A phase 1 study of the safety and pharmacokinetics of a combination of two anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in healthy volunteers (Protocol Number: RUCOV1)

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Confidentiality Statement

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Statement of Compliance

The clinical trial will be conducted in compliance with the protocol, with the International Conference on Harmonization Good Clinical Practice E6 (R2) (ICH-GCP), and with 45 CFR 46 and 21 CFR 50, 56 and 312. All protocol investigators have completed Protection of Human Subjects Training.

Signature Page 1

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 U.S. federal regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Signature Page 2

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 U.S. federal regulations and ICH guidelines.

The Investigator(s) of Record (signature(s) on 1572) from each participating clinical site should sign the Signature Page 2 as appropriate. This Signature Page 2 should be maintained at each site.

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Print/Type

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Name/Title

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List of Abbreviations

Ab	Antibody
ACE	Angiotensin Converting Enzyme
ADA	Anti-drug Antibodies
AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
AUC	Area Under the Curve
bNAbs	Broadly Neutralizing Antibodies
CD4	T-cell Surface Glycoprotein CD4
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CONSORT	Consolidated Standards of Reporting Trials
CHO	Chinese Hamster Ovary
CL/F	Clearance
COVID-19	Coronavirus Disease 2019
Cmax	Maximum Concentration Of A Drug In The Body After Dosing
CRF	Case Report Form
CRSO	Clinical Research Support Office
CTSA	Clinical and Translational Science Award
CCTS	Center for Clinical and Translational Science
DAIDS	Division Of Acquired Immunodeficiency Syndrome
DLT	Dose Limiting Toxicity
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HAHA	Human Anti-Human Antibody
HIPAA	Health Insurance Portability and Accountability Act
hu-mice	Humanized Mice
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
I.M.	Intramuscularly
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
I.V.	Intravenously
mAb	Monoclonal antibody
MCB	Master Cell Bank
MFI	Mean Fluorescence Intensity
mg/mL	Milligram Per Millileter
MTD	Maximum tolerated dose
N	Number (typically refers to participants)
nAb	Neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
NHP	Non-Human Primates
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NP	Nasopharyngeal
OHRP	Office for Human Research Protections

OHSR	Office for Human Subjects Research
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PK	Pharmacokinetics
RU	The Rockefeller University
RUH	The Rockefeller University Hospital
QA	Quality Assurance
QC	Quality Control
RBD	Receptor Binding Domain
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SARS-CoV-2	Severe Acute Respiratory Syndrome-associated Coronavirus 2
S.C.	Subcutaneously
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
$t_{1/2}$	Half-Life
T cell	T lymphocyte
UAE	Unanticipated Adverse Event

PROTOCOL SUMMARY

Title	**A phase 1 study of the safety and pharmacokinetics of a combination of two anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in healthy volunteers**
Short Title	RU Anti-SARS-CoV-2 mAbs in Healthy Volunteers
Protocol Number	RUCOV1
Phase	Phase 1
Investigational product	Two highly neutralizing antibodies directed against SARS-CoV-2 RBD: C144-LS and C135-LS. The antibodies are manufactured separately and each will be formulated in a separate vial at a concentration of 50 mg/mL.
Indication	Prevention or therapy of COVID-19
Sample size	23 to 38
Number of study sites	Single site – The Rockefeller University Hospital (RUH), New York, NY, U.S.A.
Study Objectives	Primary objectives: - To evaluate the safety and tolerability of subcutaneous injections or single intravenous infusions of C144-LS in combination with C135-LS in healthy volunteers. - To evaluate the pharmacokinetic profile of C144-LS and C135-LS in combination, administered subcutaneously or intravenously at increasing dose levels in healthy volunteers. Secondary objectives: - To assess the occurrence of anti-drug antibody responses. - To evaluate serum neutralizing activity against SARS-CoV-2 after C144-LS and C135-LS administration.
Study Outcomes/Objectives	Primary outcomes: - Rate of solicited and investigational product (IP)-related unsolicited adverse events that are Grade 2 and above (including confirmed laboratory abnormalities) 4 weeks after administration. - Rate of solicited and IP-related unsolicited adverse events that are Grade 3 and above (including confirmed laboratory abnormalities) 4 weeks after administration. - Proportion of participants with serious adverse events (SAEs) throughout the study period that are considered related to investigational products and their duration. - The pharmacokinetic profile of C144-LS and C135-LS: elimination half-life (t1/2), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve. Secondary Outcomes: - Rate and severity of investigational product (IP)-related adverse events during study follow up. - Frequency and levels of induced anti-C144-LS and anti-C135-LS antibodies in all study groups. - Serum neutralizing activity against SARS-CoV-2 before and after C144-LS and C135-LS administration.

Overview of Study Design

This is a first-in-human, single dose, dose-escalation phase 1 study to evaluate the safety and pharmacokinetics of a combination of two highly neutralizing anti-SARS-CoV-2 mAbs targeting two distinct epitopes on the receptor protein binding domain (RBD) of the SARS-CoV-2 spike protein in healthy volunteers.

The study consists of two parts. Part A has a standard 3+3 phase 1 dose escalation design. Study participants will receive subcutaneous injections of C144-LS and C135-LS at 4ml (approximately 100mg of each antibody administered separately) or 8ml (approximately 200mg of each antibody administered separately), or sequential intravenous infusions of C144-LS and C135-LS, each administered via a peripheral vein over 60 minutes at one of three increasing dose levels (1.5 mg/kg, 5 mg/kg and 15 mg/kg of each antibody). Participants in Part B will be randomized to receive subcutaneous injections of C144-LS and C135-LS at 8ml (approximately 200mg of each antibody administered separately) or placebo in a 3:1 ratio and double-blinded fashion.

Part A has started enrollment. Part B has a planned enrollment of 8 participants (see Table and Scheme below).

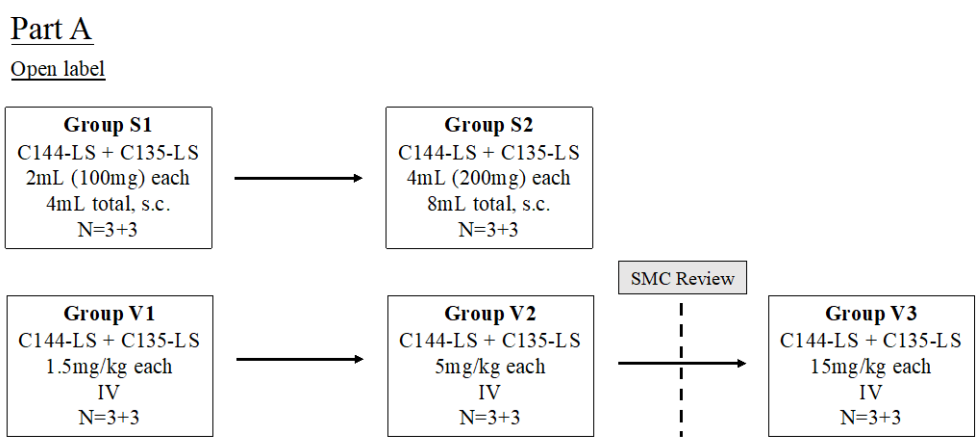
Study Groups

Part A – Open label

Group	Antibody	Dose	Route	Regimen	N
S1	C144-LS + C135-LS	100 mg each mAb	SC	Day 0	3+3
S2	C144-LS + C135-LS	200 mg each mAb	SC	Day 0	3+3
V1	C144-LS + C135-LS	1.5 mg/kg each mAb	IV	Day 0	3+3
V2	C144-LS + C135-LS	5 mg/kg each mAb	IV	Day 0	3+3
V3	C144-LS + C135-LS	15 mg/kg each mAb	IV	Day 0	3+3

Part B – Randomized, double-blinded

Group	Antibody	Dose	Route	Regimen	N
S3	C144-LS + C135-LS	200 mg each mAb or placebo	SC	Day 0	8 (6:2)



Part A - Dose escalation plan
During the subcutaneous and intravenous dose escalation phase of the study, enrollment will be staggered by 1 day for the volunteers of each group.

Subcutaneous (SC) Administration (Groups S1 and S2)

1. First, eligible participants will be enrolled in **Group S1** (C144-LS + C135-LS, 2mL each).
2. Enrollment in **Group S2** (C144-LS + C135-LS, 4mL each) will begin after all three participants enrolled in **Group S1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144- LS and/or C135-LS).

Overview of Study Design	3. If 1 DLT occurs, 3 additional participants will enroll in **Group S1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed. 4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum subcutaneous tolerated dose (MTD). 5. Enrollment in **Group S2** will follow the same rules. *Intravenous (IV) Administration (Groups V1, V2 and V3)* 1. Enrollment in **Group V1** (C144-LS + C135-LS, 1.5mg/kg each, IV) will begin at least 7 days after the first three participants enrolled in **Group S2.** 2. Enrollment in **Group V2** (C144-LS + C135-LS, 5mg/kg each, IV) will begin after all three participants enrolled in **Group V1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144-LS and/or C135-LS). 3. If 1 DLT occurs, 3 additional participants will enroll in **Group V1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed. 4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum intravenous tolerated dose (MTD). 5. Enrollment in **Group V3** (C144-LS + C135-LS, 15mg/kg each, IV) will follow the same rules. 6. Enrollment in **Group V3** will begin at least 7 days after three participants enrolled in **Group V2** and following SMC review of all available safety data. Note: As outlined in **Section 14.1**, the SMC will be asked to review safety data if one or more grade 3 or higher adverse events, deemed probably or definitely related to the study drugs (DLT) occur. No additional administration of the investigational products will take place pending a SMC review. In the event of a DLT, the SMC will make recommendations with regards to expansion of a study group from 3 to 6 participants, dose escalation to the next dose level, or halting additional enrollment. **Part B** During the subcutaneous, randomized, double-blinded phase (Part B) of the study, enrollment will be limited to a maximum of two participants per day. Enrollment in **Group S3** will begin once all participants in Part A have met eligibility criteria and have been scheduled for enrollment (day 0) and after all three participants enrolled in **Group S2** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group. **Toxicity Evaluations** Treatment toxicity will be evaluated per the FDA Guidance of Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Participants will be observed at the study site for 24 hours after antibody administration, and will return for follow visits over 48 weeks, according to Appendix A, Time of Events Schedule. Blood samples will be collected for safety testing at day 1, weeks 1, 4, 8, 12, 18 24, 36 and 48 following antibody dosing. Pharmacokinetics assessments will be performed before and after each antibody dosing and at later time points, as indicated in Appendix A (see below).
Study Duration	15 months
Inclusion and Exclusion Criteria	**Inclusion Criteria**: - Aged 18 to less than 65. - If sexually active male or female, and participating in sexual activity that could lead to pregnancy, agrees to use one effective method of contraception from 10 days prior to the antibody administration until 6 months after investigational product (IP) administration.

	Exclusion Criteria: - Weight > 110 kg for groups S1 and S2 only - History of prior positive SARS-CoV-2 RT-PCR or SARS-CoV-2 serology. - Active respiratory or non-respiratory symptoms consistent with COVID-19. - Medically attended acute illness or hospitalization (ie, >24 hours) for any reason within 30 days prior to screening. - Acute exacerbation of a chronic pulmonary condition (eg, chronic obstructive pulmonary disease [COPD], asthma exacerbations, or uncontrolled hypertension, as defined by a systolic blood pressure > 180 and/or diastolic blood pressure > 120, in the presence or absence of anti-hypertensive medications) in the past 6 months prior to screening. - Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months. - Other clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation. - Are eligible for COVID-19 vaccination prior to your entry in the study according to local guidelines (e.g. healthcare professionals, non-healthcare professionals such as teachers, firefighters, public transit workers). - Laboratory abnormalities in the parameters listed: o Absolute neutrophil count ≤ 1,500 K/mcL; o Hemoglobin ≤ 10.5 gm/dL if female; ≤ 11 gm/dL if male; o Platelet count ≤ 125,000 K/mcL; o ALT ≥ 1.25 x ULN; AST ≥ 1.25 x ULN; o Total bilirubin ≥ 1.25 x ULN; o Creatinine ≥ 1.1 x ULN; - Pregnancy or lactation. - Any vaccination within 14 days prior to SARS-CoV-2 mAbs administration (except influenza vaccine). - History of prior receipt of any SARS-CoV-2 vaccine or antibodies, including convalescent plasma. - Known allergy/sensitivity or any hypersensitivity to components of the investigational agents. - History of severe reaction to a vaccine or monoclonal antibody administration or history of severe allergic reactions. - Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.
Study Product, Dose, Route, Regimen	- Single subcutaneous injections of C144-LS and C135-LS, each mAb dosed at approximately 100 mg (two 2 mL injections administered at separate sites) or 200 mg (four 2 mL injections administered at separate sites). - Single subcutaneous injections of placebo (buffered solution) as four 2 mL injections administered at separate sites. - One intravenous infusion of C144-LS and C135-LS, each administered via a peripheral vein over 60 minutes sequentially. Starting dose level is 1.5 mg/kg of each antibody, with 0.5 log10 increases to 5 mg/kg and 15 mg/kg.

Statistical Methodology	A standard "3+3" Phase 1 trial design will be used in the dose-escalation phase (Part A) to assess safety; stopping rules (as defined above) will be based on the occurrence of dose-limiting toxicity. Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Descriptive results will be presented for the pharmacokinetic parameters by dose group. Continuous data will be summarized by descriptive statistics, including sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of participants with an outcome.

1 KEY ROLES

1.1 Study Site and associated Institutions

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2 LAY SUMMARY

The COVID-19 pandemic is currently gripping the world in the absence of any clearly effective preventive or therapeutic remedies. Aside from the health consequences, the necessary decrease in human activity has resulted in economic losses and expanding social disparities without modern precedent, especially in countries where health care and social security systems were not sufficient even prior to the pandemic.

It is hoped that one or more currently available drugs can bring a measure of mitigation to meet the medical need, however it is unclear whether a repurposed drug can be given safely in high enough doses to provide meaningful efficacy against the virus. Multiple vaccines and other preventive or therapeutic strategies are being tested in clinical trials. As of December 11, 2020 one vaccine has received Emergency Use Approval (EUA) by the FDA for the prevention of SARS-CoV-2 infection. Two monoclonal antibodies also received EUA for the treatment of mild to moderate COVID-19. At this time, the supply of both vaccine and antibodies remains extremely limited. It is also unclear at this time how long protection from the available vaccine will last. Therefore, there is a continued need for the development of additional prevention and treatment strategies that can add to the arsenal of modalities that have become recently available.

Antibodies are the active agents in most vaccines and have the added benefit of use as therapeutics when administered passively. We have identified a set of complementary human antibodies from individuals who recovered from COVID-19 that potently neutralize SARS-CoV-2 (the virus that causes COVID-19) at low concentrations. The object of this study is to evaluate the safety and pharmacokinetics of the combination of two of anti-SARS-CoV-2 monoclonal antibodies in healthy volunteers.

3 OBJECTIVES AND RATIONALE

3.1 Background

In December 2019, an outbreak of a novel viral pneumonia of unknown origin was identified in the city of Wuhan, China. Shortly thereafter, molecular techniques revealed that the rapidly spreading severe acute respiratory syndrome was caused by a novel coronavirus, which was named SARS-CoV-2. The disease caused by this new pathogen was subsequently named COVID-19. Since then, the number of reported cases surpassed 30 million and while drastic public health measures were able to curb the exponential spread of this novel pathogen in some areas of the world, the virus is continuing to infect millions of people worldwide leading to immense morbidity and mortality, and profound economic and societal damage.

SARS-CoV-2 is a member of the coronavirus family, which includes some highly pathogenic viruses such as SARS-CoV (Severe Acute Respiratory Syndrome virus; (Drosten et al. 2003) and MERS-CoV (Middle Eastern Respiratory Syndrome virus; (Zaki et al. 2012) but also less pathogenic viruses such as the common-cold coronaviruses (229E, NL63, OC43 and HKU1), which are endemic seasonal pathogens of mild upper respiratory infections (Galanti et al. 2019). Coronaviruses are positive-strand non-segmented RNA viruses, with a range of host and tissue tropisms and the potential for cross-species transmission (Masters 2006). SARS-CoV-2 was named due to its relatedness to its closest phylogenetic relative within the coronavirus family, SARS-CoV, a virus that was causative for the

first global viral pandemic of the 21st century in 2002-2003. Like SARS-CoV, SARS-CoV-2 is thought to have originated in bats from which it has made its way into humans probably via an as of yet indeterminate intermediary. Moreover, like SARS-CoV it has been shown to be able to bind to human ACE-2, facilitating its tropism for the mucosa of the upper and lower respiratory tract (Walls et al. 2020), where both pathogens exert their primary clinical pathology.

Infection with SARS-CoV-2 can lead to a wide variety of clinical outcomes (Guan et al. 2020; Richardson et al. 2020). The vast majority of infected individuals develop only mild symptoms akin to a common cold. Some individuals, however, particularly those who are elderly and/or have comorbidities can progress to a more severe phenotype, which primarily manifests as pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS), but can also impair other organ systems such as the vasculature, the heart, kidneys, and the central and peripheral nervous system among others. Severe COVID-19 disease often requires hospitalization, oxygen supplementation, mechanical ventilation and other organ replacement therapy warranting admission to an intensive care unit. Moreover, a significant fraction of severe COVID-19 cases eventually succumb to the disease, despite maximal treatment with literature reports of mortality rates varying between 10 and 90 percent (Docherty et al. 2020; Grasselli et al. 2020; Richardson et al. 2020).

While some risk factors for progression to severe disease, such as older age, cardiovascular disease, hypertension, obesity, diabetes mellitus, chronic lung/kidney disease and malignancy have emerged, it is far from clear how to predict such adverse outcomes (Williamson et al. 2020). Moreover, a significant proportion of the global population possesses above mentioned risk factors making them particularly vulnerable to an adverse course of disease. Therefore, there is a dire need to rapidly develop therapeutic and prophylactic medicines to prevent severe disease and to protect those most at risk.

Innumerable efforts are being undertaken to characterize the human immune responses and develop vaccines to SARS-CoV-2. Especially the quality and duration of the humoral immune response following natural infection with SARS-CoV-2 is of great importance.

Under protocol DRO-1006, our group began to study the humoral immune responses of a cohort of 149 COVID-19 convalescent individuals using samples collected an average of 39 days after the onset of symptoms. These early studies showed that the initial humoral responses to SARS-CoV-2 are highly variable and that 33% of affected individuals failed to develop neutralizing activity above a median geometric mean half-maximal neutralization titer (NT_{50}) of 50 (Robbiani et al. 2020). However, despite overall low plasma titers, antibody sequencing revealed expanded clones of receptor binding domain (RBD)-specific memory B cells expressing closely related antibodies in different individuals. Antibodies targeting three distinct epitopes on the RBD of the SARS-CoV-2 spike protein were identified, and some of these showed in vitro half-maximal inhibitory concentrations (IC_{50} values) as low as single digit nanograms per milliliter.

Little is known about the dynamic and durability of the humoral immune responses to SARS-CoV-2 and longitudinal studies that test the evolution of antibodies in circulating memory B cells are currently under way.

The contribution of T cells to SARS-CoV-2 immunity is yet another unresolved question. Declining peripheral blood lymphocyte counts have been observed during acute infection and found to be correlated with disease severity. This may reflect direct cytotoxic effects of the virus or rather a redistribution of lymphocytes to the lung tissue in the setting of an excessive inflammatory response (Giamarellos-Bourboulis et al. 2020). An exuberant inflammatory response seems to dominate the pathogenesis of the later stages of severe COVID-19, and increases in key inflammatory markers such as CRP, Ferritin and IL-6 have been reported. Cytokine blocking therapy (i.e. Tocilizumab) and immune suppressive therapy with systemic glucocorticoids (ie dexamethasone) have shown some promise for patients with severe late stage disease, but prognosis often remains dismal (Group et al. 2020). It is currently unclear whether the immune pathology observed in severe COVID-19 is intrinsic to this virus or whether the inability to clear the pathogen in a timely manner leads to an overwhelming and deleterious immune activation. However, it appears plausible that prevention of infection or swift clearance of infection by the adaptive immune system may prevent or curtail such phenomena.

While cellular immunity can play an ameliorating role once an infection is established, in order to achieve sterilizing protection from SARS-CoV-2 infection, neutralizing antibodies are essential. Historically, this has been illustrated by the fact that most licensed vaccines are thought to exert their preventative effects through neutralizing antibodies and even for immunity established via natural infection, antibodies are the best characterized correlates of protection from future infection (Plotkin 2010). COVID-19 antibody therapy in the form of polyclonal plasma from convalescent individuals is currently being explored as a therapeutic option and it has even been granted an emergency use authorization (EUA) by the FDA on August 23, 2020. However, therapy with convalescent plasma has not yet shown efficacy in randomized-controlled trials.

