Protocol Number: G03-52-01-002

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

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Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects
Protocol Number:	G03-52-01-002
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Revision History

Version	Date	Revisions
0.1	08-DEC-2022	Initial draft
0.2	18-JAN-2023	Second draft
1.0	09-FEB-2023	Final version
1.1	05-JUN-2024	Updates to Statistical Analysis Plan following protocol amendment for inclusion of Cohort 4: - Section 2 Study Objectives: Study objectives updated per protocol v4.0 - Section 3 Study Design: o Inclusion/exclusion criteria updated per protocol v4.0 o General Study Design sub-section updated for Cohort 4 - Section 4 Types of Planned Analyses: o Language updated regarding DSMB statistical analyses and interim analysis - Section 5 Study Endpoints: o Endpoints updated per protocol v4.0 - Section 6 Sample Size and Power: o Detail added for sample size of Cohort 4 - Section 9 Statistical Methods: o Language updated throughout for addition of Cohort 4 and its schedule of assessments as it pertains to statistical analysis (ie, study visits) o Language updated in endpoint sub-sections to describe the updated endpoints per protocol v4.0 - Section 11 Appendix: o Cohort 4 schedule of assessments added
1.2	13-AUG-2024	- Sponsor feedback addressed from v1.1 - Section 9 Statistical Methods: o Three cumulative incidence AE summaries across all cohorts added to Primary Endpoint 1a
1.3	09-MAY-2025	- Section 8.3 Handling of Missing Data and Outliers: Language added to specify handling of laboratory values with non-numeric qualifiers (eg, inequalities) - Section 9.10.1 Primary Endpoint 1a: Language added to specify that AE table summaries to include only events reported through subjects' final scheduled study visits - Protocol reference updated to v5.0 06Jan2025
2.0	23-MAY-2025	- Up-versioned to final version v2.0

Table of Contents

List of Abbreviations

Abbreviation	Explanation
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
BoNT	Botulinum Neurotoxin
C_{max}	Maximum Plasma Titer/Concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECLA	Electrochemiluminescence Assay
ELISA	Enzyme-Linked Immunosorbent Assay
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropic Hormone
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonization
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IM	Intramuscular
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
Kg	Kilogram
mAb(s)	Monoclonal Antibody(ies)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA®	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MNA	Battelle Mouse Neutralization Assay
MPV	Mean platelet volume
NAC	Neutralizing Antibody Concentration
PD	Pharmacodynamic
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
PTT	Partial Thromboplastin Time
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAS®	Statistical Analysis Software
SD	Standard Deviation

SOC	System Organ Class
SOP	Standard Operating Procedure
TFLs	Tables, Figures, Listings
WFI	Water for injection

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for the study protocol G03-52-01-002, version 5.0, “A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Immunogenicity of G03-52-01 in Adult Subjects”, dated 06-JAN-2025. The table of contents and templates for the Tables, Figures, and Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 and Good Clinical Practice (GCP) guidelines.

All data analyses and generation of TFLs will be performed using SAS® Version 9.4 or higher.

2 Study Objectives

2.1 Primary Objectives

- To evaluate the safety and tolerability of single or repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects
- For Cohorts 1-3 (Cohorts 1-2 active IP and Cohort 3 is placebo)
    - Demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90
    - To evaluate lot-to-lot variability of two doses of G03-52-01 (Note: There will be no formal statistical analysis to support evaluation of lot-to-lot variability. In table summaries, the two lots within each of Cohorts 1 and 2 will be summarized and displayed separately to visually assess lot-to-lot variability.)
- For Cohort 4 (only active IP), demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post-dose

2.2 Secondary Objectives

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

2.3 Exploratory Objective

- For Cohorts 1-3 (Cohorts 1-2 active product and Cohort 3 is placebo), to evaluate PK parameters to ensure ADA evaluation adequate of the two lots

3 Study Design

3.1 General Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity (ADA) of G03-52-01, administered by a 2-dose-regimen (Days 1 and 45) IM injections for Cohorts 1-3 and a 1-dose regimen (Day 1) for Cohort 4, in adult subjects.

In Cohorts 1-3, approximately 375 subjects between the ages of 18 and 65 years will be randomized in a 1:1:1:1:1 ratio to 5 parallel treatment groups, which constitute 3 cohorts with 150 subjects each for the two dosing cohorts (Cohort 1 50 mg G03-52-01 and Cohort 2 100 mg G03-52-01) and 75 subjects for the Cohort 3 Placebo group. Within each active dosing cohort, subjects will be randomized 1:1 to receive product from active drug Lot 1 or Lot 2. There is no lot within the Placebo cohort.

In Cohort 4, approximately 250 subjects between the ages of 18 and 65 years will be randomized in a 4:1 ratio to 2 treatment groups, which constitutes 1 cohort (Cohort 4) with 200 subjects randomized into the active group (Cohort 4 100 mg G03-52-01) and 50 subjects randomized into the Cohort 4 Placebo group.

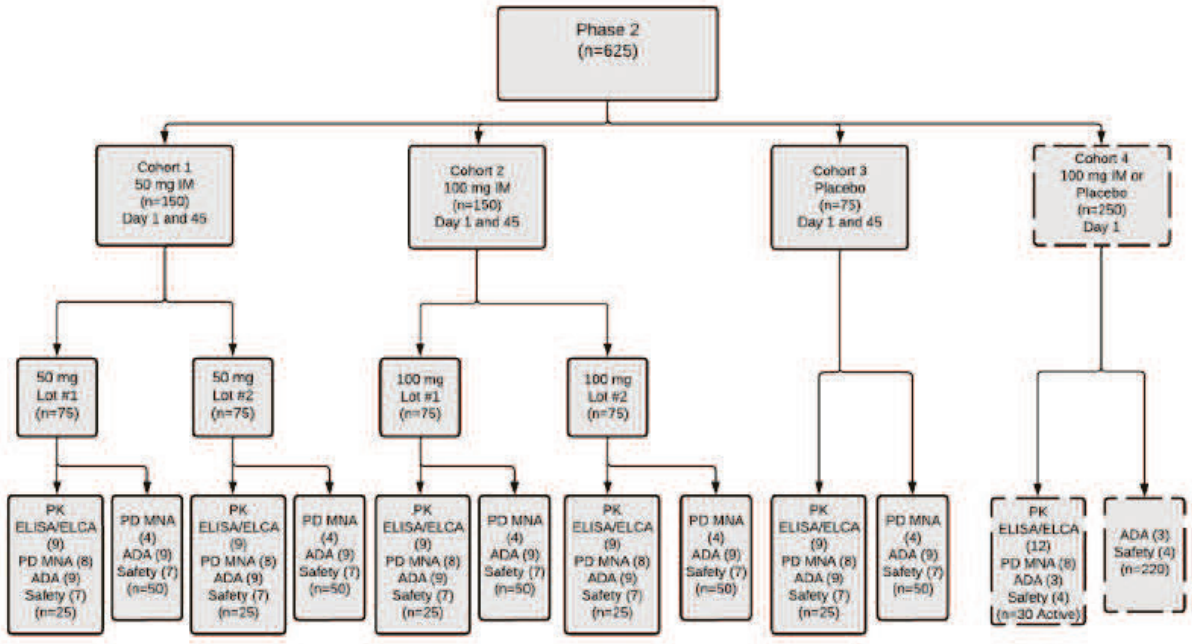
Details regarding the planned assessments for each cohort can be found in the Study Treatments and Assessments section.

See Table 1 below for further details.

Table 1: Details of Study Cohorts

Study Cohort	Expected Number of Subjects	Dosing Day(s)	Drug Product Lot	Group
Cohort 1 50 mg G03-52-01	150	1, 45	Lot 1 (n=75)	Group 1 50 mg Lot 1
			Lot 2 (n=75)	Group 2 50 mg Lot 2
Cohort 2 100 mg G03-52-01	150	1, 45	Lot 1 (n=75)	Group 3 100 mg Lot 1
			Lot 2 (n=75)	Group 4 100 mg Lot 2
Cohort 3 Placebo	75	1, 45	NA	Group 5 Placebo
Cohort 4 100 mg G03-52-01	200	1	NA	Group 6 100 mg
Cohort 4 Placebo	50	1	NA	Group 7 Placebo
Total	625			

Figure 1: Study Design



1. Numbers of time points collected are presented in the parentheses.

3.2 Key Eligibility Criteria

3.2.1 Inclusion Criteria

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

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

2. Assessed by the Investigator to be a healthy male or healthy, non-pregnant, non-lactating female between the ages of 18 and 65 inclusive on the day of dosing.

