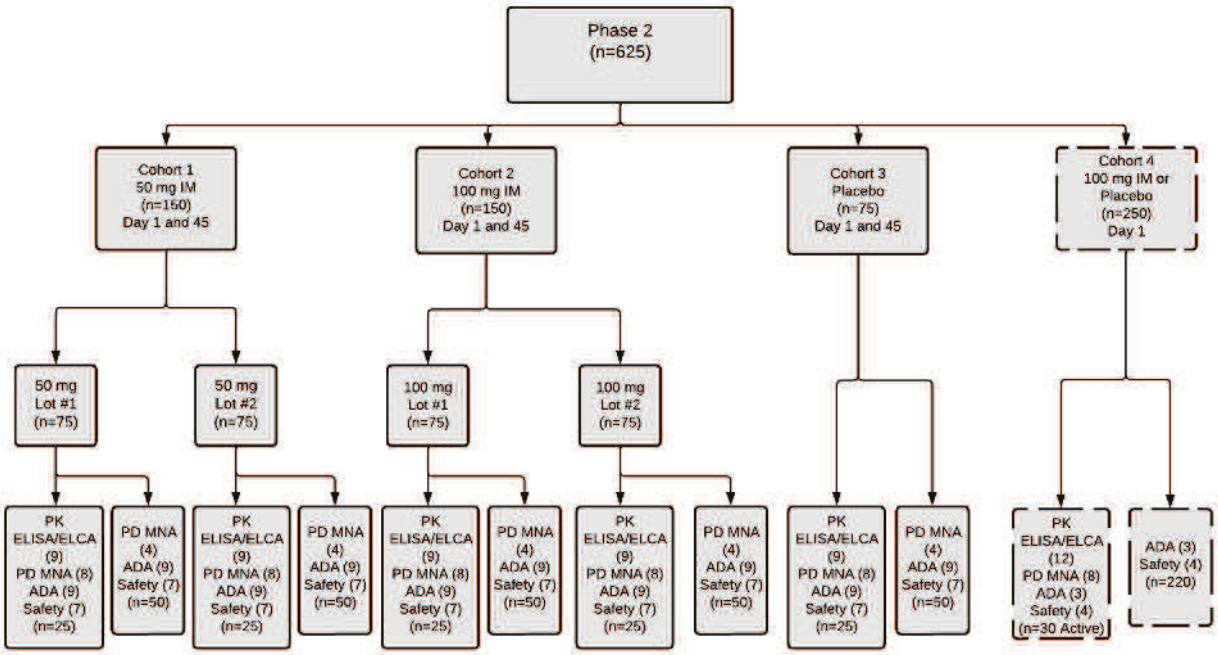


Figure 3: Study Design



5.2. Subject Inclusion Criteria

All must be answered yes for the subject to be eligible for study participation.

1. Informed consent understood and signed prior to screening procedures.
2. Assessed by the Investigator to be a healthy male or healthy, non-pregnant, non-lactating female between the ages of 18 and 65 inclusive on the day of dosing.
3. Able and willing to comply and be available for all protocol procedures and follow-up for the duration of the study.
4. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2.
5. Females of child-bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1 prior to dosing.
    - A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses) or surgically sterilized via bilateral oophorectomy, or hysterectomy or bilateral tubal ligation.
6. If the subject is female and of childbearing potential, she agrees to practice abstinence from sexual intercourse with men or use medically effective contraception (methods with a failure rate of < 1% per year when used consistently and correctly) during participation in the study. Acceptable methods include:
    - Hormonal contraception including implants, injections or oral
    - Two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide)
    - Intrauterine device (IUD) or intrauterine system
7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Appendix B will be excluded.
    - Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once.
8. The urine drug screen is negative.
    - For Cohorts 1-3, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication, (except for THC), the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria.
    - For Cohort 4, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication or positive for THC, the PI may enroll the subject if they meet all other inclusion criteria and none of the exclusion criteria.
9. Breathalyzer test is negative.
10. Available for follow-up for the duration of the study.

11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4, per Investigator discretion.

5.3. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for participation.

All must be answered no for the subject to be eligible for study participation.

1. History of a chronic medical condition that would either interfere with the accurate assessment of the objectives of the study or increase the risk profile of the subject.
    - Chronic medical conditions include but are not limited to diabetes; Asthma requiring use of medication in the year before screening; Autoimmune disorder such as lupus, Wegener's, rheumatoid arthritis, thyroid disease; coronary artery disease; chronic hypertension; History of malignancy except low-grade (squamous and basal cell) skin cancer thought to be cured; chronic renal, hepatic, pulmonary, or endocrine disease (except previous asthma which has required no treatment for the past year).
2. Known history of severe allergic reaction of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobulins.
    - Severe allergic reactions are defined as any of the following: anaphylaxis, urticaria, or angioedema.
3. Known allergic reactions to any of the study product components present in the formulation or in the processing.
4. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds).
5. Clinically significant abnormal electrocardiogram (ECG) at screening.
    - Clinically significant abnormal ECG results include but are not limited to: complete left or right bundle branch block; other ventricular conduction block except for incomplete RBB; 2nd degree or 3rd degree atrioventricular (AV) block; sustained ventricular arrhythmia; sustained atrial arrhythmia; two Premature Ventricular Contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; or any condition deemed clinically significant by a study investigator.
6. Positive serology results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies.
7. Febrile illness with temperature ≥38°C within 7 days of dosing. Subjects with acute febrile illness within 7 days of dosing may be rescreened no earlier than 7 days following resolution of symptoms.
8. Female subjects that are pregnant or breastfeeding or intending to become pregnant within the projected duration of the trial starting from the Screening visit until last dose.
9. Donation of blood or blood product within 56 days of enrollment.

10. Is currently participating or has participated in a study with an investigational product (IP) within 28 days preceding Day 1 (documented receipt of placebo in a previous trial would be permissible for trial eligibility)
11. Plans to enroll in another clinical trial that could interfere with safety assessment of the IP at any time during the study period.
    - Includes trials that have a study intervention such as a drug, biologic, or device only
12. Treatment with a mAB within 3 months of Day 1.
13. Receipt of antibody (e.g., tetanus immune globulin [TIG], varicella zoster immune globulin [VZIG], intravenous immunoglobulin [IVIG], IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given.
14. Reported active drug or alcohol or substance abuse/independence or illicit drug use that, in the opinion of the Investigator, would interfere with adherence to study requirements.
15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4 (PRN use could be allowed with MM approval).
16. Use of any prohibited medication within 28 days prior to study entry or planned use during the study period.
    - Note: Prohibited medications include immunosuppressives (except nonsteroidal anti-inflammatory drugs [NSAIDs]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents.
17. Previous exposure to botulinum toxin, receipt of antibodies against botulinum toxin, or previous treatment with equine antitoxin.
18. Any previous injection or any planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.
19. Any illness or condition that in the judgment of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.
20. Is a study site employee, staff, or close relative as defined.
    - PIs and Sub-Investigators
    - Staff who are supervised by the PI, Sub-Investigators
    - Member of the team conducting this clinical trial
    - Children, spouse, partners, siblings, and parents of site staff

5.4. Treatment Assignment Procedures

5.4.1. Number of Subjects

Approximately 625 subjects will be enrolled in this Phase 2 study.

5.4.2. Randomization Procedures

Randomized treatment assignments will be generated by centralized randomization system. The system will be used each day that a subject, who has been screened and qualified at the site, returns for a study visit. Subjects will be randomized 2:2:1 to the following concurrent cohorts:

- Cohort 1: 50-mg dose of G03-52-01 on Day 1 and repeat 50-mg dose on Day 45 (N=150)
- Cohort 2: 100-mg dose of G03-52-01 on Day 1 and repeat 100-mg dose on Day 45 (N=150)
- Cohort 3: Placebo on Day 1 and placebo on Day 45 (N=75)

Within Cohorts 1 and 2, subjects will be randomized 1:1 to receive their study drug from Lots 1 or 2 of the drug. Within each of the 4 study drug dose/lots and the placebo cohort, subjects will be randomized 2:1 to provide PD or PK specimens at visits specified in the Schedule of Assessments (Appendix A).

Subjects in Cohort 4 will be randomized in a 4:1 to receive a single 100-mg dose of G03-52-01 or Placebo on Day 1 (N=250).

All individuals with access to study subjects or subject data will remain blinded until all data are entered and verified, and database is locked.

5.4.3. Masking Procedures

The study staff participating in the administration of study product and assessment of the subjects will not be aware of the contents of the IM vial. The G03-52-01 and placebo will look identical, so the study staff and the subject will not be able to determine whether placebo or G03-52-01 is being injected.

5.4.4. Procedure for Unscheduled Breaking of the Randomization Code

The Investigator may unblind a subject's treatment assignment only in the case of an emergency or SAE when knowledge of the study treatment is essential to the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator should first discuss the options with the ICON GPHS Medical Monitor (MM) and the RGS Medical Lead (ML) or appropriately designated RGS personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the ICON GPHS MM and the RGS as soon as possible but without revealing the subject's treatment assignment. The date and reason for unblinding must be recorded on the SAE form.

6. WITHDRAWAL OR DISCONTINUATION

6.1. Withdrawal or Discontinuation by Subject

A subject may withdraw from the study at any time for any reason, without any consequence. If a subject withdraws consent, the Investigator will make all efforts to understand the reason and this information will be documented. If subjects withdraw from the study, subjects will be encouraged to remain in the study for safety follow-ups. If applicable, safety could be managed via telephone consultation for such subjects.

6.2. Withdrawal or Discontinuation by Investigator

A study subject will be discontinued from participation in the study if any of the following reasons occur prior to dosing:

- Development of any exclusion criteria
- Request by the subject to terminate participation
- Requirement for prohibited concomitant medication or treatment

A subject may be removed from the study for the following reasons post dosing; however, whenever possible the subject should be followed for safety per protocol:

- Failure to adhere to the protocol requirements.
- Lost to follow-up.
- Request of primary care provider.
- At the request of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or Food and Drug Administration (FDA)
- The subject's well-being based on the opinion of the Investigator.
- The occurrence of an SAE or AE warranting withdrawal.
- If a withdrawn subject has an active AE or SAE, they will be followed until resolution or stabilization of the event. The clinical site should make all practical effort to follow up with the withdrawn subject to complete early study termination assessments.

7. STUDY PRODUCTS

7.1. Description of Study Products

G03-52-01 DP is a mixture of five human monoclonal IgG_1 antibodies and one humanized monoclonal IgG_1 antibody, which bind to non-overlapping epitopes on BoNT/A/B. Each of the component antibodies, NX01, NX02, NX11, XB10, XB18, and XB23, is separately produced in CHO cell lines. Each mAb comprising G03-52-01 has distinct human variable regions that bind to BoNT/A/B. No subtypes of BoNT/A or BoNT/B have been described.

Placebo (0.9% Sodium Chloride Injection, USP) is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection (WFI).

7.2. Acquisition

The G03-52-01 will be supplied by Resilience Government Services (Ology Bioservices).

The normal saline for injection will be supplied by ICON.

7.3. Formulation, Packaging, and Labeling

G03-52-01

G03-52-01 is a mixture of five human IgG1 antibodies and one humanized IgG1 antibody lyophilized in a single use vial to 55 mg per vial. When reconstituted with WFI, the DP is a clear, colorless, sterile aqueous solution in a pH 6 buffered vehicle without preservatives.

The DP, serum/lyophilized, is supplied in a 3mL/13mm glass vial fitted with a 13-mm FluroTec™-coated stopper and flip-up aluminum seal.

Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied for Cohorts 1-3.

One DP Lot (DP Lot #C2300157) will be supplied for Cohort 4.

Placebo (Normal Saline, 0.9% Sodium Chloride, USP)

0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride and WFI. Each mL contains sodium chloride 9 mg and contains no preservatives, bacteriostatic, antimicrobial agent, or added buffer. The solution is clear in appearance with a pH range of 4.5 to 7.0.

7.4. Product Storage and Stability

G03-52-01

G03-52-01 DP Lots #274-190416 and #279-190722 will be shipped refrigerated at 2-8°C (36-46°F) and should be stored refrigerated at 2-8°C (36-46°F) until time of preparation. If a vial is removed from refrigeration, it must be used within 8 hours. G03-52-01 DP Lot #C2300157 will be shipped and stored at room temperature (20 to 25°C [68 to 77°F). If not used, it must be quarantined and maintained for study product accountability. G03-52-01 should be protected from direct sunlight. G03-52-01 is not light sensitive under normal shipping and storage conditions. The product should be used within 30 minutes upon reconstitution. Avoid vigorous shaking or agitation.

Placebo (Normal Saline, 0.9% Sodium Chloride, USP)

Store at 20ºC to 25ºC (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°F and 86°F) are permitted]. Protect from freezing.

7.5. Dosage, Preparation and Administration

The unblinded site Research Pharmacist will prepare the study drug on the same day as administration. Each vial should be inspected for overt signs of seal failure or other damage, the presence of particulate matter, or discoloration before use. Product Lots #274-190416 and #279-190722 that fails inspection should be quarantined at 2-8°C and Lot #C2300157 at 20ºC to 25ºC. Preparation of the product will be performed using aseptic technique under a sterile environment (e.g., Biologic Safety Cabinet or laminar flow hood). Based on the subject assigned cohort randomization, the appropriate G03-52-01 dose will be calculated, and the appropriate number of vials will be removed from storage to prepare the injection. Vials containing G03-52-01 should not be vigorously shaken. WFI will be used to reconstitute the G03-52-01 for IM injection. Any unused portion left in the vial should be retained for study product accountability. The placebo will be a normal saline injection without the addition of G03-52-01. The product should be used within 30 minutes upon reconstitution.

The subjects will be admitted to the research clinic on the day of the planned injection. Verification that the subject still meets all inclusion criteria and does not have any exclusion criteria must be made prior to randomization. The unblinded site Research Pharmacist will prepare the injection as described in the Pharmacy Manual and the injection must be completed within 30 minutes after preparation. G03-52-01 or Placebo should be administered as a single IM injection to the central, thickest portion of the deltoid muscle.

