A Phase 1, Randomized, Double-Blind, Dose Escalation Study to Evaluate the Safety and Pharmacokinetics of a Single IM Dose of G03-52-01 vs Placebo in Adult Subjects.

Ology Bioservices Protocol Number: G03-52-01.001

IND Sponsor: Ology Bioservices, Inc.

Principal Investigator: Cassandra Key, MD

Medical Monitor: Uma Arumugam, MD

Version 3.0

September 7, 2021

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.

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.

Site Investigator: Cassandra Key, MD / Principal Investigator

Signature: _____

Date: _____

Sponsor: John Abernethy, MD / Medical Director

Signature: _____ MD

Date: 14 Sep 2021

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BoNT	Botulinum Neurotoxin
BP	Blood Pressure
Bpm	Beats per Minute
BUN	Blood Urea Nitrogen
CAR	Clinical Agents Repository
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum Plasma Titer/Concentration
CPM	Clinical Project Manager
CROMS	Clinical Research Operations and Management Support
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMP	Data Management Plan
DOD	Department of Defense
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
ECLA	Electrochemiluminescence Assay
ELISA	Enzyme-Linked Immunosorbent Assay
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
Gm	Gram
gm/dL	Grams per Deciliter
HBAT	Heptavalent Equine Antitoxin
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropic Hormone
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
Hr/hr	Hour
HRPO	Human Research Protections Office
HRSA	Health Resources and Services Administration
ICH	International Conference on Harmonisation
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug
IP	Intraperitoneal
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
IUDs	Intrauterine Contraceptive Device
IV	Intravenous

KG	Kilogram
LLN	Lower Limit of Normal
mAbs/mAb	Monoclonal Antibodies
MedDRA®	Medical Dictionary for Regulatory Activities
mEq/L	Milliequivalent per Liter
Mg/mg	Milligram/milligram
mg/dl	Milligram per Deciliter
Ml/mL	Milliliter
Mm/mm	Millimeter
mmHg	Millimeters of Mercury
MNA	Battelle Mouse Neutralization Assay
MOP	Manual of Procedures
MPA	Mouse Potency Assay
MRSD	Maximum Recommended Starting Dose
N	Number
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NLM	National Library of Medicine
NOAEL	No-Observed-Adverse-Effect-Level
NSAIDS	Nonsteriodal Anti-Inflammatory Drugs
OHRP	Office for Human Research Protections
OTC	Over the Counter
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	PR Interval-Standard ECG Terminology
PREP	Public Readiness and Emergency Preparedness
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVG	Pharmacovigilance Group

PVSS	Pharmacovigilance Safety System
RBC/HPF	Red Blood Cells per High-Power Field
SAE	Serious Adverse Event
SRC	Safety Review Committee
SOP	Standard Operating Procedure
T_{max}	Time to Maximum Concentration
TTD	Time to Death
µg	Microgram
ULN	Upper Limit of Normal
WBC	White Blood Count

SUMMARY OF CHANGES FOR VERSION 3.0

Version 2.0	Version 3.0	Reason for change
Page 17: Protocol Summary Population = 30 Study Duration = 8 months	Protocol Summary Population = 40 Study Duration = 10 months	Additional Cohort added with extended follow-up period.
Page 17: Protocol Summary, Subject Participation Subjects in all cohorts will participate approximately 150 days (up to 28-day screening, 12-hour inpatient stay, up to 120 days outpatient follow-up)	Protocol Summary, Subject Participation Subjects in cohorts 1-3 will participate approximately 150 days (up to 28-day screening, 12-hour inpatient stay, up to 120 days outpatient follow-up) Subjects in cohorts 4 will participate approximately 210 days (up to a 28-day screening, 12-hour inpatient stay, up to 180-day outpatient follow-up)	Additional Cohort added with extended follow-up period.
Page 17-18: Protocol Summary, Study Outcome Measures Secondary Endpoints: Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 The assessment of Cmax, Tmax, half-life (α and β), MRT and AUC(0-t) for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or an enzyme-linked immunosorbent assay (ELISA).	Protocol Summary, Study Outcome Measures Secondary Endpoints: Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 for cohorts 1-3. Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 45, 60, 90, and 120 for cohort 4. The assessment of Cmax, Tmax, half-life (α and β), MRT and AUC(0-t) for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence	Additional Cohort added with extended follow-up period.

Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120 Samples collected to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. Samples will be tested for ADA at pre-dose and on Days 15, 30, 45, 60, 90, and 120	assay (ECLA) or an enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for cohorts 1-3. Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 6 hours post dose, and on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180 for cohort 4. Samples collected to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. Samples will be tested for ADA at pre-dose and on Days 15, 30, 45, 60, 90, and 120 for cohorts 1-3. Samples will be tested for ADA at pre-dose and on Days 45, 60, 90, 120 and 180 for cohort 4.	
Page 18: Protocol Summary, Estimated Time to Complete Enrollment: Approximately 3 months	Protocol Summary, Estimated Time to Complete Enrollment: Approximately 5 months	

Page 18: Protocol Summary, Description of Study Design: A Phase 1, randomized, double-blind, placebo-controlled dose escalation trial of three dose cohorts of 10 subjects: (A: 10mg, B: 25mg, C: 50mg)	Protocol Summary, Description of Study Design: A Phase 1, randomized, double-blind, placebo-controlled dose escalation trial of four dose cohorts as outlined below: • Cohort 1: 10 mg IM injection (8 active, 2 placebo) • Cohort 2: 25 mg IM injection (8 active, 2 placebo) • Cohort 3: 50 mg IM injection (8 active, 2 placebo) • Cohort 4: 100mg IM injection (8 active, 2 placebo)	Added cohort 4
Page 18-19: Protocol Summary, Description of Study Design Dose escalation will not occur until safety data through Day 8 is reviewed by the Safety Review Committee (SRC) composed of the Principal Investigator (PI), Ology Bioservices Medical Monitor, and the DOD Medical Monitor. Objective dose-escalation criteria and safety evaluations will be utilized.	Protocol Summary, Description of Study Design Dose escalation will not occur until safety data through Day 8 is reviewed by the Safety Review Committee (SRC) composed of the Principal Investigator (PI), Ology Bioservices Medical Monitor, and the ICON Medical Monitor. Objective dose-escalation criteria and safety evaluations will be utilized. A SRC meeting will be held at any time during the course of the study if halting criteria are met or safety concerns arise.	Revise to include which Medical Monitors will attend the SRC and when the SRC meetings will occur.
Page 19: Protocol Summary, Description of Study Design The study will consist of a twenty-eight-day screening period and 12-hour clinic stay. Follow-up visits will occur at 24 hours, 48 hours, and 72	Protocol Summary, Description of Study Design The study will consist of a twenty-eight-day screening period and 12-hour clinic stay. Follow-up visits will occur at	Additional follow-up visits for cohort 4 added

hours post dose and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for all cohorts.	24 hours, 48 hours, and 72 hours post dose and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for cohorts 1-3. Follow-up visits for subjects in cohort 4 will occur on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, 150 and 180.	
Page 19: Protocol Summary, Description of Study Design Subjects will be screened for Human Immunodeficiency Virus (HIV), Hepatitis B surface antigen (HBsAg), and antibody to Hepatitis C virus (HCV), drugs and alcohol. Safety parameters include physical examination, 12-lead Electrocardiogram (ECG), vital signs, and clinical laboratory values to include: Complete Blood Count (CBC) with differential, comprehensive metabolic panel, and urine dipstick for blood, glucose and protein.	Page 33: Protocol Summary, Description of Study Design Subjects will be screened for Human Immunodeficiency Virus (HIV), Hepatitis B surface antigen (HBsAg), and antibody to Hepatitis C virus (HCV), drugs and alcohol. Safety parameters include physical examination, 12-lead Electrocardiogram (ECG), vital signs, and clinical laboratory values to include: Complete Blood Count (CBC) with differential, comprehensive metabolic panel, and urine dipstick for protein, blood, and glucose with reflex microscopy.	Added reflex microscopy
Page 19: Protocol Summary, Description of Study Design Pharmacokinetic (PK) samples will be drawn at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120. PK samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose and on days 4, 30, 90, and 120 for all	Protocol Summary, Description of Study Design Cohorts 1-3: Pharmacokinetic (PK) samples will be drawn at pre-dose, 2, 4, 8, 24, and 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120. PK samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose and on days 4, 30, 60, 90, and 120. PK samples will be	Additional Cohort added with extended follow-up period.

cohorts. PK samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120 for all cohorts. Samples will be tested for anti-drug antibodies (ADA) at pre-dose and days 15, 30, 45, 60, 90, and 120. A Safety Review Committee (SRC) meeting will be held if halting criteria are met or safety concerns arise.	tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120. Samples will be tested for anti-drug antibodies (ADA) at pre-dose and days 15, 30, 45, 60, 90, and 120. Cohort 4: Pharmacokinetic (PK) samples will be drawn at pre-dose, 6hours post dose, and on days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180. PK samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, and on days 4, 30, 45, 60, 90, and 120. PK samples will be tested by ECLA or ELISA at pre-dose, 6 hours post-dose and on days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180. Samples will be tested for anti-drug antibodies (ADA) at pre-dose and days 45, 60, 90, 120, and 180.	
Page 20: Schematic of Study Design	Schematic of Study Design Added cohort 4 to chart design	Revised to show addition of Cohort 4
Section 1 Key Roles: Ology Bioservices Medical Monitor John.abernethy@ologybio.com	Section 1 Key Roles: Ology Bioservices Medical Monitor John.abernethy@resilience.com	Update contact information
Page 25, Section 2.2 Rationale for Use of G03-52-01 Doses will escalate to 25 mg and then to 50 mg provided there are no safety concerns.	Section 2.2 Rationale for Use of G03-52-01 Doses will escalate to 25 mg and then to 50 mg provided there are no safety concerns.	Added rationale for escalation to 100 mg dose

The nonclinical IND-enabling toxicology studies were designed to support this clinical design with intramuscular route of administration.	The nonclinical IND-enabling toxicology studies were designed to support this clinical design with intramuscular route of administration. Based on data received from the Day 60 blinded interim safety and PK analysis, it was determined to escalate to 100 mg single dose.	
Page 29, Section 3.2.2 Secondary endpoints The pharmacokinetic assessment of Cmax, Tmax and AUC(0-t) as measured by the validated Battelle Mouse Neutralization Assay (MNA) for serotypes A and B Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 The assessment of Cmax, Tmax, half-life (α and β), MRT, and AUC(0-t) for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or validated enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on	Section 3.2.2 Secondary endpoints The pharmacokinetic assessment of Cmax, Tmax and AUC(0-t) as measured by the validated Battelle Mouse Neutralization Assay (MNA) for serotypes A and B Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 for Cohorts 1-3. Pharmacokinetic samples will be tested by MNA at pre-does and on Days 4, 30, 45, 60, 90, and 120 for cohort 4. The assessment of Cmax, Tmax, half-life (α and β), MRT, and AUC(0-t) for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or validated enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on	Details for addition of Cohort 4