Highly potent neutralizing monoclonal antibodies (nAbs) against SARS-CoV-2 have several advantages compared to convalescent plasma: they can be titrated to concentrations of known neutralizing activity, they have less potential for off-target binding and subsequent immune pathology (ie Transfusion-related acute lung injury (TRALI)), and they show less of the therapeutic variability that is inherent to polyclonal remedies.

To this date, there are close to 100 FDA-approved mAbs for treatment or prevention of cancer, autoimmune diseases, infectious diseases and other conditions. Palivizumab, for example, a humanized monoclonal antibody (IgG) directed against the fusion protein of respiratory syncytial virus (RSV), is the first monoclonal antibody approved for clinical use against an infectious pathogen and it is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children. Another example which illustrates the utility of nABs against viruses, particularly the possibility for rapid development in the face of an emerging infection, is the 2014-2016 Ebola epidemic. While an initial trial of a triple monoclonal antibody cocktail, ZMapp, did not meet its efficacy endpoints (Group et al. 2016), a subsequent RCT showed superior results for day 28 mortality for Inmazeb/REGN-EB3 (a triple nAb cocktail), leading to approval by the FDA in October 2020.

The use of broadly neutralizing monoclonal antibodies (bNAbs) against HIV is yet another example illustrating the clinical translation of monoclonal antibodies to treat or prevent infectious disease. During the first decade of the 21st century, trials of first-generation bNAbs (such as 2G12, 4E10, 2F5) found them to be safe and well tolerated, but showed rather limited effects on delaying viral rebound during analytical treatment interruption of ART (Mehandru et al. 2007; Trkola et al. 2005). It was not

until the advent of single-cell cloning techniques (Scheid et al. 2009; Tiller et al. 2008) which allowed for the identification and isolation of rare but extremely potent second-generation antibodies. Some of these new antibodies showed remarkable *in vitro* neutralizing activity and breadth (over 90% of pseudoviruses from diverse clades), even at low concentrations (Klein et al. 2013; West et al. 2014) and made their way into clinical trials. Three well characterized bNAbs VRC01, 3BNC117 (targeting the CD4 binding site on the HIV envelope gp120 glycoprotein), and 10-1074 (targeting the V3 epitope of the HIV envelope) were able to significantly suppress plasma viral loads in viremic individuals when given as monotherapy (Caskey et al. 2015; Caskey et al. 2017; Lynch et al. 2015). Repeated infusions of the combination of 3BNC117 and 10-1074 in people living with HIV (PLWH) during analytical treatment interruption (ATI) of ART maintained viral suppression for a median of 15 weeks after last antibody infusions and prevented selection of escape variants while therapeutic antibody levels were maintained (Mendoza et al. 2018). These anti-HIV-1 antibodies were further modified to include amino acid mutations in the Fc region to extend biological half-lives ("LS" mutations). Studies to date demonstrate that the modified antibodies demonstrate similar safety profiles to the unmodified variants (Gaudinski et al. 2018; Gaudinski et al. 2019) and NCT03254277, NCT03554408).

Taken together, passive administration of neutralizing antibodies holds great clinical promise for the prevention and treatment of COVID-19. Monoclonal antibodies may prove to be particularly useful in preventing SARS-CoV-2 infection in populations who may not mount protective immune responses to vaccination (e.g. advanced age, immunocompromise) and as post-exposure prophylaxis in individuals at high risk to develop severe COVID-19. Several monoclonal anti-SARS-CoV-2 antibodies have been isolated by multiple groups and have entered clinical testing, including progression to efficacy phase 2/3 studies for both prevention and therapy.

This first-in-human study aims to evaluate the safety, tolerability and pharmacokinetics of two highly potent human monoclonal antibodies, C135-LS and C144-LS, that target distinct neutralizing epitopes on the RBD of the SARS-CoV-2 spike glycoprotein in healthy volunteers.

3.2 Preclinical Characterization

3.2.1 Identification of C135 and C144 and in vitro characterization

C-135 and C-144 were identified and cloned at the Rockefeller University from two individuals who recovered from Coronavirus Disease 2019 (COVID-19).

Briefly, individual B lymphocytes with receptors that bound to the SARS-CoV-2 receptor binding domain (RBD) were isolated by flow cytometry from blood samples of COVID-19 convalescent individuals. Paired IgG heavy and light chain (IGH and IGL) paired sequences were obtained by reverse transcription and subsequent PCR from individual RBD-binding B cells, and a subset of representative antibodies were expressed. The selected antibodies were tested for binding to SARS-CoV-2 RBD by ELISA and for *in vitro* neutralizing activity against a SARS-CoV-2 pseudovirus and against authentic SARS-CoV-2.

C135 and C144 showed exceptional neutralizing activities against authentic SARS-CoV-2 (strain USA-WA1/2020): C135 showed an IC_{50} of 2.98 ng/ml and C144-LS showed an IC_{50} of 2.55 ng/ml (Figure 1**,** (Robbiani et al. 2020).

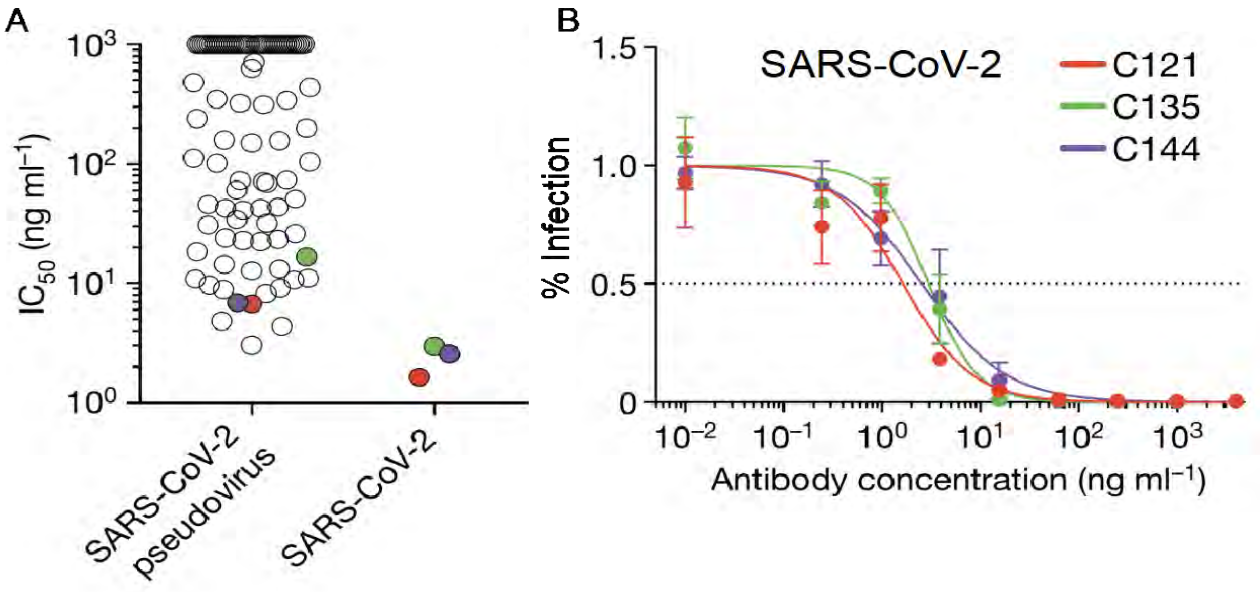

Figure 1. In vitro neutralizing activity of selected anti-SARS-CoV-2 antibodies

(a) Graph shows IC_{50}s for antibodies assayed in an in vitro neutralization assay against SARS-CoV-2 pseudovirus or against authentic SARS-CoV-2 (strain USA-WA1/2020), (b) shows authentic SARS-CoV-2 neutralization curves. Infected cells (Y axis) vs. titration of monoclonal antibodies C121, C135 and C144 in two independent experiments.

3.2.2 *In vitro* characterization of C135 and C144

The spike (S) protein of SARS-CoV-2 is a trimeric viral glycoprotein that is responsible for mediating binding to the angiotensin-converting enzyme 2 (ACE2) receptor, enabling viral entry into host cells and subsequent pathology. The S trimer is comprised of 3 copies of the S1 subunit containing the receptor-binding domain (RBD) and 3 copies of the S2 subunit, which includes the fusion and transmembrane domains. As with other coronaviruses, the RBD of SARS-CoV-2 displays steric flexibility. The RBD can present in an “up” conformation enabling it to bind ACE2 or in a “down” conformation, in which the closed, pre-fusion S trimer cannot interact with ACE2. Functional assays and structural biology methods showed multiple non-overlapping antibody binding domains (Robbiani et al. 2020), delineating them into 4 classes of highly potent RBD-specific nAbs with distinct binding approaches to the RBD: (1) VH3-53 antibodies with short CDRH3s that block ACE2 and bind only to "up" RBDs, (2) ACE2-blocking antibodies that bind both "up" and "down" RBDs and can contact adjacent RBDs, (3) nAbs that bind outside the ACE2 site and recognize "up" and "down" RBDs, and (4) other antibodies that do not block ACE2 and bind only "up" RBDs (Barnes, Jette, et al. 2020; Barnes, West, et al. 2020).

C144 is a class 2 antibody using the VH3-53 heavy chain gene with a relatively long CDRH3. It can bind to the RBDs of an S trimer in both the “up” and “down” confirmation, thus conferring the ability to attach to the spike of SARS-CoV-2 in various steric configurations. Moreover, the exact epitope of

C144 has been shown to overlap with the binding site for ACE2. This direct competition with ACE2 could partially explain its potency in neutralizing SARS-CoV-2. An additional aspect contributing to the exceptional neutralizing capacity of C144 is the aforementioned length of its CDR3H, which enables it to bridge between adjacent "down" configurated RBDs, thus locking the S trimer in a closed, prefusion conformation that is unable to engage ACE2.

C135 is a class 3 antibody of exceptional neutralizing potency *in vitro*. Its binding mechanism is distinct from C144. C135 recognizes a glycopeptide epitope on a region of the RBD near the N343$_{RBD}$ glycan and non-overlapping with the ACE2 binding site. Importantly, there is no steric competition for binding to monomeric RBD between C144 and C135, suggesting that both antibodies can bind to and neutralize SARS-CoV-2 when given in combination.

The distinct binding characteristics of C144 and C135 to the RBD of SARS-CoV-2 suggest that concurrent administration of the two antibodies could have additive neutralizing effects *in vivo* and would likely confer some degree of protection from viral escape mutations. In fact, *in vitro* experiments with a replication-competent recombinant vesicular stomatitis virus (VSV) pseudotyped with the S proteins of SARS-CoV-2 showed that escape mutations are selected in the presence of either C144 or C135 alone, but selection does not occur with the antibody combination (Figure 2, see the Investigator's Brochure) (Weisblum et al. 2020).

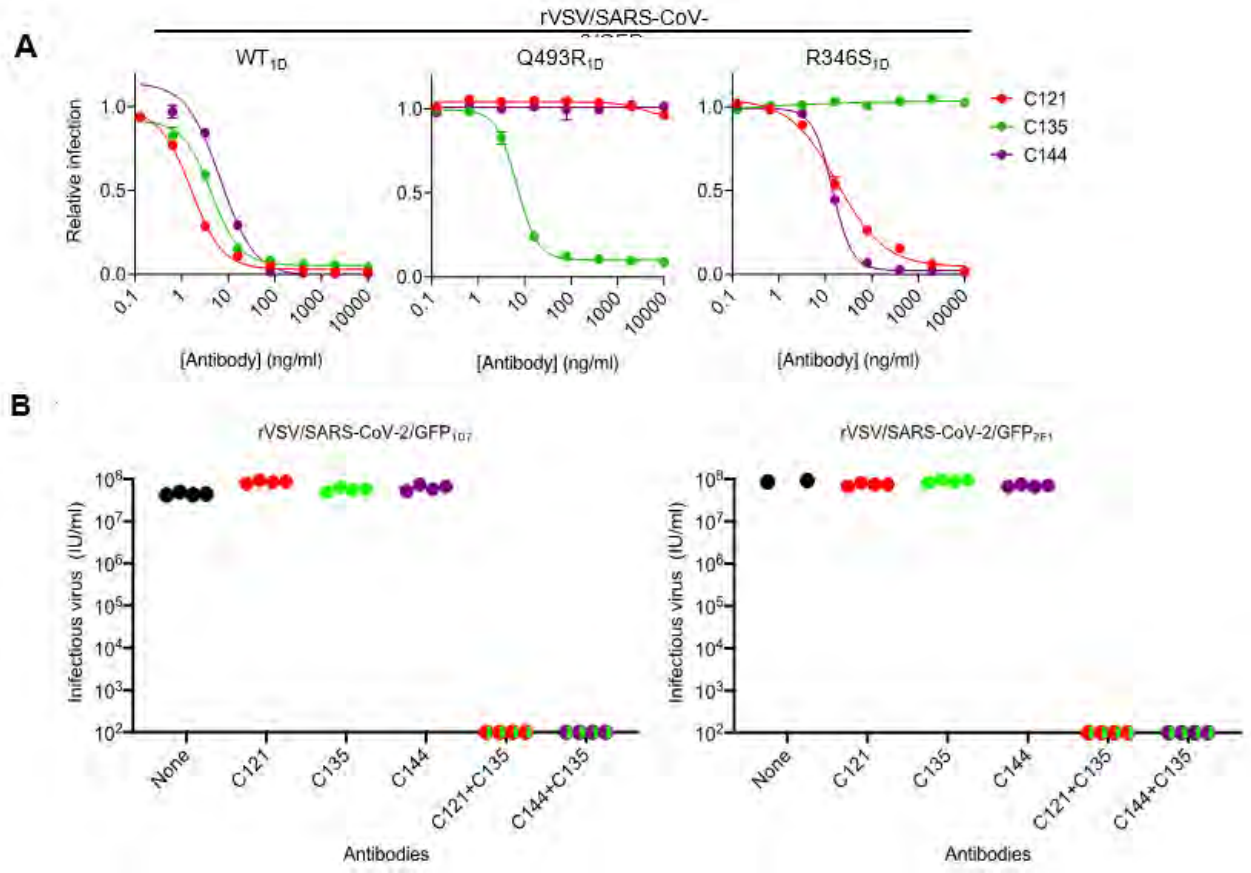

Figure 2. SARS-CoV-2 antibody combinations suppress the selection of antibody resistance

(A) Examples of neutralization resistance of rVSV/SARS-CoV-2/GFP mutants that were isolated following passage in the presence of antibodies. 293T/ACE2cl.22 cells were inoculated with WT or mutant rVSV/SARS-CoV-2/GFP in the presence of increasing amount of each monoclonal antibody, and infection quantified by FACS 16h later. Mean and SD from two independent experiments. (B) Infectious virus yield following two passages of rVSV/SARS-CoV-2/GFP in the absence or presence of individual neutralizing antibodies or combinations of two antibodies. Titers were determined on 293T/ACE2cl.22 cells. Each symbol represents a technical replicate and results from two independent experiments using rVSV/SARS-CoV-2/GFP1D7 and rVSV/SARS-CoV-2/GFP2E1 are shown.

3.2.3 *In vitro* characterization of C135-LS and C144-LS

The original C135 and C144 antibodies were modified by two single amino acid modifications (M428L/N434S) in the Fc domain to extend the antibodies' half-lives. The "LS mutations" increase the binding affinity of the antibody to FcRn, which in turn protects the bound antibody from degradation in lysosomes. These substitutions at the Fc positions do not alter the antibody-antigen binding domain or its neutralizing activity. Moreover, C135-LS and C144-LS have preserved Fc effector functions. *In vitro* experiments show that both antibodies can mediate antibody-dependent cellular cytotoxicity (ADCC), similarly to the unmodified C135 and C144 (see the Investigator's Brochure).

Several LS-modified antibodies are in clinical development for different indications, including HIV-1 therapy and prevention. In general, the LS variants have approximately 3-fold longer half-lives in comparison to the non-LS molecules, while maintaining similar safety and antiviral activity profiles (Gaudinski et al. 2018; Gaudinski et al. 2019), and NCT03254277, NCT03554408).

3.2.4 *In vivo* characterization of C135-LS and C144-LS

3.2.4.1 Preclinical studies in mice

The pharmacokinetics of C144-LS and C135-LS were evaluated in transgenic mice expressing human FcRn. These mice carry a null mutation for the mouse FcRn gene and a transgene expressing the human FcRn α-chain. Following a single intravenous dose of 0.5 mg, the estimated half-life of C135-LS was 4.3 days and of C144-LS was 8.2 days. In comparison, the anti-HIV-1 antibody 10-1074-LS, used as control, showed an estimated half-life of 9.2 days in this model and has shown a half-life of approximately 80 days in humans.

The C144-LS and C135-LS antibody combination was tested for activity *in vivo* against a mouse adapted strain of SARS-CoV-2. The antibodies were initially tested for neutralizing activity against pseudoviruses expressing the mouse adapted S protein on tissue culture cells expressing mouse ACE-2. The neutralizing activity of the 2 antibodies against the mouse adapted SARS-CoV-2 was very similar to that against authentic SARS-CoV-2. C135-LS showed an IC_{50} of 6.9 ng/mL and C144-LS showed an IC_{50} of 3.2 ng/mL.

The antibody combination was delivered intraperitoneally at different dose levels ranging from 1.8 to 16 mg/kg of total antibody (i.e. 0.9 to 8 mg/kg of each mAb) (Figure 3). The mice were challenged

with 10^5 plaque forming units (PFUs) of mouse-adapted SARS-CoV-2 intranasally 12 hours after antibody injection. Lung titers were measured by plaque forming units per lung lobe 2 days post infection, which is the kinetic peak of viral replication in this model. As expected, the isotype control antibody failed to reduce virus replication. The C135/C144 combination protected all but one animal at doses of 5.3 and 16 mg/kg of total antibody (i.e. 2.65 or 8 mg/kg each mAb). The remaining mouse showed low but measurable virus titer. Notably, the 1.8 mg/kg dose of the combination (i.e. 0.9mg/kg each mAb) significantly reduced titers as compared to isotype control antibody but was not as effective as 5.3 or 16 mg/kg of total antibody (Schafer et al. 2020).

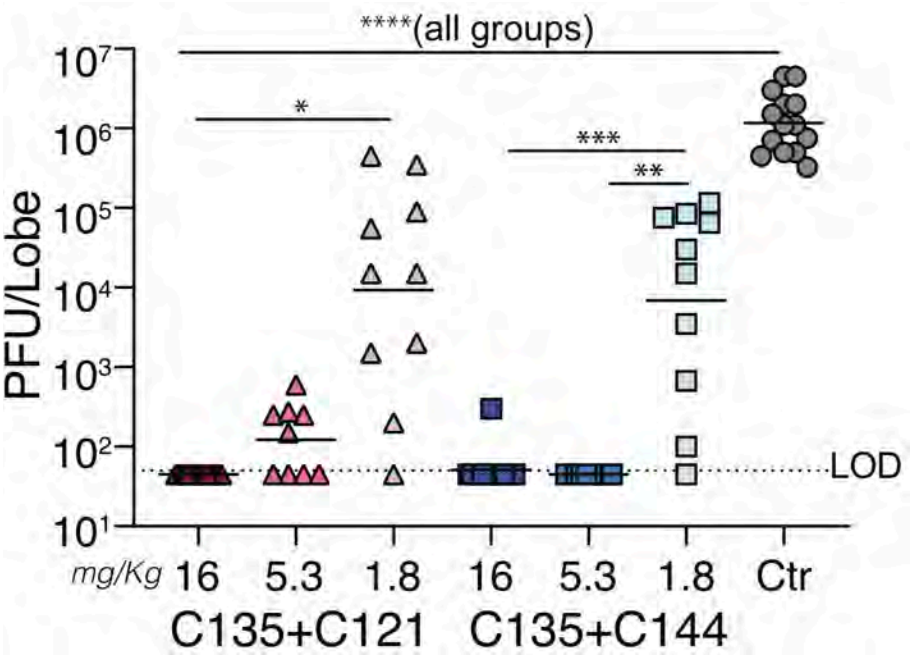

Figure 3. Antibody combinations synergize to increase in vivo potency.

SARS-CoV-2 MA lung titer following antibody prophylaxis with isotype control or combinations of C135+121 or C135+C144 mixed at a ratio of 1:1 for combined dose levels of 16, 5.3 or 1.8 mg/Kg. Antibodies were delivered intraperitoneally 12hr prior to infection with 1x105 PFU of SARS-CoV-2 MA. Combined data from two independent experiments is shown. For 16mg/kg groups, N = 14-15 mice and all other groups were 9-10 mice/group. The line is at the geometric mean and each symbol represents the titer for a single animal. Asterisks indicate statistical differences as compared to isotype control by one-way ANOVA with a Dunnet's multiple comparison test or ANOVA with a Tukey's multiple comparison test.