3. Able and willing to comply and be available for all protocol procedures and follow-up for the duration of the study.

4. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2.

5. Females of child-bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1 prior to dosing.

- A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses) or surgically sterilized via bilateral oophorectomy, or hysterectomy or bilateral tubal ligation.

6. If the subject is female and of childbearing potential, she agrees to practice abstinence from sexual intercourse with men or use medically effective contraception (methods with a failure rate of < 1% per year when used consistently and correctly) during participation in the study. Acceptable methods include:

- Hormonal contraception including implants, injections or oral

- Two barrier methods, e.g., condom and cervical cap (with spermicide) or diaphragm (with spermicide)
- Intrauterine device (IUD) or intrauterine system

7. Screening clinical laboratory results within normal ranges or are no greater than a Grade 1 and deemed not clinically significant by Medical Monitor (MM) and Principal Investigator (PI). Any subjects with results that are Grade 2 or above according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be excluded.

- Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once.

8. The urine drug screen is negative.

- For Cohorts 1-3, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication, (except for THC), the PI may enroll the subject if they meet all inclusion criteria, and none of the exclusion criteria.
- For Cohort 4, if a subject has a positive urine drug screen that the PI believes is caused by a currently prescribed medication or positive for THC, the PI may enroll the subject if they meet all other inclusion criteria and none of the exclusion criteria.

9. Breathalyzer test is negative.

10. Available for follow-up for the duration of the study.

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

3.2.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for participation. All must be answered no for the subject to be eligible for study participation.

1. History of a chronic medical condition that would either interfere with the accurate assessment of the objectives of the study or increase the risk profile of the subject.

- Chronic medical conditions include but are not limited to diabetes; Asthma requiring use of medication in the year before screening; Autoimmune disorder such as lupus, Wegener's, rheumatoid arthritis, thyroid disease; coronary artery disease; chronic hypertension; History of malignancy except low-grade (squamous and basal cell) skin cancer thought to be cured; chronic renal, hepatic, pulmonary, or endocrine disease (except previous asthma which has required no treatment for the past year).

2. Known history of severe allergic reaction of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobulins.

- Severe allergic reaction is defined as any of the following: anaphylaxis, urticaria, or angioedema.

3. Known allergic reactions to any of the study product components present in the formulation or in the processing.

4. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds).

5. Clinically significant abnormal electrocardiogram (ECG) at screening.

- Clinically significant abnormal ECG results include but are not limited to: complete left or right bundle branch block; other ventricular conduction block except for incomplete RBB; 2nd degree or 3rd degree atrioventricular (AV) block; sustained ventricular arrhythmia; sustained atrial arrhythmia; two Premature Ventricular Contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; or any condition deemed clinically significant by a study investigator.

6. Positive serology results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies.

7. Febrile illness with temperature ≥38°C within 7 days of dosing. Subjects with acute febrile illness within 7 days of dosing may be rescreened no earlier than 7 days following resolution of symptoms.

8. Female subjects that are pregnant or breastfeeding or intending to become pregnant within the projected duration of the trial starting from the Screening visit until last dose.

9. Donation of blood or blood product within 56 days of enrollment.

10. Is currently participating or has participated in a study with an investigational product (IP) within 28 days preceding Day 1 (documented receipt of placebo in a previous trial would be permissible for trial eligibility).

11. Plans to enroll in another clinical trial that could interfere with safety assessment of the investigational product (IP) at any time during the study period.

- Includes trials that have a study intervention such as a drug, biologic, or device only.

12. Treatment with a mAb (monoclonal antibody) within 3 months of Day 1.

13. Receipt of antibody (e.g., tetanus immune globulin (TIG), varicella zoster immune globulin (VZIG), intravenous immunoglobulin (IVIG), IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given.

14. Reported active drug or alcohol or substance abuse/independence or illicit drug use that, in the opinion of the Investigator, would interfere with adherence to study requirements.

15. Use of H1 antihistamines or beta-blockers within 5 days of dosing Day 1 and Day 45 for Cohorts 1-3 and Day 1 for Cohort 4 (PRN use could be allowed with MM approval).

16. Use of any prohibited medication within 28 days prior to study entry or planned use during the study period.

- Note: Prohibited medications include immunosuppressives (except nonsteroidal anti-inflammatory drugs [NSAIDs]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents.

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

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

19. Any illness or condition that in the judgment of the Investigator may affect the safety of the subject or the evaluation of any study endpoint.

20. Is a study site employee, staff, or close relative as defined.

- PIs, Sub-Investigators
- Staff who are supervised by the PI or Sub-Investigators
- Member of the team conducting this clinical trial
- Children, spouse, partners, siblings, and parents of site staff

3.3 Randomization and Blinding

For Cohorts 1-3, eligible subjects will be randomized to one of the 5 parallel treatment groups (50 mg G03-52-01 Lots 1 and 2, 100mg G03-52-01 Lots 1 and 2, and Placebo) in a 1:1:1:1:1 ratio, respectively, via the centralized randomization using Interactive Response Technology (IRT) randomization system (Table 1). Cohort 1-3 subjects will receive one dose of either G03-52-01 or Placebo on Days 1 and 45 for a total of two doses. No stratification will be performed for randomization.

For Cohort 4, eligible subjects will be randomized into one of 2 treatment groups (100 mg G03-52-01 or Placebo) in a 4:1 ratio. Cohort 4 subjects will receive one dose of either G03-52-01 or Placebo on Day 1. No stratification will be performed for randomization.

The ICON Randomization Development Team will generate the randomization schedule according to the sponsor protocol number G03-52-01-002, V4.0, 14Apr2024. The ICON team will deliver dummy and live randomization schedules to the IVRS System Development Team via a password-protected .zip file sent through e-mail.

The study staff participating in the administration of study product and assessment of the subjects and the subjects will be refrained from understanding the contents of the IM vial and are blinded from the study product information. Please refer to the Cohorts 1-3 Randomization Plan, v1.0, 16May2022 and Cohort 4 Randomization Plan, v1.0, 18Apr2024 for the detailed randomization list preparation and implementation.

The Investigator may unblind a subject's treatment assignment only in the case of an emergency or a serious adverse event (SAE) when knowledge of the study treatment is essential to the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator should first discuss the options

with the ICON IGP Medical Monitor (MM) and the Resilience Government Services, Inc. Medical Lead (ML) or appropriately designated Resilience Government Services, Inc. personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the MM and the ML 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.

Unblinding will be conducted through the IRT system. Notification to Resilience Government Services, Inc., ML, MM, unblinded statistician(s), and ICON clinical trial manager will be made for each unblinding, and a record will be kept at each study site for all unbroken treatment codes and the reason for the need to break the treatment assignment.

3.4 Study Treatments and Assessments

G03-52-01 DP is a mixture of five human monoclonal IgG1 antibodies and one humanized monoclonal IgG1 antibody, which bind to non-overlapping epitopes on BoNT/A/B. Each of the component antibodies, NX01, NX02, NX11, XB10, XB18, and XB23, is separately produced in CHO cell lines. Each mAb comprising G03-52-01 has distinct human variable regions that bind to BoNT/A/B. No subtypes of BoNT/A or BoNT/B have been described.

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

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

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

The following assessments will be collected for this study:

- Physical Examination (PE)

  An abbreviated PE will be conducted at the screening visit and on Day 1, as well as Day 240 for Cohort 1-3 subjects. Height and weight will be obtained at screening. The PE conducted on Day 1 will be for the purpose to detect signs of a hypersensitivity reaction. Symptom-directed PE will be performed at all other in-clinic study visits.