Days 4, 8, 15, 30, 45, 60, 90, and 120 Samples will be tested to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. Samples will be tested for ADA at pre-dose, 15, 30, 45, 60, 90, and 120	Days 4, 8, 15, 30, 45, 60, 90, and 120 for Cohorts 1-3. Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 6 hours post-dose, and on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180 for cohort 4. Samples will be tested to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. Samples will be tested for ADA at pre-dose, 15, 30, 45, 60, 90, and 120 for cohorts 1-3. Samples will be tested for ADA at pre-dose and on Days 45, 60, 90, 120, and 180 for Cohort 4.	
Page 29, Section 4 Study Design This is a first-in-human study consisting of three cohorts of ten subjects each. Each subject will receive a single IM injection of G03-52-01 or placebo.	Section 4 Study Design This is a first-in-human study consisting of four cohorts of ten subjects each. Each subject will receive a single IM injection of G03-52-01 or placebo.	Additional cohort added.
Page 29, Section 4 Study Design Table 1 Cohort A, B, C	Section 4 Study Design Table 1 Cohort 1, 2, 3, and 4 Cohort 4 - 100mg, 10 subjects (8 active, 2 placebo)	Additional Cohort added with extended follow-up period.
Page 30, Section 4 Study Design: Schedule for Subjects Subjects in all cohorts will participate in the study for	Page 45, Section 4 Study Design: Schedule for Subjects Subjects in Cohorts 1-3 will participate in the study for	Additional Cohort added with extended follow-up period.

approximately 150 days, including a 28-day screening period, a 12-hour inpatient stay and approximately 120-day follow-up after study product administration. Subjects will remain at the clinic and not be eligible for discharge until 8 hours after the IM injection. Last follow up visit scheduled at Day 120. The end of the study is defined as the date of the last visit of the last subject in the study.	approximately 150 days, including a 28-day screening period, a 12-hour inpatient stay and approximately 120-day follow-up after study product administration. Subjects will remain at the clinic and not be eligible for discharge until 8 hours after the IM injection. Last follow up visit scheduled at Day 120. Subjects in Cohort 4 will participate in the study for approximately 210 days, including a 28-day screening period, a 12-hour inpatient stay and approximately 180-day follow-up after study product administration. Subjects will remain at the clinic and not be eligible for discharge until 8 hours after the IM injection. Last follow up visit scheduled at Day 180. The end of the study is defined as the date of the last visit of the last subject in the study.	
Section 5.2 subject Exclusion Criteria	Section 5.2 subject Exclusion Criteria Addition of #24. Subjects with NX02 levels present at screening will be exclude from cohort 4.	
Page 34, Section 5.3.1 Randomization Procedures This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within three dosing	Section 5.3.1 Randomization Procedures This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within four dosing	Addition of cohort 4

cohorts to either active or placebo in an overall 4:1 ratio.	cohorts to either active or placebo in an overall 4:1 ratio.	
Section 6.2 Acquisition ICON Early Phase Services Attn: Jane Willman, RPh 8307 Gault Lane San Antonio, TX 78209	Section 6.2 Acquisition ICON Early Phase Services Attn: Pharmacist 8307 Gault Lane San Antonio, TX 78209	Jane Willman no longer at the site.
Page 36, Section 6.3 Formulation. Packaging, and Labeling G03-52-01 will be administered intramuscularly (IM) as a single dose at concentrations of 10 mg, 25 mg, and 50 mg by varying the administration volume.	Page 52, Section 6.3 Formulation. Packaging, and Labeling G03-52-01 will be administered intramuscularly (IM) as a single dose at concentrations of 10 mg, 25 mg, 50 mg and 100 mg by varying the administration volume.	Cohort 4 will receive 100mg dose.
Page 40, Section 7.5.1.3 Pregnancy Testing A urine pregnancy test will be repeated on Day 4, Day 45, and Day 120 (end of study).	Page 56, Section 7.5.1.3 Pregnancy Testing A urine pregnancy test will be repeated on Day 4, Day 45, and end of study (Day 120 or Day 180, depending on cohort).	Added cohort 4 with extended visit schedule
Page 42, Section 7.6.2 Anti-Drug Antibody Assay Six-mL samples of blood will be drawn on Days 0, 15, 30,45,60, 90, and 120 for determining the presence of ADA using a validated ECLA that measures total anti-drug antibody in serum. This will be done to assess immunogenicity.	Page 57, Section 7.6.2 Anti-Drug Antibody Assay Six-mL samples of blood will be drawn pre-dose on Day 0, and on Days 15, 30,45,60, 90, and 120 for determining the presence of ADA using a validated ECLA that measures total anti-drug antibody in serum for Cohorts 1-3. Six-mL samples of blood will be drawn pre-dose on Day 0 and on Days 45, 60, 90, 120,	Additional Cohort added with extended follow-up period.

	and 180 for determining the presence of ADA using a validated ECLA that measures total anti-drug antibody in serum for Cohort 4. This will be done to assess immunogenicity.	
Page 43, Table 2	Page 58, Table 2 Updated to reflect additional visits on day 180 for Cohort 4. 24hr/Day 1. 48hr/Day2 PK, MNA and ADA and Cumulative totals shown for Cohorts 1-3 and 4 separately Footnotes revised.	Additional Cohort added with extended follow-up period.
Section 8.2 Visit 2: Baseline (Day0) • Obtain blood samples for Baseline serum PK (prior to injection and at the completion of the injection and 2hr, 4hr, and 8 hr post dosing)	Section 8.2 Visit 2: Baseline (Day0) • Obtain blood samples for Baseline serum PK (prior to injection and at the completion of the injection and 2hr, 4hr, and 8hr post dosing for subjects in Cohorts 1-3. Baseline serum PK (prior to injection and at 6 hrs post-injection for subjects in Cohort 4) MNA (prior to injection for subjects in Cohorts 1-3)	Added cohort 4

	MNA (prior to injection and at 2 hours post injection for subjects in Cohort 4) ADA (prior to injection for all subjects)	

Section 8.3 visit 3: Out-patient Follow-up (24 hrs)
• Obtain blood samples for the following:
  • PK measurement
	Section 8.3 visit 3: Out-patient Follow-up (24 hrs/Day 1)
	• Obtain blood samples for the following:
	  ○ PK measurement at 24 hours for subjects in cohorts 1-3
	PK measurement at 24 hours (+/- 2houirs) for subjects in cohort 4
		Added cohort 4

Section 8.4 Visit 4: Outpatient follow-up Visit (48 hours)
• Obtain blood samples for the following:
• PK measurement
	Section 8.4 Visit 4: Outpatient follow-up Visit (48 hours/Day 2)
	• Obtain blood samples for the following:
	  ○ PK measurement at 48 hours for subjects in cohorts 1-3
	  ○ PK measurement 48 hours (+/- 2 hours) for subjects in cohort 4
		Added cohort 4

Section 8.5 visit 5: Out-patient Follow-up (72 hours)	Section 8.5 visit 5: Out-patient Follow-up (72 hours) Cohorts 1-3	Specified visit for cohort 3

Section 8.8 Visit 8: Out-patient Follow-up (Day 15 $\pm$1)
• Obtain blood samples for the following:
  ○ Clinical Safety Labs
	Section 8.8 Visit 8: Out-patient Follow-up (Day 15 $\pm$1)
	• Obtain blood samples for the following:
	  ○ Clinical Safety Labs
		Specified ADA for cohorts 1-3

○ PK measurement ○ ADA	○ PK measurement ○ ADA (cohorts 1-3)	
Section 8.9 visit 9: Out-patient Follow-up (Day30 ±1) • Obtain blood samples for the following: ○ Clinical Safety Labs ○ PK measurement ○ MNA ○ ADA	Section 8.9 visit 9: Out-patient Follow-up (Day30 ±1) • Obtain blood samples for the following: ○ Clinical Safety Labs ○ PK measurement ○ MNA ○ ADA (cohorts 1-3)	Specified ADA for cohorts 1-3
Section 8.10 Visit 10: Out-patient Follow-up (Day 45 ±3) • Obtain blood samples for the following: ○ PK measurement ○ ADA	Section 8.10 Visit 10: Out-patient Follow-up (Day 45 ±3) • Obtain blood samples for the following: ○ PK measurement ○ ADA ○ MNA (cohort 4)	Specified MNA for cohort 4
Section 8.13 Visit 13: Final Visit/Early Termination Visit (Day 120 ±3) • Obtain blood samples for the following: ○ Clinical Safety Labs ○ PK measurement ○ MNA ○ ADA	Section 8.13 Visit 13: Final Visit /Early Termination Visit for Cohorts 1-3 (Day 120 ±3) / Cohorts 4 (Day 120 +3) • Obtain blood samples for the following: ○ Clinical Safety Labs (cohorts 1-3) ○ PK measurement ○ MNA ○ ADA	Specified labs for cohorts 1-3

Section 8.14	Section 8.14 Visit 14: Final Visit/Early Termination for subjects in Cohorts 4 (Day 180 ±3)
	
	• Obtain vital signs
	• Review and update concomitant medications
	• Perform symptom directed PE
	• Obtain blood samples for the following:
	  ○ Clinical Safety Labs
	  ○ PK measurement
	  ○ ADA
	• Obtain urine sample for dipstick analysis
	• Perform urine pregnancy test on women of child-bearing potential
	• Assessment of AEs and SAEs
	• 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
		Addition of Cohort 4 final visit

Section 8.14 Unscheduled Visit	Section 8.15 Unscheduled Visit	Section number update
Section 9.3.2 Serious Adverse Events SAE Email Address: safety@ologybio.com	Section 9.3.2 Serious Adverse Events SAE Email address: olo.safety@reilience.com	Revision to correct SAE email address Revision to correct Medical Monitor

The DOD medical monitor and clinical project manager will be notified of the SAE by DOD PVG. The DOD medical monitor will review and assess the SAE for potential impact on study subject safety and protocol conduct.	The ICON medical monitor and clinical project manager will be notified of the SAE by DOD PVG. The ICON medical monitor will review and assess the SAE for potential impact on study subject safety and protocol conduct.	
Page xx, Section 9.6.3 DOD Medical Monitor The DOD Medical Monitor will communicate with the Ology Bioservices Medical Monitor for any safety related questions. The DOD MM will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.	Section 9.6.2 ICON Medical Monitor The ICON Medical Monitor will communicate with the Ology Bioservices Medical Monitor for any safety related questions. The ICON MM will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.	Revision to correct section numbering and Medical Monitor
Section 9.6.4 Ology Bioservices Medical Monitor The Ology Bioservices Medical Monitor will be the main point of contact for the ICON MM and the DOD MM, including any safety-related questions or concerns. The Ology Bioservices MM will escalate any medical or safety concerns to the DOD MM as needed.	Section 9.6.3 Ology Bioservices Medical Monitor The Ology Bioservices Medical Monitor will be the main point of contact for the ICON MM, including any safety-related questions or concerns. The Ology Bioservices MM will escalate any medical or safety concerns to the DOD as needed.	Revision to correct section numbering and Medical Monitor
Page xx, Section 9.6.5 Safety Review Committee (SRC) The SRC will be composed of: PI, or designee Ology Bioservices Medical Monitor	Section 9.6.4 Safety Review Committee (SRC) The SRC will be composed of: PI, or designee Ology Bioservices Medical Monitor	Revision to correct section numbering and name of Medical Monitor

DOD Medical Monitor or designee; The SRC recommendation to advance to the next level will be documented and provided to all the appropriate parties (PI, Ology Bioservices and DOD) involved with the study.	ICON Medical Monitor or designee; The SRC recommendation to advance to the next level will be documented and provided to all the appropriate parties (PI, Ology Bioservices, ICON, and DOD) involved with the study.	
Section 11.2 Planned Interim Analyses A blinded interim safety and PK analysis is planned for this study to analyze all PK, ADA, and MNA samples through Day 60. This will include all subject in all cohorts through Day 60. Stopping criteria are for safety and are defined in section 9.5.	Section 11.2 Planned Interim Analyses A blinded interim safety and PK analysis is planned for this study to analyze all PK, ADA, and MNA samples for Cohorts 1-3 through Day 60. A second blinded interim safety analysis is planned to analyze all PK, ADA, and MNA samples for Cohort 4 through Day 90. Stopping criteria are for safety and are defined in section 9.5.	
Appendix A: Schedule of Events	Appendix A: Schedule of Events Addition columns added for Study Day 180 Footnotes updated.	Additional Cohort added with extended follow-up period.