Virus neutralization *in vitro* is independent of antibody Fc effector functions that impact *in vivo* efficacy against other viral infections. The loss of Fc-effector function by the introduction of mutations in the Fc domain of selected SARS-CoV-2 antibodies significantly decreased the protective activity against mouse-adapted SARS-CoV-2 *in vivo* ((Schafer et al. 2020), see Investigator's Brochure). C135-LS and C144-LS do not contain mutations that interfere with Fc effector functions.

3.2.4.2 Preclinical studies in hamsters

The combination of C144-LS and C135-LS was administered intraperitoneally to hamsters 24 hours prior (prophylaxis) or 12 hours after (treatment) intranasal challenge with 10^4 Plaque forming units (PFU) of the WA1-2020 isolate of SARS-CoV-2. Three groups of four hamsters each received doses of 2, 6 and 20 mg/kg of total antibody for prophylaxis (i.e. 1, 3 and 10 mg/kg each mAb) and 4, 12 and 40 mg/kg of total antibody for treatment (i.e. 2, 6 and 20 mg/kg each mAb), respectively (Figure 4). SARS-CoV-2 lung titers were determined by plaque assay three days after viral challenge. While all animals in the control group showed high level viral infection (PFUs around 10^6), hamsters in prophylactic and therapeutic medium and high dose antibody combination groups showed complete absence of viral infection with one exception in the therapeutic 20mg/kg dose group. In the prophylaxis low dose group (2 mg/kg) 3 out of 4 animals achieved protection, and in the therapy low dose group (4 mg/kg of each antibody) all animals had undetectable or very low virus titers.

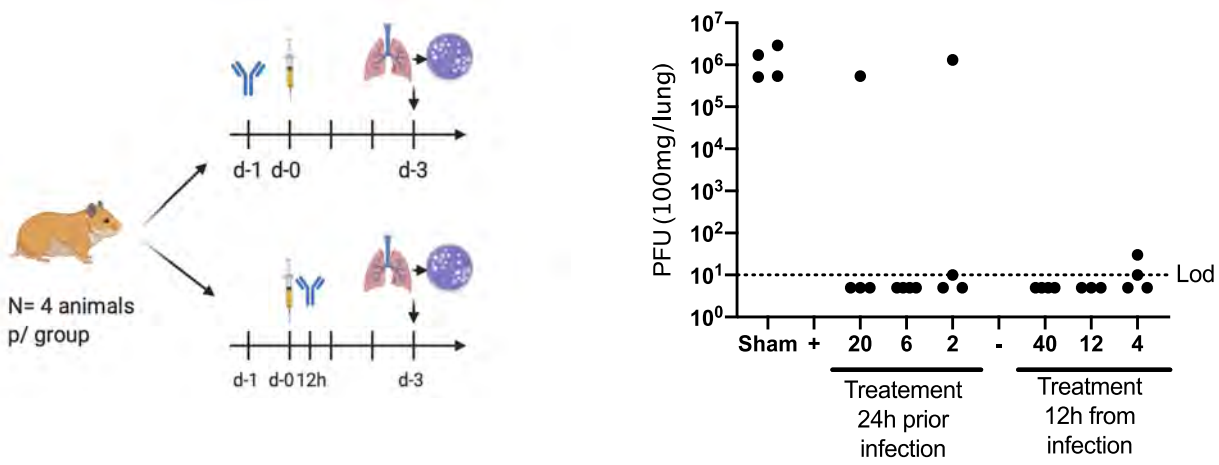

Figure 4. Evaluation of C144-LS and C135-LS for prophylactic and therapeutic efficacy against SARS-CoV-2 infection in Hamsters

Hamsters were administered with the antibody combination either 24h prior or 12h after viral challenge. Viral infection in the lung was measured by plague assays three days after viral challenge. The graph shows the number of plaque forming units for the control and different therapeutic (4, 12 and 40 mg/kg of total antibody) or prophylactic (2, 6 and 20 mg/kg of total antibody) dose groups respectively. (Lod=Limit of detection).

3.2.4.3 Preclinical studies in non-human primates

The combination of C144-LS and C135-LS was administered intravenously to 3 Indian origin rhesus macaques at a dose of 10 mg/kg of each antibody. The average neutralizing antibody concentration in plasma on day 10 after injection was 120 mcg/mL, which is about 2,000 times higher than the IC_{90} neutralization titer for the C144 plus C135 combination against SARS-CoV-2 pseudovirus (IC_{90} 61.02 ng/mL). In rhesus macaques, the estimated average half-life of the C144-LS plus C135-LS combination was approximately 46 days.

The combination of C144-LS and C135-LS was administered intravenously to rhesus macaques 24 hours prior to intranasal, intratracheal and intraocular challenge with $2x10^6$ Plaque forming units (PFU) of SARS-CoV-2. Three groups of four animals each received doses of 2, 6 and 20 mg/kg of total antibody (i.e. 1, 3 and 10 mg/kg of each mAb). SARS-CoV-2 genomic and subgenomic viral copies were determined from sequential nasopharyngeal swabs over the course of seven days after viral challenge. While genomic viral copies can detect the presence of residual challenge virus, subgenomic viral copies are a measure of *de novo* replication in infected animals. Levels of genomic viral copies were lowest in the animals that received the high dose antibody combination. More importantly, all animals in the control group showed high levels of viral copies (around 10^5), whereas all but two macaques in the lowest dose group showed sterilizing protection and absence of productive viral infection as determined by subgenomic viral copies (Figure 5).

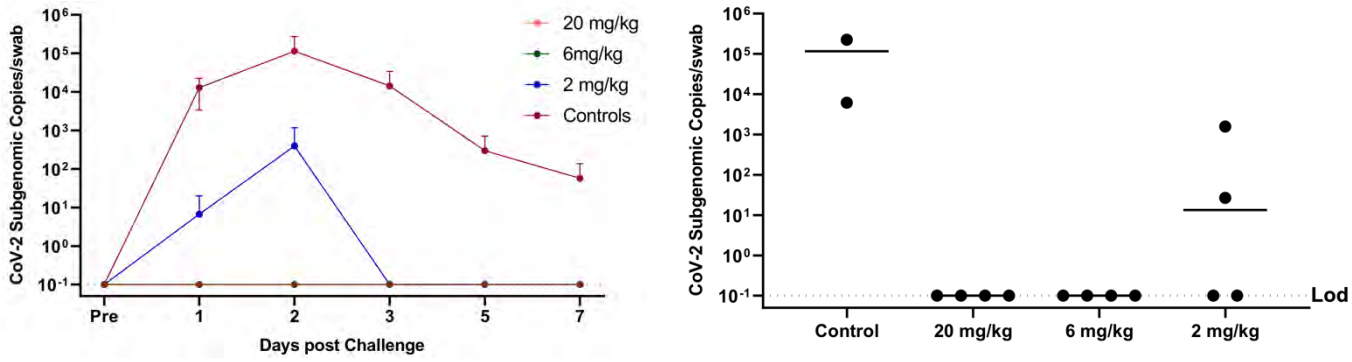

Figure 5. C144-LS and C135-LS for prophylaxis against SARS-CoV-2 infection in macaques

The antibody combination was administered intravenously to rhesus macaques 24h prior to viral challenge. Subgenomic viral copies were measured from nasopharyngeal swabs over the course of 7 days after challenge. The graph shows the number of subgenomic viral copies for the control and different dose groups (2, 6 or 20 mg/kg of total antibody) respectively. (Lod = Limit of detection)

In a separate experiment, the combination of C144-LS and C135-LS was administered intravenously to rhesus macaques 24 hours after intranasal, intratracheal and intraocular challenge with $2x10^6$ Plaque forming units (PFU) of SARS-CoV-2. Three groups of four animals each received either placebo, low dose (12 mg/Kg) or high dose (40 mg/kg) of the antibody combination (i.e. 6 or 20 mg.kg of each mAb). The animals were euthanized at 7 days after infection. Microscopic lung sections were blinded and assessed by two independent pathologists for different grades of pneumonitis based on the depicted grading system. While the placebo control group showed high levels of pneumonitis (average grade around 2.7), the animals that received the antibody combination showed significantly lower grades of pneumonitis with the high dose group (40 mg/kg of total antibody) demonstrating the lowest grades (average grade around 1). (Figure 6).

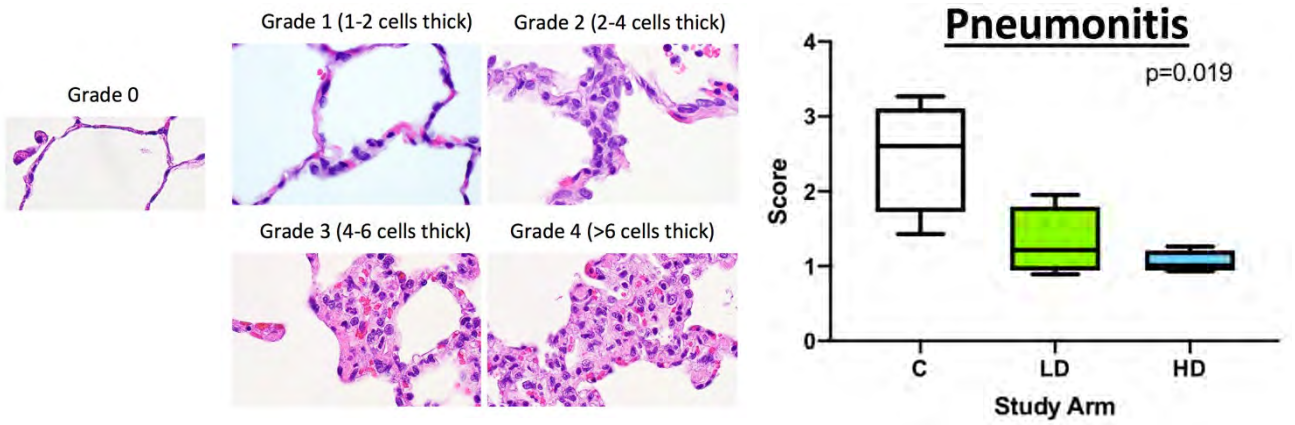

Figure 6. C144-LS and C135-LS for therapy of SARS-CoV-2 infection in macaques

Four macaques in each group were administered either with placebo (control), the antibody combination at low dose (12 mg/kg) or high dose (40 mg/kg) at 24 hours after intranasal, intratracheal and intraocular viral infection. Microscopic lung sections were blinded and assessed by two independent pathologists for different grades of pneumonitis based on the depicted grading system. The box plots on the right show the grades of pneumonitis of hundreds of lung sections from macaques of respective control or dose groups.

In summary, C135-LS and C144-LS are highly potent broadly neutralizing anti-SARS-CoV-2 RBD antibodies with evidence of significant *in vivo* activity in several relevant animal models. A single infusion of C135-LS and C144-LS prevented infection with a mouse-adapted SARS-CoV-2 strain in mice. In hamsters and non-human primates, the C135-LS/C144-LS combination conferred protection and rapid improvement or clearance of infection when administered intravenously before or within 24 hours after SARS-CoV-2 challenge. Overall, it is expected that C135-LS and C144-LS may provide protection against infection from SARS-CoV-2 and accelerate viral clearance and disease resolution in SARS-CoV-2-infected individuals.

3.2.5 Toxicology studies

The tissue cross-reactivity studies showed cytoplasmic binding to isolated tissues in both rat and human tissue panels. Since C135-LS and C144-LS are antibodies to an infectious disease antigen, no on-target binding in these tissue panels was expected. As such, observed binding was concluded to be off-target but was limited to binding in the cytoplasmic space. Monoclonal antibody binding to cytoplasmic sites in tissue cross-reactivity studies generally is considered of little to no toxicologic significance due to the limited ability of antibody therapeutics to access the cytoplasmic compartment *in vivo*.

The combination of C135-LS and C144-LS was evaluated for safety in a multidose study in Sprague Dawley rats. The purpose of this study was to evaluate the systemic toxicity, local tolerability, toxicokinetics and immunogenicity of C135-LS and C144-LS when administered twice weekly intravenously (IV) at doses ranging from 6 to 120 mg/kg of the combination, or subcutaneously (SC) at 30 mg/kg for 4 weeks (total of 8 doses) to Sprague Dawley rats, and to assess the reversibility or persistence of effects following a 47-Day recovery period. At the time of the IND submission only data from the dosing period were available, and conclusions should be viewed as interim. A summary of available data is included in Investigator's Brochure (Section 4.7 Nonclinical Toxicology).

3.3 Clinical experience

3.3.1 Anti-SARS-CoV-2 antibodies to treat or prevent infections

This is the first-in-human study of C135-LS and C144-LS, however passive administration of anti-SARS-CoV-2 antibodies is currently being evaluated in humans under multiple studies, including phase 2/3 efficacy studies.

Important caveats to the use of antibody therapies are whether they can be detrimental to endogenous responses or elicit antibody dependent enhancement (ADE). ADE consists on Fc receptor-mediated enhanced infection and it was first described in Dengue infection (Halstead and O'Rourke 1977), and later suggested for SARS-CoV (Yilla et al. 2005) and MERS (Zhou et al. 2014). Preliminary reports of vaccinated NHP do not support ADE in SARS-Cov-2 infection (Gao et al. 2020), and COVID-19 convalescent plasma therapy appears to be safe ((Joyner et al. 2020), discussed in detail below).

In the absence of alternative treatment strategies, convalescent plasma therapy was one of the first emergency approaches to enter clinical trials and to gain Emergency Use Approval by the FDA. On September 06, 2020 Joyner et al reported safety information on 20,000 hospitalized COVID-19 patients who received convalescent COVID-19 plasma. The incidence of all serious adverse events was low; these included transfusion reactions (1%), thromboembolic or thrombotic events (1%), and cardiac events (~3%). Notably, the vast majority of the thromboembolic or thrombotic events and cardiac events were judged to be unrelated to the plasma transfusion per se. The 7-day mortality rate was 13.0%, and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs 9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%). The authors concluded

that transfusion of convalescent plasma is safe in hospitalized COVID-19 patients. However, the observation that a significant proportion of convalescent COVID-19 donors have very low to undetectable neutralizing antibody responses poses an important technical challenge (Liu et al. 2020; Robbiani et al. 2020; Rogers et al. 2020) and may limit the efficacy of this approach.

In parallel to studies of convalescent COVID-19 plasma, several anti-SARS-CoV-2 mAbs have entered clinical testing in both therapeutic and preventative settings.

For example REGN-COV-2 (a combination of two mAbs), will be administered to approximately 2,000 asymptomatic adults who are household contacts of persons with SARS-CoV-2 infection. In addition to assessing safety, the trial will seek to define whether REGN-COV-2 can prevent disease symptoms in those already infected. The efficacy assessment will be a one-month period following administration of REGN-COV-2 or placebo. All trial participants will be followed for safety for seven months after efficacy assessment period ends. The study is ongoing (NCT04452318).

On November 10, the anti-SARS-CoV-2 mAb Bamlanivimab (LY-CoV555) was granted emergency use authorization (EUA) by the FDA. The antibody treatment was authorized for mild-to-moderate COVID-19 in adult and pediatric patients 12 years of age and older weighing at least 40 kilograms, and who are at high risk for progressing to severe COVID-19. The data supporting this EUA for Bamlanivimab are based on a phase two randomized, double-blind, placebo-controlled clinical trial in 465 non-hospitalized adults with mild to moderate COVID-19 symptoms. The trial participants received antibody doses ranging from 700 to 7,000 mg (the equivalent of 10 to 100 mg/kg for an average 70-kg of body weight) and the safety profile was similar in patients receiving any of the three Bamlanivimab doses (Food and Drug Administration (FDA) 2020).

3.3.2 Fc-modified antibodies to enhance binding to the FcRn receptor

VRC01LS is a human anti-HIV-1 CD4 binding site antibody that has been modified in the Fc region to include the LS substitutions (M428L/N434S), and is being evaluated for HIV-1 therapy and prevention. VRC01LS has been evaluated multiple clinical studies in HIV-infected (NCT02840474) and HIV-uninfected adults (NCT02599896, NCT02797171), and in infants (NCT02256631). VRC01LS showed good safety profile at intravenous doses ranging from 5, 20 or 40 mg/kg. Most reported AEs were of grade 1 severity. VRC01LS clearance rate was 36 ± 8 mL/d with an elimination half-life of 71 ± 18 days. VRC01LS retained its expected neutralizing activity in serum, and anti-VRC01 antibody responses were not detected (Gaudinski et al. 2018). 3BNC117-LS and 10-1074-LS, two other anti-HIV-1 long acting monoclonal antibodies, are in clinical development (NCT03254277, NCT03554408). Twenty-seven participants (6 HIV-infected individuals on suppressive ART) received 10-1074-LS at doses ranging from 150 mg or 300 mg SC up to 30 mg/kg IV, and 39 received 3BNC117-LS at the same dose levels. The admixture of the two antibodies has also been administered subcutaneously to 30 HIV-uninfected participants, and intravenously to 5 HIV-uninfected and 5 HIV-infected participants. Both intravenous infusions and subcutaneous injections have been well tolerated without Grade 3 adverse events or serious adverse events deemed possibly related to the antibodies reported to date. The safety profiles of the LS-variants so far are similar to the parental antibodies.

3.4 Hypothesis

The subcutaneous and intravenous administration of C144-LS and C135-LS in combination will be safe and well tolerated at the tested doses in healthy volunteers. The dose levels studied are expected to achieve protective or therapeutic levels of each antibody in serum (estimated as 1,000-fold the *in vitro* IC_{50} of each antibody against SARS-CoV-2).

3.5 Study Objectives

Primary objectives:

- To evaluate the safety and tolerability of subcutaneous injections or single intravenous infusions of C144-LS in combination with C135-LS in healthy volunteers.
- To evaluate the pharmacokinetic profile of C144-LS and C135-LS in combination, administered subcutaneously or intravenously at increasing dose levels in healthy volunteers.

Secondary objective:

- To assess the occurrence of anti-drug antibody responses.
- To evaluate serum neutralizing activity against SARS-CoV-2 after anti-C144-LS and anti-C135-LS administration.

3.6 Study Outcomes

Primary Outcomes:

- Rate of solicited and investigational product (IP)-related unsolicited adverse events that are Grade 2 and above (including confirmed laboratory abnormalities) 4 weeks after administration.
- Rate of solicited and IP-related unsolicited adverse events that are Grade 3 and above (including confirmed laboratory abnormalities) 4 weeks after administration.
- Proportion of participants with serious adverse events (SAEs) throughout the study period that are considered related to investigational product and their duration.
- The pharmacokinetic profile of C144-LS and C135-LS: elimination half-life (t1/2), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve.

Secondary Outcomes:

- Rate and severity of investigational product (IP)-related adverse events during study follow up.
- Frequency and levels of induced anti-C144-LS and anti-C135-LS antibodies in all study groups.
- Serum neutralizing activity against SARS-CoV-2 after C144-LS and C135-LS administration.

4 STUDY DESIGN

This proposed study is a first-in-human, single dose, dose-escalation phase 1 study to evaluate the safety and pharmacokinetics of a combination of two highly neutralizing anti-SARS-CoV-2 mAbs C144-LS and C135-LS in healthy volunteers.

The study consists of two parts.

Part A has a standard 3+3 phase 1 dose escalation design. Study participants will receive subcutaneous injections of C144-LS and C135-LS at 4ml (2ml or approximately 100mg of each antibody administered separately) or 8ml (4 ml or approximately 200mg of each antibody administered separately) or sequential intravenous infusions of C144-LS and C135-LS, each administered via a peripheral vein over 60 minutes at one of three increasing dose levels (1.5 mg/kg, 5 mg/kg and 15 mg/kg of each antibody)

Study participants in Part B will be randomized to receive subcutaneous injections of C144-LS and C135-LS at 8ml (approximately 200mg of each antibody administered separately) or placebo in a 3:1 ratio and double-blinded fashion.

Part A has started enrollment. Part B has a planned enrollment of 8 participants (see Table 1 and Scheme below).

Table 1. Study Groups

Part A – Open label

Group	Antibody	Dose	Route	Regimen	N
S1	C144-LS + C135-LS	100 mg each mAb	SC	Day 0	3+3
S2	C144-LS + C135-LS	200 mg each mAb	SC	Day 0	3+3
V1	C144-LS + C135-LS	1.5 mg/kg each mAb	IV	Day 0	3+3
V2	C144-LS + C135-LS	5 mg/kg each mAb	IV	Day 0	3+3
V3	C144-LS + C135-LS	15 mg/kg each mAb	IV	Day 0	3+3

Part B – Randomized, double-blinded

Group	Antibody	Dose	Route	Regimen	N
S3	C144-LS + C135-LS	200 mg each mAb or placebo	SC	Day 0	8 (6:2)

Following administration of the C144-LS and C135-LS antibody combination at one of three increasing dose levels, study participants will return for safety assessments on day 1, and weeks 1, 4, 8, 12, 18 and 24, 36 and 48 following antibody administration as indicated in the Time of Events Schedule **(**Appendix A, Time of Events Schedule).