- Vital Signs

Vital sign assessments will be performed at all in-clinic study visits, including systolic and diastolic blood pressure (BP), heart rate (HR), and oral temperature. During screening and follow-up, a measurement that is a Grade 1 (as referenced in Protocol G03-52-01-002, v4.0, 14Apr2024, Appendix B) may be repeated once if the principal investigator 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.

- Electrocardiogram (ECG)

  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.

- Laboratory Evaluations

  Laboratory assessment schedule will follow the Schedule of Assessments in Appendix A. Detailed laboratory tests can be found in Section 8.5.2 of Protocol G03-52-01-002, v4.0, 14Apr2024.

- Pharmacodynamic (PD) and Pharmacokinetic (PK) Assays

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

  Blood samples for PD assessment will be collected at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, and on Days 30, 45, and 90 for all subjects in Cohort 4. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hours, 4 hours, 8 hours, 24 hours, and on Days 30, 45, and 90. PD samples will be analyzed for neutralizing antibody concentration (NAC) using the validated Battelle MNA.

  Blood samples for PK assessment will be collected at pre-dose, 24 hours and 72 hours post-dose, and on Days 8, 15, 45 (prior to dosing), 49, 90, and 120 for all subjects in Cohorts 1-3. The first 25 subjects randomized for each DP lot of 50 mg and 100 mg doses and placebo will be tested at all timepoints.

  Blood samples for PK assessment will be collected at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post-dose, and on Days 8, 15, 30, 45, 90, and 120 for all subjects in Cohort 4. Cohort 4 samples for the first 30 subjects, who receive active drug product and complete sample collection at 24 hours, will be tested at pre-dose, 2 hour, 4 hours, 8 hours, 24 hours, 72 hours post-dose, and on Days 8, 15, 30, 45, 90, and 120. The PK analysis of each mAb will be assessed using a validated electrochemiluminescence assay (ECLA) or enzyme-linked immunosorbent assay (ELISA).

- Anti-Drug Antibody Assay (ADA)

Blood samples will be collected for all subjects in Cohorts 1-3 at pre-dose and Days 15, 45 (prior to dosing), 60, 90, 120, 150, 180, and 240 and pre-dose and post-dose on Days 90, and 120 for all subjects in Cohort 4 for determining the presence of ADA using a validated ECLA that measures total ADA in serum. This will be performed to assess immunogenicity.

4 Types of Planned Analyses

4.1 Interim Analyses

An interim analysis is planned for the first 125 subjects in Cohorts 1-3 who complete through Day 120. An interim Clinical Study Report (CSR) is planned for the same 125 subjects across the three cohorts through Day 120. The data cut will take place when all 125 subjects have completed their 120 visits. The safety analysis will include all available safety data obtained from all subjects enrolled in the study up to the time of the fourth Data Safety Monitoring Board (DSMB) meeting.

The objectives of this interim analyses will be to compare safety between the 3 cohorts and to evaluate lot-to-lot variation in PK and PD parameters within the two active drug cohorts.

4.2 Data Safety Monitoring Board

A centralized, independent DSMB will be established in collaboration with Resilience Government Services, Inc. and ICON and will oversee the safety conduct the study. The DSMB will make safety and tolerability recommendations.

Following data and documents will be generated for DSMB review:

- Incidences and listings of overall Adverse Events (AEs), Medically Attended Adverse Events (MAAEs), and Serious Adverse Events (SAEs)
- Summaries and listings of change from baseline in electrocardiogram, vital signs, and clinical safety laboratory values
- Other relevant data / documents:
    - Number of enrolled subjects
    - Number of subjects withdrawn and subject dispositions
    - Subject characteristics and anthropometric measures data (including age, height, weight, and BMI)
    - Protocol deviations will be summarized. Listings for Per-Protocol (PP) population will not be available for DSMB meetings and there will not be DSMB analyses based on the PP population.

Blinded tables, figures, and listings (TFLs) will be provided for the open session of DSMB meetings. A dummy randomization schedule will be used to assign the subjects to groups, whereby subjects will be summarized in their true treatment group, but treatment groups will be arbitrarily labeled and ordered in tables to preserve the blind.

Four DSMB meetings are planned for Cohorts 1-3, and one DSMB meeting is planned for Cohort 4.

4.3 Final Analyses

Final analyses will be conducted following final database lock (DBL). Unblinded TFLs and a CSR with completed time points will be provided.

5 Study Endpoints

Table 2 summarizes the study endpoints in relation to their corresponding study objectives, as well as a brief overview of the statistical methods (described in greater detail in Section 8) used to analyze each endpoint.

Table 2: Study Objective, Endpoint, and Statistical Methodology Overview

Primary Objectives	Primary Endpoints	Statistical Methodology
Primary Objective #1: To evaluate the safety and tolerability of repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects	**Primary Endpoint #1a**: The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit	Incidence rate of the various AE categories, and the counts and percentages of subjects that experienced them
	Primary Endpoint #1b: The occurrence of changes from baseline in PE, vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit	Descriptive statistics for the change/shift from baseline in laboratory (chemistry and hematology), vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry, and body temperature), and physical examination measures
Primary Objective #2: For Cohorts 1-3 (Cohorts 1-2 active IP and Cohort 3 is placebo): • Demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90 • To evaluate lot-to-lot variability of two doses of G03-52-01	**Primary Endpoint #2**: For Cohorts 1-3, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90 (Note: There will be no formal statistical analysis to support evaluation of lot-to-lot variability. In table summaries, the two lots within each of Cohorts 1 and 2 will be summarized and displayed separately to visually assess lot-to-lot variability.)	Protective NAC rate at Day 45 and Day 90, where protective NAC rate is defined as the proportion of subjects with NAC value > 0.02 U/mL against BoNT/A or NAC value > 0.03 U/mL against BoNT/B
Primary Objective #3: For Cohort 4 (active IP only), demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post-dose	**Primary Endpoint #3**: For Cohort 4, to evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 4 and 8 hours post dose	Protective NAC rate at 4 Hours and 8 Hours post dose, where protective NAC rate is defined as the proportion of subjects with NAC value > 0.02 U/mL against BoNT/A or NAC value > 0.03 U/mL against BoNT/B
Secondary Objectives	**Secondary Endpoints**	**Statistical Methodology**
Secondary Objective #1: For Cohorts 1-3 (Cohorts 1-2 active IP and Cohort 3 is placebo): Demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120	**Secondary Endpoint #1**: To evaluate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120	Protective NAC rate at Day 120, where protective NAC rate is defined as the proportion of subjects with NAC value > 0.02 U/mL against BoNT/A or NAC value > 0.03 U/mL against BoNT/B
Secondary Objective #2: For Cohorts 1-3 (Cohorts 1-2 active IP and Cohort 3 is placebo): To evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study	**Secondary Endpoint #2**: Descriptive statistics of selected PD and ADA at all timepoints tested	Summary statistics [number of subjects (n), mean, standard deviation (SD), median, first quartile, third quartile, minimum, maximum], coefficient of variation (CV, presented in percentage, CV%), geometric mean (GM), the 95%

		confidence interval (CI) for GM, the geometric coefficient of variation (GCV, presented in percentage, GCV%), and the 95% CI of GCV% calculated for each time point for each cohort and DP lot
Secondary Objective #3: For Cohort 4 (only active IP): Demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 2 hours post-dose	**Secondary Endpoint #3**: To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose	Protective NAC rate at 2 Hours post dose, where protective NAC rate is defined as the proportion of subjects with NAC value > 0.02 U/mL against BoNT/A or NAC value > 0.03 U/mL against BoNT/B
Secondary Objective #4: For Cohort 4 (only active IP): To assess pharmacokinetics (PK) at pre-dose through end of study	**Secondary Endpoint #4:** PK analysis at the determined timepoints	Summary statistics [number of subjects (n), mean, SD, median, first quartile, third quartile, minimum, maximum], CV%, GM, the 95% CI for GM, GCV%, and the 95% CI of GCV% calculated for each time point for the Cohort 4 active G03-52-01 treatment group
Secondary Objective #5: For Cohort 4 (only active IP): To evaluate pharmacodynamics (PD) and anti-drug antibody (ADA) at pre-dose through the end of study	**Secondary Endpoint #5:** Descriptive statistics of determined PD and ADA timepoints	Summary statistics [number of subjects (n), mean, SD, median, first quartile, third quartile, minimum, maximum], CV%, GM, the 95% CI for GM, GCV%, and the 95% CI of GCV% calculated for each time point for the Cohort 4 active G03-52-01 treatment group
Exploratory Objective	**Exploratory Endpoint**	**Statistical Methodology**
Exploratory Objective: For Cohorts 1-3 (Cohorts 1-2 active IP and Cohort 3 is placebo): To evaluate PK parameters to ensure ADA evaluation adequate of the two lots	**Exploratory Endpoint**: Descriptive statistics of selected PK parameters at all time points tested of the two lots	Summary statistics [number of subjects (n), mean, SD, median, first quartile, third quartile, minimum, maximum], CV%, GM, the 95% CI for GM, GCV%, and the 95% CI of GCV% calculated for each time point for each cohort and DP lot