Subjects in Cohorts 1-3 will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid, on Study Day 1 and a repeat dose on Day 45. Subjects in Cohort 4 will receive 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid muscle, on Study Day 1.

7.6. Accountability Procedures for the Study Products

The Site PI is responsible for the distribution and disposition of study product (both G03-52-01 and placebo) and has ultimate responsibility for accountability. The site PI may delegate this responsibility to the unblinded site Research Pharmacist. If delegated, the site Research Pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, temperature monitoring, and storage conditions, and final disposition of the study product.

All study products, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. Used and unused G03-52-01 vials and placebo vials will be retained until monitored and released for disposition as per requirements.

Upon completion of the study and after the final monitoring visit, any remaining unused study product will either be returned or destroyed appropriately at the clinical site as per Sponsor requirements and instructions, or in accordance with disposition plans.

7.7. Concomitant Medications

Concomitant medication information will be recorded at Screening for the prior 28 days. At each subsequent study visit, each new concomitant medication and changes to existing medications will be recorded. Subjects will be required not to utilize non-study medication or herbal supplements during the study except those deemed necessary by the site PI or Sub-Investigator. Any drug (e.g., over-the-counter [OTC] herbal supplement, vitamins or prescription) used by the subject during the course of the trial will be recorded in the subject's source documents and on the appropriate electronic Case Report Form (eCRF).

Subjects will be instructed to refrain from the receipt of any of the following during study participation unless medically indicated and deemed immediately necessary by their private physician:

- Blood or blood products
- Any antibody (e.g., TIG, VZIG, IVIG, IM gamma globulin)
- Any live vaccines
- Monoclonal antibody
- Botulinum toxin (including products such as: Botox)
- H1 antihistamines (PRN use could be allowed with MM approval)
- Immunosuppressives (except NSAIDs)
- Immune modulators
- Oral corticosteroids (topical/intranasal steroids are acceptable)
- Anti-neoplastic agents

8. STUDY PROCEDURES

8.1. Demographic/Medical History

Medical history will be obtained by direct interview. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat (HEENT), mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. The medical history will include current and past medical diagnoses, hospitalizations and major surgical procedures. Demographic information (date of birth, gender, race, ethnicity) will be obtained as part of the medical history assessment. The medical history will be obtained at screening and updated upon admittance to the unit on Day 1.

8.2. Physical Examination

An abbreviated PE will be conducted at the screening visit and on Day 1 and at the end of study visit. Height and weight will be obtained at screening. An abbreviated PE is distinguished from a complete PE as all body system assessments are not required (e.g., pelvic, rectal, etc.). On Day 1, the PE will focus assessment for the presence of the following in order to detect signs of a hypersensitivity reaction:

- General appearance including alertness and any difficulty breathing
- HEENT (confirm no swelling of lips/tongue/uvula)
- Chest (confirm no stridor or wheezing)
- Heart (assess regularity of rhythm)
- Skin (confirm no hives, examine for any eruptions)
- Joints (confirm no swelling, warmth, or tenderness)

A symptom-directed PE will be performed at all other in-clinic study visits. Symptom-directed PEs will be performed based upon an unsolicited complaint for the subject. The exam will focus on the organ system as appropriate. All symptom-directed PEs will be documented in the subject's source record. Any new findings on examination post dosing or worsening of existing conditions are to be reported as AEs.

8.3. Vital Signs

Vital sign assessments including systolic and diastolic blood pressure (BP) [measured after sitting for at least 10 minutes], heart rate (HR), and oral temperature will be performed at each in-clinic study visit. Vital signs that are thought to be aberrant due to an error in measurement may be repeated. During screening and follow-up, a measurement that is a Grade 1 (as referenced in Appendix B) may be repeated once if the PI believes a transient condition led to the aberrant value.

Vital signs obtained at screening will serve as baseline values for the subject. Grade 1 values are allowable unless deemed clinically significant by the study Investigator.

8.4. Electrocardiogram

A 12-lead ECG will be performed at screening (all cohorts) and Day 15 (Cohorts 1-3) and reviewed by the study PI or a co-Investigator to assess the cardiac status of a subjects for enrollment and for any significant changes at Day 15 (Cohorts 1-3). ECGs will be performed after the subject rests quietly for at least 10 minutes. To be eligible for participation, the QT interval should be ≤450ms, and there must be no clinically significant ECG abnormalities according to the study investigators and may be repeated once.

8.5. Laboratory Evaluations

Laboratory assessment schedule can be found in the Schedule of Assessments in Appendix A and further detailed in the Laboratory Manual.

8.5.1. Screening Laboratory Tests

8.5.1.1. Viral Serology Testing

Subjects will be screened for HIV, HBsAg, and antibody to HCV. These tests must be negative for eligibility into the study. In cases where a false positive result is suspected, confirmatory testing may be performed (e.g., Polymerase Chain Reaction).

8.5.1.2. Drug Screen

A breathalyzer test and drug urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP.

8.5.1.3. Pregnancy Testing

For women of child-bearing potential, a serum pregnancy test will be done at screening and must be negative. A urine pregnancy test will be done at Visit 2 (Day 1), which must be reported as negative before dosing. A urine pregnancy test will be repeated on Day 45 and must be negative before dosing for Cohorts 1-3 and at the end of study for all subjects.

8.5.2. Screening and Safety Laboratory Tests

The following laboratory tests will be done at screening and end of study. Subjects should be fasting. This means no food or drink (other than water) for at least 8 hours prior to sampling.

- Hematology: hemoglobin, white blood count (WBC) with differential, absolute neutrophil count and platelet count. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), which are included in a complete blood count (CBC) with differential, will not be graded.
- Chemistry: serum creatinine, blood urea nitrogen (BUN), calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, and total creatine kinase (CK).

- Urine Dipstick: Urine protein, blood and glucose must be negative or trace. Menstruating females failing with a positive blood on urine dipstick may be retested following cessation of menses.
- Urinalysis: If dipstick is abnormal, a complete urinalysis with microscopic will be performed. When a urine dipstick is more than trace positive for blood (whether a menstruating female or other subject), that subject would not be excluded if the urine microscopic exam shows <5 red blood cells per high-power field (RBC/HPF).

Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once. Laboratory values will be entered in the Clinical Labs eCRF.

All laboratory values will be evaluated based on toxicity table (modified from FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials). Safety labs with a Grade 1 value (Appendix B) will not exclude a subject from participation but will serve as their baseline value.

8.5.3. Hypersensitivity Panel

A hypersensitivity panel includes cytokine and complement panels, immunoglobulin E (IgE) and tryptase. This 14 mL sample will be drawn on Day 1 prior to dosing for Cohorts 1-3 only. The sample will be processed only if the subject has a hypersensitivity reaction. If a subject develops anaphylaxis or anaphylactoid reaction, an additional 14 mL sample will be drawn during the event and another will be drawn after the event. No sample will be collected for Cohort 4.

8.6. Special Assays or Procedures

The blood sample volumes to be collected for each test are referenced in the lab manual.

8.6.1. Pharmacodynamic Assay

Blood samples will be drawn at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (prior to dosing) 49, 90, and 120 for Cohorts 1-3. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, and on Days 30, 45, and 90. PD samples will be analyzed for neutralizing antibody concentration (NAC) using the validated Battelle MNA.

8.6.2. Pharmacokinetic Assay

Blood samples will be drawn at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (prior to dosing), 49, 90, and 120 for Cohorts 1-3. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120. The PK analysis of each mAbs will be assessed using a validated ECLA or ELISA.

8.6.3. Anti-Drug Antibody Assay

Blood samples will be drawn for Cohorts 1-3 at pre-dose and Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 and pre-dose and post-dose on Days 90, and 120 for Cohort 4 for

determining the presence of ADA using a validated ECLA that measures total ADA in serum. This will be performed to assess immunogenicity.

8.6.4. Future Use

Blood samples will be drawn for subjects who consent to have samples stored for future use. These samples will be collected at pre-dose and on Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 for Cohorts 1-3.

This blood sample may be used in new or different laboratory tests, to provide information for the development of new DPs, or for the studies of botulism or other infections.

8.6.5. Specimen Preparation, Handling, and Shipping

Details regarding the specimen preparation, handling, storage, and shipping are described in the Laboratory manual.

9. STUDY SCHEDULE

9.1. Study Schedule (Cohorts 1-3)

9.1.1. Screening Period (Day -14 to Day -1)

After providing written informed consent, each subject will be assigned a Subject ID number and undergo an eligibility assessment. Results of screening tests and procedures will be evaluated by the Investigator to determine eligibility prior to enrollment and randomization. The following will be done during the screening period (within 14 days prior to administration of study product). The following procedures will be performed.

- Record demographics including age, gender, race and ethnicity. Obtain contact information.
- Obtain medical history. The medical history will include the following:
  - Current medical diagnoses
  - Past medical diagnoses
  - Hospitalizations
  - Major surgical procedures
  - Receipt of antibody (e.g., TIG, VZIG, IVIG, IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given
  - Live vaccines within the last 28 days
  - Inactivated vaccines within the last 28 days
    - Subjects will be eligible to receive any authorized COVID-19 vaccine after they complete Study Day 8, if they desire
  - Blood donation within the last 56 days
  - Allergic reactions
  - Drug and/or alcohol use or dependence
  - Receipt of investigational drug within the last 28 days
  - Receipt of mAB within the last 3 months
  - Exposure to botulinum toxin in the past 4 months
  - Previous exposure to botulinum toxin, receipt of antibodies against botulinum toxin, or previous treatment with equine antitoxin
  - Any previous injection or planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason
- Review concomitant medication history, including all medications taken within the last 28 days

- Review current use of contraceptive methods and recent menstrual history (female subjects only)
- Perform PE by licensed clinician listed on the Form FDA 1572 (examples include Medical Doctor, Nurse Practitioner and Physician's Assistant)
- Obtain height and weight and calculate BMI
- Take vital signs (systolic and diastolic BP, pulse rate, and oral temperature)
- Obtain fasting blood samples for viral serology, clinical laboratory screening tests
- Obtain blood sample for serum pregnancy test for women of childbearing potential
- Obtain urine sample for dipstick urinalysis and urine toxicology
- Obtain 12-lead ECG
- Perform Breathalyzer test for recent alcohol use
- Counsel on the avoidance of pregnancy for women of child-bearing potential
- Counsel on the avoidance of botulinum toxin, vaccines, and drugs

9.1.2. Baseline Evaluation and Dosing Period (Day 1)

Subjects meeting inclusion/exclusion criteria will return to the clinical site the day of the injection and the following procedures will be performed prior to study drug administration:

- Review inclusion/exclusion criteria to ensure the subject remains eligible for enrollment.
- Update medical history.
- Review and update concomitant medications.
- Perform abbreviated PE.
- Obtain vital signs.
- Perform Breathalyzer test to detect recent alcohol use.
- For women of child-bearing potential, a urine human chorionic gonadotropic hormone (hCG) test will be done. The results must be confirmed to be negative before dosing.
- Obtain urine sample for urine dipstick and toxicology.
- Obtain blood samples (Pre-Dose) for:
  - MNA
  - PK
  - ADA
  - Clinical safety labs
  - Hypersensitivity panel

  - Future use samples (if consent given)
  - Distribute reactogenicity diary

Subjects will be randomized to receive 50 mg or 100 mg of G03-52-01 or placebo. Subjects will receive a single 50 mg or 100mg dose of either G03-52-01 or equal volume of placebo (Normal Saline, 0.9% Sodium Chloride, USP), administered IM in the central, thickest portion of the deltoid muscle on Day 1. Subjects will be observed at the study site for approximately 1 hour after dose administration.

9.1.3. Visit 3/24-Hour (± 2 hours) Follow-Up

- Obtain vital signs
- Review and assessment of AEs and SAEs
- Review and update concomitant medications
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
  - Clinical safety labs
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8

9.1.4. Visit 4/72-Hour (± 2 hours) Follow-Up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for PK assessment
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8

9.1.5. Visit 5/Day 8 (±1 Day) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
- Collect reactogenicity diary
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8

9.1.6. Visit 6/Day 15 (±2 Day) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain 12-lead ECG
- Obtain blood samples for the following:
  - PK
  - MNA
  - ADA
  - Clinical safety labs
  - Future use (if consent given)
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection or vaccines for 3 months

9.1.7. Visit 7/ Day 45 (±3 Day) Repeat Dose Period

- Obtain vital signs
- Review and update concomitant medications

- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples (prior to administration of G03-52-01 or Placebo) for the following:
  - PK
  - MNA
  - ADA
  - Clinical safety labs
  - Hypersensitivity panel
  - Future use (if consent given)
- Distribute reactogenicity diary
- Obtain pregnancy test
- Obtain urine dipsticks
- Obtain urine sample for toxicology
- Perform Breathalyzer test to detect recent alcohol use
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine 8 days after visit

Administration of repeat 50 mg or 100 mg G03-52-01 dose or placebo IM injection. Subjects will be observed at the study site for approximately 1 hour after dose administration.

9.1.8. Visit 8/ Day 49 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.9. Visit 9/Day 60 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - Clinical safety labs
  - ADA
  - Future use (if consent given)
- Collect reactogenicity diary
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.10. Visit 10/Day 90 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
  - ADA
  - Future use (if consent given)
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.11. Visit 11/Day 120 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE

- Obtain blood samples for the following:
  - PK
  - MNA
  - ADA
  - Clinical safety labs
  - Future use (if consent given)
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.12. Visit 12/Day 150 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - ADA
  - Future use (if consent given)
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.13. Visit 13/Day 180 (±3 Days) Follow-up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - ADA
  - Future use (if consent given)
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.1.14. Visit 14/Day 240 (±5 Days) End of Study Visit

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform abbreviated PE
- Obtain blood samples for the following:
  - ADA
  - Clinical safety labs
  - Future use (if consent given)
- Obtain urine pregnancy test
- Obtain urine dipstick
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.2. Study Schedule (Cohort 4)

9.2.1. Screening Period (Day -14 to Day -1)

After providing written informed consent, each subject will be assigned a Subject ID number and undergo an eligibility assessment. Results of screening tests and procedures will be evaluated by the Investigator to determine eligibility prior to enrollment and randomization. The following will be done during the screening period (within 14 days prior to administration of study product). The following procedures will be performed.