Serum samples for Pharmacokinetic (PK) measurements will be collected before and at the end of each mAb administration and at multiple subsequent time points during study follow up, as indicated in the Time of Events Schedule (Figure 7, Appendix A). Assessments will also include measurement of anti-drug antibody (ADA) responses. All participants will be followed for 48weeks after C144-LS and C135-LS administration.

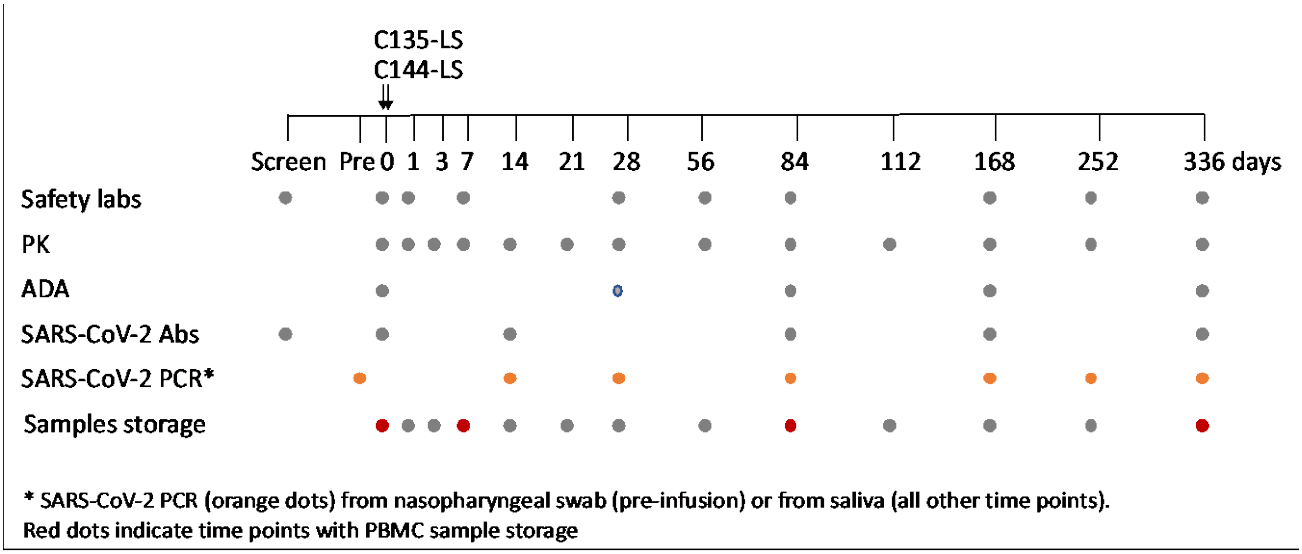

Figure 7. Schedule of Study Visits and Sample Collection

4.1 Dose Selection and Dose Escalation Plan

The proposed study doses were chosen based on *in vitro* and *in vivo* data that demonstrated the neutralizing potency of C144-LS and C135-LS in preclinical experiments in mice, hamsters and non-human primates. A protection experiment in mice challenged with a mouse adapted strain of SARS-CoV-2 intranasally showed that an equivalent dose of 2.65 mg/kg of each mAb led to sterile protection in 9 out 10 animals. In hamsters and non-human primates, prophylaxis and treatment experiments in animals challenged with SARS-CoV-2 showed that 3mg/kg of each antibody protected animals from infection, whereas 6 mg/kg of each antibody led to rapid improvement or clearance of infection

demonstrated by lower virus titers in lung tissue and lower pneumonitis scores in comparison to controls.

The planned starting dose in this first-in-human study is 1.5 mg/kg of each antibody (100mg of each antibody subcutaneously) and the target prophylactic dose is between 1.5 and 3mg/kg. It is expected that higher doses may be required for therapy. The target therapeutic dose at this time is 5 or 15 mg/kg of each antibody, if found to be safe and well tolerated. Similar and higher dose levels have been safely evaluated with anti-HIV-1 antibodies as well as with other anti-SARS-CoV-2 RBD monoclonal antibodies, according to publicly available data.

It is expected that a 15 mg/kg dose of each antibody will achieve peak serum levels of approximately 750 mcg/mL. Based on previous studies with anti-HIV-1-antibodies, it is expected that C144-LS and C135-LS will have a $t_{1/2}$ in humans of 60-80 days, and that serum concentrations will be maintained above 2.5 mcg/mL (or approximately 1,000 times the in vitro IC_{50} of either mAb) for approximately 12 months when C144-LS and C135-LS are administered at 15 mg/kg doses each.

Part A – Dose escalation phase

During the subcutaneous and intravenous dose escalation phase (Part A) of the study, enrollment will be staggered by 1 day for the volunteers of each group (Figure 8).

Subcutaneous (SC) Administration (Groups S1 and S2)

1. First, eligible participants will be enrolled in **Group S1** (C144-LS + C135-LS, 2mL each).
2. Enrollment in **Group S2** (C144-LS + C135-LS, 4mL each) will begin after all three participants enrolled in **Group S1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144- LS and/or C135-LS).
3. If 1 DLT occurs, 3 additional participants will enroll in **Group S1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed.
4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum subcutaneous tolerated dose (MTD).
5. Enrollment in **Group S2** will follow the same rules.

Intravenous (IV) Administration (Groups V1, V2 and V3)

1. Enrollment in **Group V1** (C144-LS + C135-LS, 1.5mg/kg each, IV) will begin at least 7 days after the first three participants enrolled in **Group S2.**
2. Enrollment in **Group V2** (C144-LS + C135-LS, 5mg/kg each, IV) will begin after all three participants enrolled in **Group V1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144-LS and/or C135-LS).
3. If 1 DLT occurs, 3 additional participants will enroll in **Group V1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed.
4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum intravenous tolerated dose (MTD).
5. Enrollment in **Group V3** (C144-LS + C135-LS, 15mg/kg each, IV) will follow the same rules.

6. Enrollment in **Group V3** will begin at least 7 days after three participants enrolled in **Group V2** and following SMC review of all available safety data.

The study investigators will review 1-week safety data prior to dose escalation in the subcutaneous groups (S1 and S2) and in the low and mid dose IV groups (V1 and V2). An external Safety Monitoring Committee (SMC) will review the 1-week safety data prior to dose escalation from the intravenous mid to the high dose groups step (V2 to V3). The SMC will provide a recommendation regarding enrollment in subsequent groups.

Note: As outlined in **Section 14.1**, the SMC will be asked to review safety data if one or more grade 3 or higher adverse events, deemed probably or definitely related to the study drugs (DLT) occur. No additional administration of the investigational products will take place pending a SMC review. In the event of a DLT, the SMC will make recommendations with regards to expansion of a study group from 3 to 6 participants, dose escalation to the next dose level, or halting additional enrollment.

Part B – Randomized, double-blinded phase

During the subcutaneous, randomized, double-blinded phase (Part B) of the study, enrollment will be limited to a maximum of two volunteers per day (Figure 8).

Enrollment in **Group S3** will begin once all participants in Part A have met eligibility criteria and have been scheduled for enrollment (day 0) and after all three participants enrolled in **Group S2** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group.

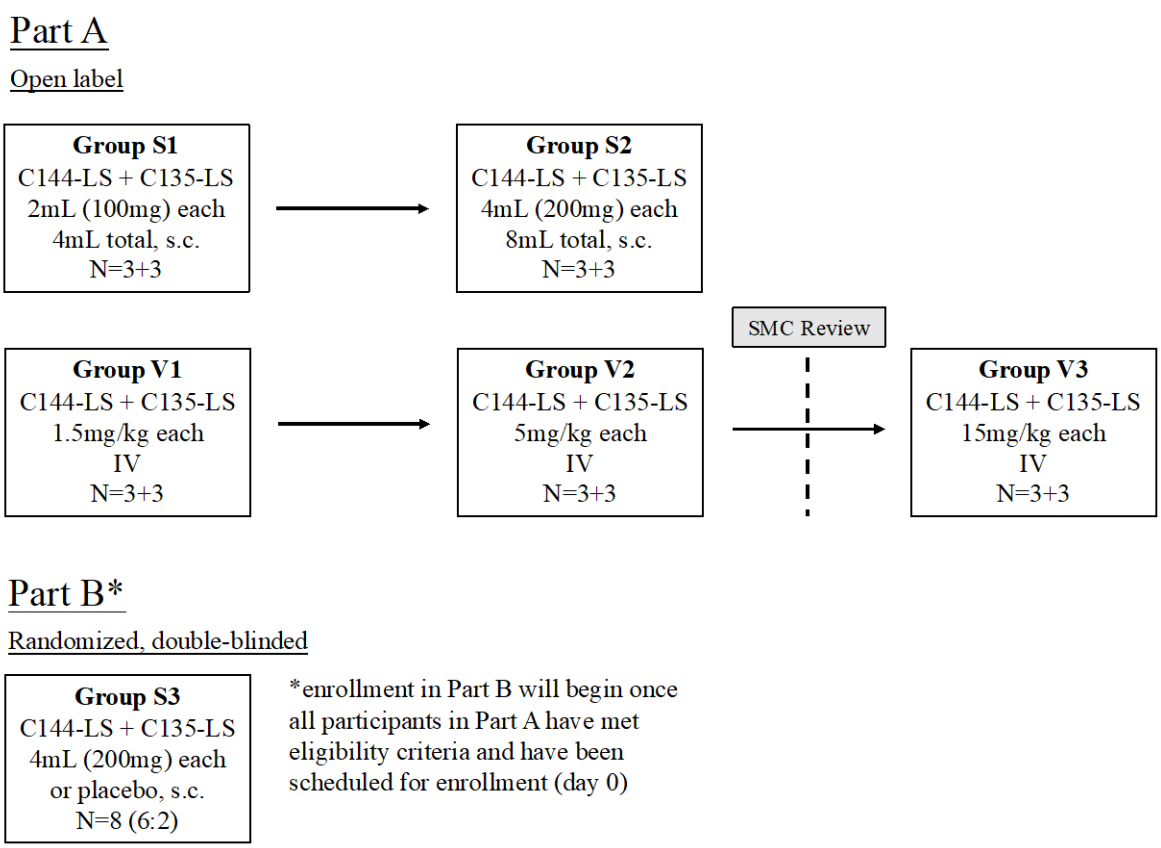

Figure 8. Study Scheme

4.2 End of the clinical trial

This clinical trial ends with the last participant's last visit.

5 STUDY POPULATION

5.1 Inclusion Criteria:

- Aged 18 to less than 65.
- If sexually active male or female, and participating in sexual activity that could lead to pregnancy, agrees to use one effective method of contraception from 10 days prior to the antibody administration until 6 months after IP administration.

Female study participants of reproductive potential are defined as pre-menopausal women who have not had a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy). Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 consecutive months.

5.2 Exclusion Criteria:

- Weight > 110 kg for groups S1 and S2 only
- History of prior positive SARS-CoV-2 RT-PCR or SARS-CoV-2 serology.
- Active respiratory or non-respiratory symptoms consistent with COVID-19.
- Medically attended acute illness or hospitalization (ie, >24 hours) for any reason within 30 days prior to screening.
- Acute exacerbation of a chronic pulmonary condition (eg, chronic obstructive pulmonary disease [COPD], asthma exacerbations, or uncontrolled hypertension, as defined by a systolic blood pressure > 180 and/or diastolic blood pressure > 120, in the presence or absence of anti-hypertensive medications) in the past 6 months prior to screening.
- Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.
- Other clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation.
- Are eligible for COVID-19 vaccination prior to your entry in the study according to local guidelines (e.g. healthcare professionals, non-healthcare professionals such as teachers, firefighters, public transit workers).
- Laboratory abnormalities in the parameters listed:
  - Absolute neutrophil count ≤ 1,500 K/mcL;
  - Hemoglobin ≤ 10.5 gm/dL if female; ≤ 11 gm/dL if male;
  - Platelet count ≤ 125,000 K/mcL;
  - ALT ≥ 1.25 x ULN; AST ≥ 1.25 x ULN;
  - Total bilirubin ≥ 1.25 x ULN;
  - Creatinine ≥ 1.1 x ULN;
- Pregnancy or lactation.
- Any vaccination within 14 days prior to SARS-CoV-2 mAbs administration (except influenza vaccine).
- History of prior therapy with any SARS-CoV-2 vaccine or antibodies, including convalescent plasma.
- Known allergy/sensitivity or any hypersensitivity to components of the investigational agents.
- History of severe reaction to a vaccine or monoclonal antibody administration or history of severe allergic reactions.
- Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.

6 METHODS AND PROCEDURES

The study will be conducted as a single-center study at the Rockefeller University Hospital, USA.

6.1 Screening Procedure and Study Visits

The Time of Events Schedule summarizes the frequency and timing of various study assessments. See Appendix A.

6.1.1 Pre-Screening

Potential participants will first undergo pre-screening by telephone to assess medical history and qualification for the study (e.g. review of ongoing medical conditions, current medications, previous history of COVID-19). Potential participants will have the opportunity to discuss the study and ask questions of the study recruiter at this time. Those who are eligible and interested in participation will attend a screening visit at the Rockefeller University Hospital (RUH) Outpatient Clinic.

6.1.2 Screening Visit

Initial Screening Visit:
Study personnel will answer any questions about the study. Written informed consent will be obtained prior to conducting any study procedures. The informed consent process may occur remotely (e.g. by telephone or zoom), if needed.

To ensure informed consent, the principal investigator or designee will discuss the following processes individually with each potential participant:

1. Risk-reduction counseling including safe-sex and pregnancy avoidance counseling;
2. That sexually active males and females, participating in sexual activity that could lead to pregnancy, should use one reliable form of contraception for the duration of the trial.

If the potential participant consents to participate, site personnel will:

- Perform complete medical history (including review of concomitant medication);
- Perform a general physical examination including height, weight, vital signs (pulse, respiratory rate, blood pressure and temperature), examination of skin, respiratory, cardiovascular and abdominal systems;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A),
- Perform a pregnancy test for female volunteers of reproductive potential.

If the initial screening visit occurs more than 70 days prior to date of the first C144-LS and C135-LS mAb administration, then study procedures for the screening visit must be repeated. The most recent set of procedures will be used if there is a discrepancy.

6.1.3 Pre-administration Visit

Obtain a nasopharyngeal or oropharyngeal swab for SARS-CoV-2 PCR testing, according to Appendix A.

Note: This sample may be collected at the screening visit if it is anticipated that enrollment will occur within 3 days from the screening visit.

6.1.4 C144-LS and C135-LS Administration Visit

- Study participants will be admitted to the RUH inpatient unit the night before or on the day of C144-LS and C135-LS administration.

Prior to drug administration, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data, including results of the SARS-CoV-2 PCR test;
- Review the informed consent form administered at screening visit with the participant;
- Perform a physical examination including weight, vital signs (pulse, respiratory rate, blood pressure and temperature) and any further examination indicated by history or observation;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- Perform pregnancy counseling;
- Perform a pregnancy test for all female volunteers of reproductive potential and obtain results prior to drug administration;
- Perform baseline assessment and record any systemic symptoms;
- C144-LS and C135-LS mAb will be prepared for administration according to the RUH Pharmacy Standard Operating Procedures;

- For the **subcutaneous administration**, C144-LS and C135-LS or placebo (buffered solution, Group S3) will be administered separately as two (approximately 100 mg of each mAb) or four 2 mL (approximately 200 mg of each mAb) injections at different sites in the abdomen, upper arms or thighs
- For the **intravenous administration**, C144-LS and C135-LS mAb will be administered via a peripheral vein over at least 60 minutes in sequential order. The IV line will be flushed with normal saline after infusion of C144-LS is completed and the participant will be observed for 1 hour before initiation of subsequent C135-LS infusion. If participants develop grade 3 acute infusion reaction, an immediate hypersensitivity reaction or a life-threatening event during C144-LS and C135-LS intravenous administration, the infusion will be discontinued and will not be reinitiated (see Section 6.1.7.1).
- For the SC groups, vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at end of mAb administration (+/- 5 minutes), 1 hour (+/- 10 min), 3 hours (+/- 10 min), 6 hours (+/- 10 min), 12 hours (+/- 10 min) post administration and prior to discharge from in-hospital observation.
- For the IV groups, vital signs will be checked at the end of each mAb infusion (+/- 5 minutes), and at 1 hour (+/- 10 min), 3 hours (+/- 10 min), 6 hours (+/- 10 min), 12 hours (+/- 10 min) after the C135-LS infusion and prior to discharge from in-hospital observation.
- Presence or absence of reactogenicity adverse events, as well as any other event that occurs, will be recorded 30 – 60 minutes after end of antibody dosing, as shown in the Time of Events Schedule (Appendix A).
- Rescue medications, including acetaminophen, diphenhydramine or an alternative antihistamine, epinephrine and glucocorticoids will be available in the RUH inpatient units for use if clinically indicated.
- For SC and IV groups blood samples for pharmacokinetics assessments will be collected (as indicated in Appendix A).

- Study participants will be discharged after at least 24 hours post C144-LS and C135-LS administration, after day 1 clinical assessment and study procedures have taken place. Hospital discharge will be delayed if clinically indicated.

Specific procedures to be performed at each treatment visit are illustrated in the Time of Events Schedule (Appendix A).

6.1.5 Post- C144-LS and C135-LS Administration Visits

Participants will be followed through study week 48.

At these follow up visits the following will be conducted:
- Review of interim medical history and use of concomitant medications;
- If symptoms are present, perform a symptom-directed physical examination;
- Local and systemic reactogenicity adverse events, as well as other adverse events, will be assessed;
- Pregnancy counseling;
- Vital Signs;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- In case of adverse event(s), the participant will be assessed and followed up by the clinical team. Supplemental visit(s) for further investigation can be planned at the discretion of the principal investigator or designee. Supplemental visit(s) may be recommended if clinically indicated or to clarify observations.

Specific procedures to be performed at each follow up visit are illustrated in the Time of Events Schedules (Appendix A).

Any abnormalities (adverse events) attributed to study drug, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

6.1.6 Final Visit/Early termination Visit

Assessments will be undertaken according to the Time of Events Schedule (Appendix A).

6.1.7 Discontinuation of study drug infusions and/or participant withdrawal from study

6.1.7.1 Discontinuation of study drug infusions

Antibody intravenous infusions will be discontinued for any of the following reasons:

1. Grade 3 acute infusion reactions that occur during infusion.
2. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal. edema; anaphylaxis; syncope).
3. Life threatening medical event during C144-LS and C135-LS infusion.

6.1.7.2 Withdrawal from the study (Participant Early Termination from study)

Participants may be withdrawn from the study permanently for the following reasons:

1. Participants may withdraw from the study at any time if they wish to do so, for any reason.
2. Following an adverse event at the discretion of the investigator (or designee).
3. Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
4. Participant judged by the investigator to be at significant risk of failing to comply with the protocol in a manner that might lead to harm to self or seriously interfere with the validity of the study results.
5. At the discretion of the FDA or investigator.

6.1.7.3 Follow up after withdrawal from study (Participant Early Termination from study)

Any adverse event resulting in withdrawal of a participant will be followed up until resolution or until the adverse event is judged by the principal investigator or designee to have stabilized where possible.

At the time of withdrawal, provided the participant is willing, all the requested termination visit procedures will be performed according to the Time of Events Schedule (Appendix A).

The date and reason for withdrawal from the study (early termination) should be collected and reported to the RU sponsor, SMC, and Rockefeller University IRB.

A pregnant participant will not receive the C144-LS and C135-LS administration. If pregnancy occurs after C144-LS and C135-LS administration, the participant will be followed until the end of the study and until delivery, if delivery occurs after the study has ended. Approximately 2-4 weeks after delivery, the baby will be examined by a pediatrician to assess his/her health status. The health status of the baby will be reported to the RU sponsor, Rockefeller University IRB, CRSO and the SMC.

6.1.7.4 Premature termination of trial

The RU sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer feasible. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial participants still under treatment at the time of termination must undergo a final examination which must be documented. The RU sponsor must be informed without delay if any investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial participant changes markedly
- It is no longer ethical to continue administration of the study drug
- The RU sponsor considers that the trial must be discontinued for safety reasons (e.g. on the advice of the SMC)
- It is no longer feasible to complete the trial
- The RU sponsor decides on whether to discontinue the trial in consultation with the and SMC.

6.1.8 Unblinding (Group S3)

Participants enrolled in Group S3 will be informed as to whether they received the study product or placebo 3 months after the participant study entry (day 0) and at least 1 month after all 8 participants enroll in Group S3.

Following unblinding, placebo recipients will remain in follow up for safety assessments. Samples will not be collected for research purposes following unblinding.