SUMMARY OF CHANGES FOR VERSION 2.0

Version 1.0	Version 2.0	Reason for Change
Page 8: List of Abbreviations	Page 9: List of Abbreviations	Added abbreviation for ELISA, HRPO, PVG, and PVSS
Page 12: Protocol Summary, Study Outcome Measures: Secondary Endpoint: The assessment of C_{max}, T_{max}, half-life (α and β), MRT and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) method. Pharmacokinetic samples will be tested by ECLA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120.	Page 17: Protocol Summary, Study Outcome Measures: Secondary Endpoint: The assessment of C_{max}, T_{max}, half-life (α and β), MRT and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or an enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120.	Added enzyme-linked immunosorbent assay (ELISA)
Page 12: Protocol Summary, Description of Study Design: PK samples will be tested by ECLA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120 for all cohorts.	Page 17: Protocol Summary, Description of Study Design: PK samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120 for all cohorts.	Added ELISA

Page 24: Section 4: Study Design Table 1 lists the IP as Dose of NTM-1634	Page 28: Section 4: Study Design Table 1 corrected name of IP to read Dose of G03-52-01	Revision to correct the name of the IP to G03-52-01
Page 24: Section 3.2.2 Secondary Endpoint: The assessment of C_{max}, T_{max}, half-life (α and β), MRT and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) method. Pharmacokinetic samples will be tested by ECLA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120.	Page 29 Section 3.2.2: Secondary Endpoint: The assessment of C_{max}, T_{max}, half-life (α and β), MRT and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or an enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120.	Added ELISA
Page 36: Section 7.6.1 Pharmacokinetic Assay Serum will be analyzed for levels of each of the antibodies using a validated ECLA. Five-mL samples of blood will be drawn to be analyzed for neutralizing antibody concentrated using the validated Battelle MNA.	Page 41: Section 7.6.1 Pharmacokinetic Assay Six-mL of blood will be drawn for the analysis of levels of each of the monoclonal antibodies in serum using a validated ECLA or ELISA. Ten-mL samples of blood will be drawn to be analyzed for neutralizing antibody concentrated using the validated Battelle MNA.	Added ELISA and revised the amount of blood to be drawn for analysis.
Page 37 Section 7.6.2 Anti-Drug Antibody Assay Six-mL samples of blood will be drawn on Days 0, 15, 30,45,60, 90, and 120 for determining the presence of	Page 42 Section 7.6.2 Anti-Drug Antibody Assay Six-mL samples of blood will be drawn on Days 0, 15, 30,45,60, 90, and 120 for determining the presence of ADA using a	Added that ECLA assay is validated

ADA using an ECLA assay that measures total anti-drug antibody in serum. This will be done to assess immunogenicity.	validated ECLA that measures total anti-drug antibody in serum. This will be done to assess immunogenicity.	
Page 38 Table 2: Laboratory Samples and Estimated Total Blood Volume (mL)	Page 43 Table 2: Laboratory Samples and Estimated Total Blood Volume (mL)	Estimated blood volume
Page 40 Section 8.2 Visit 2/Baseline	Page 45 Section 8.2 Visit 2/ Baseline: Added MNA	Added MNA
Page 42 Section 8.6 Visit 6/Day 4	Page 47 Section 8.6 Visit 6/Day 4: Added MNA	Added MNA
Page 42 Section 8.8 Visit 8/Day 15	Page 47 Section 8.8 Visit 8/Day 15: Added: 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	Added: 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
Page 43 Section 8.9 Visit 9/Day 30	Page 48 Section 8.9 Visit 9/Day 30: Added MNA	Added MNA
Page 43 Section 8.11 Visit 11/Day 60	Page 49 Section 8.11 Visit 11/Day 60: Added MNA	Added MNA
Page 44 Section 8.12 Visit 12/Day 90	Page 49 Section 8.12 Visit 12/Day 90: Added MNA	Added MNA
Page 44 Section 8.13 Visit 13/Day 120	Page 49 Section 8.13 Visit 13/Day 120: Added MNA	Added MNA

Page 47 Section 9.3.2 Serious Adverse Events: ICON Medical Monitor SAE Phone: 443-983-1332	Page 53 Section 9.3.2 Serious Adverse Events: ICON Medical Monitor SAE Phone: 410-294-2537	Revision in Medical Monitor Phone Number to Report SAE. Revision captured in Administrative Letter to Protocol dated March 5, 2020
N/A	Page 56 Section 9.6.2 ICON Medical Monitor	Added the ICON Medical Monitor and defined the role
N/A	Page 56 Section 9.6.3 DOD Medical Monitor	Added the DOD Medical Monitor and defined the role
N/A	Page 56 Section 9.6.4 Ology Bio Medical Monitor	Added the Ology Bio Medical Monitor and defined the role
Page 63 Appendix A: Schedule of Events	Page 69: Appendix A: Schedule of Events	Added MNA as a line item on the Schedule of Events

PROTOCOL SUMMARY

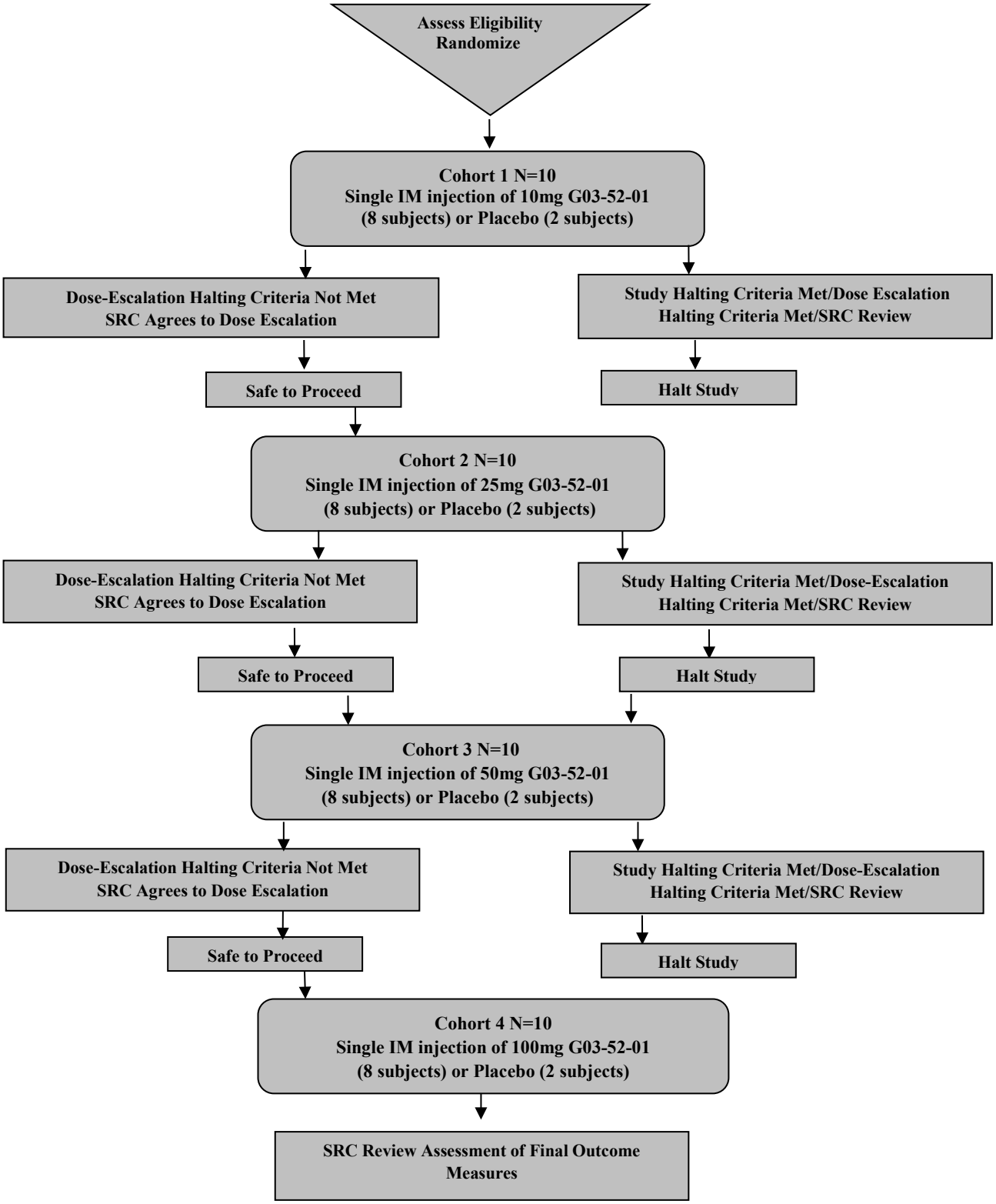
Title:	A Phase 1, Randomized, Double-Blind, Dose Escalation Study to Evaluate the Safety and Pharmacokinetics of a Single IM Dose of G03-52-01 vs Placebo in Adult Subjects.
Phase:	1
Population:	40 healthy male and female subjects between 18-45 years of age
Number of Sites:	One
Study Duration:	Approximately 10 months.
Subject Participation Duration	Subjects in Cohorts 1-3 will participate approximately 150 days (up to 28-day screening, 12-hour inpatient stay, up to 120 days outpatient follow-up) Subjects in Cohort 4 will participate approximately 210 days (up to a 28-day screening, up to 12-hour clinic stay, up to 180-day outpatient follow-up)
Description of Agent:	G03-52-01 drug product is a mixture of five human monoclonal IgG_1 antibodies (NX01, NX11, XB10, XB18, and XB23) and one humanized monoclonal IgG_1 antibody (NX02) which bind to non-overlapping epitopes on BoNT/A/B.

Study Objectives:	Primary Objective: • To assess the safety and tolerability of escalating doses of G03-52-01 administered intramuscularly (IM) in healthy adult subjects Secondary Objective: • To assess the pharmacokinetics (PK) and immunogenicity of escalating doses of G03-52-01 administered IM in healthy adult subjects
Study Outcome Measures:	Primary Endpoints: • The occurrence of Serious Adverse Events (SAE) following administration of G03-52-01 to the final follow-up visit. • The occurrence of Adverse Events (AE) from administration of G03-52-01 to the final follow-up visit. • The occurrence of changes from baseline in physical examination, vital signs and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit. Secondary Endpoints: • The pharmacokinetic assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ as measured by the validated Battelle Mouse Neutralization Assay (MNA) for serotypes A and B. o Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 for Cohorts 1-3. o Pharmacokinetic samples will be tested by MNA at pre-dose, 2-hour post-dose (for future use), and on Days 4, 30, 45, 60, 90, and 120 for Cohort 4. The assessment of C_{max}, T_{max}, half-life (α and β), MRT and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or an enzyme-linked immunosorbent assay (ELISA). o Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for Cohorts 1-3. o Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 6 hours post dose, and on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180 for Cohort 4.