- Record demographics including age, gender, race and ethnicity. Obtain contact information.
- Obtain medical history. The medical history will include the following:
  - Current medical diagnoses
  - Past medical diagnoses
  - Hospitalizations
  - Major surgical procedures
  - Receipt of antibody (e.g., TIG, VZIG, IVIG, IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given
  - Live vaccines within the last 28 days
  - Inactivated vaccines within the last 28 days
    - Subjects will be eligible to receive any authorized COVID-19 vaccine after they complete Study Day 8, if they desire

  - Blood donation within the last 56 days
  - Allergic reactions
  - Drug and/or alcohol use or dependence
  - Receipt of investigational drug within the last 28 days
  - Receipt of mAB within the last 3 months
  - Exposure to botulinum toxin in the past 4 months
  - Previous exposure to botulinum toxin, receipt of antibodies against botulinum toxin, or previous treatment with equine antitoxin
  - Any previous injection or planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason
- Review concomitant medication history, including all medications taken within the last 28 days
- Review current use of contraceptive methods and recent menstrual history (female subjects only)
- Perform PE by licensed clinician listed on the Form FDA 1572 (examples include Medical Doctor, Nurse Practitioner and Physician's Assistant)
- Obtain height and weight and calculate BMI
- Take vital signs (systolic and diastolic BP, pulse rate, and oral temperature)
- Obtain fasting blood samples for viral serology, clinical laboratory screening tests
- Obtain blood sample for serum pregnancy test for women of childbearing potential
- Obtain urine sample for dipstick urinalysis and urine toxicology
- Obtain 12-lead ECG
- Perform Breathalyzer test for recent alcohol use
- Counsel on the avoidance of pregnancy for women of child-bearing potential
- Counsel on the avoidance of botulinum toxin, vaccines, and drugs

9.2.2. Baseline Evaluation and Dosing Period (Day 1)

Subjects meeting inclusion/exclusion criteria will return to the clinical site the day of the injection and the following procedures will be performed prior to study drug administration:

- Review inclusion/exclusion criteria to ensure the subject remains eligible for enrollment.
- Update medical history.
- Review and update concomitant medications.
- Perform abbreviated PE.

- Obtain vital signs.
- Perform Breathalyzer test to detect recent alcohol use.
- For women of child-bearing potential, a urine human chorionic gonadotropic hormone (hCG) test will be done. The results must be confirmed to be negative before dosing.
- Obtain urine sample for urine dipstick and toxicology.
- Obtain blood samples for:
  - MNA at pre-dose and 2 hours, 4 hours, and 8 hours post-dose
  - PK at pre-dose and 2 hour, 4 hours, 8 hours post-dose
  - ADA at pre-dose
- Distribute reactogenicity diary

Subjects will be randomized to receive 100 mg of G03-52-01 or placebo. Subjects will receive a single 100mg dose of either G03-52-01 or equal volume of placebo (Normal Saline, 0.9% Sodium Chloride, USP), administered IM in the central, thickest portion of the deltoid muscle on Day 1. Subjects will be observed at the study site for approximately 8 hours after dose administration.

9.2.3. Visit 3/24-Hour (± 2 hours) Follow-Up

- Obtain vital signs
- Review and assessment of AEs and SAEs
- Review and update concomitant medications
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8

9.2.4. Visit 4/72-Hour (± 2 hours) Follow-Up

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs

- Perform symptom-directed PE
- Obtain blood samples for PK assessment
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8

9.2.5. Visit 5/ Day 8 (±1 Day)

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for PK assessment
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection
- Counsel the subject on eligibility to receive any authorized COVID-19 vaccine after they complete Study Day 8
- Collect reactogenicity diary

9.2.6. Visit 6/ Day 15 (±2 Day)

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - Clinical safety labs
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.2.7. Visit 7/ Day 30 (±3 Day)

- Obtain vital signs

- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for the following:
  - PK
  - MNA
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.2.8. Visit 8/ Day 45 (±3 Day)

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Perform pregnancy test
- Obtain blood samples for the following:
  - PK
  - MNA
  - Clinical safety labs
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.2.9. Visit 9/ Day 90 (±3 Day)

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform symptom-directed PE
- Obtain blood samples for ADA, MNA, and PK assessment.
- Counsel women of child-bearing potential on the avoidance of pregnancy
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.2.10. Visit 10/Day 120 (±3 Days) End of Study Visit

- Obtain vital signs
- Review and update concomitant medications
- Review and assessment of AEs and SAEs
- Perform abbreviated PE
- Obtain blood samples for the following:
  - PK
  - ADA
  - Clinical safety labs
- Obtain urine pregnancy test
- Obtain urine dipstick
- Counsel the subject not to receive any botulinum toxin preparation (e.g., Botox) for 4 months after injection

9.3. Study Completion

A subject is considered to have completed the study if he/she completes all the study visits.

9.4. Unscheduled visits

A subject may return to the clinic for an unscheduled visit at any time. The following activities at a minimum should be performed:

- Obtain vital signs
- Perform symptom-directed PE as appropriate
- Review and update concomitant medications
- Assessment of AEs and SAEs

9.5. Lost to Follow-Up

A subject will be considered as lost to follow-up if a subject is unreachable for a minimum of 3 consecutive visits/follow-ups including telephone consultation. Subjects will be asked to provide an emergency contact at the time of consent process. All attempts will be made using all contact information available and all such attempts will be documented. All data that would have been collected at subject visits will be marked as missing.

9.6. Study Site Discontinuation

RGS, the Investigator, or IRB/IEC can decide to discontinue a study site participation in the study based on medical or safety reasons or based on regulations, laws and Good Clinical Practice (GCP) guidelines.

9.7. Assessment of Safety

Regulatory requirements including the FDA regulations and International Conference on Harmonization (ICH) Guidelines for GCP set forth safety monitoring and reporting responsibilities of sponsors and investigators to ensure the safety and protection of human subjects participating in clinical trials.

Responsibilities

Investigators participating in this clinical trial are responsible for and will:

- evaluate subject safety including assessment of AEs for seriousness, severity, and causality;
- notify the Sponsor (RGS) of SAEs immediately;
- provide detailed written reports, including necessary documentation requested by the Sponsor or IRB promptly following immediate initial reports;
- inform the IRB of AEs as required by applicable regulatory requirements, and;
- have emergency staff and medications, such as epinephrine, corticosteroids, bronchodilators, and emergency tool kits for emergent intubation and initial acute cardiopulmonary resuscitative care available at all clinical sites in the event they are needed during and immediately after IM injections.

9.8. Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The PI is responsible for ensuring familiarity and adherence to this section.

9.8.1. Adverse Events

ICH E6(R2) defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

9.8.2. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  **Life-threatening AE. An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.*

9.8.3. Unexpected

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an unapproved IP or package insert/summary of product characteristics for an approved product).

9.8.4. Medically-Attended Adverse Event

A medically-attended AE is any AE or SAE that leads to an unscheduled visit to a healthcare practitioner. A medically-attended AE may include but is not limited to:

- Local (injection site) or systemic symptoms, PE findings, laboratory abnormalities, new clinical conditions or syndromes, or worsening of pre-existing conditions, in study subjects that result in an encounter with a medical professional in either an outpatient or inpatient setting, at any time from receipt of study drug/placebo through the end of the study.

Medically-attended AEs must be documented and graded according to the toxicity grading scale in Appendix B.

9.9. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.9.1. Adverse Events

AEs will be collected at Day 1 during and after dosing. Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if the condition increases in severity or frequency at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product based on the Investigator's assessment.

The Investigator will assess the intensity of AEs based on the following definitions per Toxicity Table (modified from FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials):

- Mild: Grade 1 (awareness of sign or symptom, but easily tolerated)
- Moderate: Grade 2 (discomfort sufficient to cause interference with normal activities)
- Severe: Grade 3 (incapacitating, with inability to perform normal activities)
- Potentially Life Threatening: (Grade 4)

- Death: (Grade 5)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.8.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

9.9.2. Relationship to Study Product

AEs and SAEs must be assessed by the Investigator to determine relationship to study product. All AEs must have their relationship to study product assessed using the following terms:

- Definitely Related: There is a definite probability that the study product caused the AE.
- Possibly Related: There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related: There is not a reasonable possibility that the administration of the study product caused the event.

To help assess, the following factors may be considered:

- Temporal relationship of the event to the administration of study product
- Whether an alternative etiology has been identified
- Biological plausibility
- Existing therapy and/or concomitant medications

9.10. Reporting Procedures

9.10.1. Adverse Events

AEs to include medically-attended AEs not meeting the criteria for “SAEs” will be captured on the appropriate Case Report Form (CRF). Information to be collected for AEs includes event description, date of onset, investigator assessment of severity, relationship to study product, date of resolution of the event, seriousness, and outcome.

The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the patient to discontinue, and the outcome.

9.10.2. Serious Adverse Events

The following procedures will apply to all SAEs:

- The PI will report any SAE to ICON Pharmacovigilance Safety System (PVSS) within 24 hours of awareness.
- ICON PVSS will perform an initial check of the SAE and contact the site for any missing elements and then inform the ICON MM of the SAE.
- ICON PVSS will record the information on the appropriate SAE report form and send to RGS.
- Each SAE will be reviewed and followed to resolution or stability by a study physician.
- SAEs will be collected on each subject up to 60 days after his/her last study visit.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to ICON PVSS, at the following address and ICON PVSS will send AE/SAE information to Resilience Government Services, Inc.

ICON PVSS	ICON plc PVSS [redacted]
ICON Medical Monitor	[redacted]
ICON PVSS will send AE/SAE information to Resilience Government Services, Inc.	
Resilience Government Services	Resilience Government Services, Inc. 13200 NW Nano Court Alachua, FL 32615, USA SAE Fax Number: [redacted] SAE Email Address: [redacted]

Other supporting documentation of the event may be requested by ICON PVSS and should be provided as soon as possible.

ICON plc PVSS will send SAEs with the ICON Drug Safety Physician assessment of causality, expectedness, and any impact on the benefit-risk ratio of the IP to RGS. The DOD and the FDA will be notified of SAEs as appropriate, by RGS. HRPO and IRB will be informed of any safety issues as appropriate, per safety management plan by ICON and the PI.

If the Investigator becomes aware of an SAE that is suspected to be related to study product up to 60 days after the subject completes the study, the Investigator will report the event to ICON PVSS.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON within one day as described above. For a non-serious AE that becomes serious, but which is not fatal or life-threatening, a report should be received within 5 days.

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the CRF. The Investigator is responsible for informing the IEC of the SAE as per local requirements. The Investigator should report to ICON, who will forward the report to the appropriate Sponsor representative.

Pregnancy

Pregnancies that occur during the study period will be reported to ICON PVSS on the Pregnancy Report form within 5 days of site awareness.

Efforts will be made to follow all pregnancies occurring prior to 56 days post product administration through to outcome, as described in the Safety Management Plan (e.g., delivery, spontaneous abortion or therapeutic abortion).

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the patient has been withdrawn from the study.

Male subjects participating in this study should report pregnancies of their partners and outcome of the pregnancy, if fathered during the conduct of the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Sponsor on a pregnancy outcomes report form.

A positive urine pregnancy test for a female subject will result in subject discontinuation from the study. Such subject will have follow-ups for pregnancy outcomes. The outcome of pregnancy will be documented even after completion of the study.

All reports of congenital abnormalities/birth defects/preterm (< 37 weeks gestation) are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as a follow-up report for outcome of the pregnancy. All outcomes of pregnancy must be reported to ICON on a Pregnancy Outcomes Report Form.

9.11. Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be followed until resolution or stability even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the subject's CRFs.

9.12. Halting Rules

9.12.1. Halting Criteria for the Study

Study dosing may be halted after review of data by the MM in consultation with RGS ML. The Data Safety Monitoring Board (DSMB) will be informed and a review of available safety data will be conducted by the DSMB if any of the following occur:

- Death of a subject following injection and prior to the subject’s last visit that was possibly related to study product
- Two Grade 4 non-laboratory AE (as per FDA guidance toxicity table as modified in Appendix B) related to study treatment, or

- One life-threatening allergic/hypersensitivity reaction (anaphylaxis) in any subject, manifested by bronchospasm with or without urticaria or angioedema, or
- Requiring hemodynamic support with pressor medications or mechanical ventilation, or
- One SAE that is considered definitely or possibly related to study product
- Four or more subjects with a Grade 3 AE in the same organ class (systemic toxicity, clinical laboratory tests or vital signs) possibly related to study drug

9.13. Safety Oversight

9.13.1. ICON Medical Monitor

The ICON MM is the clinical site's primary point of contact for eligibility or safety related questions. The ICON MM is responsible for liaising with RGS ML to ensure that all medical concerns are communicated and will provide any potential pertinent medical communication update to the project team as needed. As well as make a recommendation that the DSMB be convened to review any safety concerns.

The ICON MM will communicate with the RGS ML for any safety related questions. The ICON MM will participate in the planned DSMB meetings and make recommendations that the DSMB be convened to review any safety concerns.

9.13.2. Resilience Government Services (RGS) Medical Lead

The RGS ML will be the main point of contact for the ICON MM including any safety-related questions or concerns. The RGS ML will escalate any medical or safety concerns to the DOD as needed. The RGS ML will participate in the planned DSMB meetings and can make a recommendation that the DSMB be convened to review any safety concerns.

9.13.3. Data Safety Monitoring Board (DSMB)

A centralized, independent DSMB will be established in collaboration with RGS and ICON. The DSMB will review blinded safety data and make safety and tolerability recommendations. More details on the role of and the data provided to the DSMB will be described in a DSMB Charter. See Section 11.2 for more details on planned interim analyses.

The DSMB will periodically review accumulating blinded safety data by group. Prior to each meeting, the ICON statistician will provide the DSMB with AE data. Reports will be cumulative, generated from an up-to-date data file. Based on the reports, the DSMB will determine whether to recommend that the study should be continued, modified, or stopped for safety reasons.