6.2 Study Procedures

6.2.1 Consent Procedure

Prior to the initiation of any study related procedures, the potential participants will be given a copy of the most recent IRB stamped and approved informed consent to read. Additionally, the PI or study staff member who has been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the participant. Participants will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the participant.

A private, confidential setting will be provided for the potential participant to read and discuss the informed consent free from coercion, undue influence or constraints of time. The informed consent process may occur remotely (e.g. by telephone or zoom), if needed.

All participants will be given a chance to ask questions and express concerns. They will be given the option to take the consent home and discuss it with family, friends, and /or health care providers. After a participant and the person conducting the consenting process sign and date the consent, the participant will be given a copy of the signed informed consent form.

A note will be written in the source document as to who obtained consent, how, when, were questions asked and answered, and that a copy of the informed consent was given to the participant.

The "Teach Back" method will be used in the clinical research setting to ask research participants to repeat or “teach back” the information, concepts and directions that the staff member has attempted to convey to the participant. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the participant's rights described in the Informed Consent process. This will be assessed with the questionnaire included in Appendix D, Assessment of Understanding Questionnaire.

6.2.2 Study Assignment

Part A: Enrollment will be open-label, and study participants will be enrolled sequentially as they meet enrollment criteria. The RUH pharmacist will dispense C144-LS and C135-LS according to the

study dose group. Over-enrollment will only be permitted to replace participants lost to follow up prior to week 2, as discussed in Section 8.2 Sample Size Considerations.

Part B: Enrollment in Part B will begin once all participants in Part A have met eligibility criteria and have been scheduled for enrollment (day 0). Participants will be randomized in a 3:1 ratio to receive the study drugs or placebo. Participants will be enrolled sequentially as they meet enrollment criteria, according to the randomization schedule.

Randomization will be performed by the Rockefeller University Hospital pharmacy. The 8 participants in S3 will be randomized in a ratio of 6 study drug recipients to 2 placebo recipients. Randomization will be generated using SAS 9.4. The study drugs or placebo preparation will be provided to the study nurses for injection under a coded, masked identification. The nurses, study staff, investigators, and participants will be blinded as to the identity of the study preparation. Participants in Part B will be unblinded according to Section 6.1.8. To accomplish this, study investigators will be provided with the randomization code and they will notify each participant. In the event of a medical emergency wherein knowledge of the treatment assignment will influence the participant's care, the Principal Investigator may unblind the treatment assignment.

6.2.3 C144-LS and C135-LS Administration Procedure

C144-LS and C135-LS will be provided in single-use vials containing 6 ml of the product at concentration of 50 mg/ml.

Part A

Subcutaneous administration:
The RUH research pharmacist will provide each study drug in a separate syringe ready for administration. The number of injections of C144-LS and C135-LS will follow study assignment: Group S1, 2 mL of C144-LS and 2 mL of C135-LS, separately. Group S2, 4 mL of C144-LS and 4 mL of C135-LS , separately. The total volume of the antibodies will be dispended in two (Group S1) or four (Group S2) separate syringes containing either C144-LS or C135-LS for administration in two or four separate sites, respectively. The antibodies will be administered subcutaneously in the abdomen, upper arms or thighs. Each SC injection should be administered carefully to avoid inadvertent deposition into muscular tissue or leakage after needle removal. If leakage occurs, it should be noted in the study records.

Intravenous administration:
The volume of C144-LS to be administered will be calculated by the RUH research pharmacist according to study group allocation. Weight measurement collected at the pre-infusion visit or at day 0 will be used to calculate the dose of C144-LS. The appropriate volume of C144-LS will be diluted in sterile normal saline to a total volume of 100 ml, and will be administered as a slow intravenous infusion over 60 minutes.

After infusion of C144-LS is completed, the participant will be observed for 1 hour before initiation of subsequent C135-LS infusion.

The volume of C135-LS to be administered will be calculated by the RUH research pharmacist according to study group allocation. Weight measurement collected at the pre-infusion visit or at day 0 will be used to calculate the dose of C135-LS. The appropriate volume of C135-LS will be diluted in sterile normal saline to a total volume of 100 ml, and will be administered as a slow intravenous infusion over 60 minutes sequentially.

The study drugs will be administered intravenously, via a peripheral vein in one of the upper extremities. The administration site should be free of potentially complicating dermatologic conditions. At the end of infusion, the IV line will be flushed with Normal Saline to ensure all study drug has been delivered.

Part B

Subcutaneous administration (Group S3):
The RUH research pharmacist will provide the study drugs or placebo in separate syringes ready for administration. The number of injections of C144-LS and C135-LS will be 4 mL of C144-LS and 4 mL of C135-LS, separately or 8ml of placebo. The total volume of the antibodies or placebo will be dispended in four (Group S3) separate syringes containing either C144-LS or C135-LS or placebo for administration in four separate sites. The antibodies or placebo will be administered subcutaneously in the abdomen, upper arms or thighs. Each SC injection should be administered carefully to avoid inadvertent deposition into muscular tissue or leakage after needle removal. If leakage occurs, it should be noted in the study records.

6.2.4 Medical History and Physical Examination

At the time of screening, participant's past medical history will be collected and will include details of any previous reaction to vaccination, and contraceptive practices. Interim medical histories will be collected at time-points according to the Time of Events Schedule (Appendix A).

A general physical examination will be conducted including weight, height, vital signs, and examination of skin, respiratory, cardiovascular, neurological and abdominal systems. At the time of C144-LS and C135-LS administration and at selected time-points thereafter, general and/or directed physical examinations will be performed according to the Time of Events Schedule (Appendix A). A directed physical examination will include vital signs, examination of administration site, and any further examination indicated by history or observation.

6.2.5 Monitoring for cytokine release associated adverse events and treatment of cytokine release syndrome

Based on previous clinical experience with similar monoclonal antibodies, it is unlikely that administration of C144-LS and C135-LS would lead to cytokine release syndrome. However, a potential side effect of a monoclonal antibody can be the stimulation of a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity, and myocardial, lung, liver, and kidney functions. If cytokine release syndrome occurs, the participant may need to be treated with therapies that include, but are not limited to, intravenous fluids, vasopressors, and high-dose corticosteroids and/or may require ventilatory support.

Study participants will be admitted to the Rockefeller University Hospital the night before or on the day of C144-LS and C135-LS administration for 24 hours of monitoring. Participants will be closely observed for at least 30 – 60 minutes after administration. Access to a twenty-four hour on-call physician is available. The RUH outpatient and inpatient units are equipped with crash carts for immediate medical care, should the need arise. In case of an emergency at the Rockefeller University Hospital, after stabilization of the volunteer, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care.

6.2.6 SARS-CoV-2 Infection

Participants who develop symptoms suggestive of COVID-19 during study follow up will be mailed a kit for collection of saliva specimens (see Appendix C). The specimens will be returned for SARS-CoV-2 PCR testing at the RU Laboratory of Molecular Neuro-Oncology. The participants will also be advised to seek medical care for management of SARS-CoV-2 infection. Participants acquiring SARS-CoV-2 may remain on study. These participants will not return for in person follow up visits until deemed no longer infectious, according to CDC and local institutional guidelines. During this period, virtual study visits will be conducted for safety assessments, according to Appendix A.

6.2.7 SARS-CoV-2 Vaccination

At this time, it is not known if the prior receipt of anti-SARS-CoV-2 antibodies can interfere with the efficacy of SARS-CoV-2 vaccines, if the vaccine is administered while the anti-SARS-CoV-2 antibodies are still present. Similarly, the pharmacokinetics and time to clearance of C144-LS and C135-LS when administered at different doses are not yet known. As discussed in Section 4.1, based on previous studies with anti-HIV-1-antibodies, it is expected that C144-LS and C135-LS will have a $t_{1/2}$ in humans of 60-80 days, and that serum concentrations will be maintained above 2.5 mcg/mL (or approximately 1,000 times the in vitro IC_{50} of either mAb) for approximately 12 months when C144-LS and C135-LS are administered at 15 mg/kg doses each.

Study participants will be allowed to receive a FDA-approved SARS-CoV-2 vaccine after administration of the study antibodies and will be advised that the CDC currently recommends that vaccination be delayed for 90 days after receipt of anti-SARS-CoV-2 antibodies and that the period of C144-LS and C135-LS clearance is expected to be longer at the higher doses evaluated in this protocol (Appendix C, COVID-19 Considerations).

Participants who receive a SARS-CoV-2 vaccine following receipt of C135-LS and C144-LS in this study will be offered enrollment in an ongoing observational study (Protocol DRO-1006 “Peripheral Blood of Coronavirus Survivors to Identify Virus-Neutralizing Antibodies”). This study aims to evaluate both B and T cell responses longitudinally in individuals who recovered from COVID-19 and in SARS-CoV-2 vaccine recipients.

6.2.8 Other COVID-19 Considerations

In the event of travel restrictions, virtual study visits will be conducted for safety assessments, according to Appendix A. During such restrictions, if feasible, in person visits will be offered on study weeks 1, 4, 12, 24, and 48. These visits will follow Appendix A.

Appendix C. COVID-19 Considerations provides detailed guidance on study conduct in the context of the COVID-19 pandemic.

6.2.9 Family Planning Counseling

During screening and subsequent study visits, study personnel will counsel participants about the importance of prevention of pregnancies and the use of condoms, as well as other effective family planning methods.

Study participants engaging in sexual activity that could lead to pregnancy will be advised to use one effective method of contraception from 10 days prior to the C144-LS and C135-LS administration until 6 months after IP administration.

Examples of effective contraception methods are: condom with or without spermicide, diaphragm with spermicide, hormone-eluting IUD (Mirena), hormone-based contraceptive pills, injections or implants.

Should pregnancy occur, a pregnant participant will not receive the C144-LS and C135-LS administration. If pregnancy occurs after C144-LS and C135-LS administration, the participant will be followed until the end of the study and until delivery, if it occurs after the study has ended. Approximately 2-4 weeks after delivery, a pediatrician will examine and assess the health status of the baby. The baby's health status will be reported to the RU sponsor, the RU IRB and the SMC.

6.2.10 Safety Assessments

6.2.10.1 Solicited Adverse Events

Solicited systemic adverse events in this study include presence of feverishness, chills, headache, nausea, vomiting, malaise, myalgia and arthralgia occurring 2 weeks following C144-LS and C135-LS administration.

Solicited local adverse events in this study include presence of pain, tenderness, erythema and induration at injection site or infusion site occurring 2 weeks following C144-LS and C135-LS.

Solicited adverse events will be collected prospectively by structured interviews on administration and post-administration follow up visits; recorded and graded according to pre-established criteria (see Appendix B**)** in the source document and in specific Reactogenicity eCRFs. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) will be used to grade adverse events. In addition, the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading scale will be used for reporting and grading adverse events related to administration reactions and cytokine release syndromes within 24 hours of the start of

C144-LS and C135-LS administration that are considered administration reactions or cytokine release syndromes. Symptoms that may constitute an administration reaction or cytokine release syndrome include: fever and/or shaking chills, flushing and/or pruritus, alterations in heart rate and blood pressure, dyspnea or chest discomfort, back or abdominal pain, nausea, vomiting, and/or diarrhea, skin rash.

Vital signs (pulse, respiratory rate, blood pressure and temperature) will be measured according to **Section 6.1.4** and Appendix A. Vital signs during the 24-hour period after antibody administration will be graded according to The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). All medications required for treatment of adverse events will be recorded.

6.2.10.2 Unsolicited Adverse Events

During all follow up visits, the occurrence of unsolicited adverse events will be assessed following an open question to participants, with the dates of commencement and resolution and any medication required. All adverse events will be followed to resolution. Serious Adverse Events (SAEs) will be collected during the entire study period. They will be graded as indicated in Appendix B.

Laboratory abnormalities that are considered clinically significant and are grade 3 or higher will be reported as adverse events.

6.2.11 Blood Collection, Storage and Shipment

Venous blood will be collected at every study visit, usually from the antecubital fossa, according to the Time of Events Schedule (Appendix A). Up to 100 ml will be collected at day 0. Up to 60 ml will be collected at other visits. At no time will the total volume of blood collected exceed 550 ml over an 8-week period. The total volume of blood samples that will be collected during the entire study will be 775ml.

All specimens will be handled according to SOPs that were developed in the GLP-Processing Lab within the Laboratory of Molecular Immunology.

Frozen PBMCs, plasma and serum will be processed and stored in the Laboratory of Molecular Immunology at Rockefeller University.

6.2.12 Routine Laboratory Parameters

Specimens collected for safety labs at RUH will be transported to Memorial Sloan Kettering Cancer Center laboratory (MSKCC) via a courier. Specimens for Weill Cornell Medical Center (WCMC), LabCorp or Quest will be picked up by WCMC, LabCorp or Quest staff at RUH.

Laboratory parameters will routinely include hematology (WBC and differential, hemoglobin/hematocrit, platelets), clinical chemistry (Creatinine, Glucose, Total and Direct bilirubin, Alkaline phosphatase, AST and ALT), and urinalysis (RBC, WBC, protein). Female participants of

reproductive potential will have urine beta-HCG measured at screen, on the day of C144-LS and C135-LS administration, at selected follow up visits and as clinically indicated. The laboratory samples for these tests will be collected at the time points indicated in the Time of Events Schedule (Appendix A).

In the event of an abnormal laboratory value, participants may be asked to have additional sample(s) collected at the discretion of the principal investigator or designee.

At screening, participants will be screened for HIV, hepatitis B and C.

SARS-CoV-2 serology will be performed at screen, day 0, weeks 2, 12, 24 and 48.

A nasopharyngeal or oropharyngeal swab will be collected for SARS-CoV-2 PCR at the pre-administration visit. Saliva samples will be collected for SARS-CoV-2 PCR at weeks 2, 4, 12, 24, 36 and 48.

In the event a participant develops symptoms suggestive of COVID-19 during study follow up, a kit for collection of saliva specimens will be mailed to the participant's residence. The specimens will be returned for SARS-CoV-2 PCR testing at the RU Laboratory of Molecular Neuro-Oncology.

6.2.13 Pharmacokinetics and Immunogenicity Assessments

1. Pharmacokinetics:

Measurement of C144-LS and C135-LS levels by sandwich ELISA will be performed by PPD Laboratory Services (a contract research organization). C144-LS and C135-LS levels will be measured before and at the end of the administration, at 1 ,3, 6, 9 and 12 hours, 1, 3, 7 days and on weeks 2, 3, 4 weeks after administration, and at later time points as outlined in Appendix A.

Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Pharmacokinetic parameters to be assessed will include elimination half-life ($t_{1/2}$), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve. Descriptive results will be presented for the pharmacokinetic parameters by dose group.

2. Immunogenicity:

Anti-drug (C144-LS and C135-LS) antibody responses in serum. Assays will be performed by PPD Laboratory Services. The presence of anti-drug antibodies will be assessed at baseline and at weeks 4, 12, 24 and 48.

Optimal sample collection, processing, cryopreservation, archiving and storage will be maintained. Additional studies will be performed as warranted at the discretion of the investigators.

6.2.14 Other Laboratory Assessments

Serum neutralizing activity: An in vitro neutralization assay will be performed to determine serum neutralizing activity against a SARS-CoV-2 pseudovirus following C135-LS and C144-LS administration in the Laboratory of Molecular Immunology.

SARS-CoV-2 serology: will be performed at screen, day 0, weeks 2, 12, 24 and 48.

SARS-CoV-2 PCR:

- A nasopharyngeal or oropharyngeal swab will be collected for SARS-CoV-2 PCR at the pre-administration visit. The sample will be assayed at Memorial Sloan Kettering Cancer Center.

- Saliva samples will be collected for SARS-CoV-2 PCR at weeks 2, 4, 12, 24, 36 and 48. These samples will be collected at home using a collection kit and brought in during the designated study visit. These samples will be assayed at the RU Laboratory of Molecular Neuro-Oncology and results will be used for research purposes. In the event of a positive result, the study team will contact the participant and refer him/her to have a coronavirus PCR test performed by a commercial lab.

  In the event a participant develops symptoms suggestive of COVID-19 during study follow up, a kit for collection of saliva specimens will be mailed to the participant's residence. The specimens will be returned for SARS-CoV-2 PCR testing at the RU Laboratory of Molecular Neuro-Oncology.

6.2.15 Compensation

Participants will be compensated according to standards at the study site.

7 INVESTIGATIONAL PRODUCT

Investigational Drug Name:	C144-LS, C135-LS and Placebo for C144-LS and C135-LS
Manufacturer name of drug:	Bristol Myers Squibb (BMS)
IND Number:	150929
IND Sponsor:	The Rockefeller University

7.1 Regimen

C144-LS and C135-LS will be administered subcutaneously (separately) at 4ml (approximately 100mg of each antibody) or 8ml (approximately 200mg of each antibody) or intravenously (sequentially) at one of three increasing dose levels 1.5 mg/kg, 5 mg/kg and 15 mg/kg of each antibody on day 0.

7.2 Study Product Formulation and Preparation

Formulation:

- **C135-LS** will be provided by Bristol Myers Squibb (BMS) in single-use vials containing 50 mg/mL of protein in 6ml of buffered solution. C135-LS is a clear to opalescent, colorless to yellow liquid, which may contain light (few) particulates (consistent in appearance to protein particulates). The drug product is monitored for particulates in the stability program and is in compliance with USP particulate limits.

  The drug product is a sterile, nonpyrogenic, single-use, preservative-free, isotonic aqueous solution for intravenous (IV) administration formulated at 50 mg/mL in a buffered solution

consisting of histidine, sucrose, pentetic acid (diethylenetriaminepentaacetic acid, DTPA), polysorbate 80, and water for injection, at pH 6.0. Each vial includes a 0.5-mL overfill to account for vial, needle, and syringe (VNS) holdup. The drug product is supplied in a 6-mL Type I flint glass vial stoppered with a fluoropolymer film-laminated rubber stopper and sealed with an aluminum seal.

- **C144-LS** will be provided by Bristol Myers Squibb (BMS) in single-use vials containing 50 mg/mL of protein in 6 ml of buffered solution. C144-LS is a clear to opalescent, colorless to yellow liquid, which may contain light (few) particulates (consistent in appearance to protein particulates). The drug product is monitored for particulates in the stability program and is in compliance with USP particulate limits.

  The drug product is a sterile, nonpyrogenic, single-use, preservative-free, isotonic aqueous solution for intravenous or subcutaneous administration formulated at 50 mg/mL in a buffered solution consisting of histidine, sucrose, pentetic acid, polysorbate 80, and water for injection, at pH 6.0. Each vial includes a 0.5-mL overfill to account for VNS holdup. The drug product is supplied in a 6-mL Type I flint glass vial stoppered with a fluoropolymer film-laminated rubber stopper and sealed with an aluminum seal.

- **Placebo for C135-LS and C144-LS** will be a buffered solution provided by BMS in single-use vials containing 2 ml of buffered solution. The placebo is a sterile, nonpyrogenic, preservative-free, single-use, subcutaneous injectable product consisting of a buffered solution of histidine, sucrose, pentetic acid (diethylenetriaminepentaacetic acid, DTPA), polysorbate 80 and water for injection at pH 6.0. It is packaged in a 6-mL Type I flint glass vial, stoppered with a 20-mm fluoropolymer film-laminated rubber stopper, and sealed with a 20-mm aluminum flip-off seal. The placebo for BMS-C44-LS and C135-LS injection contain the same formulation as the respective active drug products, but without the active drug products.

Preparation:
- Each mAb will be diluted in normal saline (NaCl 0.9%) to a volume of 100 mL for intravenous infusion. Normal saline will be obtained by the local site pharmacy.
- C144-LS-LS and C135-LS are stored at 5 ± 3°C. The appropriate dose of each mAb should be drawn soon after vials are removed from the refrigerator. Vials should be inspected for particulate matter and discoloration. Discard if cloudy, discolored, or contain extraneous particulate matter. Do not shake (see Investigator's Brochure).
- Placebo for C135-LS and C144-LS should be stored at the site Pharmacy at 5 ± 3°C. The appropriate dose of placebo should be drawn soon after vials are removed from the refrigerator.

Part A:

Subcutaneous groups
- Subcutaneous groups: The RUH research pharmacist will provide each mAb in a syringe ready for administration (in 3 mL syringes attached to a 18G x 1.5 inch needle). The volume of C144-LS and C135-LS will follow study assignment. In both groups the mAbs will be prepared separately and the total volume of the individual antibodies will be dispended in two or four separate syringes for administration in two or four separate sites respectively.

Intravenous groups

- The appropriate dose will be calculated by the site research pharmacist according to participant's weight (measured at the pre-infusion or day 0 visits) and study group allocation. C144-LS and C135-LS will be dispensed in a small volume parenteral infusion, diluted in normal saline (NaCl 0.9%) ready for administration by the study investigators. Standard 18G needles are recommended to draw the required dose of each mAb to decrease the preparation time. Prior to injection of the mAb solution into the IV bag, remove air from the syringe and inject slowly, to avoid foaming. After preparation, infusion bags should be handled gently to avoid foaming (do not shake). Infusion bags should also be checked for particulates.
- C144-LS and C135-LS should be administered through a 0.2 or 0.22 micron in-line filter.