6 Sample Size and Power

This phase 2 trial is not powered to conduct formal hypothesis testing. The target enrollment of 375 subjects for Cohorts 1-3 and 250 subjects for Cohort 4 were based on previous experiences from studies conducted with similar products.

7 Analysis Populations

7.1 Description of Analysis Populations

7.1.1 Intention-to-Treat (ITT) Population

The ITT population includes all subjects who are randomized. Subjects in this population will be analyzed according to their randomized treatment assignment.

7.1.2 Safety Population

The Safety population includes all subjects in the ITT population who receive at least one dose of IP. Subjects in this population will be analyzed according to the actual treatment received.

7.1.3 Per-Protocol (PP) Population

The PP population includes all ITT subjects who received all planned treatments and have no major/key excluding protocol deviations. Subjects in this population will be analyzed according to their randomized treatment assignment. Subjects excluded from the PP population will be identified and documented prior to unblinding of the trial database; however, the PP population will not be used for any TFL summaries. All TFL summaries will be presented among one or more of the ITT, Safety, PK, and/or PD populations.

7.1.4 Pharmacodynamic (PD) and Pharmacokinetic (PK) Populations

The PK and PD populations include all Safety population subjects who have sufficient evaluable PK or PD samples, respectively. The evaluable PK or PD samples should be able to provide reliable estimation of PK or PD parameters for at least one of the mABs or serotypes BoNT/A or BoNT/B. Subjects in these samples will be analyzed according to the actual treatment received.

7.2 Protocol Deviations/Violations and Exclusions from Analysis Sets

Protocol deviation data will be captured in the clinical trial management system. Extracts of all protocol deviations will be reviewed periodically and prior to final analysis. All protocol deviations and the exclusion of participants from analysis sets will be identified prior to unblinding, through clinical review input provided by Resilience Government Services, Inc. using supportive participant listings, provided by the ICON biostatistician based upon data recorded in the clinical trial management system.

Further, deviations from the protocol will be classified as major/key or minor/non-key. Classification of major and minor protocol deviations is determined prior to participant enrollment and is outlined in detail in the protocol deviation criteria documentation managed by the clinical trial management team.

8 Statistical Considerations and Analysis

8.1 Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, baseline derivation and other important derivations applicable for this segment of the trial.

Table 3: Derived Variables

Variable	Formula
Demographic and Baseline Characteristics	
Body Mass Index	weight (kg) / [height (m)]^2
Age	Calculated at the time of informed consent. Sample SAS code to calculate age is: age = floor((informed consent date - date of birth)/365.25)
Baseline	Baseline is defined as the last measurement prior to the first treatment administration
Derivation of Durations	
Study day at any visit	date of visit – date of first dose. One day is added if the difference is ≥ 0.
Duration of any events	end date of event – start date of event + 1
Other Derivations	
Incidence in a group	The proportion of the participants experiencing the outcome of interest compared to the total number of participants at risk of experiencing the outcome of interest. (e.g., the incident rate of SAEs after injection are the number of participants with an SAE reported after injection divided by the number of participants that received the injection).
Pharmacodynamic (PD) Parameters	
$AUC_{(0-t)}$	Area under the concentration time-curve from the time of dosing to the time of the last measurable (positive) concentration
C_{max}	Maximum observed concentration, occurring at time $T_{max.}$
T_{max}	Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.
$t_{1/2}$	Terminal half-life defined as ln(2)/ λ_z as measured during steady-state
Pharmacokinetic (PK) Parameters	

Variable	Formula
Kel	First-order rate constant associated with the terminal (log-linear) portion of the curve, estimated by linear regression of time vs. log concentration during steady-state elimination
$AUC_{(0-t)}$	Area under the concentration time-curve from the time of dosing to the time of the last measurable (positive) concentration
$AUC_{(0-\infty)}$	Area under the concentration time-curve from time of dosing extrapolated to infinity, based on the last observed concentration or last predicted concentration defined as $AUC_{(0-t)} + (C_{(0-t)}/\lambda_z)$
$t_{1/2}$	Terminal half-life defined as $\ln(2)/ \lambda_z$ as measured during steady-state
CL/F	Total body clearance for extravascular administration defined as Dose/ $AUC_{(0-\infty)}$
V_Z/F	Volume of distribution based on the terminal phase. For non-steady-state data defined as Dose/[λ_z ($AUC_{(0-\infty)}$)]

8.2 Missing Data Analysis Methods

8.3 Handling of Missing Data and Outliers

All attempts will be made to collect data as prescribed by the clinical protocol. No imputations will be conducted for missing data except for the following scenarios:

- BLQ (Below Limit of Quantitation) results for PD and PK analyses: BLQ values will be treated as zero prior to the first measurable concentration. After the first measurable concentration, subsequent BLQ values will be treated as missing. In the calculation of geometric means and coefficients of variation, 0.001 will be imputed for zero values.
- Titer results below detectable threshold for ADA analysis: Titer values presented as inequalities due to being below the detectable threshold will be reported as their numeric value without the inequality qualifier
- Laboratory results below detectable threshold for laboratory analysis: Laboratory results presented as inequalities (or which otherwise have a non-numeric qualifier) will be presented as the numeric value without its non-numeric qualifier

Outliers identified in the PK analyses will be discussed in the analysis report.

8.4 Handling of Missing or Incomplete Dates

Imputation rules for missing or partial adverse event start/stop dates

- If the AE end date day is missing (month and year provided) then set the date to the last day of the month.

- If the AE end date month is missing (day and year provided) then set the date to the latest calendar month consistent with the day.
- If the AE end date day and month are missing (year is provided) then set the date to December 31.
- If the year of the AE start date or AE end date are missing, then a query to the site must be made to gather additional information.
    - If the start date is completely missing, then set the start date to the date of first dose. If the end date is completely missing, then set the end date to the date of last follow-up.
    - If the start date day is missing (month provided), then set the date to the first of the month, unless the month and year are the same as the month and year of first dose. In this case, set the date to the date of first dose. If the end date day is missing (month provided), then set the date to the last day of the month.
    - If the start date month is missing (day provided), then set the month date to January, unless the day and year are the same as the month and year of first dose. In this case, set the date to the date of first dose. If the end date month is missing (day provided), then set the date to the latest calendar month consistent with the day.
    - If the start date year is missing (day and month provided), then set the year to the year in which the subject was first screened, unless the day and month are the same as the day and month of first dose. In this case, set the date to the date of first dose. If the end date year is missing (day and month provided), then set the date to the latest calendar year in which the subject is followed.

Imputation rules for missing or partial prior/concomitant medication start/stop dates

- Start dates will not be imputed.
- Partial stop dates of prior/concomitant medications will be assumed to be the latest possible date consistent with the partial date. If day, month, and year are missing, then assign ‘continuing’ status to the stop date.