The DSMB may recommend any steps to ensure the safety of study participants and the integrity of the trial. Furthermore, the DSMB may recommend that the trial be terminated or that specific groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. To guarantee the unrestricted performance of its task, the DSMB may receive the individual study morbidity and mortality data from the ICON unblinded statistician.

10. CLINICAL MONITORING

10.1. Direct Access to Source Data/Documents

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a DOD-affiliated, or manufacturer-sponsored study, the site will permit authorized representatives of the sponsor(s), DOD, and regulatory agencies to review (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Forms for use as source document will be derived from the eCRFs provided to site by ICON. Additional source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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, and subject files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. If data is recorded directly into the eCRF with no paper source, then that data should be listed as being a direct electronic data entry with no paper source available.

10.2. Study Monitoring

The Investigator shall permit the Site Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall provide access to medical records for the Monitor in order that entries in the CRF may be verified. The Investigator, as part of his/her responsibilities, is expected to co-operate with ICON in ensuring that the study adheres to GCP requirements.

The Investigator may not recruit subjects into the study until such time that a visit, or with the agreement of the Sponsor, attendance at the Site Initiation Visit (SIV), has been made by a sponsor/ICON monitor to conduct a detailed review of the protocol and CRF.

Clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to RGS.

10.3. Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protection, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines. Site visits may be conducted by an authorized representative of ICON, the IRB, and other regulatory or government agencies to inspect study data, subjects' medical records, and eCRFs in accordance

with ICH guidelines, GCP and the respective local and national government and local regulations and guidelines.

The Investigator will permit authorized representatives of ICON and the respective local and national health authorities to inspect facilities and records relevant to this study, if needed.

A separate monitoring plan, to be developed by ICON, will describe protocol-specific items to be monitored.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Considerations

No formal sample size calculations were performed for this Phase 2 study, as there is no planned formal hypothesis testing, and the target enrollment of subjects was based on previous experiences from studies conducted with similar products.

11.2. Planned Interim Analysis

An interim Clinical Study Report (CSR) is planned for the first 125 subjects across the first three cohorts through Day 120. The data cut will be taken when all 125 subjects have completed their Day 120 visit for PD, PK, and ADA analysis. All available safety from subjects in Cohorts 1-3 will be included until the data cutoff for the DSMB report. The objectives of this interim CSR will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK, PD and immunogenicity parameters within drug dose levels as defined in the SAP.

11.3. Statistical Analysis Plan

A formal Statistical Analysis Plan (SAP) will be developed with mock tables, listings, and figures (TLFs). The ICH Guidance Document E9 (Statistical Principles for Clinical Trials) will be followed for all statistical content. For categorical data, summaries of frequencies and percentages will be presented. Summaries for continuous data will include minimum, lower quartile, median, mean, standard deviation, upper quartile, and maximum. PD, PK and ADA continuous data will include additional summary statistics as described below and in the SAP.

11.4. Analysis Populations

Analysis populations for statistical analyses include intent-to-treat (ITT), safety, per-protocol (PP) and PD and PK populations as shown in Table 1.

Table 1: Analysis Populations

Population	Description
Intention-to-Treat (ITT)	All subjects who were randomized. They will be analyzed according to the treatment group to which they were randomized.
Safety	All randomized subjects who received any study drug. They will be analyzed according to the treatment they actually received.
Per-Protocol (PP)	All subjects in the ITT population who have received all planned study drug, have no major excluding protocol deviations and will be analyzed according to the group to which they are randomized.
Pharmacodynamic (PD)	All Safety population subjects who have sufficient evaluable PD result following dosing. They will be analyzed according to the treatment they actually received.
Pharmacokinetic (PK)	All Safety Population subjects who have sufficient evaluable PK result following dosing.

	They will be analyzed according to the treatment they actually received.

11.5. Statistical Methods

For continuous variables, descriptive statistics will include the number of available records for evaluation, mean, standard deviation, Q1, median, Q3, minimum and maximum. For categorical variables, frequencies and percentages will be calculated for each category. Geometric means, coefficients of variation (%), geometric coefficients of variation (%) and the geometric coefficient of variation 95% confidence intervals will be presented for selective PD, PK, and ADA endpoints. All results will be presented for all subjects and by treatment group using analysis population as appropriate.

All statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4 (or higher), R version 4.0.2 (or higher) and Phoenix WinNonlin version 8.3.1 (or higher).

11.5.1. Enrollment and Disposition

Subject enrollment and disposition will be summarized by treatment group in the ITT population.

11.5.2. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by treatment group in the ITT population.

11.5.3. Safety and Tolerability

All safety analyses will be based on the safety population, unless otherwise stated.

AEs will be coded using Medical Dictionary for Regulatory Activities® (MedDRA® Version 24.0). All AEs that occur after the initiation of study medication will be summarized using frequency counts and percentages. Summaries will be presented by treatment group. The following summaries will be presented for AEs and SAEs:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, or severe)
- By relationship to study medication
- By MedDRA® level hierarchy (system organ class and preferred term)

Unless otherwise specified, at each level of subject summarization in reporting the incidence of an AE, a subject will only be counted once if the subject reported one or more occurrence of an event. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

Vital signs (HR, BP, respiratory rate, pulse oximetry and body temperature), PEs, and clinical laboratory values, including change from baseline, will be summarized descriptively by treatment group, including both visit values and change from baseline (measured at admission) to each visit. In addition, shift tables, showing individual subject changes from baseline will be presented for laboratory parameters using toxicity grading. Subjects with graded values of vital

sign and laboratory parameters will be identified in listings, along with significant changes identified in the symptom-directed physical examinations.

11.5.4. Pharmacodynamics (PD)

Descriptive summary statistics of BoNT/A or BoNT/B toxin neutralization across visits will be compared between the two dose cohorts. by drug dose cohort. Summary statistics will include the number of available records for evaluation, mean, standard deviation, Q1, median, Q3, minimum, maximum, geometric mean, coefficient of variation (%), geometric coefficient of variation (%) and the geometric coefficient of variation 95% confidence interval. Details will be described in the SAP. When evaluable, PD estimates will include the following parameters:

- $AUC_{(0\text{-}t)}$: Area under the concentration time-curve from the time of dosing to the time of the last measurable (positive) concentration.
- T_{max}: Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.
- C_{max}: Maximum observed concentration, occurring at time T_{max}.

11.5.5. Pharmacokinetics (PK)

PK parameters will be estimated for each of the six mAbs separately using noncompartmental methods in WinNonlin or a similar software package. Parameters will be estimated by drug dose cohort. Summary statistics will include the number of available records for evaluation, mean, standard deviation, Q1, median, Q3, minimum, maximum, geometric mean, coefficient of variation (%), geometric coefficient of variation (%) and the geometric coefficient of variation 95% confidence interval. Details will be described in the SAP. When evaluable, PK estimates will include the following parameters:

- $AUC_{(0\text{-}t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation
- Kel: Elimination rate constant
- $AUC_{(0\text{-}\infty)}$: Area under the concentration time-curve extrapolated to infinity
- $t_{1/2}$: Terminal elimination half-life
- CL: Total clearance
- V_z: Volume of distribution

11.5.6. Immunogenicity

Immunogenicity will be evaluated by the incidence of ADA and antibody titers by timepoint. ADA titers will be evaluated over the course of the post-injection period. Descriptive summary statistics of antibody titers will be presented in Cohorts 1, 2 and for subjects receiving active drug in Cohort 4. Details will be described in the SAP.

11.5.7. Missing Values and Outliers

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Handling of outliers identified during the PK, PD and Immunogenicity analysis will be discussed in the SAP.

11.5.8. Multiplicity

There will be no statistical adjustments made for multiple comparisons.

12. QUALITY CONTROL AND QUALITY ASSURANCE

ICON shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures (SOPs) to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with FDA regulations (CFR, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

Following a written Sponsor-accepted site quality management plan, the investigational site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The PI will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities. The PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

The Investigator will ensure that this study is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6(R2); 62 Federal Regulations 25691 (1997), if applicable. The Investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

13.2. Institutional Review Board

Prior to the start of the study, ICON is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant, central IRB listed on the FWA. Any amendments to the protocol or consent materials must also be approved before they are placed into use unless change is for the safety of the subject. Only those IRB members who are independent of the investigators and the Sponsor should provide an opinion on study related matters. Verification of IRB approval of the protocol and the written informed consent will be transmitted by the Investigator or designee prior to the shipment of study product. No deviations from or changes to the protocol will be initiated without prior approval of an appropriate amendment unless change is for the safety of the subject.

13.3. Informed Consent Process

13.3.1. Informed Consent

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. Informed consent should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46. Information should be presented both orally and in written form.

An investigator or designee will describe the protocol to potential subjects face-to-face. The Subject Information and Consent Form may be read to the subjects, but, in any event, the Investigator shall give the subjects ample opportunity to inquire about details of the study and ask any questions before the signing and dating the consent form.

Study staff must inform subjects that the trial involves research, and explain the purpose of the trial, those aspects of the trial that are experimental, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, the procedures of the research study, including all invasive procedures, and the probability for random assignment to treatment groups. Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available, and the important potential benefits and risks of these available alternative procedures. Subjects must

receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed of whom to contact (e.g., the Investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in the trial. The extent of the confidentiality of the subjects' records must be defined, and subjects must be informed that applicable data protection legislation will be followed. Subjects must be informed that the monitor(s), auditors(s), IRB, DOD, RGS, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form (ICF), the subject is authorizing such access. Subjects must be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

Consent forms must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been provided and all questions have been answered to the prospective participant's satisfaction. Each subject's signed ICF must be kept on file by the Investigator for possible inspection by Regulatory Authorities and/or the Sponsor and Regulatory Compliance persons. The subject should receive a copy of the signed and dated written ICF and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

13.4. Exclusion of Women, Minorities, and Children (Special Populations)

Pregnant women, lactating women and children are excluded for safety reasons.

13.5. Subject Confidentiality

Subject confidentiality is held strictly in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval from the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

13.6. Study Discontinuation

RGS has the right to terminate this study or the site's participation at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of AEs indicates a potential health hazard;
- Data recording is inaccurate or incomplete;
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

13.7. Future Use of Stored Specimens

Samples will be collected as outlined in the protocol. Subjects will be given a choice during the informed consent process to have their residual linked samples stored indefinitely for future research, have their residual samples de-linked from any subject information and stored indefinitely, or have their residual linked samples destroyed at completion of the study. The use of long-term stored linked samples will be conducted under the restrictions regarding confidentiality, as outlined in the preceding paragraphs.

Only coded specimens will be sent to the Sponsor with the code identifiers maintained by the PI. Any future research studies will utilize only the residual long-term stored specimens from subjects consenting to future use.

14. DATA HANDLING AND RECORD KEEPING

The Investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **Do not erase, overwrite, or use correction fluid or tape on the original.**

Copies of the eCRF will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

RGS and/or its designee will provide guidance to investigators on making corrections to the data collection forms/source documents and eCRFs.

14.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs must be graded, assessed for severity and causality, and reviewed by the site PI or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the Investigator must maintain complete and accurate documentation for the study.

ICON will serve as the Statistical and Data Coordinating Center (DCC) for this study, and will be responsible for data management, quality review, analysis, and reporting of the study data.

14.2. Data Capture Methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21CFR11-compliant Internet Data Entry System (IDES) provided by ICON. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data must be identified in the protocol.

14.3. Case Report Form/Source Data Handling

The Investigator shall be provided with standardized CRFs and shall ensure that all data from subject visits are promptly entered into the CRFs in accordance with the specific instructions given. The Investigator must sign each CRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. All samples as outlined in Laboratory Manual will be analyzed by the by the central laboratory managed by ICON.

The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and PE reports.

14.4. Retention of Essential Documents

The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

14.5. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6(R2):

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to ICON/RGS.

All protocol deviations, as defined above, must be addressed in study subject source documents. A completed copy of the Protocol Deviation log must be maintained in the Regulatory File, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

15. PUBLICATION POLICY

All manuscripts resulting from this trial will be reviewed by representatives from the sites, DOD and the product manufacturer. Each institution will have at least thirty days to review the publication prior to submission.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine (NLM). Other biomedical journals are considering adopting similar policies. This trial will be registered in NLM in accordance with the new NLM requirements under the Food and Drug Administration Amendments Act (FDAAA).