Part B:

Subcutaneous Group S3

- The RUH research pharmacist will provide each mAb or placebo in a syringe ready for administration (in 3 mL syringes attached to a 18G x 1.5 inch needle). The volume of C144-LS and C135-LS or placebo will be dispended in four (Group S3) separate syringes containing either C144-LS or C135-LS or placebo for administration in four separate sites respectively.

7.3 Dispensing and Handling of Investigational Product:

C144-LS, C135-LS and placebo will be shipped from Bristol Myers Squibb (BMS) and will be stored in the RUH Pharmacy at 5 ± 3°C. C144-LS, C135-LS and placebo will be dispensed by the RUH pharmacist. Trial personnel will ensure that the study ID number on the syringe or infusion bag matches the study ID assigned to the participant prior to administration.

7.4 Accountability and Disposal of Used and Unused Investigational Product

The date, allocation number and location of storage of the vials will be recorded in a log. During the trial, the product accountability form, and the dispensing log will be monitored. At the end of the trial, unused vials will be returned to Bristol Myers Squibb (BMS), transferred to the Laboratory of Molecular Immunology at RU or destroyed.

7.5 Concomitant Medications and Procedures

Use of concomitant medications will be reviewed at each study visit. Each participant will have a medication reconciliation record, which will be updated if schedule or dose level changes, and if new medications are initiated.

7.6 Permitted Medications and Procedures

Significant drug interactions with the study products are not anticipated at this time, therefore, if clinically necessary, participants can be initiated on other medications for intercurrent illnesses that might occur during their study participation.

Study participants will be allowed to receive a FDA-approved SARS-CoV-2 vaccine after after administration of the study antibodies, but will be advised that the CDC currently recommends that vaccination be delayed for 90 days after receipt of anti-SARS-CoV-2 antibodies and that it is expected that C144-LS and C135-LS will take longer to clear when dosed at the higher doses of 5 and 15 mg/kg. (Appendix C, COVID-19 Considerations).

7.7 Prohibited Medications and Procedures

Significant drug interactions with the study products are not anticipated at this time. Participants who enroll in the study agree to not participate in other studies of investigational drugs. In addition, they should not participate in studies that require frequent blood sample collection.

Use of systemic corticosteroids (long term use), immunosuppressive anti-cancer, interleukins, systemic interferons, systemic chemotherapy within 6 months of study enrollment is not permitted. Short term use of systemic steroids (e.g. steroid taper for allergic or administration reactions or asthma exacerbation) is permitted.

7.8 Precautionary Medications and Procedures

Significant drug interactions with the study products are not anticipated at this time. Participants who enroll in the study agree to not participate in other studies of investigational drugs. In addition, they should not participate in studies that require frequent blood sample collection.

7.9 Required Medications

Not applicable.

7.10 Rescue Medications

If participants develop grade 3 acute infusion reaction, an immediate hypersensitivity reaction or a life-threatening event during study drug administration, the infusion will be discontinued and will not be reinitiated (see Section 6.1.7.1). Rescue medications, including acetaminophen, diphenhydramine, epinephrine and glucocorticoids will be available at the clinical sites for use if clinically indicated.

8 DATA ANALYSIS

The proposed study is a first-in-human, single dose, dose-escalation phase 1 study of C144-LS and C135-LS in healthy volunteers (Table 1, Study groups and Section 4, Study Design - Dose escalation plan). Study participants will be enrolled sequentially.

Study participants will be administered C144-LS and C135-LS subcutaneously or intravenously at increasing dose levels. In Group S3 participants will be administered C144-LS and C135-LS or placebo subcutaneously in a 3:1 ratio.

This is an exploratory proof of concept trial and analysis will be descriptive. A standard “3+3” Phase 1 trial design is used; stopping rules will be based on the occurrence of dose-limiting toxicity.

8.1 Analysis of Safety, PK and Antiretroviral effects

Primary Outcomes

Safety: The safety population will include all participants who receive C144-LS and C135-LS. A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after C144-LS and C135-LS administration may be required for inclusion in the analysis of a specific safety parameter.

The number and percentage of participants experiencing one or more AEs will be summarized by study group, relationship to study drug, and severity. AEs will be summarized by the number and percentage of participants who experienced the event, according to system organ class (SOC) and preferred term. AEs will also be summarized by severity grade and by relationship to study drug according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The CTCAE v5.0 grading scale will be used for reporting and grading adverse events related to administration reactions and cytokine release syndromes in all groups (Appendix A). Changes in hematology, chemistry, and other laboratory values will be summarized descriptively. Changes will be calculated relative to the values collected at baseline.

Pharmacokinetic parameters: will be calculated using standard non-compartmental analysis methods. Descriptive results will be presented for the pharmacokinetic parameters by dose group. Pharmacokinetic parameters, including AUC, Cmax, $T_{1/2}$, Tmax and others will be summarized. ANOVA model will be used to compare group differences for AUC and Cmax. The dose proportionality for the 2 parameters (AUC and Cmax) will be examined by regression analysis. Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacodynamic parameters, and variance based on population intrinsic factors such as weight and gender will be explored.

Secondary outcomes

Anti-C144-LS and anti-C135-LS antibodies: The frequency of induced anti-C144-LS or anti-C135-LS antibodies will be reported. Occurrence of anti-drug antibodies (ADA) will be evaluated by a three-tiered approach using validated screening and confirmatory assays, followed by tittering of responses to determine if responses were treatment-induced or treatment-boosted.

Serum neutralizing activity against SARS-CoV-2: The SARS-CoV-2 neutralizing activity in serum will be determined by an in vitro neutralization assay before and after anti-C144-LS and anti-C135-LS administration.

Continuous data will be summarized by descriptive statistics, including the sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of participants.

The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Summary statistics will be calculated, along with point and interval estimates of solicited and unsolicited adverse events. The pharmacokinetic profile of a single administration of C144-LS

and C135-LS will also be determined. This study is exploratory, and any statistical inferences will be hypothesis generating and not confirmatory.

8.2 Sample Size Considerations

The sample size will be of 23 to 38 participants according to the dose escalation design used to characterize the safety and the pharmacokinetics profile of combined C144-LS and C135-LS administration at increasing dose levels, to healthy volunteers. Replacement of 2 participants lost to follow up prior to week 4 will be allowed.

- Pharmacokinetics:

The pharmacokinetic profile of C144-LS and C135-LS will be evaluated in this study. The target dose of C144-LS and C135-LS at this time is 5 mg/kg or 15 mg/kg. Based on the PK profile of other human monoclonal antibodies with the LS mutations, it is expected that the half-life of C144-LS and C135-LS will be 60 to 80 days.

- Safety:

It is expected that the administration of C144-LS in combination with C135-LS will be generally safe and well tolerated.

The sample size of 21 participants receiving C-144-LS and C-135-LS in combination will provide 95% probability of observing a treatment-related AE that would occur in 13.4% or more of treated participants. If none of the participants experiences a grade 2 or higher AE related to C-144-LS and/or C-135-LS, the one-sided 95% upper confidence bound for the rate of AEs in the population is 13.3%.

9 DATA AND SAMPLE STORAGE

The Principal Investigator will oversee how the data are collected, entered, and protected. All study data will be collected by the clinical study staff using designated source documents and entered onto the appropriate electronic case report forms (eCRFs). Data collection forms (DCFs) will be provided by Emmes Corporation for use as source documents as appropriate. All study data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the clinical site and remain separate from participant identification information (name, address, etc.) to ensure confidentiality. All medical records (when not being reviewed by the research team) will be kept under lock and key in the Medical Record Department of the hospital with access limited to the appropriate RUH personnel, members of the RU IRB and the FDA. Source documentation will be available for review to ensure that the collected data are consistent with the eCRFs.

All eCRFs and laboratory reports will be reviewed by the clinical team, who will ensure that they are accurate and complete.

All research samples will have a unique identifier. The PI will be responsible for ensuring project compliance, data analysis and entry, regulatory monitoring, and coordination of the activities of the entire study team. Standard GCP practices will be followed to ensure accurate, reliable and consistent data collection.

Source documents include, but are not limited to:
- Signed Informed Consent Documents
- Dates of visits including date of C144-LS and C135-LS administration
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications
- Reactogenicity adverse events

10 RECRUITMENT AND ADVERTISING

Both men and women aged 18 or older will be recruited for the study from the community at large and will be referred by physicians in the community. We will make every effort to recruit minorities and women.

Advertisements – The RUH Clinical Research Support Office (CRSO) will utilize the Volunteer Repository. Advertisements will also be placed: online (e.g. Craigslist, Centerwatch, etc), and in newspapers (Metro, AMNY).

Centralized Call Management – The RUH CRSO will conduct telephone screenings of selected Volunteer Repository members, and of volunteers who call 1800-RUCARES, to facilitate screening efficiently. Based on IRB approved eligibility criteria, potentially eligible candidates pre-screened by CRSO staff will be referred to the study coordinator/investigator for further evaluation. The research team and CRSO will work together on a protocol-specific pre-screening script to optimize the process.

11 POTENTIAL BENEFITS TO PARTICIPANTS

This is the first-in-human study of these monoclonal antibodies. There are no direct benefits to healthy volunteers that enroll in this study.

12 POTENTIAL RISKS TO THE PARTICIPANT INCLUDING TO THE FETUS

While each mAb product has unique safety issues related to its mechanism of action, the major safety concern related to monoclonal antibodies (mAbs) in general is an administration/hypersensitivity reaction. These types of reactions are more common for mAbs that contain murine elements compared to human mAbs, such as C144-LS and C135-LS. Passive administration of antiviral antibodies has been evaluated in humans in the past. As observed with other monoclonal antibodies, e.g. anti-HIV-1 antibodies were generally safe and well tolerated and most adverse events observed were infusion-related events and grade 1 in severity.

This study entails “significant” risk to participants since C144-LS and C135-LS have not been tested in humans yet. Potential study participants will be informed about the possible risks associated with C144-LS and C135-LS mAb administration and that there may be unknown risks.

- Immunologic symptoms such as listed below are possible with administration of a monoclonal antibody and will be considered adverse events of interest. Potential allergic-type reactions during

and immediately following the administration of C144-LS and C135-LS will be carefully monitored.

- Constitutional symptoms, such as fever, rigors/chills;
- Administration site reaction/extravasation changes, pruritus, urticaria;
- Serum sickness like syndromes as evidenced by fever, rash, arthralgia, arthritis, nephritis;
- Deposition of immune complexes in the kidneys leading to renal insufficiency;
- Adult Respiratory Distress Syndrome, bronchospasm/wheezing, anaphylaxis;
- Cytokine release syndrome/ acute administration reaction.

- There is a theoretical concern that non-neutralizing or decaying levels of antibodies could lead to antibody-dependent enhancement of infection should a participant acquire SARS-CoV-2 after receiving C144-LS and C135-LS. However, this phenomenon has not been observed in multiple studies of SARS-CoV-2 convalescent plasma transfusions, which contain polyclonal antibodies of varying neutralizing potencies.

- There is also a theoretical concern that the receipt of anti-SARS-CoV2- antibodies, such as C144-LS and C135-LS may interfere with the efficacy of COVID-19 vaccines, if the vaccine is given while the anti-SARS-CoV-2 antibodies are still present. It is not yet known how long it will take for C144-LS and C135-LS to be cleared when given at different doses.

- Blood drawing and phlebotomy can be associated with pain, bruising, anemia or infection at the site of venipuncture. Rarely, fainting may follow phlebotomy.

- The adverse effects C144-LS and C135-LS administration would have in a fetus are unknown.

- Participants may engage in increased risk taking after receiving anti-SARS-CoV-2 mAbs. One to one counseling will be routinely performed.

13 PROCEDURES TO MINIMIZE RISK

- As outlined above, this study will be a first-in-human dose escalation phase 1 trial of C144-LS and C135-LS in humans. Potential study participants will be informed about possible risks of the monoclonal antibodies and that there may be unknown risks.

- Medical records and routine laboratory data will be handled with HIPAA compliance and protected by the rules and regulations of the RUH.

- With any new medicine or monoclonal antibody, there is a possibility of totally unexpected side effects. Participants will be admitted the night prior or on the day of C144-LS and C135-LS administration for close monitoring for 24 hours after administration. The RUH inpatient unit is equipped for providing emergency medical interventions in the unlikely event of acute allergic or other reactions. In case of an emergency at the Rockefeller University Hospital, after stabilization of the participant, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care.

- To minimize risks associated with antibody administration, C144-LS and C135-LS will be administered as separate subcutaneous injections. During the sequential intravenous infusions, the participants will be observed for 1 hour after the first C144-LS infusion before proceeding with subsequent infusion of C135-LS.

- Enrollment will be staggered by 1 day for participants enrolled in each subcutaneous or intravenous dose group in Part A of the study. If 1 DLT occurs, 3 additional participants will enroll in each respective dose group. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum subcutaneous tolerated dose (MTD).

- The study investigators will review 1 week safety data prior to dose escalation from the low to the mid dose groups step. An external Safety Monitoring Committee (SMC) will review the 1 week safety data prior to dose escalation from the mid to the high intravenous dose groups step. The SMC will provide a recommendation regarding enrollment in subsequent groups.

- If, at any time, a fatal, life-threatening or permanently disabling SAE with a suspected causal relationship to C144-LS and C135-LS occurs, no further administration of the investigational product will occur until a consensus plan forward has been approved by investigators, SMC, the IRB and the FDA.

- Participants will be advised that the CDC currently recommends that vaccination be delayed for at 90 days after receipt of anti-SARS-CoV-2 antibodies and that it is expected that C144-LS and C135-LS will take longer to clear when dosed at the higher doses of 5 and 15 mg/kg. In addition, participants who are eligible to SARS-CoV-2 vaccination according to current local guidelines will be excluded from participation.

- To minimize risks associated with phlebotomy, blood drawing will be performed by experienced phlebotomists. Should discomfort occur, they will provide appropriate treatment.

- To minimize risks associated with blood drawing, participants will be closely monitored for signs and symptoms of anemia.

- Females of childbearing potential and who participate in sexual activity that might lead to pregnancy will be advised to use one reliable form of contraception (i.e. condom with spermicide, diaphragm with spermicide, hormone-eluting IUD, hormone-based contraceptive with condom) from 10 days prior to and until 6 months after the C144-LS and C135-LS administration. In addition, a pregnancy test will be performed at screening, on the day of antibody administration, and throughout the course of the study according to Appendix A and as clinically indicated. Males who are not anatomically sterile and who participate in sexual activity that might lead to pregnancy will be advised to use one reliable form of contraception from 10 days prior to and until 6 months after the C144-LS and C135-LS administration until the end of the study to avoid pregnancy in a spouse or partner. Condoms will be provided.

- Participants will have regularly scheduled visits to the outpatient clinic and routine safety laboratories will be checked according to the Time of Events Schedule (Appendix A).

- Adverse events will be monitored and graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The CTCAE v5.0 grading scale will be used for reporting and grading adverse events related to administration reactions and cytokine release syndromes in all groups (Appendix A).

- Adverse events will be managed by the clinical trial team who will assess and treat the event as appropriate, including referral to an independent physician and/or department.

- Safety monitoring will be conducted by the study investigators and by an external Study Monitoring Committee (SMC). The RU IRB will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious adverse events. Any serious and unanticipated adverse events will be immediately reviewed by the study investigators. Investigators will notify the local IRB and the RU sponsor within 2 working days from the investigators being made aware of the event. The RU sponsor will notify the FDA, per 21 CFR 312. The SMC will be available to the investigators for consultation and review of severe adverse events if needed.

14 DATA AND SAFETY MONITORING PLAN

This is a first-in-human phase 1 study, which exposes study participants to "significant risk". A Study Monitoring Committee (SMC) will be established to monitor the study.

14.1 Safety Monitoring Committee

The charter of the Safety Monitoring Committee (SMC) is to provide an ongoing assessment of participant safety during the conduct of the study. The SMC consists of three independent individuals who have no relationship to the Principal Investigator and Co-Investigators involved in the trial. No member of the SMC will have any direct responsibility for the clinical care of study participants. No representative of Bristol Myers Squibb (BMS), the Rockefeller University, or their designees may be a member of the SMC. However, the SMC may invite the principal investigator (PI) or designee and a BMS, and/or Rockefeller University representative to an open session of a SMC meeting to provide information on study conduct, present data, or to respond to the members' questions.

The names, university affiliation and title, area of expertise, and contact information of each of the SMC members are provided below:

1. Trevor Crowell, MD PhD
Assistant Professor of Medicine, Division of Infectious Diseases
F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences
Associate Director, Department of Epidemiology and Threat Assessment
Henry M. Jackson Foundation for the Advancement of Military Medicine/U.S. Military HIV Research
Phone: 301-500-3990
tcrowell@hivresearch.org

Clinical expertise: infectious diseases, HIV vaccines and monoclonal antibodies.

2. Christopher Palma, MD
Assistant Professor of Medicine, Division of Allergy Immunology and Rheumatology
University of Rochester School of Medicine & Dentistry
Phone: 585-486-0901
Christopher_palma@urmc.rochester.edu
Clinical expertise: immunotherapy, COVID-19 interventional trials (including anti-SARS CoV2 mAbs).

3. Sanjay Mehta, MD
Associate Professor of Medicine and Pathology, Division of Infectious Diseases and Global Public Health
University of California, San Diego
Phone: 858-552-7446
sanjay.mehta2@va.gov
Clinical expertise: clinical management of HIV and SARS-CoV-2 infection.

3. Randall L. Tressler, MD (non-voting member)
Medical Officer
Division of AIDS/NIAID/NIH
5601 Fishers Lane, Rm 9E49
Rockville, MD 20852
Email: randall.tressler@nih.gov
Areas of expertise: clinical evaluation of antiretrovirals

At least two members of the SMC must be in attendance (phone, video, or in-person meetings) to constitute a quorum for an SMC meeting. SMC members may also review and comment by email, if scheduling cannot be worked out in a timely manner. One member of the SMC will be appointed as chair of the committee. The SMC chair (or his/her alternate) will be responsible for summarizing and communicating in writing SMC acknowledgments and recommendations to the PI within 3 business days following each SMC meeting and/or review.

The SMC will be asked to review on an interim basis and in the following scenarios:

1. The SMC will review the 1-week safety data prior to dose escalation from the mid to the high dose intravenous groups step. The SMC will provide a recommendation regarding enrollment in subsequent groups.

2. The SMC will review all available safety and PK data when 4-wk safety and 2-wk PK data from the last enrolled group (V3) becomes available. Following review, the SMC will provide a recommendation regarding initiation of future phase 2 studies.

3. Grade 3 solicited and unsolicited adverse events judged by the principal investigator or designee to be possibly, probably or definitely related to C135-LS and/or C144-LS.

4. Grade 3 laboratory adverse events confirmed on retest and judged by the principal investigator or designee to be possibly, probably or definitely related to C135-LS and/C144-LS.

5. The investigator will report any "late occurring" DLT (i.e., a DLT occurring after 12 weeks of dosing) to the SMC. The investigators and SMC will mutually assess this information, along with safety from other participants, to determine whether a change to study conduct is warranted.

6. If one or more grade 3 or higher adverse events, deemed probably or definitely related to the study drugs occur, no additional administration of the investigational products will take place pending a Safety Monitoring Committee (SMC) review. In the event of a DLT, the SMC will make recommendations with regards to expansion of a study group from 3 to 6 participants, dose escalation to the next dose level, or halting additional enrollment. The investigators and SMC will mutually assess available information, along with safety from subsequent study groups, to determine whether a change to study conduct is warranted.

7. SAEs, which are deemed possibly, probably or definitely related to C144-LS and C135-LS by the principal investigator or designee, and unanticipated adverse events will be reported to the SMC within 2 working days of the site becoming aware of the event.

   If there is one SAE, grade 3 or higher, and judged as possibly, probably or definitely related to the administration of C144-LS and C135-LS by the principal investigator or designee, no additional administration of the investigational product will take place pending a review by at least two members of the SMC. Following this review, the SMC will make a recommendation to the principal investigator regarding the continuation of investigational product administration.

8. If, at any time, a fatal, life-threatening or permanently disabling SAE with a suspected causal relationship to C144-LS and C135-LS occurs, no further administration of the investigational product will occur until a consensus plan forward has been approved by investigators, SMC, the IRB and the FDA.

All updated versions of the protocol will be provided to the SMC. The review of trial data by the SMC will take place at least bi-annually. Prior to data review, the study team will provide the SMC with updated records of all adverse events (AEs) of a grade 2 or higher.

The SMC will acknowledge receipt of annual reports and will indicate if there are concerns with the continuation of the study. The SMC will provide a written report to the RU sponsor and the site PIs after each evaluation. The PIs in turn will distribute these reports to the study team and the local IRB.