	• Samples collected to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o Samples will be tested for ADA at pre-dose and on Days 15, 30, 45, 60, 90, and 120 for Cohorts 1-3. o Samples will be tested for ADA at pre-dose and on Days 45, 60, 90, 120, and 180 for Cohort 4.
Estimated Time to Complete Enrollment:	Approximately 5 months.
Description of Study Design:	A Phase 1, randomized, double-blind, placebo-controlled dose escalation trial of four dose cohorts outlined below: • Cohort 1: 10 mg IM injection (8 active, 2 placebo) • Cohort 2: 25 mg IM injection (8 active, 2 placebo) • Cohort 3: 50 mg IM injection (8 active, 2 placebo) • Cohort 4: 100mg IM injection (8 active, 2 placebo) Dosing for each cohort is as follows: Two sentinel subjects will be administered a single IM dose (one G03-52-01, one placebo). The dosing of the remaining eight subjects within that cohort will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining eight subjects in the cohort will be admitted as scheduled without delay. Dose escalation will not occur until safety data through Day 8 is reviewed by the Safety Review Committee (SRC) composed of the Principal Investigator (PI), Ology Bioservices Medical Monitor, and the ICON Medical Monitor. Objective dose-escalation criteria and safety evaluations will be utilized. A SRC meeting will be held at any time during the course of the study if halting criteria are met or safety concerns arise. The study will consist of a twenty-eight-day screening period and up to 12-hour clinic stay. Follow-up visits will occur at 24 hours, 48 hours, and 72 hours post dose and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for Cohorts 1-3. Follow-up visits for subjects in Cohort 4 will occur at on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180. Subjects will be screened for Human Immunodeficiency Virus (HIV), Hepatitis B surface antigen (HBsAg), and antibody to Hepatitis C virus (HCV), drugs and alcohol. Safety parameters include physical examination, 12-lead Electrocardiogram (ECG), vital signs, and clinical laboratory values to include:

	Complete Blood Count (CBC) with differential, comprehensive metabolic panel, and urine dipstick for protein, blood, and glucose with reflex microscopy. Cohorts 1-3: Pharmacokinetic (PK) samples will be drawn at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120. PK samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose and on days 4, 30, 60, 90, and 120. PK samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post dose and on days 4, 8, 15, 30, 45, 60, 90, and 120. Samples will be tested for anti-drug antibodies (ADA) at pre-dose and days 15, 30, 45, 60, 90, and 120. Cohort 4: PK samples will be tested by the Battelle Mouse Neutralization Assay (MNA) for serotypes A and B at pre-dose, 2-hours post-dose (future use) and on days 4, 30, 45, 60, 90, and 120. PK samples will be tested by ECLA or ELISA at pre-dose, 6 hours post-dose, and on days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180. Samples will be tested for anti-drug antibodies (ADA) at pre-dose and days 45, 60, 90, 120, and 180. A Safety Review Committee (SRC) meeting will be held if halting criteria are met or safety concerns arise.

Schematic of Study Design



1. KEY ROLES

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CRO Safety and Pharmacovigilance Contractor:	ICON Pharmacovigilance & Safety Services Unit 2, Globeside Business Park Marlow SL7 1HZ United Kingdom PV email: ICON-Safety-CentralReceipt@iconplc.com

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Back up Laboratory for Safety Testing:	Quest Diagnostic Clinical Laboratories Inc. 4770 Regent Blvd. Irving, TX 75063
Research Laboratory for PK and ADA Samples:	Ology Bioservices, Inc. 2601 Challenger Drive, Suite 101 Alameda, CA 94501
Research Laboratory for MNA Samples:	Battelle 1425 State Route 142 West Jefferson, OH 43162

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. 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.

2.1.2. 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 equine antitoxin (HBAT) 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] HBAT 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] HBAT 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 HBAT, can vary significantly for sub-serotypes where there is significant sequence difference between the immunizing sub-serotype and other sub-serotypes.

2.1.3. G03-52-01 Development

G03-52-01 drug product is being investigated for the treatment of botulinum neurotoxin and prophylaxis of inhalation botulism from serotypes A and B in adults. G03-52-01 is a mixture of five human IgG1 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 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 drug products 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 drug product.

A GLP 12-week repeat dose toxicity study was performed to evaluate the safety of G03-52-01 in rate when administered by intramuscular 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, injection site (Draize) reactogenicity scoring; body weights; food consumption; body temperature measurements; clinical pathology parameters (clinical chemistry, hematology, and coagulation); serum drug levels/toxicokinetics; 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 botulinum neurotoxins 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.

2.1.4. Public Readiness and Emergency Preparedness Act

This protocol and the study product tested are covered under the Public Readiness and Emergency Preparedness (PREP) act. The PREP Act provides compensation to participants in the event of serious physical injury or death caused by covered drugs and vaccines, and liability protection for persons conducting the clinical trial and the manufacturer of the drug or vaccine.

On October 10, 2008, an amendment was issued to the Declaration for use of the PREP act to include countermeasures to treat, identify, or prevent adverse health consequences or death from exposure to botulinum toxin. (Federal Register, Volume 73, Number 202, Pages: 61864-61866). The study product used in this clinical trial is one such countermeasure. The PREP act provides immunity for covered persons (such as Manufacturers, Distributers, Program planners and other qualified persons who prescribe, administer or dispense the study product) from tort liability, unless the injury was caused by willful misconduct.

The PREP Act also authorized a "Covered Countermeasures Process Fund" to provide compensation to eligible individuals who suffer specified injuries from administration or use of a countermeasure pursuant to the declaration. Any requests for compensation must be filed within one year of administration or use of the countermeasure. Requests would go to the HRSA Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp). Compensation may then be available for medical benefits, lost wages and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from the administration and use of the study product must first seek compensation from the Covered Countermeasures Process Fund. A serious physical injury means an injury that is life threatening, results in, or requires medical or surgical intervention to prevent, permanent impairment of a body function or permanent damage to body structure. Any compensation will be reduced by public or private insurance or worker's compensation available to the injured individual.

If no funds have been appropriated to the compensation program, the Secretary does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, the individual does not have a tort claim that can be filed in a US Federal or a State court.

2.2. Rationale For Use of G03-52-01

Based on nonclinical and clinical experience with other anti-BoNT mAbs, use of G03-52-01 for the treatment of botulism and prophylaxis 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 similar product targeting BoNT serotype A was well tolerated and no safety concerns were observed in a Phase 1 clinical study
  - A similar product targeting BoNT serotype B was well tolerated and no safety concerns were observed in a Phase 1 clinical trial
- 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 proposed starting dose for G03-52-01 dose escalation (10 mg IM) is based on previous toxicology and clinical studies of anti-BoNT mAbs that included intravenous dosing. The 10 mg IM dose includes 5 mg of anti-BoNT/A mAbs (NX01, NX02, and NX11; similar to NTM-1631, formerly XOMA 3AB) and 5 mg of anti-BoNT/B mAbs (XB10, XB18 and XB23; similar to NTM-1632, formerly XOMA 3B).

NTM-1631 and NTM-1632 have undergone Phase 1 clinical testing under protocols very similar to Protocol G03-52-001.001. These studies were placebo-controlled, double-blind, dose escalation studies to evaluate the safety and tolerability of each drug. Each subject received a single intravenous (IV) infusions of study drug or placebo administered over one hour, as an inpatient, at one of three dose levels (0.33, 0.165, or 0.033 mg/kg) equating to approximately 25, 12, or 2.5 mg assuming a 75 kg subject. All three doses of each drug were safe and generally well tolerated during and following infusion. No pattern of treatment emergent adverse events was seen at any of the doses. None of the three NTM-1631 mAbs induced an antibody response or augmentation of preexisting antibodies in the few subjects who had them and similar analysis of NTM-1632 antibody response is underway.

Doses will escalate to 25 mg and then to 50 mg up to 100mg provided there are no safety concerns. The nonclinical IND-enabling toxicology studies were designed to support this clinical design with intramuscular route of administration. Based on data received from the Day 60 blinded interim safety and PK analysis, it was determined to escalate to 100mg single dose.

2.3. Potential Risks and Benefits

2.3.1. 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

As G03-52-01 has not been administered to humans, the potential risks are based on adverse events associated with NTM-1631and NTM-1632 in the Phase 1 studies, infusion or injection of other antibody products, in particular other monoclonal antibody preparations against non-human targets, and the possibility of allergic reactions, especially IgE-mediated and serum sickness-like reactions.

Adverse Events with a Similar Product

A summary of all Adverse Events (AEs) assessed as related on the NTM-1631 clinical protocol following administration of NTM-1631 follows:

NTM-1631 dose level 0.033mg/kg:

- One female subject experienced a moderate decrease in hemoglobin reported 1-week post infusion. She also had a mild elevation in Alanine Aminotransferase (ALT) 2 weeks post infusion.
- One male subject experienced moderate protein in the urine one-week post infusion and a mild elevation in Aspartate Aminotransferase (AST) two months post infusion.
- One male subject experienced a moderate elevation in blood sugar three days post infusion and then again two weeks post infusion.

NTM-1631 dose level 0.165mg/kg:

- One female subject experienced a mild increase in neutrophils starting one-month post infusion.

NTM-1631 dose level 0.330mg/kg:

- No associated AEs were reported in subjects receiving NTM-1631 at this dose.

No safety signals or trends were identified on this protocol and a placebo subject also had a mild increase in AST and ALT three days post infusion.

A summary of all AEs assessed as related with the NTM-1632 clinical protocol following administration of NTM-1632 is as follows:

NTM-1632 dose level 0.033mg/kg:

- One female subject experienced mild throbbing pressure on forehead during infusion
- One female subject experienced mild lightheadedness during infusion

NTM-1632 dose level 0.33mg/kg

- One female subject experienced mild loose stools 1-day post infusion

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.

2.3.2. 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.

3. OBJECTIVES

3.1. Study Objectives

Primary Objective:

- To assess the safety and tolerability of escalating doses of G03-52-01 administered IM in healthy adult subjects.

Secondary Objective:

- To assess the (PK) and immunogenicity of escalating doses of G03-52-01 administered IM in healthy adult subjects.

3.2. Study Outcome Measures

3.2.1. Primary Endpoints

- The occurrence of Serious Adverse Events following administration of G03-52-01 to the final follow-up visit.
- The occurrence of Adverse Events from administration of G03-52-01 to the final follow-up visit.
- The occurrence of changes from baseline in physical examination, vital signs and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit.

3.2.2. Secondary Endpoints

- The pharmacokinetic assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ as measured by the validated Battelle Mouse Neutralization Assay (MNA) for serotypes A and B
    - Pharmacokinetic samples will be tested by MNA at pre-dose and on Days 4, 30, 60, 90, and 120 for Cohorts 1-3.
    - Pharmacokinetic samples will be tested by MNA at pre-dose, 2-hours post-dose (future use), and on Days 4, 30, 45, 60, 90, and 120 for Cohort 4.
- The assessment of C_{max}, T_{max}, half-life (α and β), MRT, and $AUC_{(0-t)}$ for each of the monoclonal antibodies of G03-52-01 as measured by a validated electrochemiluminescence assay (ECLA) or validated enzyme-linked immunosorbent assay (ELISA).
    - Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection, and on Days 4, 8, 15, 30, 45, 60, 90, and 120 for Cohorts 1-3.
    - Pharmacokinetic samples will be tested by ECLA or ELISA at pre-dose, 6 hours post-dose, and on Days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180 for Cohort 4.
- Samples will be tested to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts.
    - Samples will be tested for ADA at pre-dose, 15, 30, 45, 60, 90, and 120 for Cohorts 1-3.
    - Samples will be tested for ADA at pre-dose and on Days 45, 60, 90, 120, and 180 for Cohort 4.