*Journal Citation :

De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

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16. APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 2: Schedule of Assessments (Cohorts 1-3)

Study Visit	**Screening[1] 1**	**Baseline/ Dosing 2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Unscheduled**
Day of Study	-14 to -1	**D 1**	**1-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 45**	**D49**	**D 60**	**D 90**	**D 120**	**D 150**	**D 180**	**D 240**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±5D)**	
Review Inc/Excl Criteria	X	X														
Demographics	X															
Review Medical History	X	X														
Randomization		X														
Study Drug Administration		X						X								
Concomitant Medications[2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[3]	X	X	(SD)[4]	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	X	SD
Vital Signs[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential[7]	X	X		X			X	X		X		X			X	
Chemistry[6]	X	X		X			X	X		X		X			X	
Serology Panel[12]	X															
Pregnancy Test[8]	X (serum)	X (urine)						X (urine)							X (urine)	
Drug Screening[9]	X	X						X								
Breathalyzer test	X	X						X								
Urine Dipstick[10]	X	X						X							X	
12-lead ECG[11]	X						X									
PK samples[15]		X		X	X	X	X	X[18]	X		X	X				
MNA samples[16]		X		X		X	X	X[18]	X		X	X				
Immunogenicity (ADA) samples[17]		X					X	X[18]		X	X	X	X	X	X	
Future Use Sample[13]		X					X	X[18]		X	X	X	X	X	X	

Study Visit	Screening[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	11	12	13	14	Unscheduled
Day of Study	-14 to -1	**D 1**	**1-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 45**	**D49**	**D 60**	**D 90**	**D 120**	**D 150**	**D 180**	**D 240**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±5D)**	
Hypersensitivity Panel[14]		X						X								
Subject Diary Review[19]			X	X	X	X		X	X	X						

1. Screening will be completed within 14 days prior to administration of study drug and may require more than one visit.
2. Concomitant medications including all of the following: prescription drugs, over-the–counter drugs, herbs, vitamins, nutritional supplements, illicit and recreational substance use, birth control information.
3. PE includes height and weight at screening.
4. Symptom-directed only.
5. Vital Signs to include sitting diastolic and systolic BP, HR, and oral temperature. Vital signs will be checked just before injection on Day1 and Day 45 and every visit.
6. Chemistry panel that will include serum creatinine, BUN, calcium, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, albumin, PT, PTT, INR, total CK, carbon dioxide, and chloride. Subjects should be fasting for the chemistry panel.
7. A CBC with differential will be obtained including WBC, RBC, hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, RDW, MPV, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
8. A serum pregnancy test will be obtained at screening for all women of reproductive capacity. A urine pregnancy test will be obtained and must be resulted prior to Day 1 dosing. Results must be confirmed as negative before study product is dosed.
9. Urine drug screening.
10. A urine dipstick will be done to evaluate for presence of protein, glucose or blood in urine. If dipstick is abnormal (>+1), a complete urinalysis with microscopic will be performed.
11. A 12-lead ECG will be done during screening. Subjects with a QTc interval >450 milliseconds will be excluded from participation.
12. Viral Serology includes HIV, HBsAg and antibody to HCV.
13. Serum from subjects who give consent will be stored for future use.
14. The Hypersensitivity Panel includes cytokine and complement panels, IgE, and tryptase. Refer to lab manual for further processing instructions. .
15. PK samples will be collected for all subjects at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120.
16. Serological samples (PD) will be collected for all subjects at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120.
17. ADA samples will be collected and tested for all subjects at pre-dose and Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240.
18. Samples to be collected pre-dose prior to Day 45 repeat dose.
19. Subjects will be provided a reactogenicity diary prior to leaving the clinic on baseline/dosing Day 1 . Subjects will be asked to complete daily diary records study Day 1-7 and dairy is to be collected by site staff on Day 8 for review. Subjects will be provided a reactogenicity diary prior to leaving the clinic on baseline/dosing Day 45. Subjects will be asked to complete daily diary records study Day 46-52 and dairy is to be collected by site staff on Day 60 for review.

Table 3: Schedule of Assessments (Cohort 4)

Study Visit	Screening[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	Unscheduled
Day of Study	-14 to -1	**D 1**	**8-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 30**	**D 45**	**D 90**	**D 120**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	
Review Inc/Excl Criteria	X	X										
Demographics	X											
Review Medical History	X	X										
Randomization		X										
Study Drug Administration		X										
Concomitant Medications[2]	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[3]	X	X	(SD)[4]	SD	SD	SD	SD	SD	SD	SD	SD	SD
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential[7]	X						X		X		X	
Chemistry[6]	X						X		X		X	
Serology Panel[12]	X											
Pregnancy Test[8]	X (serum)	X (urine)							X (urine)		X (urine)	
Drug Screening[9]	X	X										
Breathalyzer test	X	X										
Urine Dipstick[10]	X	X										
12-lead ECG[11]	X											
PK samples[13]		X	X[16]	X	X	X	X	X	X	X	X	
MNA samples[14]		X	X[17]	X				X	X	X		

Study Visit	Screening[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	Unscheduled
Day of Study	-14 to -1	**D 1**	**8-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 30**	**D 45**	**D 90**	**D 120**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	
Immunogenicity (ADA) samples[15]		X								X	X	
Subject Diary Review[18]			X	X	X	X						

1. Screening will be completed within 14 days prior to administration of study drug and may require more than one visit.
2. Concomitant medications including all of the following: prescription drugs, over-the–counter drugs, herbs, vitamins, nutritional supplements, illicit and recreational substance use, birth control information.
3. PE includes height and weight at screening.
4. Symptom-directed only.
5. Vital Signs to include sitting diastolic and systolic BP, HR, and oral temperature. Vital signs will be checked just before injection on Day 1 and every visit.
6. Chemistry panel that will include serum creatinine, BUN, calcium, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, albumin, PT, PTT, INR, total CK, carbon dioxide, and chloride. Subjects should be fasting for the chemistry panel.
7. A CBC with differential will be obtained including WBC, RBC, hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, RDW, MPV, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
8. A serum pregnancy test will be obtained at screening for all women of reproductive capacity. A urine pregnancy test will be obtained and must be resulted prior to Day 1 dosing. Results must be confirmed as negative before the study product is dosed.
9. Urine drug screening.
10. A urine dipstick will be done to evaluate for presence of protein, glucose or blood in urine. If dipstick is abnormal (>+1), a complete urinalysis with microscopic will be performed.
11. A 12-lead ECG will be done during screening. Subjects with a QTc interval >450 milliseconds will be excluded from participation.
12. Viral Serology includes HIV, HBsAg and antibody to HCV.
13. PK samples will be collected for all subjects at pre-dose, 2 hours (± 10 minutes), 4 hours (± 15 minutes), 8 hours (± 15 minutes), 24 hours (± 2 hour), 72 hours (± 2 hour) post dose, and on Days 8, 15, 30, 45, 90, and 120.
14. Serological samples (PD) will be collected for all subjects at pre-dose, 2 hours (± 10 minutes), 4 hours (± 15 minutes), 8 hours (± 15 minutes), 24 hours (± 2 hour) and on Days 30,45, and 90.
15. ADA samples will be collected and tested for all subjects at pre-dose and post-dose on Days 90 and 120.
16. PK samples will be collected at pre-dose, 2 hours (± 10 minutes), 4 hours (± 15 minutes), and 8 hours (± 15 minutes) post-dose.
17. PD samples will be collected at pre-dose, 2 hours (± 15 minutes), 4 hours (± 15 minutes), and 8 hours (± 15 minutes) post-dose.
18. Subjects will be provided with a reactogenicity diary prior to leaving the clinic on baseline/dosing Day 1. Subjects will be asked to complete daily diary records study Day 1-7 and diary is to be collected by site staff on Day 8 for review.

APPENDIX B. TOXICITY TABLE OF CLINICAL ADVERSE EVENTS
(MODIFIED FROM FDA TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS)

Local Reaction to Injectable Product				
Clinical Abnormality	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness	2.5 − 5 cm	5.1 − 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 − 5 cm and does not interfere with activity	5.1 − 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Systemic (General)				
Clinical Abnormality	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) (°F)	38.0 − 38.4 100.4 − 101.1	38.5 − 38.9 101.2 − 102.0	39.0 − 40 102.1 − 104	> 40 > 104
Nausea/vomiting	No interference with activity or 1 − 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Vital Signs				
Vital Signs	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever(°C)	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40

(°F)	100.4 – 101.1	101.2 – 102.0	102.1 – 104	> 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension(systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension(diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	> 25	Intubation

Abbreviations: DHHS = Department of Health and Human Services; ER = emergency room.

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

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

[c] Oral temperature; no recent hot or cold beverages.

[d] Subject should be at rest for all vital sign measurements.

[e] When resting heart rate is between 60-100 beats per minutes. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Source: [DHHS 2007].

*Will not be used as halting criteria

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis

Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
LFTs –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in LFT increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when LFT is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

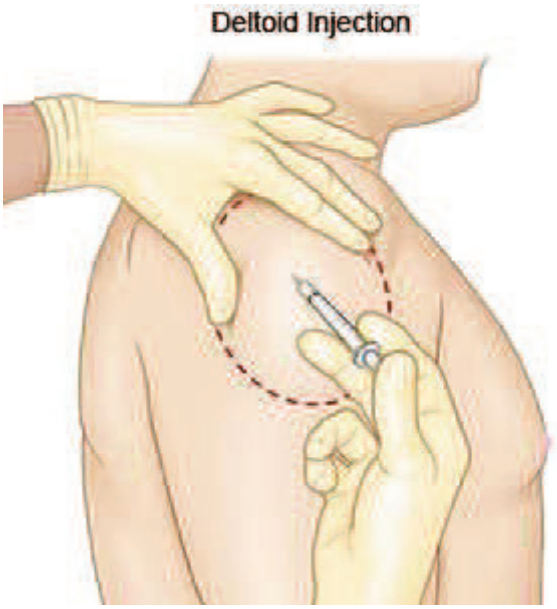
Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 –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

Abbreviations: CPK = creatine phosphokinase; DIC = disseminated intravascular coagulation; LFT = liver function test; ULN = upper limit of normal.

APPENDIX C. INTRAMUSCULAR (IM) INJECTION ADMINISTRATION

G03-52-01 or placebo will be administered via IM injections on Days 1 and 45 for Cohorts 1-3 and on Days 1 for Cohort 4.

Please refer to the Pharmacy Manual for additional dose preparation and administration detail.



APPENDIX D. SUMMARY OF CHANGES

Table 4: Summary of Changes for Version 4.0

Version 3.0	Version 4.0	Reason for Change
PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects	Addition of Cohort 4 (single dose of G03-52-01)
Name of Sponsor/Company: Ology Bioservices, Inc.	Name of Sponsor/Company: Resilience Government Services, Inc.	Resilience Government Services, (previously Ology Bioservices) updated
ICON Medical Monitor: [redacted]	ICON Medical Monitor: [redacted]	New medical monitor
Deltoid	Deltoid muscle	Clarification on the administration of injection in the deltoid muscle
Page 19: Protocol Synopsis, Subject Participation Each subject's participation in the study is approximately 254 days (up to a 14-day screening, 1-hour inpatient stay and 240 days outpatient follow-up)	Page 15: Protocol Synopsis, Subject Participation Subject's participation Cohorts 1-3 of in the study is approximately 254 days (up to a 14-day screening, 1-hour inpatient stay and 240 days outpatient follow-up) Subject's participation in Cohort 4 is approximately 134 days (up to a 14-day screening, 8-hour inpatient stay and 120 days outpatient follow-up)	Addition of Cohort 4
Page 19: Protocol Synopsis, Objectives and Endpoints Primary Objectives: • To evaluate the safety and tolerability of repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects • Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90 • To evaluate lot-to-lot variability of the two doses of G03-52-01	Page 15-16: Protocol Synopsis, Objectives and Endpoints Primary Objectives: • To evaluate the safety and tolerability of single or repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects • Cohorts 1-3 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90	Addition of Cohort 4 and new objectives and endpoints

Primary Endpoints: • The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit • The occurrence of changes from baseline in physical examination (PE), vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit • To evaluate target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90	○ To evaluate lot-to-lot variability of the two doses of G03-52-01 ○ For Cohort 4, demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post dose Primary Endpoints: • The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit • The occurrence of changes from baseline in physical examination (PE), vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit • For Cohorts 1-3, to evaluate target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90 • For Cohort 4, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 4 and 8 hours post dose	
Page 19: Protocol Synopsis, Objectives and Endpoints Secondary Objectives: • Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 120 • Pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study Secondary Endpoints:	Page 16: Protocol Synopsis, Objectives and Endpoints Secondary Objectives: • Cohorts 1-3 ○ Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 120 ○ To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at	Addition of Cohort 4 and new objectives and endpoints

• To evaluate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 • Descriptive statistics of selected PD and ADA at all-time points tested	pre-dose through the end of study • Cohort 4 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 2 hours post dose o To assess pharmacokinetics (PK) at pre-dose through end of study o To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study Secondary Endpoints: • Cohorts 1-3 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 o Descriptive statistics of selected PD and ADA at all-time points tested • Cohort 4 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose o PK analysis at the determined timepoints o Descriptive statistics of determined PD and ADA timepoints	
Page 19-20: Protocol Synopsis, Objectives and Endpoints	Page 16: Protocol Synopsis, Objectives and Endpoints	Addition of Cohort 4 and new objectives and endpoints

Exploratory Objectives: • To evaluate pharmacokinetic (PK) parameters to ensure ADA evaluation adequate of the two lots Exploratory Endpoints: • Descriptive statistics of selected PK parameters at all time points tested of the two lots	Exploratory Objectives: • For Cohorts 1-3, to evaluate pharmacokinetic (PK) parameters to ensure ADA evaluation adequate of the two lots Exploratory Endpoints: • For Cohorts 1-3, descriptive statistics of selected PK parameters at all time points tested of the two lots	
Page 20: Protocol Synopsis, Methodology This study is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, PD, and immunogenicity of a repeat dose (50 mg and 100 mg) of G03-52-01 administered by IM injection(s) in adult subjects. Approximately 375 subjects will be enrolled in this study. No formal sample size calculations will be performed for this Phase 2 study, as there is no planned formal hypothesis testing, and the target enrollment of 375 subjects was based on previous experiences from studies conducted with similar products. Subjects will be randomized 2:2:1 to the following concurrent cohorts: • Cohort 1: 50-mg dose of G03-52-01 on Day 1 and repeat 50-mg dose on Day 45 (N=150) • Cohort 2: 100-mg dose of G03-52-01 on Day 1 and repeat 100-mg dose on Day 45 (N=150) • Cohort 3: Placebo on Day 1 and placebo on Day 45 (N=75) Subjects who receive 50 mg dose of G03-52-01, 100 mg dose of G03-52-01, or placebo on Day 1 will receive a repeat injection of the same dose on Day 45. Within Cohorts 1 and 2, subjects will be randomized 1:1 to Lot 1 or Lot 2 of each respective dose.	Page 16-17: Protocol Synopsis, Methodology This study is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, PD, and immunogenicity of a repeat dose (50 mg and 100 mg) or single dose (100 mg) of G03-52-01 administered by IM injection(s) in adult subjects. Approximately 625 subjects will be enrolled in this study. No formal sample size calculations will be performed for this Phase 2 study, as there is no planned formal hypothesis testing, and the target enrollment of subjects was based on previous experiences from studies conducted with similar products. Subjects will be randomized 2:2:1 to the following cohorts 1-3: • Cohort 1: 50-mg dose of G03-52-01 on Day 1 and repeat 50-mg dose on Day 45 (N=150) • Cohort 2: 100-mg dose of G03-52-01 on Day 1 and repeat 100-mg dose on Day 45 (N=150) • Cohort 3: Placebo on Day 1 and placebo on Day 45 (N=75) Subjects in Cohort 4 will be randomized in a 4:1 to receive a single 100 mg dose of G03-52-01 or Placebo on Day 1 (n=250). Subjects who receive 50 mg dose of G03-52-01, 100 mg dose of G03-52-01, or placebo on Day 1 will receive a repeat injection of the same dose on	Updates to study design to support addition of Cohort 4and new objectives/endpoints