9 Statistical Methods

9.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) of 0.05. Two-sided 95% confidence intervals (CI) will be provided where relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum, and maximum. Means, medians, and quartiles (if averaged value) will be rounded to one more decimal place than what is reported in the data. SDs will be rounded to two more decimal places than what is reported in the data.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline is defined as the last measurement prior to the first treatment administration. All summaries will be presented by treatment group and for all subjects, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order within subject listings. All listings will be stratified by treatment group and sorted by subject ID in ascending numerical order, and date/time in ascending chronological order. The subject's race, sex, and age will be stated on each listing. Unless otherwise stated, data listings will be based on all randomized subjects (ITT Population).

9.2 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The table summary will include the total number of screened subjects, as well as the frequency and percentage of subjects who were screen failures and those who re-screened, with the percentages being based on the total number of screened subjects. Additionally, the total number of subjects who were randomized, dosed with IP, and completed the study per protocol will also be summarized using counts and percentages, using the total number of enrolled subjects as the denominator for percentages. The primary reason for study discontinuation will also be tabulated, using the total number of randomized subjects as the denominator for the proportion calculation. Subject disposition will be listed along with inclusion or exclusion criteria that were not met for randomization. The counts and percentages of subjects in each analysis set will also be tabulated.

A separate table summary will display subject enrollment by site using counts and percentages. The summary will include the name of the investigator at the site.

Data to be included in subject disposition listings will include:

- End of study status for randomized subjects, including reason for discontinuation for discontinued subjects
- Screen failure reason(s) for subjects who failed at screening
- Re-screened and re-consented subjects, along with any associated collected laboratory data

Treatment misallocations occur when a subject receives a different treatment than to what they were randomized. In these cases:

- If a subject were randomized but not treated, the subject will be included according to their randomized study arm assignment in the subject disposition summaries. The subject will be included in the ITT population only.
- If a subject were treated but not randomized, the subject will be excluded from the trial.
- If a subject were randomized but received a different treatment regimen, then the subject will be included according to their randomized study arm assignment in the ITT population but will be excluded from the PP population. The subject will be included according to the treatment regimen actually received for all safety analyses using the Safety population.

9.3 Protocol Deviations/Violations

All protocol deviations will be tabulated using counts and percentages by category and specific deviation classification within each category by treatment group and overall, among all randomized subjects. Subjects who experienced more than one event for a given category or deviation will be counted only once for that category or deviation.

All protocol deviations will be available in a subject listing. Additionally, a listing of subjects excluded from ITT, Safety, PP, PK, and PD analysis sets will be presented. These two listings will list all subjects randomized into the study.

9.4 Demographics and Baseline Characteristics

9.5 Demographics

Age at informed consent, sex, race, ethnicity, weight, height, BMI, and BMI category at baseline will be summarized descriptively [number of subjects (n), mean, SD, median, Q1, Q3, minimum, and maximum] for the ITT population.

9.6 Medical History

Medical and surgical histories will be coded using MedDRA (Medical Dictionary for Regulatory Activities) version 25.0 and tabulated by System Organ Class and Preferred Term for all treatment groups and overall. Subjects with more than one reported history for a given System Organ Class or Preferred Term will be included only once in that category.

Medical history will be presented in a subject listing for the ITT population.

9.7 Prior and Concomitant Medications

Data for all prior and concomitant medications will be summarized with counts and percentages by treatment group and overall for the ITT population. Prior medications are defined as those with an end date before the date of informed consent. Concomitant medications are defined as those with an end date on or after the date of informed consent. Medications with missing end dates will have their end date imputed as "Continuing" and will therefore be considered as concomitant medications. Please refer to Section 8, Statistical Considerations and Analysis, for further detail on imputed dates for prior and concomitant medications.

Prior and concomitant medications will also be presented in a subject listing for the ITT population.

9.8 Extent of Exposure

9.9 Treatment Duration and Compliance

For Cohorts 1-3, study treatment exposure and compliance will be summarized in the following manner:

- As a continuous summary of the number of doses received per subject
- As a categorical summary of the number of subjects receiving no, one, or both doses of IP
- As a categorical summary of the number of doses administered outside of the study window, and the count and percentage of subjects that received at least one dose out of the study window
- As a categorical summary of the reasons a dose was not administered

For Cohort 4, study treatment exposure and compliance will be summarized in the following manner:

- As a categorical summary of the number of subjects receiving no or one dose of IP
- As a categorical summary of the reasons the dose was not administered

The above summaries will be presented by treatment group and overall in the ITT population.

9.10 Analysis of Study Endpoints

9.10.1 Primary Endpoint 1a – Adverse Events, Cohorts 1-4

In order to evaluate primary objective #1, to evaluate the safety and tolerability of repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects, primary endpoint #1a will be used:

> The occurrence of adverse events (AEs) and serious adverse events (SAEs) following administration of G03-52-01 to the final visit

Adverse events (AEs) will be captured in a log at all scheduled visits from Baseline/Dosing [Visit 2 (Day 1)] through the end of study. Unless specified otherwise, AEs summaries will include all events starting from the date of initial administration of G03-52-01 up to and including the date of each subject's final scheduled

study visit. AEs with a start date after subjects' final scheduled study visit will not be included in table summaries. All AEs captured in the database will be included in subject listings.

All AEs with the exception of reactogenicity events will be classified by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 25.0. All AEs that occur after the initiation of study medication will be included in TFL summaries. Table summaries will include the frequency and percentage of subjects experiencing each event, as well as the total number of events experienced at each level of summarization (i.e., SOC and PT within SOC). The following summaries will be presented for all AEs, medically attended adverse events (MAAEs), and serious adverse events (SAEs) by SOC and PT and by treatment group and for all subjects:

- Overall (i.e., regardless of severity or relationship to treatment)
- By maximum severity grade (mild, moderate, or severe)
- By closest relationship to study medication

Additionally, an overall summary irrespective of SOC/PT categorization will be presented separately for all AEs with the exception of reactogenicity events. This overall summary will tabulate the number of subjects and events for: AEs, MAAEs, Grade 3 or greater AEs, AEs related to IP (possibly related or definitely related), Grade 3 or greater AEs related to IP (possibly related or definitely related), AEs with outcome of death, SAEs, SAEs related to IP (possibly related or definitely related), AEs leading to study discontinuation, AEs leading to discontinuation of IP, and AEs related to IP that led to discontinuation of IP.

Furthermore, a separate table will summarize the frequency and percentage of subjects experiencing each reactogenicity event and the total number of events experienced per term. The summary will be broken down by dose (i.e., Dose 1 and Dose 2) for Cohorts 1-3. Events that occur on or after date of first dose and before date of second dose will be summarized under Dose 1. Events that occur on or after date of second dose will be summarized under Dose 2. Reactogenicity events will be broken down into local reactions (injection site pain, injection site tenderness, injection site redness, injection site swelling) and systemic reactions (fever, headache, myalgia, abdominal pain, anorexia, nausea, vomiting, diarrhea, and malaise/fatigue).

Finally, three AE tables will be produced combining data across all four cohorts with the goal of comparing AE rates following initial administration of IP and before subjects in the first three cohorts received their second dose. For Cohorts 1-3, all AEs will be included that occur starting from the date of initial administration of G03-52-01 and prior to the date of each subjects' second dose. For Cohort 4, all AEs will be included that occur starting from the date of initial administration of G03-52-01 and prior to the date each subject's Day 45 study visit. If a Cohort 4 subject does not attend their Day 45 study visit, then all AEs will be included that occur up to and including 44 days from the subject's initial administration of G03-52-01. For these three AE summaries, Cohort 1 and Cohort 2 subject groupings will include both DP lots and the two Placebo groups (Cohorts 3 and 4) will be pooled together, such that the treatment groupings are as follows: Cohort 1, 50 mg (Both Lots); Cohort 2, 100 mg (Both Lots); Cohort 4, 100 mg; Cohorts 3 and 4, Placebo; and

Total. The number of AEs and the number and percentage of subjects that experienced the given AE will be summarized by the above mentioned treatment groupings.