4. STUDY DESIGN

This is a Phase 1, single-center, placebo-controlled, double-blind, dose-escalation study to evaluate the safety and tolerability of G03-52-01 in healthy adults. This is a first-in-human study consisting of four Cohorts of ten subjects each. Each subject will receive a single IM injection of G03-52-01 or placebo.

Table 1: Cohorts

Cohort	Dose of G03-52-01	Number of Subjects
1	10 mg	10 subjects (8 active, 2 placebo)
2	25 mg	10 subjects (8 active, 2 placebo)
3	50 mg	10 subjects (8 active, 2 placebo)
4	100 mg	10 subjects (8 active, 2 placebo)

Schedule for Subjects

Subjects in Cohorts 1-3 will participate in the study for approximately 150 days, including a 28-day screening period, up to12-hour inpatient stay and approximately 120-day follow-up after study product administration. Subjects will remain at the clinic and not be eligible for discharge until 8 hours after the IM injection. Last follow up visit scheduled at Day 120.

Subjects in Cohort 4 will participate in the study for approximately 210 days, including a 28-day screening period, up to a 12-hour clinic stay and approximately 180-day follow-up after study product administration. Subjects will remain at the clinic and not be eligible for discharge until approximately 8 hours after the IM injection. Last follow up visit scheduled at Day 180.

The end of the study is defined as the date of the last visit of the last subject in the study.

Schedule for Cohorts

Since this is a first-in-human study, administration of the study products to subjects in a cohort will occur over a period of up to two weeks to allow careful observation of individuals for adverse events. Two sentinel subjects within each cohort will be admitted initially and will be administered a single IM injection, and the randomization scheme will be designed to ensure that one subject will receive G03-52-01 and the other will receive placebo. The dosing of the remaining eight subjects within that cohort will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining eight subjects in the cohort will be admitted as scheduled without delay. An alternate subject will be admitted to the unit for each two-subject group. Up to four alternates per cohort will be recruited. Dose escalation will not occur until safety data through Day 8 is reviewed by the Safety Review Committee (SRC) composed of the Principal Investigator (PI), Ology Bioservices Medical Monitor, and the ICON Medical Monitor.

4.1 Study Enrollment and Withdrawal

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. No exemptions are granted on Inclusion/Exclusion Criteria in DOD-sponsored studies.

Forty healthy male and female subjects, ages 18 to 45 years old, will be enrolled in four cohorts. Up to four alternates per cohort will be recruited. Alternates who meet all eligibility criteria may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 24 hours after the initial two subjects are dosed (Cohorts 1-3). Alternates not enrolled into a dosing group within a cohort are eligible for enrollment into the next group for that cohort. Alternates not enrolled into the cohort are eligible for enrollment in subsequent cohorts but would have to undergo re-screening with the exception of the viral serology labs listed in section 7.5.1.1 if more than 28 days have passed since collection of screening laboratory parameters.

4.1.1 Subject Inclusion Criteria

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

1. Informed consent understood and signed
2. Healthy male or healthy, non-pregnant, non-lactating female
3. Willingness to comply and be available for all protocol procedures
4. Between 18 and 45 years of age on the day of IM injection
5. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2
6. If the subject is female and of childbearing potential, she has a negative serum pregnancy test at screening and negative urine test within 24 hours prior to IM injection
    - *Note: 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 or successful Essure placement with documented confirmation test at least 3 months after the procedure.*
7. If the subject is female and of childbearing potential, she agrees to practice abstinence from sexual intercourse with men or use acceptable contraception during participation in the study
    - *Note: Acceptable contraception methods are restricted to effective devices (Intrauterine Contraceptive Devices)*
8. The hemoglobin, platelet count, white blood cell count and absolute neutrophil count are not below the LLN and ≤ULN x 10%
    - *Abnormalities in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), and nucleated red blood cell count (NRBC CT), which are included in a complete blood count with differential, will not be exclusions.*
9. The urine dipstick results on protein, glucose and blood are negative or trace
    - *Note: Menstruating females failing inclusion criteria due to a positive blood on urine dipstick may be retested following cessation of menses.*

- *Note: When a urine dipstick is more than trace positive for blood (whether a menstruating female or other subjects), that subject would not be excluded if the urine microscopic exam shows <5 rbcs/hpf.*

10. Chemistry screening laboratory tests as outlined in Section 7.5.1.4 are in the normal reference range
    - *Note: The following exceptions to laboratory normal reference ranges are allowed: Creatinine, Blood Urea Nitrogen (BUN), total bilirubin, AST, ALT, lipase, amylase, Prothrombin Time (PT), Partial Thromboplastin Time (PTT) below the lower limit of normal (LLN); CK less than 400U/L; Glucose, potassium, total protein, and alkaline phosphatase with a toxicity grade of 1 is allowable; albumin above the upper limit of normal (ULN).*
    - *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.*
11. The urine drug screen is negative
12. Breathalyzer test is negative
13. Available for follow-up for the duration of the study
14. Agrees not to participate in vigorous activity 72 hours prior to dosing through day 15 post dosing

4.1.2 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.
    - *Note: 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. History of severe allergic reaction of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobulins.
    - *Note: Severe allergic reaction is defined as any of the following: anaphylaxis, urticaria, or angioedema*
3. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds)
4. Clinically significant abnormal electrocardiogram at screening.

- *Note: Clinically significant abnormal ECG results include but not limited to: complete left or right bundle branch block; other ventricular conduction block; 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*

5. Positive serology results for HIV, HBsAg, or HCV antibodies

6. Febrile illness with temperature ≥38°C within 7 days of dosing

7. Pregnant or breastfeeding

8. Donated blood within 56 days of enrollment

9. Known allergic reactions to any of the study product components present in the formulation or in the processing, as listed in the Investigator Brochure

10. Treatment with another investigational drug within 28 days of dosing

11. Treatment with a monoclonal antibody within 3 months of enrollment.

12. 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

13. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements

14. Use of H1 antihistamines or beta-blockers within 5 days of dosing

15. 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; any vaccine (licensed or investigational). Subjects will be eligible to receive any authorized COVID-19 vaccine after they complete Study Day 8*

16. Previous exposure to botulinum toxin, receipt of antibodies against botulinum toxin, or previous treatment with equine antitoxin

17. Any previous injection or planned injection within 4 months after enrollment of botulinum toxin for cosmetic reasons, spastic dysphonia, torticollis, or any other reason

18. Any specific condition that in the judgment of the investigator precludes participation because it could affect subject safety

19. Plans to enroll or is already enrolled in another clinical trial* that could interfere with safety assessment of the investigational product at any time during the study period

    - *Note: Includes trials that have a study intervention such as a drug, biologic, or device*

20. Is a study site employee or staff
    - *Note: Site employees or staff include the PIs and sub-investigators or staff who are supervised by the PI or Sub-Investigators*

21. Systolic blood pressure >140mm Hg or diastolic blood pressure >90 mm Hg
    a. *Grade 1 values may be repeated once if the PI believes a transient condition let to the aberrant value and are allowable unless deemed clinically significant by the PI.*

22. Resting heart rate <50 or >100 beats per minute

23. Oral temperature ≥ 38°C (100.4°F)

24. Subjects with NX02 antibody levels present at screening will be excluded from Cohort 4.

4.2 Treatment Assignment Procedures

4.2.1 Randomization Procedures

Randomized treatment assignments will be generated by a statistician at ICON PLC. Randomization will occur following admittance to the unit and confirmation of eligibility is confirmed.

This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within four dosing Cohorts to either active or placebo in an overall 4:1 ratio. For each dosing cohort, the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control. An alternate subject will be admitted to the unit for each two-subject group. If one of the first two subjects is not randomized for any reason, then the alternate subject will receive the next consecutive randomization number. The product assignment of the remaining eight subjects in each cohort will be a simple random sample to ensure the 4:1 ratio for the dosing cohort. The randomization list will be generated by the unblinded study biostatistician and transferred to the unblinded study pharmacist prior to start of the study.

If 2 or more subjects withdraw, are lost to follow up or terminate prior to Day 8, those subjects need to be replaced to ensure that data for at least 7 subjects is available for review.

If 2 or more subjects withdraw, are lost to follow up or terminate prior to Day 60 or are not compliant with all PK draws through Day 15, they may be replaced.

If more than 2 subjects withdraw, are lost to follow up or terminate following the Day 8 SRC review of safety data, the site will attempt to replace those subjects in that dose group at the time of the next planned cohort.

4.2.2 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 G03-52-001 is being injected.

The Investigator may unblind a subject's treatment assignment only in the case on 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 Ology Bioservices Medical Monitor or appropriately designated Ology Bioservices personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Ology Bioservices 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.

4.2.3 Reasons for Withdrawal

A subject may withdraw from the study at any time for any reason, without any consequence.

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)/Ethics committee, Food and Drug Administration (FDA), or DOD;
- The subject's well-being based on the opinion of the investigator;
- The occurrence of a Serious Adverse Event (SAE) or (AE warranting withdrawal).

4.2.4 Handling of Withdrawals

Subjects who are withdrawn prior to dosing may be replaced. Following dosing, one subject per cohort may withdraw prior to the completion of Visit 11 (Day 60) or was noncompliant with all PK draws through Visit 6 (Day 4) without being replaced. Should more than one subject from the same cohort voluntarily withdraw from the study who did not meet the above criteria, those subjects may be replaced. Subjects who withdraw or are withdrawn from the study who received any amount of the study product will be encouraged to continue follow-up (with subjects' consent) for safety. Subjects withdrawing will be asked to complete a final termination visit if they do not wish to be followed per protocol.

4.2.5 Lost to Follow-up

In the case of subjects who fail to appear for a follow-up assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mail, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subjects' records.

4.2.6 Termination of Study

Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study at any time for clinical or administrative reasons.

5. STUDY PRODUCTS

5.1. Description of Study Products

G03-52-01 drug product 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 is 0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection.

5.2. Acquisition

The G03-52-01 will be supplied by Ology Bioservices, Inc. Study product will be shipped to the following address:

ICON Early Phase Services

Attn: Pharmacist

8307 Gault Lane

San Antonio, TX 78209

The normal saline for injection will be supplied by ICON.

5.3. 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 water for injection (WFI), the drug product is a clear, colorless, sterile aqueous solution in a pH 6 buffered vehicle without preservatives.

Cohorts 1-3: The drug product will be supplied in 2-mL, pyrogen-free, Type 1 glass vials fitted with Teflon-coated butyl rubber stoppers and flip-up aluminum seals.

Cohort 4: The drug product is supplied in a 3mL/13mm glass serum/lyophilized vial fitted with a 13-mm FluroTec™-coated stopper and flip-up aluminum seal.

G03-52-01 will be administered intramuscularly (IM) as a single dose at concentrations of 10 mg, 25 mg, 50 mg, and 100 mg by varying the administration volume.

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

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

5.4. Product Storage and Stability

G03-52-01

G03-52-01 drug product 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. If not used, it must be quarantined and maintained for study product accountability as per Section 6.6. 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.

5.5. Dosage, Preparation and Administration

The unblinded site Research Pharmacist will prepare the study drug on the same day as administration. Prior to using any of the parenteral products, inspect for discoloration or

particulate matter before use. Any product that fails inspection should be quarantined at 2-8°C for inspection by the Sponsor. 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. Water for injection 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 as per Section 6.6. 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 Phase 1 unit 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 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.