	Day 45 for Cohorts 1-3. Within Cohorts 1 and 2, subjects will be randomized 1:1 to Lot 1 or Lot 2 of each respective dose. Subjects in Cohort 4 will be randomized 4:1 to receive G03-52-01 (Lot #C2300157) or Placebo.	
Page 21: Protocol Synopsis, Methodology The study will include up to 14-day screening period and an approximately 1-hour stay in the clinic after dosing is complete on Day 1 and Day 45 for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240. Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240. Subjects within each dose lot and placebo cohort will be randomized 2:1 to contribute PD or PK samples according to the following schedules. PD samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. The first 25 subjects randomized for each drug product (DP) lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using MNA at pre-dose and Days 45, 90, and 120. PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. A total of 25 subjects for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints.	Page 17-18: Protocol Synopsis, Methodology The study will include up to 14-day screening period and an approximately 1-hour stay in the clinic after dosing is complete on Day 1 and Day 45 for subjects in Cohorts 1-3 for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240 for Cohorts 1-3. Cohort 4 subjects will have an 8 hour stay at the clinic after dosing for safety, PD, and PK assessment. and safety follow up. Follow-up visits will occur at 24 hours, 72 hours, and on Days 8, 15, 30, 45, 90, and 120. Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240 for Cohorts 1-3. Subjects in Cohort 4 will have safety labs drawn at screening and Day 15, 45, and 120. For Cohorts 1-3, subjects within each dose lot and placebo cohort will be randomized 2:1 to contribute PD or PK samples according to the following schedules for Cohorts 1-3: PD samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. The first 25 subjects randomized for each drug product (DP) lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using	Updates to study design to support addition of Cohort 4and new objectives/endpoints

ADA samples will be tested at pre-dose and Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240 on all study subjects. An interim Clinical Study Report (CSR) is planned for the first 125 subjects through Day 120.	MNA at pre-dose and Days 45, 90, and 120. PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (before repeat-dose), 49, 90, and 120. A total of 25 subjects for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints. For Cohort 4, PK and PD samples will be tested for the first 30 subjects who receive active drug and complete sample collection at 24 hours. PD samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours and on Days 30, and 45 and 90. PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120. ADA samples will be tested at pre-dose and Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240 for study subjects in Cohorts 1-3; and at pre-dose and post-dose on Days 90 and 120 for Cohort 4. An interim Clinical Study Report (CSR) is planned for the first 125 subjects in Cohorts 1-3 through Day 120.	
Page 21: Protocol Synopsis, Study Population 375 healthy male and female subjects between the ages of 18 and 65 years of age	Page 18: Protocol Synopsis, Study Population 625 healthy male and female subjects between the ages of 18 and 65 years of age	Addition of Cohort 4 (n=250 subjects)
Page 21: Protocol Synopsis, Inclusion Criteria 8. The urine drug screen is negative	Page 18: Protocol Synopsis, Inclusion Criteria 8. The urine drug screen is negative. • For Cohorts 1-3, if a subject has a positive urine drug screen that the PI believes is caused by	Clarification on drug screening and inclusion criteria

	a currently prescribed medication (except for THC) the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria. • For Cohort 4, If a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication or positive for THC, the PI may enroll the subject if they meet all other inclusion criteria and none of the exclusion criteria.	
Page 22: Protocol Synopsis, Inclusion Criteria 11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45, per Investigator discretion.	Page 18: Protocol Synopsis, Inclusion Criteria 11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4, per Investigator discretion.	Clarification on vigorous activity
Page 23: Protocol Synopsis, Exclusion Criteria 15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 (PRN use could be allowed with MM approval).	Page 19: Protocol Synopsis, Exclusion Criteria 15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4 (PRN use could be allowed with MM approval).	Clarification on use of H1 antihistamines or betablockers
Page 23: Protocol Synopsis, Test Product, Dose and Mode of administration G03-52-01 DP is a mixture of five human monoclonal immunoglobulin G (IgG)1 antibodies (NX01, NX11, XB10, XB18, and XB23) and one humanized monoclonal IgG1 antibody (NX02) which bind to non-overlapping epitopes on BoNT/A/B. • Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied. All subjects will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central,	Page 20: Protocol Synopsis, Test Product, Dose and Mode of administration G03-52-01 DP is a mixture of five human monoclonal immunoglobulin G (IgG)1 antibodies (NX01, NX11, XB10, XB18, and XB23) and one humanized monoclonal IgG1 antibody (NX02) which bind to non-overlapping epitopes on BoNT/A/B. • Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied for Cohorts 1-3. • One DP lot (DP Lot #C2300157) for Cohort 4.	Addition of Cohort 4 and new DP lot

thickest portion of the deltoid on Study Day 1 and Day 45.	Subjects in Cohorts 1-3 will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid on Study Day 1 and Day 45. Subjects in Cohort 4 will receive a single 100 mg G03-52-01 or equal volume of placebo in the central, thickest portion of the deltoid on Study Day 1.	
Page 25: General Information Central Laboratory for Safety Testing (Cohorts 1-3): [redacted]	Page 22: General Information Central Laboratory for Safety Testing (Cohorts 1-3): [redacted] Central Laboratory for Safety Testing (Cohort 4): ICON Laboratory Services	New central laboratory for safety testing of Cohort 4 samples
Page 28: Currently Available Treatments, G03-52-01 Development G03-52-01 drug product (DP) is being investigated to prevent (pre-exposure) and reduce the incidence or progression of disease following exposure to BoNT/A and /B in adults.	Page 25: Currently Available Treatments, G03-52-01 Development G03-52-01 drug product (DP) is being investigated for pre-exposure and post-exposure prophylaxis of botulism from BoNT/A and/or BoNT/B in adults.	Update to include pre-exposure and post-exposure prophylaxis
Page 28: Currently Available Treatments, G03-52-01 Development The safety and pharmacokinetics (PK) of G03-52-01 are currently being evaluated in a Phase 1 clinical study of a single IM injection of G03-52-01 conducted by Ology Bioservices (Ology Bio). To date, there are no safety concerns with the administration of the DP (G03-52-01).	Page 26: Currently Available Treatments, G03-52-01 Development The safety and pharmacokinetics (PK) of G03-52-01 were evaluated in a Phase 1 clinical study of a single IM injection of G03-52-01 conducted by Resilience Government Services (RGS). There were no safety concerns with the administration of the DP. All subjects in Cohorts 1-3 of the Phase 2 clinical study completed their last subject visit. All available safety data was reviewed by the DSMB and no safety concerns were identified.	Updates to include available Phase 1 clinical data
Page 29-30: Rationale For Use of G03-52-01 The ongoing Phase 1 clinical trial is evaluating the safety and tolerability of a single IM injection of G03-52-01 administered to healthy adults. Sentinel dosing occurred within each cohort as described in the full protocol (G03-52-001.001). The starting dose in the clinical trial was 10 mg, which was escalated to 25 mg, 50 mg, and 100 mg with no safety concerns identified.	Page 27: Rationale For Use of G03-52-01 The Phase 1 clinical trial evaluated the safety and tolerability of a single IM injection of G03-52-01 administered to healthy adults. Sentinel dosing occurred within each cohort as described in the full protocol (G03-52-001.001). The starting dose in the clinical trial was 10 mg, which was escalated to 25 mg, 50 mg, and 100 mg with no safety concerns identified.	Updates to include available Phase 1 clinical data

Based on the Day 60 and Day 120 interim analysis, G03-52-01 was safe and well tolerated in Cohorts 1-3. To date, Cohort 4 did not show safety concerns and the product was well tolerated. The nonclinical Investigational New Drug (IND)-enabling toxicology studies were designed to support this clinical design, including the dose levels and IM route of administration. Based on the potency of the G03-52-01 lots manufactured to date, the doses evaluated are anticipated to support PK analyses with serum drug concentrations in the range for the prevention (pre-exposure) and reduction of the incidence or progression of botulism from BoNT/A and/or BONT/B .	G03-52-01 was safe and well tolerated in all subjects who participated in the Phase 1 study and in the Phase 2 study to date. The nonclinical Investigational New Drug (IND)-enabling toxicology studies were designed to support this clinical design, including the dose levels and IM route of administration. Based on the potency of the G03-52-01 lots manufactured to date, the doses evaluated are anticipated to support PK analyses with serum drug concentrations in the range for pre-exposure and post-exposure prophylaxis of botulism from BoNT/A and/or BoNT/B.	
Page 32: Study Objectives Primary Objectives: • To evaluate the safety and tolerability of repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects • Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90 • To evaluate lot-to-lot variability of the two doses of G03-52-01 Secondary Objectives: • Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 120 • Pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study Exploratory Objectives: • To evaluate PK parameters to ensure ADA evaluation adequate of the two lots	Page 29: Study Objectives Primary Objectives: • To evaluate the safety and tolerability of single or repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects • Cohorts 1-3 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90 o To evaluate lot-to-lot variability of the two doses of G03-52-01 o For Cohort 4, demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post dose Secondary Objectives: • Cohorts 1-3 o Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 120	Addition of Cohort 4 and new objectives

	○ To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study • Cohort 4 ○ Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 2 hours post dose ○ To assess pharmacokinetics (PK) at pre-dose through end of study ○ To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study Exploratory Objectives: • For Cohorts 1-3, to evaluate PK parameters to ensure ADA evaluation adequate of the two lots	
Page 32: Study Outcome Measures Primary Endpoints: • The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit • The occurrence of changes from baseline in physical examination (PE), vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit • To evaluate target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90 Secondary Endpoints: • To evaluate target protective concentration (NAC) value >	Page 29-30: Study Outcome Measures Primary Endpoints: • The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit • The occurrence of changes from baseline in physical examination (PE), vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit • For Cohorts 1-3, to evaluate target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90 • For Cohort 4, to evaluate the proportion of subjects with target protective concentration	Addition of Cohort 4 and new endpoints

0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 • Descriptive statistics of selected PD and ADA at all-time points tested Exploratory Endpoints • Descriptive statistics of selected PK parameters at all time points tested of the two lots	(NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 4 and 8 hours post dose Secondary Endpoints: • Cohorts 1-3 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 o Descriptive statistics of selected PD and ADA at all-time points tested • Cohort 4 o To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose o PK analysis at the determined timepoints o Descriptive statistics of determined PD and ADA timepoints Exploratory Endpoints • For Cohorts 1-3, descriptive statistics of selected PK parameters at all time points tested of the two lots	
Page 33: Study Design This is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, pharmacodynamics (PD), and immunogenicity of a repeat dose (50 mg and 100 mg) of G03-52-01 administered by IM injection(s) in adult subjects (Appendix C).	Page 31-32: Study Design This is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the safety, tolerability, pharmacodynamics (PD), and immunogenicity of a repeat dose (50 mg and 100 mg) and a single dose (100 mg) of G03-52-01 administered by IM injection(s) in adult subjects (Appendix C).	Updates to study design to support addition of Cohort 4and new objectives/endpoints

Approximately 375 subjects will be enrolled in this study to receive active product or placebo on Day 1 and Day 45, and will be randomized to the following concurrent cohorts: • Cohort 1 (N=150, 75 lot #1, 75 lot #2): 50-mg dose • Cohort 2 (N=150, 75 lot#1, 75 lot#2): 100-mg dose • Cohort 3 (N=75): Placebo The study will include up to 14-day screening period and an approximately 1-hour stay in the clinic after dosing is complete for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur at 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240. Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240. PD will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using MNA at pre-dose and Days 45, 90, and 120. See Figure 2 . PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 24 hours and 72 hours post-dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and	Approximately 625375 subjects will be enrolled in this study to receive active product or placebo on Day 1 or Day 1 and Day 45, and will be randomized to the following concurrent cohorts: • Cohort 1 (N=150, 75 lot #1, 75 lot #2): 50-mg dose • Cohort 2 (N=150, 75 lot#1, 75 lot#2): 100-mg dose • Cohort 3 (N=75): Placebo • Cohort 4 (N=250): 100 mg dose or Placebo The study will include up to 14-day screening period and an approximately 1-hour stay for Cohorts 1-3 and 8 hours stay for Cohort 4 in the clinic after dosing is complete for PK assessment and to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur at 24 hours and 72 hours post dose, and on Days 8, 15, 45, 49, 60, 90, 120, 150, 180, and 240 for Cohorts 1-3. For Cohort 4, follow-up visits will occur 24 hours, 72 hours, and on Days 8, 15, 30, 45, 90, and 120. Safety Analysis: Safety labs will be drawn at pre-dose, 24 hours post dose, and on Days 15, 45 (before repeat-dose or placebo), 60, 120, and 240 for Cohort 1-3. Subjects in Cohort 4 will have safety labs drawn at screening and on Day 15, 45, and 120. PD Analysis: PD samples will be collected for all subjects. Analysis will be completed by the Battelle Mouse Neutralization Assay (MNA) for Serotypes A and B. PD will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B Samples for subjects in Cohorts 1-3 will be tested at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all 8 timepoints. The remaining samples from the subjects who received either dose or lot of G03-52-01 (including placebo) will only be tested using MNA at pre-dose and Days 45, 90, and 120.	