The three AE summaries will consist of:

- Overall Summary of Adverse Events within First 45 Days of Initial Administration of IP
- Adverse Events within First 45 Days of Initial Administration of IP by System Organ Class, Preferred Term, and Maximum Severity
- Adverse Events within First 45 Days of Initial Administration of IP by System Organ Class, Preferred Term, and Closest Relationship to Study Medication

Unless otherwise specified, at each level of subject summarization of AEs, a subject will be counted once, even if they reported more than one event. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized. In summaries by SOC and PT, adverse events will be sorted in descending frequency by SOC and PTs within each SOC according to the total number of events among all subjects.

All AE summaries will be presented for the Safety population.

9.10.2 Primary Endpoint 1b – Physical Examination, Vital Signs, ECG, & Laboratory Results, Cohorts 1-4

To further evaluate primary objective #1, to evaluate the safety and tolerability of repeat intramuscular (IM) administration of G03-52-01 in healthy adult subjects, primary endpoint #1b will be used:

> The occurrence of changes from baseline in PE, vital signs, and clinical safety laboratory values following administration of G03-52-01 to the final follow-up visit

Clinical laboratory parameters for chemistry, hematology, urine dipstick, and urine toxicology will be summarized in tables and listed, using System International (SI) units where applicable. In table summaries, continuous parameters will be evaluated using descriptive statistics [number of subjects (n), mean, SD, median, first quartile, third quartile, minimum, and maximum] at each time point and each change from baseline to follow-up time point. Categorical parameters will be summarized using counts and percentages and shifts from baseline will be separately summarized. Shift tables will include both the shift from baseline to each post-baseline visit as well as the maximum shift from baseline. If a lab value is reported using a non-numeric qualifier [e.g., less than (<) a certain value, or greater than (>) a certain value], then the given numeric value will be used in the summary statistics, and the nonnumeric qualifier will be dismissed; however, results with non-numeric qualifiers will be listed as-is in the listings. Laboratory parameters will be listed by subject at each time point, which will display the result, change from baseline (if applicable), the normal range for the parameter, and whether the result was clinically significant (either clinically low or clinically high). For the urine dipstick laboratory assessment, if any of the parameter results are abnormal (>+1), then a complete urinalysis will be performed and presented in a separate subject listing.

Serology samples will be collected at Screening (Visit 1) that assess for presence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV), and will be presented in a subject listing.

Breathalyzer test and urine toxicology results will also be collected at Screening (Visit 1) and Baseline/Dosing [Visit 2 (Day 1)] for all subjects and Visit 7 (Day 45) for Cohorts 1-3 only. The results will be presented in subject listings.

For female subjects, urine/serum pregnancy test results will be collected at for Cohorts 1-3 at Screening (Visit 1), Baseline/Dosing [Visit 2 (Day 1)], Visit 7 (Day 45), and Visit 14 (Day 240) and for Cohort 4 at Screening (Visit 1), Baseline/Dosing [Visit 2 (Day 1)], Visit 8 (Day 45), and Visit 10 (Day 120). Female subjects' reported contraceptive methods and the start date of their last menstrual period at Screening will be presented in a separate subject listing.

Finally, for Cohorts 1-3 only, a hypersensitivity panel will be drawn prior to the first dose on the Baseline/Dosing [Visit 2 Day 1)] visit and prior to repeat dose on Visit 7 (Day 45). The sample will be processed if the subject has a hypersensitivity (anaphylaxis or anaphylactoid) reaction. If a hypersensitivity reaction occurs, an additional sample will be collected during the reaction and again after the reaction. A subject listing will display the results of the panel.

Vital signs data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oral temperature (degrees Celsius), and heart rate (BPM) will be summarized continuously by treatment group at Screening, Baseline/Dosing, Visit 3 (24 Hours), and then all subsequent visits and listed by subject and parameter at the aforementioned time points. For subjects who have repeat vital signs measurements within the same visit, the latest measurements will be used for analysis in table summaries and all measurements will be listed.

A 12-lead electrocardiogram (ECG) will be performed for each subject at Screening and for Cohorts 1-3 at Visit 6 (Day 15). Results will be categorized as normal sinus rhythm, normal variant, and abnormal, and summarized categorically using counts and percentages. The table summary will further summarize the number of subjects with a QTc interval greater than 450 milliseconds, with those subjects' QTc values summarized using continuous descriptive statistics for each group. An ECG subject listing will also be displayed.

Abbreviated physical examinations will be conducted for all subjects at Screening and Baseline/Dosing and for Cohorts 1-3 at Visit 14 (Day 240). The examinations will consist of the following tests/parameters: HEENT, Respiratory, Extremities, Neurological, Cardiovascular/Heart, Musculoskeletal, Dermatologic, Pulmonary, Gastrointestinal/Abdominal, Genitourinary, Endocrine, and General Appearance. Results will be summarized categorically [Normal, Abnormal Clinically Significant (CS), Abnormal Not Clinically Significant (NCS), or Not Done] for each test/parameter at each of the three visits. A subject listing will display all physical examination results by time point and test/parameter. Finally, symptom-directed physical examinations will be conducted based on an unsolicited compliant from the subject, whose results will be

displayed in a separate listing. Symptom-directed physical examinations can be performed at any visit, scheduled or unscheduled.

Unscheduled visit data for all safety analyses will be presented in listings but not included in table summaries, with the exception that an unscheduled visit result will serve as a subject's baseline result if it is their last result prior to first treatment administration.

All safety analyses will be presented for the Safety population.

9.10.3 Primary Endpoint 2 – Target Protective NAC (Day 45 and Day 90), Cohorts 1-2

To evaluate primary objective #2, to demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B through Day 45 and Day 90 for Cohorts 1-2, primary endpoint #2 will be used:

> For Cohorts 1-2, to evaluate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 45 and Day 90

PD samples will be collected and analyzed by the Battelle MNA against serotypes BoNT/A and BoNT/B at Baseline/Dosing [Visit 2 (Day 1)] pre-dose, Visit 3 (24 Hours), Visit 5 (Day 8), Visit 6 (Day 15), Visit 7 (Day 45) pre-dose, Visit 8 (Day 49), Visit 10 (Day 90), and Visit 11 (Day 120).

At Visit 7 (Day 45) and Visit 10 (Day 90), the frequency and percentage of subjects with a NAC > 0.02 U/mL against BoNT/A, a NAC > 0.03 against BoNT/B, and those with either a NAC > 0.02 U/mL against BoNT/A or a NAC > 0.03 U/mL against BoNT/B will be presented. Percentages will be based on the total number of subjects at the respective time point with evaluable concentrations. Summaries will be presented for each lot separately within each of the two active drug cohorts.

The PD population will be used for the analysis of this primary endpoint.

9.10.4 Primary Endpoint 3 – Target Protective NAC (4 Hours and 8 Hours), Cohort 4

To evaluate primary objective #3, to demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 Hours post-dose for Cohort 4 (active only), primary endpoint #3 will be used.

At 4 Hours post-dose and 8 Hours post-dose, the frequency and percentage of subjects with a NAC > 0.02 U/mL against BoNT/A, a NAC > 0.03 against BoNT/B, and those with either a NAC > 0.02 U/mL against BoNT/A or a NAC > 0.03 U/mL against BoNT/B will be presented. Percentages will be based on the total number of subjects at the respective time point with evaluable concentrations. Summaries will be presented for each lot separately within each of the two active drug cohorts.

The PD population will be used for the analysis of this primary endpoint.

9.10.5 Secondary Endpoint 1 – Target Protective NAC (Day 120), Cohorts 1-2

To evaluate secondary objective #1 demonstrate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120 (Cohorts 1-2), secondary endpoint #1 will be used:

To evaluate target protective concentration (NAC) value > 0.02 U/mL (BoNT/A) or > 0.03 U/mL (BoNT/B) at Day 120

At Visit 11 (Day 120), the frequency and percentage of subjects with a NAC > 0.02 U/mL against BoNT/A, a NAC > 0.03 against BoNT/B, and those with either a NAC > 0.02 U/mL against BoNT/A or a NAC > 0.03 U/mL against BoNT/B will be presented. Percentages will be based on the total number of subjects at the respective time point with evaluable concentrations. Summaries will be presented for each lot separately within each of the two active drug cohorts.

The PD population will be used for the analysis of this secondary endpoint.