5.6. Accountability Procedures for the Study Products

The Site Principal Investigator is responsible for the distribution and disposition of study product (both G03-52-01 and placebo) and has ultimate responsibility for accountability. The site Principal Investigator 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.

5.7. Assessment of Subject Compliance with Study Product

Because each dose of G03-52-01 will be administered by site personnel, subject compliance is not anticipated to be an issue.

5.8. 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 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 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 vaccines (licensed or investigational)

  *Subjects will be eligible to receive any authorized COVID-19 vaccine after they complete Study Day 8
- Monoclonal antibody
- Botulinum toxin
- H1 antihistamines
- Beta-blockers
- Immunosuppressives (except NSAIDS)
- Immune modulators
- Oral corticosteroids (topical/intranasal steroids are acceptable)
- Anti-neoplastic agents

6. STUDY PROCEDURES

6.1. 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 0.

6.2. Physical Examination

An abbreviated physical examination (PE) will be conducted at the screening visit and Day 0. 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

0, 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. Refer to the MOP for further details. Any new findings on examination post dosing or worsening of existing conditions are to be reported as AEs.

6.3. 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 Toxicity Grading) 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.

6.4. 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 in a supine position 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.

6.5. Laboratory Evaluations

Venipuncture schedule and volumes are displayed in Table 2.

6.5.1. Screening Laboratory Tests

6.5.1.1. 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).

7.5.1.2 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.

7.5.1.3 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 0), which must be reported as negative before dosing. A urine pregnancy test will be repeated on Day 4, Day 45, and end of study (Day 120 or Day 180 (Cohort 4 only).

7.5.1.4 Screening Laboratory Tests

- Hematology: hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded.
- Chemistry: serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
- Urinalysis: 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. 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 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.

6.5.2. 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 eight hours prior to sampling.

Safety labs with a Grade 1 value (Appendix B) will not exclude a subject from participation but will serve as their baseline value.

- Hematology: hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded.

- Chemistry: serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
- Urinalysis: 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.

6.5.3. Hypersensitivity Panel

A hypersensitivity panel includes cytokine and complement panels, IgE and tryptase. This 14 mL sample will be drawn on Day 0 prior to dosing. 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. Refer to the Manual of Procedures for further details.

6.6. Special Assays or Procedures

6.6.1. Pharmacokinetic Assay

Six-mL of blood will be drawn for the analysis of levels of each of the monoclonal antibodies in serum using a validated ECLA or ELISA. Three ten-mL samples of blood will be drawn to be analyzed for neutralizing antibody concentrated using the validated Battelle MNA.

6.6.2. Anti-Drug Antibody Assay

Six-mL samples of blood will be drawn pre-dose on Day 0, and on Days 15, 30, 45, 60, 90, and 120 for determining the presence of ADA using a validated ECLA that measures total anti-drug antibody in serum for Cohorts 1-3. This will be done to assess immunogenicity.

Six-mL samples of blood will be drawn pre-dose on Day 0 and on Days 45, 60, 90, 120, and 180 for determining the presence of ADA using a validated ECLA that measures total anti-drug antibody in serum for Cohort 4. This will be done to assess immunogenicity.

6.6.3. 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 Day 0, 8 and 30 for all cohorts and 2 hours post dose for cohort 4.

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

6.6.4. Specimen Preparation, Handling, and Shipping

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

Table 2: Laboratory Samples and Estimated Total Blood Volume (mL)

Study Visit	01	02	03	04	05	06	07	08	09	10	11	12	13	14	Total Cohorts 1-3	Total for Cohort 4
Day	-28 to -3	Baseline	24 hr	48 hr/	72 hr	4	8 ±1	15 ±1	30 ±1	45 ±3	60 ±3	90 ±3	120 ±3	180 ±3		
Dosing		X														
HIV, HBV,HCV Serum β-HCG	4														4	4
Screening Labs	9														9	9
Safety Labs		9					9	9	9				9[e]	9	45	45
PK[a] (cohorts 1-3)		24[a]	6	6	6	6	6	6	6	6	6	6	6	6	90	
PK[a] (cohorts 4)		12	6	6		6	6	6	6	6	6	6	6	6		78
MNA (cohorts 1-3)		30				30			30		30	30	30		180	
MNA (cohorts 4)		30				30			30	30	30	30	30			210
ADA (cohorts 1-3)		6						6	6	6	6	6	6		42	
ADA (cohorts 4)		6								6	6	6	6	6		36
Future Use[c]		5					5		5						15	15
Hypersensitivity panel		14[b]													14	14
Total Volume/ Visit (cohorts 1-3)	13	88	6	6	6	36	20	21	56	12	42	42	51	51	399[e]	
Total Volume/ Visit (cohort 4)	13	76	6	6		36	20	15	50	42	42	42	42	27		417
Cumulative Total[d] Cohorts 1-3	13	101	107	113	119	155	175	196	252	264	306	348	399[e]			

Cumulative Total Cohorts 4	13	89	95	101	101	137	157	172	222	264	306	348	390	417		

[a] PK serum samples taken prior to injection and 2hr, 4hr, 8hr, 24hr, 48hr, 72hr post-dose, and on days 4, 8, 15, 30, 45, 60, 90, and 120 for cohorts 1-3; PK serum samples taken prior to injection and 6-hr post-dose, and on days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120 and 180 for Cohort 4.

[b] If a subject develops anaphylaxis or anaphylactoid reaction, an additional 14ml will be drawn during the event and after the event. In this instance an additional 28 ml may be drawn from a subject than is reflected in the table totals.

[c] For subjects consenting to future use

[d] Total estimated volume drawn will vary slightly depending on future use consent and need for additional draws for the occurrence of hypersensitivity

e Subjects in Cohorts 1-3 only

7. STUDY SCHEDULE

The Schedule of Events is included as Appendix A.

7.1. Visit 1: Screening (Day -28 to Day -3)

After providing written informed consent, each subject will be assigned a Subject ID number and undergo an eligibility assessment. The following will be done during the screening period (within 28 days prior to administration of study product). Results of screening tests and procedures will be evaluated by the investigator to determine eligibility prior to enrollment and randomization. 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
    - blood transfusions or immunoglobulin within the last 6 months
    - live vaccines within the last 28 days
    - killed vaccines within the last 28 days
    - *Subjects will be eligible to receive any authorized COVID-19 vaccine after they complete Study Day 8
    - 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 monoclonal antibody in the past
    - Exposure to botulinum toxin in the past 4 months
- 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 abbreviated 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 blood pressure, 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 child bearing potential
- Obtain blood to assess NX02 antibody levels (Cohort 4 subjects only)
- 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 listed in section 6.8.

7.2. Visit 2: Baseline (Day 0)

Subjects meeting inclusion/exclusion criteria will be admitted to the clinical unit 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 physical examination
- Obtain vital signs
- Perform Breathalyzer test to detect recent alcohol use
- For women, a urine hCG test will be done. The results must be confirmed to be negative before dosing
- Obtain urine sample for toxicology
- Obtain blood samples for
    - Baseline serum PK (prior to injection and at the completion of the injection and 2hr, 4hr, and 8 hr post dosing for subjects in Cohorts 1-3)
    - Baseline serum PK (prior to injection and at 6 hours post-injection for subjects in Cohort 4)
    - Serum sample to store for future use samples (for subjects who consent)
    - MNA (prior to injection for subjects in Cohorts 1-3)

- MNA (prior to injection and at 2 hours post-injection (optional) for subjects in Cohort 4)
- ADA (prior to injection for all subjects)
- Hypersensitivity panel
- Clinical Safety Labs

- Randomize the subject and obtain study product from the pharmacy
- Perform IM Administration of study product
- Assessment of AEs and SAEs after administration of study product
- The subject is eligible for discharge after all assessments have been performed, including the 8-hour post injection blood draw and there are no signs of anaphylaxis.

7.3. Visit 3: Out-patient Follow-up (24 hours/Day 1)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - PK measurement at 24 hours (+/- 2 hours)
- 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.
- Assessment of AEs and SAEs

7.4. Visit 4: Out-patient follow-up Visit (48 hours/Day 2)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
- PK measurement at 48 hours (+/- 2 hours) 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
- Assessment of AEs and SAEs

7.5. Visit 5: Out-patient Follow-up (72 hours) Cohorts 1-3

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - PK measurement at 72 hours (+/- 2 hours)
- 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.
- Assessment of AEs and SAEs

7.6. Visit 6: Out-patient Follow-up (Day 4)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - PK measurement
    - MNA
- Obtain urine sample urine HCG for women of child bearing potential
- 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.
- Assessment of AEs and SAEs

7.7. Visit 7: Out-patient Follow-up (Day 8± 1)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - Clinical Safety Labs
    - PK measurement
    - Serum sample to store for future use (if subject gave consent)
- 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
- Assessment of AEs and SAEs

7.8. Visit 8: Out-patient Follow-up (Day 15± 1)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - Clinical Safety Labs
    - PK measurement
    - ADA (Cohorts 1-3 only)
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status

7.9. Visit 9: Out-patient Follow-up (Day 30 ± 1)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - Clinical Safety Labs
    - PK measurement
    - MNA
    - ADA (Cohorts 1-3 only)
    - Serum sample to store for future use (if subject gave consent)
- Assessment of AEs and SAEs
- 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

- Assessment of COVID-19 vaccination status.

7.10. Visit 10: Out-patient Follow-up (Day 45± 3)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - PK measurement
    - ADA
    - MNA (Cohort 4 only)
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status.

7.11. Visit 11: Out-patient Follow-up (Day 60 ± 3)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - PK measurement
    - MNA
    - ADA
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status.

7.12. Visit 12: Out-patient Follow-up (Day 90±3)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - PK measurement
    - MNA
    - ADA
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status.

7.13. Visit 13: Final Visit / Early Termination Visit for Cohorts 1-3 (Day 120±3) / Cohort 4 (Day 120±3)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
    - Clinical Safety labs (Cohorts 1-3 Only)
    - PK measurement
    - MNA
    - ADA
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status.

7.14. Visit 14: Final Visit/ Early Termination for Subjects in Cohort 4 (Day 180±3)

- Obtain vital signs
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety Labs
  - PK measurement
  - ADA
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of AEs and SAEs
- 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
- Assessment of COVID-19 vaccination status.

7.15. Unscheduled Visit

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
- Assessment of COVID-19 vaccination status.

8. ASSESSMENT OF SAFETY

Regulatory requirements including the FDA regulations and 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 (Ology Bioservices) of SAEs immediately;
- provide detailed written reports, including necessary documentation requested by the sponsor or IRB/Independent Ethics Committee (IEC), promptly following immediate initial reports, and;
- Inform the IRB/IEC of AEs as required by applicable regulatory requirements.

8.1. Specification of Safety Parameters

Definitions

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.

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 adverse event. An adverse event 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 adverse event, had it occurred in a more severe form, might have caused death.

Unexpected

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

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

8.2.1. Adverse Events

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.

Severity of adverse events will be graded as follows based on the Investigator's assessment unless otherwise specified in Appendix B.:

Mild: Events require minimal or no treatment and do not interfere with the subject's daily activities.

Moderate: Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning.

Severe: Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

8.2.2. 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. In a clinical trial the study product must always be suspect.

- **Definitely Related:** There is a definite probability that the study product caused the adverse event.
- **Possibly Related:** There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event
- **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.

8.3. Reporting Procedures

8.3.1. Adverse Events:

AEs not meeting the criteria for "SAEs," will be captured on the appropriate case report form. Information to be collected for AEs includes event description, time of onset, investigator assessment of severity, relationship to study product, date of resolution of the event, seriousness, and outcome.