placebo will be tested at all timepoints. See Figure 2. ADA will be evaluated by ECLA at pre-dose and on Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240. See Figure 2.	All subjects in Cohort 4 will have samples collected at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours and on Days 30, 45, and 90. Samples will be analyzed for the first 30 subjects in Cohort 4, who receive active drug and complete the sample collection at 24 hours. See Figure 2 and Figure 3. PK Analysis: PK samples will be collected for all subjects. Analysis will be completed by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA). Samples for subjects in Cohorts 1-3 will be tested PK samples will be tested by electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA) at pre-dose, 24 hours and 72 hours post-dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints. All subjects in Cohort 4 will have samples collected at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120. Samples will be analyzed for the first 30 subjects in Cohort 4, who receive active drug and complete sample collection at 24 hours. See Figure 2 and Figure 3. ADA Analysis: ADA will be evaluated by ECLA at pre-dose and on Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240 for study subjects in Cohorts 1-3 and at pre-dose and post-dose on Days 90 and 120 for subjects in Cohort 4. See Figure 2 and Figure 3.	
Page 35: Subject Inclusion Criteria 8. The urine drug screen is negative	Page 34: Subject Inclusion Criteria 8. The urine drug screen is negative. • For Cohorts 1-3, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication (except for THC) the PI may enroll the subject if they meet all	Clarification on drug screening and inclusion criteria

	inclusion criteria, and none of the exclusion criteria. • For Cohort 4, If a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication or positive for THC, the PI may enroll the subject if they meet all other inclusion criteria and none of the exclusion criteria.	
Page 35: Subject Inclusion Criteria 11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45, per Investigator discretion.	Page 35: Subject Inclusion Criteria 11. Agrees not to participate in vigorous activity 2 days prior to dosing and 2 days post-dose Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4, per Investigator discretion.	Clarification on vigorous activity
Page 37: Subject Exclusion Criteria 15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 (PRN use could be allowed with MM approval).	Page 36: Subject Exclusion Criteria 15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4 (PRN use could be allowed with MM approval).	Clarification on use of H1 antihistamines or betablockers
Page 37: Treatment Assignment Procedures, Number of subjects Approximately 375 subjects will be enrolled in this Phase 2 study.	Page 37: Treatment Assignment Procedures, Number of subjects Approximately 625 subjects will be enrolled in this Phase 2 study.	Addition of Cohort 4 (n=250 subjects)
Page 38: Treatment Assignment Procedures, Randomized Procedures	Page 37: Treatment Assignment Procedures, Randomized Procedures Subjects in Cohort 4 will be randomized in a 4:1 to receive a single 100-mg dose of G03-52-01 or Placebo on Day 1 (N=250).	Addition of Cohort 4 (n=250 subjects)
Page 40: Formulation, Packaging, and Labeling Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied.	Page 39: Formulation, Packaging, and Labeling Two DP lots (DP Lots #274-190416 and #279-190722) will be supplied for Cohorts 1-3. One DP Lot (DP Lot #C2300157) will be supplied for Cohort 4.	Addition of Cohort 4 and new DP lot
Page 40: Product Storage and Stability G03-52-01 DP will be shipped refrigerated at 2-8°C (36-46°F) and should be stored refrigerated at 2-8°C	Page 39: Product Storage and Stability G03-52-01 DP Lots #274-190416 and #279-190722 will be shipped refrigerated at 2-8°C (36-46°F) and	Addition of new DP lot

(36-46°F) until time of preparation. If a vial is removed from refrigeration, it must be used within 8 hours.	should be stored refrigerated at 2-8°C (36-46°F) until time of preparation. If a vial is removed from refrigeration, it must be used within 8 hours. G03-52-01 DP Lot #C2300157 will be shipped and stored at room temperature (20 to 25°C [68 to 77°F]).	
Page 41: Dosage, Preparation, and Administration Any product that fails inspection should be quarantined at 2-8°C for inspection by the Sponsor.	Page 40: Dosage, Preparation, and Administration Product Lots #274-190416 and #279-190722 that fails inspection should be quarantined at 2-8°C and Lot #C2300157 at 20ºC to 25ºC.	Addition of new DP lot
Page 41: Dosage, Preparation, and Administration All subjects will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid, on Study Day 1 and a repeat dose on Day 45.	Page 40: Dosage, Preparation, and Administration Subjects in Cohorts 1-3 will receive a 50 mg or 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid, on Study Day 1 and a repeat dose on Day 45. Subjects in Cohort 4 will receive 100 mg G03-52-01 injection or equal volume of placebo in the central, thickest portion of the deltoid, on Study Day 1.	Addition of Cohort 4 (single 100 mg dose)
Page 43: Physical Examination An abbreviated PE will be conducted at the screening visit and on Days 1 and 240.	Page 42: Physical Examination An abbreviated PE will be conducted at the screening visit and on Days 1 and at the end of study visit.	Examination to be conducted at end of study visit for all cohorts
Page 44: Electrocardiogram A 12-lead ECG will be performed at screening and Day 15 and reviewed by the study PI or a co-Investigator to assess the cardiac status of a subjects for enrollment and for any significant changes at Day 15.	Page 43: Electrocardiogram A 12-lead ECG will be performed at screening (all cohorts) and Day 15 (Cohorts 1-3) and reviewed by the study PI or a co-Investigator to assess the cardiac status of a subjects for enrollment and for any significant changes at Day 15 (Cohorts 1-3).	EEG screening to be completed at screening for all cohorts and at Day 15 for Cohorts 1-3
Page 44: Laboratory Evaluations, Drug Screen A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. If a subject has a positive urine	Page 43: Laboratory Evaluations, Drug Screen A breathalyzer test and drug urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP.	Updated drug screening evaluation

drug screen that the PI believes is caused by a currently prescribed medication (except for THC), the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria. A breathalyzer test will also be performed and results must be negative for eligibility into the study.		
Page 44: Laboratory Evaluations, Pregnancy Testing A urine pregnancy test will be repeated on Day 45 and must be negative before dosing and end of study (Day 240).	Page 43: Laboratory Evaluations, Pregnancy Testing A urine pregnancy test will be repeated on Day 45 must be negative before dosing for Cohorts 1-3 and at the end of study for all subjects.	Testing to be conducted at end of study visit for all cohorts.
Page 45: Laboratory Evaluations, Hypersensitivity Panel A hypersensitivity panel includes cytokine and complement panels, immunoglobulin E (IgE) and tryptase. This 14 mL sample will be drawn on Day 1 prior to dosing.	Page 44: Laboratory Evaluations, Hypersensitivity Panel A hypersensitivity panel includes cytokine and complement panels, immunoglobulin E (IgE) and tryptase. This 14 mL sample will be drawn on Day 1 prior to dosing for Cohorts 1-3 only. The sample will be processed only if the subject has a hypersensitivity reaction. If a subject develops anaphylaxis or anaphylactoid reaction, an additional 14 mL sample will be drawn during the event and another will be drawn after the event. No sample will be collected for Cohort 4.	Panel will only be collected for Cohorts 1-3
Page 45: Special Assays or Procedures	Page 45: Special Assays or Procedures The blood sample volumes to be collected for each test are referenced in the lab manual.	Clarification on the blood sample volumes
Page 45: Special Assays or Procedures, Pharmacodynamic Assay Two 10-mL samples of blood will be drawn at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (prior to dosing) 49, 90, and 120 to be analyzed for neutralizing antibody concentration (NAC) using the validated Battelle MNA.	Page 44: Special Assays or Procedures, Pharmacodynamic Assay Blood samples will be drawn at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (prior to dosing) 49, 90, and 120 for Cohorts 1-3. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, and on Days 30,45, and 90. PD samples will be analyzed for neutralizing antibody concentration	Addition of PD assessments for Cohort 4

	(NAC) using the validated Battelle MNA.	
Page 46: Special Assays or Procedures, Pharmacokinetic Assay Six-mL of blood will be drawn at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (prior to dosing), 49, 90, and 120 for the analysis of levels of each of the mAbs in serum using a validated ECLA or ELISA.	Page 45: Special Assays or Procedures, Pharmacokinetic Assay Blood samples will be drawn at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (prior to dosing), 49, 90, and 120 for Cohorts 1-3. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post dose, and on Days 8, 15, 30, 45, 90, and 120. The PK analysis of each mAb will be assessed using a validated ECLA or ELISA.	Addition of PK assessments for Cohort 4
Page 46: Special Assays or Procedures, Anti-Drug Antibody Assay Six-mL samples of blood will be drawn pre-dose and Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 for determining the presence of ADA using a validated ECLA that measures total ADA in serum. This will be performed to assess immunogenicity.	Page 45: Special Assays or Procedures, Anti-Drug Antibody Assay Blood samples will be drawn for Cohorts 1-3 at pre-dose and Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 and pre-dose and post-dose on Days 90, and 120 for Cohort 4 for determining the presence of ADA using a validated ECLA that measures total ADA in serum.	Addition of ADA assessments for Cohort 4
Page 46: Special Assays or Procedures, Future Use Five-mL samples of blood will be drawn for subjects who consent to have samples stored for future use. These samples will be collected at pre-dose and on Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240.	Page 45: Special Assays or Procedures, Future Use Five-mL samples of blood will be drawn for subjects who consent to have samples stored for future use. These samples will be collected at pre-dose and on Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 for Cohorts 1-3.	Future use samples collected for Cohorts 1-3 only
Page 47- 54: Study Schedule	Page 46-53: Study Schedule (Cohorts 1-3) Page 54-59: Study Schedule (Cohort 4)	Addition of study schedule for Cohort 4
Page 61: Halting Rules, Halting Criteria Study dosing may be halted after review of data by the Data Safety Monitoring Board (DSMB) at any time if medically indicated. Study dosing may be stopped, and a review of available safety data will be conducted	Page 65: Halting Rules, Halting Criteria Study dosing may be halted after review of data by the MM in consultation with RGS ML. The Data Safety Monitoring Board (DSMB) will be informed if medically indicated and a review of available safety data will be	Clarification on halting criteria and rule

by the DSMB if any of the following occur: • Death of a subject following injection and prior to the subject's last visit that was possibly related to study product • One Grade 4 non-laboratory AE (as per FDA guidance toxicity table as modified in Appendix B) related to study treatment, or • One life-threatening allergic/hypersensitivity reaction (anaphylaxis) in any subject, manifested by bronchospasm with or without urticaria or angioedema, or • Requiring hemodynamic support with pressor medications or mechanical ventilation, or • One SAE that is considered definitely or possibly related to study product • Two or more subjects with a Grade 3 AE in the same organ class (systemic toxicity, clinical laboratory tests or vital signs) possibly related to study drug	conducted by the DSMB if any of the following occur: • Death of a subject following injection and prior to the subject's last visit that was possibly related to study product • Two Grade 4 non-laboratory AE (as per FDA guidance toxicity table as modified in Appendix B) related to study treatment, or • One life-threatening allergic/hypersensitivity reaction (anaphylaxis) in any subject, manifested by bronchospasm with or without urticaria or angioedema, or • Requiring hemodynamic support with pressor medications or mechanical ventilation • One SAE that is considered definitely or possibly related to study product • Four or more subjects with a Grade 3 AE in the same organ class (systemic toxicity, clinical laboratory tests or vital signs) possibly related to study drug	
Page 65: Planned Interim Analysis An interim Clinical Study Report (CSR) is planned for the first 125 subjects across the three cohorts through Day 120. The data cut will be taken when all 125 subjects have completed their Day 120 visit. The objectives of this interim CSR will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK, PD and immunogenicity parameters within drug dose levels as defined in the SAP.	Page 69: Planned Interim Analysis An interim Clinical Study Report (CSR) is planned for the first 125 subjects across the first three cohorts through Day 120. The data cut will be taken when all 125 subjects have completed their Day 120 visit for PD, PK, and ADA analysis. All available safety from subjects in Cohorts 1-3 will be included until the data cutoff for the DSMB report. The objectives of this interim CSR will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK, PD and immunogenicity parameters within drug dose levels as defined in the SAP.	Clarification on interim CSR population.
Page 65: Statistical Analysis Plan	Page 70: Statistical Analysis Plan	Statistical analysis updates to reflect addition of Cohort 4

	PD, PK and ADA continuous data will include additional summary statistics as described below and in the SAP.	
Page 66: Statistical Methods Geometric means and coefficients of variation will be presented for selective PD and PK endpoints.	Page 71: Statistical Methods Geometric means, and coefficients of variation (%), geometric coefficients of variation (%) and the geometric coefficient of variation 95% confidence intervals will be presented for selective PD, and PK, and ADA endpoints.	Statistical analysis updates to reflect addition of Cohort 4
Page 67: Statistical Methods, Pharmacodynamics (PD) Descriptive summary statistics of BoNT/A or BoNT/B toxin neutralization across visits will be compared between the two dose cohorts. Details will be described in the SAP.	Page 72: Statistical Methods, Pharmacodynamics (PD) Descriptive summary statistics of BoNT/A or BoNT/B toxin neutralization across visits will be compared by drug dose cohort. Summary statistics will include the number of available records for evaluation, mean, standard deviation, Q1, median, Q3, minimum, maximum, geometric mean, coefficient of variation (%), geometric coefficient of variation (%) and the geometric coefficient of variation 95% confidence interval. Details will be described in the SAP. When evaluable, PD estimates will include the following parameters: • $AUC_{(0-t)}$: Area under the concentration time-curve from the time of dosing to the time of the last measurable (positive) concentration • T_{max}: Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used. • C_{max}: Maximum observed concentration, occurring at time T_{max}	Statistical analysis updates to reflect addition of Cohort 4
Page 67: Statistical Methods, Pharmacokinetics (PK) Summary statistics will include the mean, median, coefficient of variation, and range.	Page 92: Statistical Methods, Pharmacokinetics (PK) Summary statistics will include the number of available records for evaluation, mean, standard deviation, Q1, median, Q3, minimum, maximum, geometric mean, coefficient of	Statistical analysis updates to reflect addition of Cohort 4

	variation (%), geometric coefficient of variation (%) and the geometric coefficient of variation 95% confidence interval.	
Page 67: Statistical Methods, Immunogenicity Immunogenicity will be evaluated by the incidence of ADA and antibody titers. ADA titers will be evaluated over the course of the post-injection period. Descriptive summary statistics of antibody titers will be compared between the 3 study cohorts. Details will be described in the SAP.	Page 72: Statistical Methods, Immunogenicity Immunogenicity will be evaluated by the incidence of ADA and antibody titers by time point. ADA titers will be evaluated over the course of the post-injection period. Descriptive summary statistics of antibody titers will be presented in Cohorts 1, 2 and for subjects receiving active drug in Cohort 4. Details will be described in the SAP.	Statistical analysis updates to reflect addition of Cohort 4
Page 78- 79: Appendix A: Schedule of Assessments Table 2: Schedule of Assessments	Page 84-88: Appendix A: Schedule of Assessments Table 2: Schedule of Assessments (Cohorts 1-3) Table 3: Schedule of Assessments (Cohort 4) added	Addition of schedule of assessments for Cohort 4
Page 84: Appendix C: Intramuscular (IM) Injection Administration G03-52-01 or placebo will be administered via IM injections on Days 1 and 45.	Page: 93: Appendix C: Intramuscular (IM) Injection Administration G03-52-01 or placebo will be administered via IM injections on Days 1 and 45 for Cohorts 1-3 and on Day 1 for Cohort 4.	Addition of Cohort 4 administration of a single 100 mg dose