14.2 Monitoring

Safety monitoring will be conducted by the study investigators and by the external Study Monitoring Committee (SMC). The RU IRB will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious adverse events. External monitoring will occur at least quarterly, and will be conducted by the Emmes Corporation.

14.3 Adverse Event Definition and Classification

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Scales to be used: the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The CTCAE v5.0 grading scale will be used for reporting and grading adverse events related to administration reactions and cytokine release syndromes in all groups (Appendix B).

14.4 Reporting Adverse Events

All adverse events will be reported to the IRB and the SMC at least annually. Serious Adverse Events, (SAEs) will be reported to the IRB and the SMC, within two (2) working days of identification of the SAE. SAEs will be reported directly to the FDA, per 21 CFR 312.

An adverse event is reported as a SAE if it meets any of the following criteria (as per International Conference on Harmonisation [ICH] guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.):

Any untoward medical occurrence that at any dose:
• Results in death Is life-threatening

• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity, or
• Is a congenital anomaly/birth defect or spontaneous abortion
• Any other important medical condition that requires medical or surgical intervention to prevent permanent impairment of a body function or structure

Elective surgery for pre-existing condition that did not increase in severity or frequency is not considered an SAE.

14.5 Reporting Unanticipated AEs

Any adverse event that is not consistent with the known, predicted possible effects of the research protocol. An unanticipated adverse event varies in nature, intensity or frequency from information on the investigational product provided in the Investigator's Brochure, package insert, safety reports, clinical protocol, or listed in the consent form.

Unanticipated Adverse Events (UAEs) will be reported to the IRB and SMC. UAEs that are related and greater than moderate severity must be reported to the IRB and SMC, within two working days of identification of the UAE. UAEs will be reported to the FDA, per 21 CRF 312.

14.6 Clinical Laboratory Improvement Amendment/Clinical Laboratory Evaluation Program (CLIA/CLEP)

This study includes tests that are not CLIA/CLEP certified. The results of such tests will not be used in clinical decision-making or shared with participants or their health care providers.

14.7 Toxicity Management and Stopping Rules

A dose limiting toxicity (DLT) will be defined as any adverse event of Grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144-LS and C135-LS mAb. Grade 3 laboratory abnormalities must be confirmed by a repeat test, obtained as soon as possible following the initial result.

In general, the following rules in dose escalation will be followed:

During the subcutaneous and intravenous dose escalation phase (**Part A**) of the study, enrollment will be staggered by 1 day for the volunteers of each group.

Subcutaneous (SC) Administration (Groups S1 and S2)

1. First, eligible participants will be enrolled in **Group S1** (C144-LS + C135-LS, 2mL each).
2. Enrollment in **Group S2** (C144-LS + C135-LS, 4mL each) will begin after all three participants enrolled in **Group S1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144- LS and/or C135-LS).
3. If 1 DLT occurs, 3 additional participants will enroll in **Group S1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed.
4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum subcutaneous tolerated dose (MTD).
   Enrollment in **Group S2** will follow the same rules.

Intravenous (IV) Administration (Groups V1, V2 and V3)

1. Enrollment in **Group V1** (C144-LS + C135-LS, 1.5mg/kg each, IV) will begin at least 7 days after the first three participants enrolled in **Group S2.**
2. Enrollment in **Group V2** (C144-LS + C135-LS, 5mg/kg each, IV) will begin after all three participants enrolled in **Group V1** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group (DLT: any adverse event of grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144-LS and/or C135-LS).
3. If 1 DLT occurs, 3 additional participants will enroll in **Group V1**. If no additional dose limiting toxicities occur, enrollment in the next dose level will proceed.
4. If 2 or more DLTs occur, dosing will be halted and the prior lower dose level will be declared the maximum intravenous tolerated dose (MTD).
5. Enrollment in **Group V3** (C144-LS + C135-LS, 15mg/kg each, IV) will follow the same rules.
6. Enrollment in **Group V3** will begin at least 7 days after three participants enrolled in **Group V2** and following SMC review of all available safety data.

During the subcutaneous, randomized, double-blinded phase (**Part B**) of the study, enrollment will be limited to a maximum of two volunteers per day.

Subcutaneous (SC) Administration (Group S3)

Enrollment in **Group S3** will begin once all participants in Part A have met eligibility criteria and have been scheduled for enrollment (day 0) and after all three participants enrolled in **Group S2** reach at least 7 days without a dose limiting toxicity (DLT) reported in the group.

Note: As outlined in **Section 14.1**, the SMC will be asked to review safety data if one or more grade 3 or higher adverse events, deemed probably or definitely related to the study drugs (DLT) occur. No additional administration of the investigational products will take place pending a SMC review. In the event of a DLT, the SMC will make recommendations with regards to expansion of a study group from 3 to 6 participants, dose escalation to the next dose level, or halting additional enrollment.

The study investigators will review 1-week safety data prior to dose escalation from the low (Group V1 and S1) to the mid (Group V2 and S2) dose groups step. An external Safety Monitoring Committee (SMC) will review the 1-week safety data prior to dose escalation from the mid (Group V2) to the high (Group V3) dose groups step. The SMC will provide a recommendation regarding enrollment in subsequent groups.

The SMC will review the 4-week safety and 2-week PK data after dosing in all study groups is completed. Following review, the SMC will provide a recommendation regarding initiation of future phase 2 studies.

14.8 Other Disease Events

Adverse events will be followed until resolved or considered stable during each scheduled study visit or during unscheduled study visits if warranted. If adverse events deemed related to the study drugs are not resolved at the time of final study visit, participants will be referred for appropriate medical care until the symptoms resolve or the participant's condition becomes stable.

15 CLINICAL TRIAL REGISTRATION

The proposed study involves testing of FDA regulated drugs or biologics and will be registered at www.ClinicalTrials.gov.

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STATISTICAL ANALYSIS PLAN

for

Rockefeller Protocol: RUCOV1

Study Title:

A Phase 1 Study of the Safety and Pharmacokinetics of a Combination of Two Anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in Healthy Volunteers

IND # 150929

DAIDS-ES ID 38798

Version 2.0

09 JUN 2022

Title	A phase 1 study of the safety and pharmacokinetics of a combination of two anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in healthy participants
Short Title	RU Anti-SARS-CoV-2 mAbs in Healthy Participants
Protocol Number	RUCOV1
Phase	Phase 1
Investigational product	Two highly neutralizing antibodies directed against SARS-CoV-2 RBD: C144-LS and C135-LS. The antibodies are manufactured, and each will be formulated in a separate vial at a concentration of 50 mg/mL.
Indication	Prevention or therapy of COVID-19
Sample size	23 to 38
Number of study sites	Single site – The Rockefeller University Hospital (RUH), New York, NY, U.S.A.
Study Objectives	**Primary objectives:** • To evaluate the safety and tolerability of subcutaneous injections or single intravenous infusions of C144-LS in combination with C135-LS in healthy participants. • To evaluate the pharmacokinetic profile of C144-LS and C135-LS in combination, administered subcutaneously or intravenously at increasing dose levels in healthy participants. **Secondary objectives:** • To assess the occurrence of anti-drug antibody responses. • To evaluate serum neutralizing activity against SARS-CoV-2 after C144-LS and C135-LS administration.
Study Outcomes/ Objectives	**Primary outcomes:** • Rate of solicited and investigational product (IP)-related unsolicited adverse events that are Grade 2 and above (including confirmed laboratory abnormalities) 4 weeks after administration. • Rate of solicited and IP-related unsolicited adverse events that are Grade 3 and above (including confirmed laboratory abnormalities) 4 weeks after administration. • Proportion of participants with serious adverse events (SAEs) throughout the study period that are considered related to investigational products and their duration. • The pharmacokinetic profile of C144-LS and C135-LS: elimination half-life ($t_{1/2}$), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve. **Secondary Outcomes:** • Rate and severity of investigational product (IP)-related adverse events during study follow up. • Frequency and levels of induced anti-C144-LS and anti-C135-LS antibodies in all study groups. • Serum neutralizing activity against SARS-CoV-2 before and after C144-LS and C135-LS administration.

Study Duration	15 months
Study Product, Dose, Route, Regimen	Single subcutaneous injections of C144-LS and C135-LS, each mAbs dosed at approximately 100 mg (two 2 mL injections administered at separate sites) or 200 mg (four 2 mL injections administered at separate sites). Single subcutaneous injections of placebo (sterile saline) as four 2 mL injections administered at separate sites. One intravenous infusion of C144-LS and C135-LS, each administered via a peripheral vein over 60 minutes sequentially. Starting dose level is 1.5 mg/kg of each antibody, with 0.5 log10 increases to 5 mg/kg and 15 mg/kg.

This study was performed in compliance with Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL RUCOV1

A Phase 1 Study of the Safety and Pharmacokinetics of a Combination of Two Anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in Healthy Volunteers

I have read this Statistical Analysis Plan and approve its contents.

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMS	Bristol Myers Squibb
BQL	Below the Limit of Quantification
CHEM	Clinical Chemistry
CI	Confidence Interval
CV	Coefficient of Variation
DLT	Dose Limiting Toxicity
FDA	Food and Drug Administration
FWCL	Family Wise Confidence Level
GM	Geometric Mean
HEM	Hematology
ICH	International Conference on Harmonisation
IP	Investigational Product
IV	Intravenous
LLOQ	Lower Limit of Quantification
mAb	Monoclonal Antibody
Max	Maximum Value
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum Value
mL	Milliliter
N	Number (typically refers to participants)
PK	Pharmacokinetic
PT	Preferred Term
RBC	Red Blood Cell
RBD	Receptor Protein Binding Domain
RUH	Rockefeller University Hospital
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

List of Abbreviations *(continued)*

SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
UA	Urinalysis
ULN	Upper Limit of Normal
VNS	Vial, Needle, and Syringe
VS	Vital Signs
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

This Statistical Analysis Plan (SAP) for "A phase 1 study of the safety and pharmacokinetics of a combination of two anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in healthy participants" (Rockefeller University Protocol RUCOV1) covering the study follow-up period through 48 weeks of follow-up after IP administration describes and expands upon the statistical information presented in the protocol and SAP version 1.0 that covered interim analyses through 24 weeks of follow-up after IP administration.

This document describes all planned safety, pharmacokinetic (PK), and immunogenicity analyses for the Clinical Study Report (CSR) that reflect all collected safety, PK, and immunogenicity data in the study to date and provides reasons and justifications for these analyses. It also includes shells for the tables, figures, and listings planned for the safety, PK, and immunogenicity analyses. Regarding the safety, PK, and immunogenicity analyses in the CSR, this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail for pre-specification of all analyses in accordance with FDA and ICH guidelines.

Any deviation from this SAP will be described and justified in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

2.1. Purpose of the Analyses

These analyses will assess safety, PK, and immunogenicity data from a Phase 1 study of two monoclonal antibodies (mAbs), C144-LS and C135-LS over the entire planned study follow-up (48 weeks after IP administration). The goal of the analysis is to present PK profiles for each study drug and cumulative outcome data for safety and immunogenicity of the investigational product (IP).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

- To evaluate the safety and tolerability of subcutaneous injections or single intravenous infusions of C144-LS in combination with C135-LS in healthy participants.
- To evaluate the pharmacokinetic profile of C144-LS and C135-LS in combination, administered subcutaneously or intravenously at increasing dose levels in healthy participants.

3.1.2. Secondary Objectives

- To assess the occurrence of anti-drug antibody responses.
- To evaluate serum neutralizing activity against SARS-CoV-2 after anti-C144-LS and anti-C135-LS administration.

3.2. Outcomes

3.2.1. Primary Outcomes

- Rate of solicited and investigational product (IP)-related unsolicited adverse events that are Grade 2 and above (including confirmed laboratory abnormalities) 4 weeks after administration.
- Rate of solicited and IP-related unsolicited adverse events that are Grade 3 and above (including confirmed laboratory abnormalities) 4 weeks after administration.
- Proportion of participants with serious adverse events (SAEs) throughout the study period that are considered related to investigational product and their duration.
- The pharmacokinetic profile of C144-LS and C135-LS: elimination half-life ($t_{1/2}$), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve.

3.2.2. Secondary Outcomes

- Rate and severity of investigational product (IP)-related adverse events during study follow up.
- Frequency and levels of induced anti-C144-LS and anti-C135-LS antibodies in all study groups.
- Serum neutralizing activity against SARS-CoV-2 after C144-LS and C135-LS administration.

3.3. Study Definitions and Derived Variables

3.3.1. Study Group

Study Groups in the SAP are defined to match identically with study groups as defined in the protocol. All the study groups in Part A of the study, 2 of the subcutaneous (SC) and all the intravenous (IV) study groups, are open label and do not include any placebo participants.

Subcutaneous study groups:

- Part A, S1: All participants assigned to receive 4 mL (approximately 100 mg of each mAbs) of C144-LS and C135-LS in two separate SC injections (3 to 6 participants) in an unblinded fashion.
- Part A, S2: All participants assigned to receive 8 mL (approximately 200 mg of each mAbs) of C144-LS and C135-LS in two separate SC injections (3 to 6 participants) in an unblinded fashion.
- Part B, S3 Active and Placebo: All participants assigned to receive 8 mL (approximately 200 mg of each mAbs) of C144-LS and C135-LS in two separate SC injections (6 participants) or matching placebo (2 participants) in a blinded fashion.

Intravenous injection study groups:

- Part A, V1: All participants assigned to receive sequential IV infusions of C144-LS then C135-LS, each administered via peripheral vein over 60 minutes at a dose level of 1.5 mg/kg (3 to 6 participants) in an unblinded fashion.
- Part A, V2: All participants assigned to receive sequential IV infusions of C144-LS then C135-LS, each administered via peripheral vein over 60 minutes at a dose level of 5 mg/kg (3 to 6 participants) in an unblinded fashion.
- Part A, V3: All participants assigned to receive sequential IV infusions of C144-LS then C135-LS, each administered via peripheral vein over 60 minutes at a dose level of 15 mg/kg (3 to 6 participants) in an unblinded fashion.

3.3.2. Dose Group

Dose Group defines a grouping of participants for statistical analysis, where participants within a dose group received the same study product and dose under the same administration method. Three pooled dose groups, the Any Dose Group, SC Dose Group, and IV Dose Group, will include all participants who received a dose of the IP (not placebo), regardless of the dose received, and will be used for high-level demographic and safety summaries. For data from a participant to be analyzed as part of their dose group, the participant must also qualify for inclusion into the respective analysis population (Section 6.3) for that data. The pooled dose groups in the order they will be presented in the high-level demographic and safety analyses (Table 6, Table 7, and Table 9 through Table 16) are defined as follows:

- Any Dose Group: All participants who received a complete or incomplete dose of the IP regardless of dose or administration method.
- SC Dose Group: All participants who received a complete or incomplete dose of the IP via SC administration, regardless of dose.
- IV Dose Group: All participants who received a complete or incomplete dose of the IP via IV infusion, regardless of dose.

The high-level demographic and safety summary tables (Table 6, Table 7, and Table 9 through Table 16) will display the following pooled dose group break-down in the order specified:

[Pooled Safety Group 1] Any Dose Group (S1+S2+S3 Active +V1+V2+V3)	[Pooled Safety Group 2] Any SC Dose Group (S1+S2+S3 Active)	[Pooled Safety Group 3] Any IV Dose Group (V1+V2+V3)

The individual safety, immunogenicity, and PK dose groups described below will be used to present results in the tables, figures, and listings. Specified high-level demographic and safety summary tables will be presented by pooled dose group in addition to the summaries by individual dose group (Table 6, Table 7, and Table 9 through Table 16).

The individual dose groups in the order they will be presented in the detailed safety analyses are defined as follows:

- 100 mg, SC: All participants who received a complete or incomplete dose of 100 mg of the IP via SC administration;
- 200 mg, SC: All participants who received a complete or incomplete active dose of 200 mg of the IP via SC administration;
- 1.5 mg/kg, IV: All participants who received a complete or incomplete dose of 1.5 mg/kg of the IP via IV administration;
- 5 mg/kg, IV: All participants who received a complete or incomplete dose of 5 mg/kg of the IP via IV administration;
- 15 mg/kg, IV: All participants who received a complete or incomplete dose of 15 mg/kg of the IP via IV administration;
- Placebo, SC: All participants who received a complete or incomplete dose of placebo via SC administration.

The safety summary tables/figures will display the following individual study group break-down in the order specified:

[Safety Group 1] 100 mg, SC (S1)	[Safety Group 2] 200 mg, SC (S2 + S3 Active)	[Safety Group 3] 1.5 mg/kg, IV (V1)	[Safety Group 4] 5 mg/kg, IV (V2)	[Safety Group 5] 15 mg/kg, IV (V3)	[Safety Group 6] Placebo, SC (S3)

The immunogenicity summary tables/figures will use the same individual study group break-down as for the safety summary tables/figures:

[Immunogenicity Group 1] 100 mg, SC (S1)	[Immunogenicity Group 2] 200 mg, SC (S2 + S3 Active)	[Immunogenicity Group 3] 1.5 mg/kg, IV (V1)	[Immunogenicity Group 4] 5 mg/kg, IV (V2)	[Immunogenicity Group 5] 15 mg/kg, IV (V3)	[Immunogenicity Group 6] Placebo, SC (S3)

The PK summary tables/figures will display the following dose group break-down in the order specified:

[PK SC Group 1] 100 mg SC (S1)	[PK SC Group 2] 200 mg SC (S2+S3 Active)	[PK IV Group 1] 1.5 mg/kg IV (V1)	[PK IV Group 2] 5 mg/kg IV (V2)	[PK IV Group 3] 15 mg/kg IV (V3)

The example table, figure, and listing shells (Appendix 1, Appendix 2, and Appendix 3, respectively) display generic dose group names in brackets which will be replaced with the final determined dose group names above in the actual CSR.

Appendix A of the study protocol detail the analysis timepoints at which safety, PK, and immunogenicity assessments will be conducted. Outcomes analyzed by timepoint include vital sign (VS) results; clinical laboratory results: hematology clinical laboratory results (HEM), chemistry clinical laboratory results (CHEM), and urinalysis laboratory results (UA); PK results; and immunogenicity results.

3.3.3. Baseline

Baseline for VS, clinical laboratory results, PK, and immunogenicity samples is defined as the last result obtained before the study product administration. For the IV dose groups this is defined as the last result obtained before start of infusion of either mAb.

Baseline height, weight, and body mass index (BMI) will be the measurements obtained at Day 0 prior to IP administration. Age will be based on age at the time of enrollment. Age at enrollment is an integer value with units of years, calculated from the participant's enrollment date (ENRCONDT) and birth date (BRTHDT) using the following algorithm.

- If month(ENRCONDT) > month(BRTHDT), then AGE = year(ENRCONDT) – year(BRTHDT)
- If month(ENRCONDT) < month(BRTHDT), then AGE = year(ENRCONDT) – year(BRTHDT) – 1
- If month(ENRCONDT) = month(BRTHDT) and day(ENRCONDT) ≥ day(BRTHDT), then AGE = year(ENRCONDT) – year(BRTHDT)
- If month(ENRCONDT) = month(BRTHDT) and day(ENRCONDT) < day(BRTHDT), then AGE = year(ENRCONDT) – year(BRTHDT) – 1

3.3.4. Study Day

Study Day will primarily be used to refer to the timing of assessments and events relative to study product administration. Study day will be defined differently in the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. In SDTM, the day that the IP was received is considered Study Day 1 for each participant in each study group. The day prior to IP administration is Day -1. In compliance with CDISC standards, there is no Day 0 in SDTM datasets. In the ADaM datasets (ADY, Analysis Day), the day that the IP was received is considered Study Day 0 for each participant in each study group. The day prior to IP administration is considered Study Day -1. In all tables, figures, and listings, study day will be presented as defined in the protocol and in the ADaM datasets.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is first-in-human, single dose, dose-escalation phase 1 study to evaluate the safety and pharmacokinetics of a combination of two highly neutralizing anti-SARS-CoV-2 mAbs targeting two distinct epitopes on the receptor protein binding domain (RBD) of SARS-CoV-2 spike protein in healthy participants.

This study consists of two parts. Part A has a standard 3+3 phase 1 dose escalation design. Study participants will receive subcutaneous injections of C144-LS and C135-LS at one of two increasing dose levels (4 mL, approximately 100 mg of each antibody administered separately or 8 mL, approximately 200 mg of each antibody administered separately), or sequential intravenous infusions of C144-LS and C135-LS, each administered via peripheral vein over 60 minutes at one of three increasing dose levels (1.5 mg/kg, 5 mg/kg, and 15 mg/kg of each antibody). Participants in Part B will be randomized to receive subcutaneous injections of C144-LS and C135-LS at 8 mL (approximately 200 mg of each antibody administered separately) or placebo in a 3:1 ratio and double-blinded fashion.