9.10.6 Secondary Endpoint 2 – PD and ADA Evaluation, Cohorts 1-2

To evaluate secondary objective #2, to evaluate pharmacodynamic (PD) and anti-drug antibody (ADA) at pre-dose through the end of study (Cohorts 1-2), secondary endpoint #2 will be used.

The following PD parameter estimates for samples analyzed using the Battelle Mouse Neutralization Assay (MNA) method will be reported:

- $AUC_{(0-t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation (reported in day*U/mL)
- C_{max}: Maximum observed concentration (reported in U/mL)
- T_{max}: Time of maximum observed concentration (reported in days)
- $t_{1/2}$: Terminal elimination half-life (reported in days)

PD parameters will be summarized by lot and active cohort using descriptive statistics against each serotype (BoNT/A and BoNT/B) separately. Parameters will be calculated and presented separately for Dose 1 and Dose 2 where applicable.

Additionally, NAC values will be summarized descriptively for each serotype separately at Baseline/Dosing [Visit 2 (Day 1)] pre-dose, Visit 3 (24 Hours), Visit 5 (Day 8), Visit 6 (Day 15), Visit 7 (Day 45) pre-dose, Visit 8 (Day 49), Visit 10 (Day 90), and Visit 11 (Day 120). Concentration-time profiles will be displayed graphically on linear and semi-log scales by serotype and active treatment group. One set of plots will include error bars (presented as SD) and one set will not include error bars.

The summary statistics used for all PD parameters and concentrations will include number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, coefficient of variation (CV, presented in percentage, CV%), geometric mean (GM), the 95% CI of the GM, the geometric coefficient of variation (GCV, presented in percentage, GCV%), and the 95% CI of the GCV%.

The GM, 95% CI of GM, GCV%, and 95% CI of GCV% will be calculated using the following SAS® procedure:

```
proc ttest data=indata dist=lognormal;
```

```
        var x;
        ods select ConfLimits;
run;
```

, where `indata` is the data set with PD parameters and `x` is a parameter.

Additionally, PD parameters and NAC values will be listed separately at the subject level.

The PD population will be used for all pharmacodynamic tables, listings, and figures.

Immunogenicity (ADA) samples will be tested at Baseline/Dosing [Visit 2 (Day 1)] pre-dose, Visit 3 (24 Hours) and Visit 4 (72 Hours) post-dose, and at Visit 5 (Day 8), Visit 6 (Day 15), Visit 7 (Day 45) pre-dose, Visit 8 (Day 49), Visit 10 (Day 90), Visit 11 (Day 120), Visit 12 (Day 150), Visit 13 (Day 180), and Visit 14 (Day 240).

The frequency and percentage of subjects with a positive immunogenicity response will be summarized by time point across the active treatment arms. Additionally, anti-drug antibody titers will be summarized using continuous descriptive statistics [number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, CV%, GM, GCV%, and the 95% CI of the GCV] by time point. Both the categorical and continuous ADA table summaries will include a subgroup analysis for only those subjects that have a negative immunogenicity response at baseline. Anti-drug antibody status and titer values will be listed by subject and time point.

The ITT population will be used for all immunogenicity summaries.

9.10.7 Secondary Endpoint 3 – Target Protective NAC (2 Hours), Cohort 4

To evaluate secondary objective #3, demonstrate target protective concentration (NAC) value of BoNT/A and BoNT/B at 4 and 8 hours post-dose (Cohort 4), secondary endpoint #3 will be used.

> To evaluate the proportion of subjects with target protective concentration (NAC) value > 0.02 U/mL (botulinum neurotoxin [BoNT]/A) or > 0.03 U/mL (BoNT/B) at 2 hours post dose

At the 4 Hour and 8 Hour post-dose time points, the frequency and percentage of subjects with a NAC > 0.02 U/mL against BoNT/A, a NAC > 0.03 against BoNT/B, and those with either a NAC > 0.02 U/mL against BoNT/A or a NAC > 0.03 U/mL against BoNT/B will be presented. Percentages will be based on the total number of subjects at the respective time point with evaluable concentrations.

The PD population will be used for the analysis of this secondary endpoint.

9.10.8 Secondary Endpoint 4 – PK Evaluation, Cohort 4

To evaluate secondary objective #4, to assess pharmacokinetics (PK) at pre-dose through end of study (Cohort 4), secondary endpoint #4 will be used.

PK summaries will include the NX01, NX02, NX11, XB10, XB18, and XB23 mAbs. The following PK parameter estimates for sample tested by ECLA or ELISA will be reported at each of the aforementioned time points:

- $AUC_{(0-t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation (reported in day*ng/mL)
- $AUC_{(0-\infty)}$: Area under the concentration time-curve extrapolated to infinity (reported in day*ng/mL)
- C_{max}: Maximum observed concentration (reported in ng/mL)
- Kel: Elimination rate constant (reported in 1/day)
- $t_{1/2}$: Terminal elimination half-life (reported in days)
- CL/F: Total clearance (reported in L/day)
- V_z/F: Volume of distribution (reported in L)

Concentrations of each mAb will be summarized descriptively in tables by active treatment group and time point. Concentration-time profiles will be displayed graphically on linear and semi-log scales by mAb and active treatment group. One set of plots will include error bars (presented as SD) and one set will not include error bars.

The summary statistics used for all PK parameters and concentrations will include number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, CV%, GM, 95% CI of the GM, GCV%, and the 95% CI of the GCV. PK parameters will be presented by Dose 1 and Dose 2 where applicable.

Additionally, PK parameters and concentrations will be listed separately at the subject level.

The PK population will be used for all pharmacokinetic tables, listings, and figures.

9.10.9 Secondary Endpoint 5 – PD and ADA Evaluation, Cohort 4

To evaluate secondary objective #5, to evaluate pharmacodynamics (PD) and anti-drug antibody (ADA) at pre-dose through the end of study (Cohort 4), secondary endpoint #5 will be used:

Descriptive statistics of determined PD and ADA timepoints

The following PD parameter estimates for samples analyzed using the Battelle Mouse Neutralization Assay (MNA) method will be reported:

- $AUC_{(0-t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation (reported in day*U/mL)
- C_{max}: Maximum observed concentration (reported in U/mL)
- T_{max}: Time of maximum observed concentration (reported in days)
- $t_{1/2}$: Terminal elimination half-life (reported in days)

Dose 1 PD parameters will be summarized for the Cohort 4 active treatment group using descriptive statistics against each serotype (BoNT/A and BoNT/B) separately.

Additionally, NAC values will be summarized descriptively for each serotype separately at Baseline/Dosing [Visit 2 (Day 1)] pre-dose, Visit 3 (24 Hours), Visit 7 (Day 30), Visit 8 (Day 45), and Visit 9 (Day 90). Concentration-time profiles will be displayed graphically on linear and semi-log scales by serotype and active treatment group. One set of plots will include error bars (presented as SD) and one set will not include error bars.

The summary statistics used for all PD parameters and concentrations will include number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, CV%, GM, the 95% CI of the GM, GCV%, and the 95% CI of GCV%.

The GM, 95% CI of GM, GCV%, and 95% CI of GCV% will be calculated using the following SAS® procedure:

```
proc ttest data=indata dist=lognormal;
      var x;
      ods select ConfLimits;
run;
```

, where `indata` is the data set with PD parameters and `x` is a parameter.

Additionally, PD parameters and NAC values will be listed separately at the subject level.

The PD population will be used for all pharmacodynamic tables, listings, and figures.

Immunogenicity (ADA) samples will be collected at Baseline/Dosing [Visit 2 (Day 1)] pre-dose, Visit 9 (Day 90), and Visit 10 (Day 120).

The frequency and percentage of subjects with a positive immunogenicity response will be summarized by mAb and time point across the active treatment arms. Results will be categorized as Detected, Not Detected, and NRR (No Recorded Result). Additionally, anti-drug antibody titers for the overall drug product will be summarized using continuous descriptive statistics [number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, CV%, GM, 95% CI of the GM, GCV%, and the 95% CI of the GCV] by the aforementioned time points. Both the categorical and continuous ADA table summaries will include a subgroup analysis for only those subjects that have a negative immunogenicity response at baseline. Anti-drug antibody status and titer values will be listed by subject and time point.