All AEs will be followed until resolved or considered stable by the investigator.

8.3.2. Serious Adverse Events

The following procedures will apply to all serious adverse events:

- The Principal Investigator will report any SAE to ICON PVSS within 24 hours of awareness.
- ICON PVSS will perform an initial check of the SAE for missing elements and then inform the ICON MM, and the ISM.
- ICON PVSS will record the information on the appropriate serious adverse event report form and send to DOD PVG and to Ology Bioservices
- Each SAE will be reviewed and followed to resolution or stability by a study physician
- SAEs will be collected on each subject until 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 Ology Bioservices at the following address:

ICON PVSS	**ICON plc PVSS** **3rd Floor Marlow International, Parkway, Marlow,** **Buckinghamshire, SL7 1YL, United Kingdom** **SAE Email Address: ICON-Safety-CentralReceipt@iconplc.com**
ICON Medical Monitor:	**Uma Arumugam, MD** **ICON Early Phase Services**

820 West Diamond Ave., Suite 100

Gaithersburg, MD 20878, USA

SAE Phone: 410-294-2537

SAE Email Address: uma.arumugam@iconplc.com

ICON PVSS will send AE/SAE information to Ology Bioservices, Inc.

Ology Bioservices

Ology Bioservices, Inc.

13200 NW Nano Court

Alachua, FL 32615, USA

SAE Hotline: 352-213-5757

SAE Fax Number: 888-551-1691

SAE Email Address: olo.safety@resilience.com

Other supporting documentation of the event may be requested by Ology Bioservices 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 IMP to Ology Bioservices and DOD PVG. The ICON medical monitor and clinical project manager will be notified of the SAE by DOD PVG. The ICON medical monitor will review and assess the SAE for potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to ICON PVSS.

8.3.3. Regulatory Reporting

Following notification from the investigator, Ology Bioservices, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected to the FDA. Ology Bioservices will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE. Ology Bioservices will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Ology Bioservices will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, Ology Bioservices will submit to FDA any additional data or

information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.3.4. Reporting of Pregnancy

Pregnancies that occur during the study period will be reported to the Sponsor on the Pregnancy Report form within five 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).

8.4. 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 case report forms.

8.5. Halting Rules

8.5.1. Halting Criteria for the Study

Study dosing can be halted at any time if medically indicated. Study dosing must be stopped, and a review of available safety data will be conducted by the SRC if any of the following occur:

1. Death of a dosed subject following injection and prior to the subject's last visit that was not the result of trauma or accident, and possibly related to study product.
2. Occurrence of a 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.
3. One subject with an SAE.
4. Two or more subjects with a Grade 3 AE in the same organ class (systemic toxicity, clinical laboratory tests or vital signs) regardless of relatedness to study drug. An exception to this includes scenarios where there are obvious and acceptable physiological explanations for a Grade 3 abnormality (e.g., Grade 3 hematuria in a menstruating female).

8.5.2. Dose Escalation Halting Criteria

If any of the following criteria are met, escalation to the next planned dose cohort will not proceed until all available study data have been reviewed by the SRC.

- More than 25% of the subjects in the cohort experience an AE, grade 2 or above in the same organ class
- A specific AE increases in severity from one cohort to the next AND the number of subjects reporting that AE (at the higher severity level) in the cohort is the same or greater. An exception would be headaches going from a grade 1 to a grade 2.

8.5.3. Evaluation of Dose Escalation

The SRC must agree unanimously on the following criteria prior to dose escalation:

- A review of all available unmonitored and uncoded safety data from at least 7 subjects per cohort to Day 8, at a minimum, demonstrate that study halting criteria as outlined in Section 9.5.2 have not been met.
- A review of all available unmonitored and uncoded safety data from at least 7 subjects per cohort to Day 8, at a minimum, demonstrate that no safety signals of any nature were observed.

8.6. Safety Oversight

8.6.1. Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. The ISM will review SAEs and other AEs as needed and provide an independent assessment.

8.6.2. ICON Medical Monitor

The ICON Medical Monitor (MM) is the clinical site's primary point of contact for eligibility or safety related questions. The ICON MM is responsible for liaising with Ology Bioservices Medical Monitor to ensure that all medical concerns are communicated and will provide any potential pertinent medical communication update to the project team as needed. Can make a recommendation that the SRC be convened to review any safety concerns.

The ICON Medical Monitor will communicate with the Ology Bioservices Medical Monitor for any safety related questions. The ICON MM will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.

8.6.3. Ology Bioservices Medical Monitor

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

8.6.4. Safety Review Committee (SRC)

The SRC will be composed of:

- PI, or designee
- Ology Bioservices Medical Monitor
- ICON Medical Monitor or designee;

Objective dose-escalation criteria and safety evaluations will be utilized. For Cohorts 1, 2, and 3 the SRC will evaluate unmonitored and uncoded safety and tolerability data for at least 7 subjects out to Day 8 to determine whether dose escalation can occur. If none of the events described in 9.5.1 Study Halting Criteria or in 9.5.2 Dose Escalation Halting Criteria are observed, dose escalation will proceed. Should any of the study halting criteria or dose escalation halting criteria be met, the SRC will meet to evaluate the data and recommend appropriateness of further dosing. The SRC recommendation to advance to the next level will be documented and provided to all the appropriate parties (PI, Ology Bioservices, ICON and DOD) involved with the study.

If 2 or more subjects withdraw prior to Day 8, those subjects need to be replaced to ensure that data for at least 7 subjects is available for review.

If 2 or more subjects withdraw prior to Day 60 or are not compliant with all PK draws through Day 15, they may be replaced.

If more than 2 subjects withdraw following the Day 8 SRC review of safety data, the site will attempt to replace those subjects in that dose group at the time of the next planned cohort.

9. CLINICAL MONITORING

9.1. 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 or other regulatory agencies to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCP and the respective local and national government 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.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Considerations

This is a Phase 1 study first in humans with four dosing Cohorts and no formal sample size calculations based on testing a statistical hypothesis were constructed. Four dosing groups of ten each with eight participants assigned the active group and two assigned to the control group are

practical and provide sufficient information for a total sample size of 40 for a Phase 1 trial primarily designed to assess safety. If ten subjects are studied, then the probability of at least one subject experiencing an event of toxicity can range from 0.728 to 0.996 assuming true event rates between 0.15 and 0.5 Additionally, if no events are observed in a cohort of six dosed subjects receiving G03-52-01 the upper bound of an exact 95% confidence interval for the true proportion is 0.46

10.2. Planned Interim Analyses

A blinded interim safety and PK analysis is planned for this study to analyze all PK, ADA, and MNA samples for Cohorts 1-3 through Day 60 and Day 120. A second blinded interim safety analysis is planned to analyze all PK, ADA, and MNA samples for Cohort 4 through Day 90. Stopping criteria are for safety and are defined in section 9.5.

10.3. Final Analysis Plan

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

10.3.1. Analysis Populations

All subjects who received study product will be included in the safety population and analyzed as treated. The PK analysis population will consist of all subjects who complete G03-52-01 injection and have sufficient evaluable PK samples for the estimation of PK parameters.

10.3.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by dose cohort and control group.

10.3.3. Safety Analysis Plan

10.3.3.1. Adverse and Serious Adverse Events

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. 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 the AEs, a subject will be counted once if the subject reported one or more events. 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.

10.3.3.2. Additional Safety Analyses

Vital signs, physical examinations, and clinical laboratory values, including change from baseline, 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 the baseline value, will be calculated. Shift tables, showing individual subject changes from baseline will be presented for laboratory parameters using toxicity grading (Appendix B). Subjects with Graded values of vital sign and laboratory parameters will be identified in listings.

10.3.4. PK Analysis Plan

PK parameters will be estimated for each of the six monoclonal antibodies 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, estimated PK parameters will include:

- $AUC_{(0\text{-}t)}$: 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
- 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

Additionally, multi-compartmental models will be considered based on inspection of concentration-time curves. If models are fit, base models will assume first-order elimination from the central compartment, and models will be parameterized in terms of clearance, volume of distribution and inter-compartmental rates. Standard objective goodness of fit measures will be used to determine the final model.

10.3.5. Immunogenicity

Immunogenicity will be measured by the development of antibody titers. The presence of ADA will be measured over the course of the post-injection period.

10.3.6. Missing values and outliers

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Outliers identified during the PK analysis will be discussed in the analysis report.

11. SOURCE DOCUMENTS AND 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 documents will be derived from the electronic CRFs and will be provided 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.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DOD-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.

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 Ology Bioservices.

ICON will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

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 for federally funded research.

13.2. Institutional Review Board

The site will provide for the review and approval of this protocol and the associated informed consent documents, by an appropriate ethics review committee or 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, Ology Bioservices, 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, 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 informed consent form 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 informed consent form 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)

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

Ology Bioservices 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 adverse events 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 principal investigator. 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 electronic CRF (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.

Ology Bioservices 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. Adverse Events must be graded, assessed for severity and causality, and reviewed by the site Principal Investigator or designee.

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

ICON will serve as the Statistical and 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 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.

14.3. Types of Data

Data for this study will include clinical safety assessments, safety laboratory assessments, immunology and PK.

14.4. Timing/Reports

A final report will be prepared following the availability of all the safety and immunogenicity data.

14.5. Study Records Retention

Study files (except for future use consent forms) must be maintained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in and ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the

responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Consent forms for future use will be maintained as long as the sample exists.

14.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP 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/Ology Bioservices.

All protocol deviations, as defined above, must be addressed in study subject source documents. A completed copy of the Protocol Deviation Form 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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APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Study Visit	Screening[1] 01	Baseline 02	03	04	05 Cohort 1-3 Only	06	07	08	09	10	11	12	13 / Early Term	14 Cohort 4 Only
Study Day (Window)	-28 to -3	**0**	**24 hr**	**48 hr**	**72 hr**	**4**	**8±1**	**15±1**	**30±1**	**45±3**	**60±3**	**90±3**	**120±3**	**180±3**
Review Inc/ ExcI Criteria	X	X												
Review Medical History	X	X												
Review Contraception/menses	X													
Perform Abbreviated PE[3]	X	X												
Perform Symptom-Directed PE[13]		X	X	X	X	X	X	X	X	X	X	X	X	X
Obtain Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Obtain Screening Labs[5]	X													
Obtain Clinical Safety Labs[6]		X					X	X	X				X[18]	X
Serum β-HCG	X[7]													
Urine pregnancy test		X				X				X			X[18]	X
Urine Dipstick[8]	X	X											X[18]	X
Urine Toxicology	X	X												
Breathalyzer test	X	X												
Immunogenicity (ADA)[14]		X						X	X	X	X	X	X	X
Hypersensitivity Panel[15]		X												
12-lead ECG[9]	X													
Viral Serology[10]	X													
PK samples[11]		X	X	X	X	X	X	X	X	X	X	X	X	X
MNA		X[16]				X			X	X[17]	X	X	X	
Concomitant Medications[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Study Drug Administration		X												
Future Use Sample[12]		X					X		X					