Table 5: Summary of Changes for Version 3.0

Version 2.0	Version 3.0	Reason for Change
Page 21: Protocol Synopsis An interim analysis is planned for the first 25 subjects of each lot of each dose and placebo subjects through Day 60 and Day 90, including comparing descriptive statistics of selected PD and PK parameters between lots within each of the 50 and 100 mg dose cohorts. An interim Clinical Study Report (CSR) is planned for the first 125 subjects through Day 120, including comparing descriptive statistics of selected PD and PK parameters between lots within each of the 50 and	Page 21: Protocol Synopsis An interim Clinical Study Report (CSR) is planned for the first 125 subjects through Day 120.	Removed interim analyses and updated interim CSR

100 mg dose cohorts and placebo cohort.		
Page 62: Data Safety Monitoring Board (DSMB) A centralized, independent DSMB will be established in collaboration with Ology Bio and ICON. The DSMB will review interim analyses of previously decided timepoints on unblinded data. The DSMB will make safety and tolerability recommendations. More details on the role of and the data provided to the DSMB will be described in a DSMB Charter. See Section 12.2 for more details on planned interim analyses. The DSMB will periodically review accumulating unblinded safety data by group. Prior to each meeting, the ICON statistician will provide the DSMB with AE data. Reports will be cumulative, generated from an up-to-date data file. Based on the reports, the DSMB will determine whether to recommend that the study should be continued, modified, or stopped, including for safety reasons.	Page 62: Data Safety Monitoring Board (DSMB) A centralized, independent DSMB will be established in collaboration with Ology Bio and ICON. The DSMB will review blinded safety data and make safety and tolerability recommendations. More details on the role of and the data provided to the DSMB will be described in a DSMB Charter. See Section 12.2 for more details on planned interim analyses. The DSMB will periodically review accumulating blinded safety data by group. Prior to each meeting, the ICON statistician will provide the DSMB with AE data. Reports will be cumulative, generated from an up-to-date data file. Based on the reports, the DSMB will determine whether to recommend that the study should be continued, modified, or stopped for safety reasons.	Updated DSMB roles and reviews
Page 65: Planned Interim Analysis Two interim analyses are planned for the first 25 subjects of each lot of each dose and in the placebo group through Day 60 and Day 90. An interim Clinical Study Report (CSR) is planned for the first 125 subjects across the three cohorts through Day 120. For each interim analysis, the data cut will be taken when all 125 subjects have completed their Day 60, 90 and 120 visits. The objectives of these interim analyses will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK, PD and immunogenicity parameters within drug dose levels.	Page 65: Planned Interim Analysis An interim Clinical Study Report (CSR) is planned for the first 125 subjects across the three cohorts through Day 120. The data cut will be taken when all 125 subjects have completed their Day 120 visit. The objectives of this interim CSR will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK, PD and immunogenicity parameters within drug dose levels as defined in the SAP.	Removed interim analyses and updated interim CSR
Page 78-79: Schedule of Assessments Visit 8, Day 49 visit window ±1D	Page 78-79: Schedule of Assessments Visit 8, Day 49 visit window ±3D	Updated visit window

Table 6: Summary of Changes for Version 2.0

Version 1.0	Version 2.0	Reason for Change
Page 3: Sponsor Signature Page PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat IM Dose of G03-52-01 in Adult Subjects	Page 3: Sponsor Signature Page PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	Editorial error removed IM from title
Page 4: Signature of Investigator PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat IM Dose of G03-52-01 in Adult Subjects	Page 4: Signature of Investigator PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	Editorial error removed IM from title
Page 14: Protocol Synopsis Title of Study: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat IM Dose of G03-52-01 in Adult Subjects	Page 19: Protocol Synopsis Title of Study: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	Editorial error removed IM from title
Page 16-17: Protocol Synopsis: Inclusion Criteria 7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Appendix B will be excluded.	Page 21: Protocol Synopsis: Inclusion Criteria 7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be excluded.	Updated to FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix B)
Page 17: Protocol Synopsis: Inclusion Criteria 8. The urine drug screen is negative.	Page 22: Protocol Synopsis: Inclusion Criteria 8. The urine drug screen is negative. *If a subject has a positive urine drug screen (except for THC) that the PI believes is caused by a currently prescribed medication, the PI may enroll the subject if they meet all*	Added clarification on positive urine drug screens

	inclusion criteria, and none of the exclusion criteria.	
Page 18: Subject Exclusion Criteria 18. Any previous injection or planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.	Page 23: Subject Exclusion Criteria 18. Any previous injection or any planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.	Added clarification for planned injection
Page 18: Subject Exclusion Criteria 20. Is a study site employee or staff. • *Site employees or staff include the PIs and Sub-Investigators or staff who are supervised by the PI or Sub-Investigators.*	Page 23: Subject Exclusion Criteria 20. Is a study site employee, staff, or close relative as defined. • *PIs and Sub-Investigators* • *Staff who are supervised by the PI, Sub-Investigators* • *Member of the team conducting this clinical trial* • *Children, spouse, partners, siblings, and parents of site staff*	Added definitions of study site employee, staff, or close relative
Page 20: General Information A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	Page 25: General Information A Phase 2, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of a Repeat Dose of G03-52-01 in Adult Subjects	Editorial error removed IM from title
Page 20: General Information Research Laboratory for PK and ADA Samples: [redacted]	Page 26: General Information Research Laboratory for PK and ADA Samples: [redacted]	Updated PK and ADA sample general information
Page 24: G03-52-01 Development The safety and pharmacokinetics (PK) of G03-52-01 are currently being evaluated in a Phase 1 clinical study of a single IM injection of G03-52-01 conducted by Ology Bioservices (Ology Bio). To date, there are no safety concerns with the administration of the DP (G03-52-01) for Cohorts 1-3. An additional Phase 1 cohort (Cohort	Page 29: G03-52-01 Development The safety and pharmacokinetics (PK) of G03-52-01 are currently being evaluated in a Phase 1 clinical study of a single IM injection of G03-52-01 conducted by Ology Bioservices (Ology Bio). To date, there are no safety concerns with the administration of the DP (G03-52-01).	Added Cohort 4 safety data

4) was added and is underway to evaluate a single 100-mg IM injection as the maximum administered dose for the study.		
Page 24: Rationale For Use of G03-52-01 BoNTs considered the most potent biologic toxins known and are classified as a Category A biothreat, with BoNT are /A most likely to be used in this scenario.	Page 29: Rationale For Use of G03-52-01 BoNTs considered the most potent biologic toxins known and are classified as a Category A biothreat with BoNT/A most likely to be used in this scenario.	Editorial error
Page 24-25: Rationale For Use of G03-52-01 The ongoing Phase 1 clinical trial is evaluating the safety and tolerability of a single IM injection of G03-52-01 administered to healthy adults. Sentinel dosing occurred within each cohort as described in the full protocol (G03-52-001.001). The starting dose in the clinical trial was 10 mg, which was escalated to 25 mg, 50 mg, and 100 mg with no safety concerns identified. Based on the Day 60 and Day 120 interim analysis, G03-52-01 was safe and well tolerated in Cohorts 1-3.	Page 29-30: Rationale For Use of G03-52-01 The ongoing Phase 1 clinical trial is evaluating the safety and tolerability of a single IM injection of G03-52-01 administered to healthy adults. Sentinel dosing occurred within each cohort as described in the full protocol (G03-52-001.001). The starting dose in the clinical trial was 10 mg, which was escalated to 25 mg, 50 mg, and 100 mg with no safety concerns identified. Based on the Day 60 and Day 120 interim analysis, G03-52-01 was safe and well tolerated in Cohorts 1-3. To date, Cohort 4 did not show safety concerns and the product was well tolerated.	Addition of Cohort 4 safety data
Page 30: Subject Inclusion Criteria 7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be excluded.	Page 35: Subject Inclusion Criteria 7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according Appendix B will be excluded.	Updated to FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix B)
Page 30: Subject Inclusion Criteria 8. The urine drug screen is negative.	Page 35: Subject Inclusion Criteria 8. The urine drug screen is negative. *If a subject has a positive urine drug screen (except for THC) that the PI believes is caused by a currently prescribed medication, the PI may enroll the subject if they meet all*	Added clarification on positive urine drug screens

	inclusion criteria, and none of the exclusion criteria	
Page 32: Subject Exclusion Criteria 18. Any previous injection or planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.	Page 37: Subject Exclusion Criteria 18. Any previous injection or any planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason.	Added clarification for planned injection
Page 32: Subject Exclusion Criteria 21. Is a study site employee or staff. • *Site employees or staff include the PIs and Sub-Investigators or staff who are supervised by the PI or Sub-Investigators.*	Page 37: Subject Exclusion Criteria 21. Is a study site employee, staff, or close relative as defined. • *PIs and Sub-Investigators* • *Staff who are supervised by the PI, Sub-Investigators* • *Member of the team conducting this clinical trial* • *Children, spouse, partners, siblings, and parents of site staff*	Added definitions of study site employee, staff, or close relative
Page 33: Randomization Procedures Within each of the 4 study drug lots and the placebo cohort, subjects will be randomized 2:1 to provide PD or PK specimens at visits specified in the Schedule of Assessments (Appendix A).	Page 38: Randomization Procedures Within each of the 4 study drug dose/lots and the placebo cohort, subjects will be randomized 2:1 to provide PD or PK specimens at visits specified in the Schedule of Assessments (Appendix A).	Added study drug dose/lots
Page 34: Withdrawal or Discontinuation by Investigator • At the request of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), Food and Drug Administration (FDA), or Department of Defense (DOD).	Page 39: Withdrawal or Discontinuation by Investigator • At the request of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or Food and Drug Administration (FDA)	Added clarification for reasons a subject may be removed
Page 39: Electrocardiogram A 12-lead ECG will be performed at screening and reviewed by the study PI or a co-Investigator to assess the cardiac status of a subject for eligibility for enrollment. ECGs will be performed after the subject rests quietly	Page 44: Electrocardiogram A 12-lead ECG will be performed at screening and Day 15 and reviewed by the study PI or a co-Investigator to assess the cardiac status of subjects for enrollment and for any significant changes at Day 15. ECGs will be	Added a 12-lead ECG at study visit 6, day 15

in a supine position for at least 10 minutes.	performed after the subject rests quietly for at least 10 minutes.	
Page 39: Drug Screen A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. A breathalyzer test will also be performed and results must be negative for eligibility into the study.	Page 44: Drug Screen A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. If a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication (except for THC), the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria. A breathalyzer test will also be performed and results must be negative for eligibility into the study.	Added clarification on positive urine drug screens
Page 45: Visit 6/Day 15 (±2 Day) Follow-up	Page 50: Visit 6/Day 15 (±2 Day) Follow-up • Obtain 12-lead ECG	Added a 12 lead ECG at study visit 6, day 15
Page 55: Reporting Procedures: Serious Adverse Events ICON plc PVSS will send SAEs with the ICON Drug Safety Physician assessment of causality, expectedness, and any impact on the benefit-risk ratio of the IP to Ology Bio. The DOD will be notified of SAE by Ology Bio.	Page 59: Reporting Procedures: Serious Adverse Events ICON plc PVSS will send SAEs with the ICON Drug Safety Physician assessment of causality, expectedness, and any impact on the benefit-risk ratio of the IP to Ology Bio. The DOD and the FDA will be notified of the SAEs as appropriate, by Ology Bio. HRPO and IRB will be informed of any safety issues as appropriate, per safety management plan by ICON and the PI.	Added safety reporting and clarified notification responsibilities
Page 60-61: Analysis Populations Pharmacodynamic (PD) Description: All Safety population subjects who have at least one non-missing evaluable PD result following dosing. They will be analyzed according to the treatment they actually received.	Page 65: Analysis Populations Pharmacodynamic (PD) Description: All Safety population subjects who have sufficient evaluable PD result following dosing. They will be analyzed according to the treatment they actually received.	Added subjects who have sufficient evaluable PD result
Page 61: Analysis Populations Pharmacokinetic (PK) Description: All Safety Population subjects who have at least one non-missing evaluable PK result following dosing. They will be	Page 65: Analysis Populations Pharmacokinetic (PK) Description: All Safety Population subjects who have sufficient evaluable PK result following dosing. They will be analyzed	Added subjects who have sufficient evaluable PK result

analyzed according to the treatment they actually received.	according to the treatment they actually received.	
Page 73: Appendix A: Schedule of Assessments	Page 78: Appendix A: Schedule of Assessments Added 12-Lead ECG at Visit 6, D15 (±2D)	Added a 12 lead ECG at study visit 6, day 15
Page 74: Appendix A: Schedule of Assessments 13. Serum from subjects who give consent will be stored for future use on Days 0, 8, and 30.	Page 79: Appendix A: Schedule of Assessments 13. Serum from subjects who give consent will be stored for future use.	Removed the days for future use collection
Page 76-77: Appendix B	Page 81: Appendix B Vital signs: Fever, Tachycardia, Bradycardia, Hypertension (systolic), Hypertension (diastolic), Hypotension (systolic), respiratory rate	Added vital signs to toxicity table of clinical adverse events