The ITT population will be used for all immunogenicity summaries.

9.10.10 Exploratory Endpoint 1 – PK and ADA Evaluation, Cohorts 1-2

To evaluate the exploratory objective, to evaluate pharmacokinetic (PK) parameters to ensure ADA evaluation adequate of the two lots (Cohorts 1-2), exploratory endpoint #1 will be used:

PK summaries will include NX01, NX02, NX11, XB10, XB18, and XB23 mABs. The following PK parameter estimates for sample tested by ECLA or ELISA will be calculated and summarized using descriptive statistics by dose (where applicable):

- $AUC_{(0-t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation (reported in day*ng/mL)
- $AUC_{(0-\infty)}$: Area under the concentration time-curve extrapolated to infinity (reported in day*ng/mL)
- C_{max}: Maximum observed concentration (reported in ng/mL)
- Kel: Elimination rate constant (reported in 1/day)
- $t_{1/2}$: Terminal elimination half-life (reported in days)
- CL/F: Total clearance (reported in L/day)
- V_z/F: Volume of distribution (reported in L)

Concentrations of each mAb will be summarized descriptively in tables by active treatment group and time point. Concentration-time profiles will be displayed graphically on linear and semi-log scales by mAb and active treatment group. One set of plots will include error bars (presented as SD) and one set will not include error bars.

The summary statistics used for all PK parameters and concentrations will include number of subjects (n), mean, SD, median, Q1, Q3, minimum, maximum, CV%, GM, 95% CI of the GM, GCV%, and the 95% CI of the GCV.

Additionally, PK parameters and concentrations will be listed separately at the subject level.

The PK population will be used for all pharmacokinetic tables, listings, and figures.

10 Changes to Planned Analysis from Study Protocol

N/A

11 Appendix

11.1 Appendix A. Schedule of Assessments

Cohorts 1-3:

Study Visit	Screen-ing[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	11	12	13	14	Unsched-uled
Day of Study	**-14 to -1**	**D 1**	**1-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 45**	**D49**	**D 60**	**D 90**	**D 120**	**D 150**	**D 180**	**D 240**	**Unsched-uled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±5D)**	
Review Inc/Excl Criteria	X	X														
Demographics	X															
Review Medical History	X	X														
Randomization		X														
Study Drug Administration		X						X								
Concomitant Medications[2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[3]	X	X	(SD)[4]	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	X	SD
Vital Signs[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential[7]	X	X		X			X	X		X		X			X	
Chemistry[6]	X	X		X			X	X		X		X			X	

Study Visit	Screen-ing[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	11	12	13	14	Unsched-uled
Day of Study	**-14 to -1**	**D 1**	**1-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 45**	**D49**	**D 60**	**D 90**	**D 120**	**D 150**	**D 180**	**D 240**	**Unsched-uled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±5D)**	
Serology Panel[12]	X															
Pregnancy Test[8]	X (serum)	X (urine)						X (urine)							X (urine)	
Drug Screening[9]	X	X						X								
Breathalyzer test	X	X						X								
Urine Dipstick[10]	X	X						X							X	
12-lead ECG[11]	X						X									
PK samples[15]		X		X	X	X	X	X[18]	X		X	X				
MNA samples[16]		X		X		X	X	X[18]	X		X	X				
Immunogenicity (ADA) samples[17]		X					X	X[18]		X	X	X	X	X	X	
Future Use Sample[13]		X					X	X[18]		X	X	X	X	X	X	
Hypersensitivity Panel[14]		X						X								
Subject Diary Review[19]			X	X	X	X		X	X	X						

1. Screening will be completed within 14 days prior to administration of study drug and may require more than one visit.
2. Concomitant medications including all of the following: prescription drugs, over-the–counter drugs, herbs, vitamins, nutritional supplements, illicit and recreational substance use, birth control information.
3. PE includes height and weight at screening.

4. Symptom-directed only.
5. Vital Signs to include sitting diastolic and systolic BP, HR, and oral temperature. Vital signs will be checked just before injection on Day and Day 45 and every visit.
6. Chemistry panel that will include serum creatinine, BUN, calcium, total bilirubin, alkaline phosphatase, ALT, AST, sodium, potassium, albumin, PT, PTT, INR, total CK, carbon dioxide, and chloride. Subjects should be fasting for the chemistry panel.
7. A CBC with differential will be obtained including WBC, RBC, hemoglobin, hematocrit, platelet count, MCV, MCH, MCHC, RDW, MPV, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
8. A serum pregnancy test will be obtained at screening for all women of reproductive capacity. A urine pregnancy test will be obtained and must be resulted prior to Day 1 dosing. Results must be confirmed as negative before study product is dosed.
9. Urine drug screening.
10. A urine dipstick will be done to evaluate for presence of protein, glucose or blood in urine. If dipstick is abnormal (>+1), a complete urinalysis with microscopic will be performed.
11. A 12-lead ECG will be done during screening. Subjects with a QTc interval >450 milliseconds will be excluded from participation.
12. Viral Serology includes HIV, HBsAg and antibody to HCV.
13. Serum from subjects who give consent will be stored for future use on Days 0, 8, and 30.
14. The Hypersensitivity Panel includes cytokine and complement panels, IgE, and tryptase. Refer to lab manual for further processing instructions. .
15. PK samples will be collected for all subjects by ECLA or ELISA at pre-dose, 24 hours and 72 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120.
16. Serological samples (PD) will be collected for all subjects by MNA for serotypes A and B at pre-dose, 24 hours post dose, and on Days 8, 15, 45 (before repeat-dose or placebo), 49, 90, and 120.
17. ADA samples will be collected and tested for all subjects at pre-dose and Days 15, 45 (before repeat-dose or placebo), 60, 90, 120, 150, 180, and 240.
18. Samples to be collected pre-dose prior to Day 45 repeat dose.
19. Subjects will be provided a reactogenicity diary prior to leaving the clinic on baseline/dosing Day 1. Subjects will be asked to complete daily diary records study Day 1-7 and dairy is to be collected by site staff on Day 8 for review. Subjects will be provided a reactogenicity diary prior to leaving the clinic on baseline/dosing Day 45. Subjects will be asked to complete daily diary records study Day 46-52 and dairy is to be collected by site staff on Day 60 for review.

Cohort 4:

	Screening[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	Unscheduled
Day of Study	**-14 to -1**	**D 1**	**8-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 30**	**D 45**	**D 90**	**D 120**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	
Review Inc/Excl Criteria	X	X										
Demographics	X											
Review Medical History	X	X										
Randomization		X										
Study Drug Administration		X										
Concomitant Medications[2]	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review		X	X	X	X	X	X	X	X	X	X	X
Physical Exam[3]	X	X	(SD)[4]	SD	SD	SD	SD	SD	SD	SD	SD	SD
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential[7]	X						X		X		X	
Chemistry[6]	X						X		X		X	
Serology Panel[12]	X											
Pregnancy Test[8]	X (serum)	X (urine)							X (urine)		X (urine)	
Drug Screening[9]	X	X										
Breathalyzer test	X	X										
Urine Dipstick[10]	X	X										
12-lead ECG[11]	X											
PK samples[13]		X	X16	X	X	X	X	X	X	X	X	
MNA samples[14]		X	X17	X				X	X	X		

Study Visit	Screening[1] 1	Baseline/ Dosing 2		3	4	5	6	7	8	9	10	Unscheduled
Day of Study	**-14 to -1**	**D 1**	**8-Hour Stay**	**24 Hours**	**72 Hours**	**D 8**	**D 15**	**D 30**	**D 45**	**D 90**	**D120**	**Unscheduled**
Visit Windows				**(±2 hrs)**	**(±2 hrs)**	**(±1D)**	**(±2D)**	**(±3D)**	**(±3D)**	**(±3D)**	**(±3D)**	
Immunogenicity (ADA) samples[15]		X								X	X	
Subject Diary			X	X	X	X						

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