Study Visit	Screening[1] 01	Baseline 02	03	04	05 Cohort 1-3 Only	06	07	08	09	10	11	12	13 / Early Term	14 Cohort 4 Only
Study Day (Window)	-28 to -3	**0**	**24 hr**	**48 hr**	**72 hr**	**4**	**8±1**	**15±1**	**30±1**	**45±3**	**60±3**	**90±3**	**120±3**	**180±3**
Counsel on the avoidance of pregnancy	X		X	X	X	X	X	X	X	X	X	X	X	X
Counsel on avoidance of botulinum toxin and vaccines	X		X	X	X	X	X	X	X	X	X	X	X	X
AE Review		X	X	X	X	X	X	X	X	X	X	X	X	X
SAE Review		X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening will be completed within 28 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. Vital Signs to include sitting diastolic and systolic blood pressure, heart rate, and oral temperature. Vital signs will be checked just before injection and every visit.
5. Subjects should be fasting for Screening Laboratory Tests that will include hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded, serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK. Subjects in cohort 4 only will have NX02 levels drawn at screening
6. Subjects should be fasting for Clinical Safety Laboratory Tests that will include hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded, serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
7. A serum pregnancy test will be obtained for all women of reproductive capacity. Results must be confirmed as negative before study product is dosed.
8. A urine dipstick will be done to evaluate for presence of protein, glucose or blood in urine. If dipstick is abnormal, a complete urinalysis with microscopic will be performed.
9. A 12-lead ECG will be done during screening.
10. Viral Serology includes HIV, HBsAg and antibody to HCV.
11. Subjects in Cohorts 1-3 will have PK samples taken at the following times: pre-dose, 2, 4, 8, 24, 48, and 72 hours post injection and on days 4, 8, 15, 30, 45, 60, 90, and 120. . Subjects in Cohort 4 will have PK samples taken at pre-dose, 6 hours post-dose, and on days 1, 2, 4, 8, 15, 30, 45, 60, 90, 120, and 180.
12. Serum from subjects who give consent will be stored for future use. On Days 0, 8, and 30.
13. The subject will be under direct observation during at least the initial 30 minutes of the injection. A physical examination will be performed at approximately 30 minutes after starting the injection and again in response to subject symptoms which will include the following: General appearance including alertness and any difficulty breathing, HEENT, Chest, Heart, Skin and Joints.

14. Draw prior to dosing at baseline for all Cohorts. Subjects in Cohorts 4 will not have ADA blood draws on Day 15 or Day 30. Cohort 4 will have ADA drawn on follow- up Days 45, 60, 90, 120 and 180.

15. The Hypersensitivity Panel includes cytokine and complement panels, IgE, and tryptase. Draw 14ml prior to dosing. 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.

16. MNA: To be drawn pre-dose for All Cohorts. Cohort 4 subjects will also have a 2-hour post dose optional (+/- 10 minutes) draw.

18. Cohorts 1-3 only.

APPENDIX B: TOXICITY GRADING

Clinical Adverse Events			
VITAL SIGNS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe Grade 3**
Fever - °C	38.0-38.4	38.5-38.9	>38.9
Tachycardia - bpm	101-115	116-130	>130 or ventricular dysrhythmias
Bradycardia – bpm • Baseline ≥60 OR, if Baseline <60	• 50-54 OR, if Baseline <60, • 45-50	• 45-49 OR, if baseline <60, • 40-44	• <45 OR, if baseline <60 • <40
Hypertension (systolic) - mmHg	141-150	151-160	>160
Hypertension (diastolic) - mmHg	91-95	96-100	>100
Hypotension (systolic) - mmHg	85-89	80-84	<80
Tachypnea – breaths per min	23-25	26-30	>30
CARDIOVASCULAR	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Arrhythmia		Asymptomatic; transient signs; no medical intervention required	Recurrent/persistent; symptomatic medical intervention required
Hemorrhage, Blood Loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL; no transfusion required	Transfusion required
QTc (Fridericia's correction)[1]	Asymptomatic, QTc interval 450-479 msec	Asymptomatic; QTc interval 480 to 499 msec OR Increase in interval 30-59 msec above baseline	Asymptomatic; QTc interval ≥ 500 msec OR Increase in interval ≥ 60 msec above baseline
PR Interval (prolonged)[1]	PR interval 0.21-0.25 sec	PR interval >0.25	Type II 2nd degree AV block OR Ventricular pause >3.0 sec
RESPIRATORY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient; no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, Acute	Transient; no treatment; FEV1 71-80% of predicted peak flow	Requires medical intervention; normalizes with bronchodilator; FEV1 60-70% of predicted peak flow	No normalization with bronchodilator; FEV1 <60% of predicted peak flow
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities; no treatment	Prevents daily and usual social activity OR requires treatment
GASTROINTESTINAL	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**

[1]Inclusion dependent upon protocol requirements.

Nausea	No interference with activity	Some interference with activity	Prevents daily activities
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 IV hydration OR requires medical intervention
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	≥6 loose or watery stools or >800g/24 hours OR requires IV hydration OR requires medical intervention
REACTOGENICITY			
LOCAL REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pain – experienced without touching the injection site (spontaneous discomfort)	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours OR interferes with activity	Any use of narcotic pain reliever OR prevents daily activity
Tenderness – hurts only when injection site is touched, or the arm is moved	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Nodule	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ulcer	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Erythema (Redness)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Induration (Hardness)/Swelling*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Nodule	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Ulcer	1 mm – 50 mm	51 mm – 100 mm	>100 mm
SYSTEMIC REACTIONS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Allergic Reaction	Pruritus without rash	Localized urticaria OR requires oral therapy	Generalized urticaria; angioedema OR

			anaphylaxis OR requires epinephrine
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours OR some interference with activity	Significant; any use of narcotic pain reliever OR prevents daily activity OR requires triptans
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

*Will not be used as halting criteria

Laboratory and Vital Signs Reference Ranges, Eligibility Ranges, and Toxicity Grading

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	ICON Normal Lab Values
Blood, Serum, or Plasma				
Sodium (hyponatremia) – mEq/L	131-132	129-130	<129	133 – 143
Sodium (hypernatremia) – mEq/L	144 – 145	146 – 147	>147	133 – 143
Potassium (hyperkalemia) – mEq/L	5.2 – 5.4	5.5 – 5.6	>5.6	3.5 - 5.1
Potassium (hypokalemia) – mEq/L	3.2-3.4	3.0 – 3.1	<3.0	3.5 - 5.1
Glucose (hypoglycemia) – mg/dL	65 – 69	55 – 64	<55	70 – 105
Glucose (hyperglycemia) – mg/dL Fasting	106 – 125	126 – 200	>200	70 – 105
Blood Urea Nitrogen – mg/dL	21-26	27 – 31	> 31	6 – 20
Creatinine (Male) – mg/dL	1.3 – 2.0	2.1-2.3	>2.3	0.7-1.2
Creatinine (Female) – mg/dL	1.0 – 1.7	1.8 – 2.0	>2.0	0.5 - 0.9
Calcium (hypocalcemia) – mg/dL	8 - <LLN	7.5 – 7.9	<7.5	8.7 - 10.3
Calcium (hypercalcemia) – mg/dL	ULN - 10.8	10.9 – 11.4	>11.4	8.7 - 10.3
CK-U/L	309-1000	1001-1500	>1500	39-308
Albumin (hypoalbuminemia) – g/dL	2.8 – 3.4	2.5 – 2.7	< 2.5	3.5 - 5.2
AST – U/L (Male)	40-97	98-195	>195	<40
AST – U/L (Female)	32-77	78-155	>155	<32
ALT – U/L (Male)	41-100	101-200	>200	<41
ALT – U/L (Female)	33-80	81-160	>160	<33
Alkaline phosphatase – IU/L (Male)	131-260	261-390	>390	40-130
Alkaline phosphatase – IU/L (Female)	106-210	211-315	>315	35-105
Total Bilirubin (serum) – mg/dL	1.3-1.5	1.6-1.9	>1.9	0 - 1.2
Direct Bilirubin – mg/dL	NA	NA	NA	0.0-0.2
Chloride –mEq/L (hypochloremia)	NA	NA	NA	96-108
Chloride –mEq/L (hyperchloremia)	NA	NA	NA	96-108
CO2 –mEq/L (hypo)	NA	NA	NA	20- 30
CO2 –mEq/L (hyper)	NA	NA	NA	20- 30
Total Protein – g/dL	5.5 - 5.9	5.0 - 5.4	<5.0	6.0 - 8.0
Phosphorus- mg/dl (hypo)	2.3-2.4	2.1-2.2	<2.0	2.5 – 4.5
Phosphorus-mg/dl (hyper)	NA	NA	NA	2.5 – 4.5
Total Cholesterol-mg/dl	NA	NA	NA	<201
Triglycerides-mg/dl	NA	NA	NA	<151
HDL – mg/dl	NA	NA	NA	>65 F >55 M

Laboratory Adverse Events*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	ICON Normal Lab Values
LDL Direct – mg/dl	NA	NA	NA	<130
Hemoglobin (Male) – g/dL	11.2 - 12.2	10.0 – 11.1	<10.0	12.3-17.3
Hemoglobin (Female) – g/dL	9.8 - 10.8	8.5 - 9.7	<8.5	10.9 - 14.6
WBC Increase – cell/mm^3	10,001– 15,000	15,001 – 20,000	> 20,000	4,000-10,000
WBC Increase – cell/mm^3 (African America Males)	9,001 – 14, 000	14,001 – 19, 000	>19,000	4,000-10,000
WBC Increase – cell/mm^3 (African American Females)	11,001 – 15,000	15,001 – 20,000	>20,000	4,000-10,000
WBC Decrease – cell/mm^3	2,500– 3,999	1,500 – 2,499	< 1,500	4,000-10,000
WBC Decrease – cell/mm^3 (African American Males)	2,200 – 2,499	1,200 – 2,199	<1,200	4,000-10,000
WBC Decrease – cell/mm^3 (African American Females)	2,200 – 2,499	1,500 – 2,199	<1,500	4,000-10,000
Neutrophils Decrease – cell/mm^3	1,300 – 1,699	1,000 – 1,299	< 1,000	1,700-7,000
Neutrophils Decrease – cell/mm^3 (African American Males)	1,000 – 1,299	800 - 999	<800	1,700-7,000
Neutrophils Decrease – cell/mm^3 (African American Females)	1,100 – 1,299	1,000 – 1,099	<1,000	1,700-7,000
Platelets Decreased – 10^3/mm^3	120 – 149	100 – 119	<100	150-400
Hematocrit (Male) - %	33.0 -36.1	29.8 - 32.9	< 29.8	36.2-51.1
Hematocrit (Female) - %	29.5 - 32.6	26.0 – 29.4	< 26.0	32.7 - 43.5
RBC (Male) – x 10^6/uL	3.9 - 4.1	3.4 - 3.8	< 3.4	4.2-5.8
RBC (Female) – x 10^6/uL	3.5 - 3.7	3.0 - 3.4	< 3.0	3.8 - 5.8
Lymphocytes - cell/mm^3 decrease	600- 799	500 – 599	< 500	800 - 3600
Monocytes – cell/mm^3 increase	1001-2000	2001-3000	>3000	100 - 1000
Eosinophils - cell/mm^3 increase	871 - 950	951 - 1700	>1700	60- 870
Basophils - cell/mm^3 increase	101 - 300	301 - 800	> 800	10-100
PT (prothrombin time) – seconds	11.1-12.1	12.2-13.2	>13.2	9.1 - 11.0
PT INR (Prothrombin INR)	1.2-1.4	1.5-1.9	2.0 or higher	.9-1.1
PTT (partial thromboplastin time) –seconds	34.1-40.8	40.9-47.6	>47.6	22 - 34
Urine				
Protein	1+	2+	>2+	Neg.
Glucose	1+	2+	>2+	Neg.
Blood (microscopic) - red blood cells per high power field (rbc/hpf)**	5-10*	11-50*	>50 and/or gross blood**	<5*