This study will be conducted at a single site and will enroll a maximum of 38 participants. A schedule of study procedures is detailed in Appendix A of the study protocol. Screening, baseline, and follow-up procedures will follow the same process for all study groups.

4.2. Selection of Study Population

Only participants 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. Up to 38 healthy male and female participants, ages 18 to less than 65, will be enrolled into the study groups listed in Section 3.3. Neither women nor minorities will be excluded from participation in this study. Women of childbearing potential may be included as per the inclusion criteria (See inclusion criteria below). Participants will be recruited without regard to gender or race. It is expected that race will reflect that within the community. The demographics in the local population should ensure that male and female minorities will be represented in the enrolled population.

Eligibility criteria from version 2.1 of the study protocol are listed below:

Inclusion Criteria:

- Aged 18 to less than 65.
- If sexually active male or female, and participating in sexual activity that could lead to pregnancy, agrees to use one effective method of contraception from 10 days prior to the antibody administration until 6 months after investigational product (IP) administration.

Exclusion Criteria:

- Weight > 110 kg for groups S1 and S2 only.
- History of prior positive SARS-CoV-2 RT-PCR or SARS-CoV-2 serology.
- Active respiratory or non-respiratory symptoms consistent with COVID-19.
- Medically attended acute illness or hospitalization (i.e., >24 hours) for any reason within 30 days prior to screening.
- Acute exacerbation of a chronic pulmonary condition (e.g., chronic obstructive pulmonary disease [COPD], asthma exacerbations, or uncontrolled hypertension, as defined by a systolic blood pressure > 180 and/or diastolic blood pressure > 120, in the presence or absence of anti-hypertensive medications) in the past 6 months prior to screening.
- Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.
- Other clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation.
- Are eligible for COVID-19 vaccination prior to your entry in the study according to local guidelines (e.g. healthcare professionals, non-healthcare professionals such as teachers, firefighters, public transit workers).
- Laboratory abnormalities in the parameters listed:
  - Absolute neutrophil count ≤ 1,500 K/mcL;
  - Hemoglobin ≤ 10.5 gm/dL if female; ≤ 11 gm/dL if male;
  - Platelet count ≤ 125,000 K/mcL;
  - ALT ≥ 1.25 x ULN; AST ≥ 1.25 x ULN;
  - Total bilirubin ≥ 1.25 x ULN;
  - Creatinine ≥ 1.1 x ULN.
- Pregnancy or lactation.
- Any vaccination within 14 days prior to SARS-CoV-2 mAbs administration (except influenza vaccine).
- History of prior receipt of any SARS-CoV-2 vaccine or antibodies, including convalescent plasma.
- Known allergy/sensitivity or any hypersensitivity to components of the investigational agents.
- History of severe reaction to a vaccine or monoclonal antibody administration or history of severe allergic reactions.
- Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.

4.3. Treatments

4.3.1. Treatments Administered

Participants will receive a single dose of each C144-LS and C135-LS, either administered subcutaneously at 4 mL (approximately 100 mg of each mAb administered separately) or 8 mL (approximately 200 mg of each mAb administered separately) or administered intravenously at a dose of 1.5 mg/kg, 5 mg/kg, or 15 mg/kg of each mAb according to study group. Placebo treatments will only be administered as part of study group S3 (200 mg of each mAb or placebo, administered SC) in Part B.

Each antibody will be administered separately in both the SC and IV study groups. Subcutaneous administration will occur in 2 (2 mL) or 4 (4 mL) injections at the same number of sites as injections: abdomen, upper arms, or thighs. Each SC injection will be administered carefully to avoid inadvertent deposition into muscular tissue and leakage after needle removal. The volume of C144-LS and C135-LS to be administered via intravenous administration will be calculated by the Rockefeller University Hospital (RUH) research pharmacist, according to the baseline weight measurement. The appropriate volume of each antibody will be diluted in sterile normal saline to a total volume of 100 mL. First C144-LS will be administered as a slow IV infusion over 60 minutes. After infusion of C144-LS is completed, the participant will be observed for 1 hour before initiation of subsequent C135-LS infusion. The appropriate volume of C135-LS will be diluted similarly to C144-LS to a volume of 100 mL and will be administered as a slow IV infusion over 60 minutes. IV administration of study drugs will occur via a peripheral vein in one of the upper extremities. At the end of infusion, the IV line will be flushed with normal saline to ensure all study drug has been delivered.

4.3.2. Identity of Investigational Product(s)

Both C144-LS and C135-LS will be provided by Bristol Myers Squibb (BMS) in single-use vials containing 50 mg/mL of protein in 6 mL of buffered solution. Both mAbs are clear to opalescent, colorless to yellow liquid, and may contain light (few) particulates (consistent in appearance to protein particulates). The drug products are monitored for particulates in the stability program and is in compliance with USP particulate limits.

Both products are sterile, nonpyrogenic, single-use, preservative-free, isotonic aqueous solutions. C135-LS is for intravenous administration and C144-LS is for intravenous or subcutaneous administration formulated at 50 mg/mL in a buffered solution consisting of histidine, sucrose, pentetic acid (diethylenetriamine pentacetic acid, DTPA), polysorbate 80, and water for injection at pH 6.0. Each vial includes a 0.5-mL overfill to account for vial, needle, and syringe (VNS) holdup. The drug products are supplied in a 6-mL Type I flint glass vial stoppered with a fluoropolymer film-laminated rubber stopper and sealed with an aluminum seal.

Placebo for both C144-LS and C135-LS will be a buffered solution provided by BMS in single-use vials containing 2 mL of buffered solution. The placebo is a sterile, nonpyrogenic, preservative-free, single-use, subcutaneous injectable product consisting of a buffered solution of histidine, sucrose, pentetic acid (diethylenetriamine pentacetic acid, DTPA), polysorbate 80, and water for injection at pH 6.0. It is packaged in a 6 mL Type I flint glass vial, stoppered with a 20-mm fluoropolymer film-laminated rubber stopper, and sealed with a 20-mm aluminum flip-off seal. The placebo for BMS-C144-LS and C135-LS injection contain the same formulation as the respective active drug products, but without the active drug products.

4.3.3. Method of Assigning Participants to Dose Groups (Randomization)

Enrollment in Part A of the study is open-label, and study participants will be enrolled sequentially as they meet enrollment criteria. C144-LS and C135-LS will be dispensed according to study group. Part B of the study (study group S3) is double-blinded. The packaging and formulation of study drugs and placebo will look identical to maintain the blind. Enrollment in Part B will be randomized in a 3:1 ratio (study drugs to placebo, 6 study drug recipients to 2 placebo recipients). Study product administration will follow the procedures outlined in the study protocol. Participants will be enrolled sequentially as they meet enrollment criteria, according to the randomization schedule. Randomization will be performed by the RUH pharmacy. Randomization will be generated using SAS 9.4. Preparation of study drugs or placebo will be provided to study nurses for injection under a coded, masked identification. Nurses, study staff, investigators, and participants will be blinded as to the identity of the study preparation. Participants enrolled in Group S3 will be unblinded 23 months after participant study entry (Day 0) and at least 1 month after all participants enrolled in Group S3. Following unblinding, placebo recipients will remain in follow up for safety assessments. Samples will not be collected for research purposes following unblinding.

4.3.4. Selection of Doses in the Study

The proposed study doses were chosen based on *in vitro* and *in vivo* data that demonstrated the neutralizing potency of C144-LS and C135-LS in preclinical experiments in mice, hamsters, and non-human primates. Similar and higher dose levels have been safely evaluated with anti-HIV-1 antibodies as well as other anti-SARS-CoV-2 RBD mAbs, according to publicly available data. See **Section 4.1** of the study protocol (v2.1) for further details of the rationale for dose selection.

4.3.5. Concomitant Therapy

Use of concomitant medications will be reviewed at each study visit. Concomitant medications will be listed in Listing 19.

4.3.6. Treatment Compliance

Study products will be administered at RUH by site personnel in accordance with treatment assignment or randomization. Participant compliance is not anticipated to be an issue. Complete information regarding any partial or interrupted dosing will be documented. Start times and administration site of each SC injection, and start and end times of each IV infusion will be recorded (Listing 7).

4.4. Safety, Pharmacokinetic, and Immunogenicity Variables

The following section describes the safety, PK, and immunogenicity outcomes of this study. Refer to Section 3 for a list of the primary and secondary objectives and outcomes. Definitions of baseline measurements are included in Section 3.3.

Incidence, relatedness, and severity of treatment-emergent AEs and SAEs will be recorded from the time of IP administration to the final study visit. Any AEs due to study related procedures and prior to IP administration will also be listed. AEs and SAEs are defined in **Section 14.3** and **Section 14.4** of the study protocol (v2.1). Adverse events will be graded using the FDA Guidance of Industry Toxicity Grading Scale for Healthy Adult and Adolescent Participants

Enrolled in Preventive Vaccine Clinical Trials (2007). For the dose-escalation part of the study (Part A), dose limiting toxicities (DLTs) will be monitored. A dose limiting toxicity (DLT) will be defined as any adverse event of Grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to C144-LS and C135-LS mAb. In addition to AEs, the following safety outcomes will be assessed. Blood and urine samples for the assessment of clinical laboratory results will be collected according to the schedule of study procedures listed in Appendix A of the study protocol (v2.1).

- VS parameters: pulse, respiration rate, systolic blood pressure, diastolic blood pressure, temperature
- Clinical laboratory safety parameters:
  - HEM parameters: white blood cell count (WBC), neutrophils, lymphocytes, monocytes (toxicity grading criteria not defined, so will not be graded), eosinophils, basophils (toxicity grading criteria not defined, so will not be graded), hemoglobin, hematocrit, and platelet count.
  - CHEM parameters: creatinine, non-fasting glucose, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).
  - UA parameters: red blood cell count (RBC), WBC, and protein.
- Physical exams:
  - General physical exams include: weight, height, vital signs, and examination of skin, respiratory, cardiovascular, neurological, and abdominal systems.
  - Directed physical exams include: vital signs, examination of administration site, and any further examination indicated by history or observation. Directed physical exams will be performed at all other times, according to Appendix A of the study protocol, Times of Events Schedule.

VS, HEM, CHEM, and UA results will also be assessed using the FDA Guidance of Industry Toxicity Grading Scale for Healthy Adult and Adolescent Participants Enrolled in Preventive Vaccine Clinical Trials (2007).

Assays for PK and ADA will be performed by PPD Laboratory Services, according to the schedule of study procedures listed in Appendix A of the study protocol. For PK, C144-LS and C135-LS levels will be measured by sandwich ELISA.

5. SAMPLE SIZE CONSIDERATIONS

The sample size of 23 to 38 participants was determined according to the dose escalation design used to characterize the safety and the pharmacokinetics profile of combined C144-LS and C135-LS administration at increasing dose levels, to healthy participants. Replacement of 2 participants lost to follow up prior to Week 4 will be allowed.

A sample size of 21 participants receiving C144-LS and C135-LS in combination will provide 95% probability of observing a treatment-related AE that would occur in 13.4% or more of treated participants. If none of the participants experiences a grade 2 or higher AE related to C144-LS and/or C135-LS, the one-sided exact Clopper-Pearson 95% upper confidence bound for the rate of AEs in the population is 13.3%.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Summary statistics for continuous data will include the number of participants included in the analysis (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). Summary statistics for discrete data will include frequencies and proportions, and may include confidence intervals (CIs) for the proportion. When 95% CIs are given for a proportion, exact (Clopper-Pearson) CIs will be used, unless otherwise specified. All enrolled participants will be included in the summaries of participant demographics. The Safety Population will be used for summaries of safety outcomes, the PK Population will be used for summaries of PK outcomes, and the Immunogenicity Population will be used for summaries of the immunogenicity outcomes.

Denominators for safety outcomes will be the number of participants in the Safety Population. Denominators for VS and clinical laboratory results at planned study timepoints will be the number of participants with available results at the specified timepoint for that parameter. Denominators for the conceptual “Maximum Severity Post Baseline” timepoint for VS and clinical laboratory results will be the number of participants with an observed result for that parameter, obtained post-dose.

The sort order of VS and clinical laboratory test parameters is described in Section 9. The sort order for listings will be by: dose group, participant ID, mAb (if applicable, PK and immunogenicity only), and sequence number or date field (whichever is presented first). For participants in Safety Group 2, PK SC Group 2 (200 mg, SC; S2+S3 Active), or Immunogenicity SC Group 2 (200 mg, SC; S2+S3 Active), the listings will be separated out and sorted in the order of "200 mg, SC (S2)" and "200 mg, SC (S3 Active)". All safety, PK, and immunogenicity analyses will be performed by dose group as described in Section 3.3.2. Participant ID will be USUBJID (not PATID) for purposes of de-identification.

6.2. Timing of Analyses

The safety, PK and immunogenicity analyses will occur after all study groups have enrolled and all participants have been followed through the final study visit (Week 48) (or terminated the study early). The final analysis will include/present cumulative safety, PK, and immunogenicity data from the entire study follow-up period.

6.3. Analysis Populations

All analysis populations to be used in the final analysis are described in this section. A tabular listing of all enrolled participants excluded from an analysis population (Safety Population, PK Population, or Immunogenicity Population) will be included in the CSR (Listing 4). Participant enrollment in the study follows the standard definition of participants meeting eligibility criteria, signing informed consent, and being included in the study via either assignment of the IP for participants in Part A, or via randomization to the active study IP or placebo in Part B. In the case that there are multiple reasons for exclusion from the PK Analysis Population, only one reason will be counted when summarizing reasons for exclusion from analysis populations in Table 4. The order that reasons will be considered for exclusion from the PK Population will be: the participant received placebo, the assigned dose was not received or completed, the participant had no measurable antibody (C144-LS or C135-LS) concentration in serum, and the participant had a protocol deviation with potential impact to PK. The order that reasons will be considered for exclusion from the Immunogenicity Population will be: the participant did not have any post dose samples with valid results reported, and/or the participant did not contribute a pre dose baseline sample.

6.3.1. Safety Population

The Safety Population will include all participants that received any amount of the IP, including placebo. This population will be analyzed by the defined dose groups for both high-level and detailed analyses as outlined in Section 3.3.

6.3.2. PK Population

The PK Population will consist of all participants who received an active dose of the IP (C144-LS and/or C135-LS), have at least 1 quantifiable post dose serum sample with a measurable antibody concentration, and who did not have a protocol deviation with potential impact to PK (such as drug administration errors, not meeting eligibility criteria for body weight, or prior/baseline positivity for SARS-CoV-2). Protocol deviations for PK samples taken outside of the protocol window will not result in exclusion. Results from the PK Population will be analyzed by dose group and by antibody (C144-LS or C135-LS). Participants enrolled and assigned to receive some dose of the IP who did not complete their dose, or otherwise received an incorrect dose, will not be included in the respective dose group for analysis. However, listings will include concentrations and parameter estimates for those participants. Regardless of the participant's inclusion in the PK Population, all C144-LS and C135-LS results will be included in listings, including any results from placebo participants from samples taken before unblinding occurred.

6.3.3. Immunogenicity Populations

The C144-LS Immunogenicity Population will consist of all participants who received an active dose of C144-LS, contributed a pre-dose serum immunogenicity sample, and have at least 1 quantifiable post-baseline serum immunogenicity sample for which valid results were reported.

The C135-LS Immunogenicity Population will consist of all participants who received an active dose of C135-LS, contributed a pre-dose serum immunogenicity sample, and have at least 1 quantifiable post-baseline serum immunogenicity sample for which valid results were reported.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

6.5. Missing or Unquantifiable Data

All attempts will be made to collect data per protocol. Any missing data or data anomalies will be communicated to the study site for clarification and resolution. Missing collection times for PK samples may be imputed as the nominal time if the sample was confirmed to have been collected within the protocol defined window. Further details on imputation of BQL sample concentrations and missing PK collection times are included in Section 10.1. Samples which are negative for the presence of ADA will be represented in summary tables and figures with a titer value of one (equivalent to a log titer value of 0). Positive but unquantifiable ADA titration results (samples confirmed positive for ADA but that have titration results lower than the minimum required dilution of 100) will be imputed as 50 for summary tables and figures but presented as "<100" in listings. No further imputation of missing or unquantifiable data is planned.

6.6. Interim Analyses and Data Monitoring

The Safety Monitoring Committee (SMC) will provide ongoing assessment of participant safety during the conduct of the study. Interim reviews of safety data by the SMC will occur at the following pre-determined study milestones:

- When the 1-week safety data is available prior to dose escalation from study group V2 to study group V3;
- Prior to enrolling participants in Part B (study group S3) of the study;
- If any Grade 3 solicited or unsolicited AEs occur that are deemed to be possibly, probably, or definitely related to C144-LS and/or C135-LS; The SMC will review safety data;
- If any grade 3 laboratory AE is reported, confirmed on retest, and is judged by the principal investigator or designee to be possibly, probably, or definitely related to C144-LS and/or C135-LS;
- Any "late occurring" DLT (DLT occurring after 12 weeks of dosing);
- SAEs, which are deemed possibly, probably, or definitely related to C144-LS and C135-LS by the principal investigator or designee, and unanticipated AEs.

In addition, interim analysis of safety and PK endpoints was conducted according to SAP version 1.0 once all study groups were enrolled, and each participant completed follow-up through Week 24 or discontinued the study prior to their Week 24 visit. The interim analysis was not part of the planned analyses in the protocol, but was conducted to facilitate provision of data to support an Emergency Use Authorization (EUA) application for the study IPs.

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

This is a Phase 1 first-in-human study with multiple primary outcomes. Because analyses of primary safety outcomes are descriptive rather than hypothesis tests, no adjustments for multiple testing are planned for analysis of safety outcomes.

ANOVA pairwise comparisons of PK exposure parameters will be adjusted using Tukey's correction for multiple hypotheses, with a 90% Family Wise Confidence Level (FWCL). Additional details are included in the Statistical Analysis section (Section 10.3).

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

The number of participants included in each analysis population will be included in Table 3. Screened participants who were ineligible for enrollment in the study (screen failures) or eligible but not enrolled will be summarized by analysis population exclusion criteria (Table 5). Enrolled participants who were ineligible for inclusion in analysis populations will be summarized by dose group and reason for exclusion (Table 4). The number of enrolled participants who met criteria for each analysis population will also be summarized in Table 3. Individual listings of participants who were excluded from the Safety Population, PK Population, or Immunogenicity Population will be listed (Listing 4).

Participant disposition will be summarized (Table 1), showing the number of participants who were screened, enrolled, received the study product, received all scheduled study product administrations, completed all safety blood draws and urine sample collections, completed all planned PK samples, completed all planned immunogenicity samples, completed final study visit, early termination, and completed the study per protocol.

Participants who discontinued dosing or terminated early from the study will be listed (Listing). A flowchart displaying the disposition of study participants will be included (Figure 1). This figure will present the number of participants screened, enrolled, and lost-to follow up by dose group.

7.2. Protocol Deviations

A summary of protocol deviations will be presented by deviation category, deviation type, and dose group (Table 2). This table will provide both the number of participants and the number of deviations for each deviation category and type. All participant specific and non-protocol specific protocol deviations will be listed in Listing 2 and Listing 3, respectively.

8. EFFICACY EVALUATION

There are no efficacy outcomes included in this report.

9. SAFETY EVALUATION

All safety analyses will be performed using the Safety Population and results will be presented by individual dose group. In addition, demographic and safety results will be presented twice: by individual dose group and at a high-level by pooled dose group (Section 3.3.2). Any medical condition that is present at the time of screening will be considered baseline and will not be reported as an AE, unless the condition worsens in severity or increases in frequency during the study. The denominators for proportions will be indicated within the table or table header.

Solicited AEs, VS and clinical laboratory results will also be used to assess safety. Results from these assessments will be graded by severity and presented in tables and figures by dose group for each post baseline timepoint. See Appendix A of the study protocol, the Times of Events Schedule, for the analysis timepoints that will be summarized are presented for each safety assessment.

Toxicity grading scales for clinical adverse events, solicited AEs, VS results, and clinical laboratory results are provided in the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Participants Enrolled in Preventive Vaccine Clinical Trials (2007).

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, and race for all participants will be summarized by dose group (Table 6). Ethnicity will be categorized as “Hispanic or Latino”, “Not Hispanic or Latino”, “Unknown”, or “Not Reported” in accordance with National Institutes of Health (NIH) reporting policies. Participants may self-designate as belonging to more than one race or may refuse to identify a race. Age, height, weight, and BMI at enrollment will be summarized by dose group (Table 7). Demographic data for all participants will also be listed (Listing 5).

9.1.1. Medical History

All current illnesses and past pre-existing medical conditions (medical history) will be MedDRA coded using MedDRA dictionary version 24.1. Summaries of participant pre-existing medical conditions will be presented by MedDRA system organ class (SOC) and dose group (Table 8). Individual participant listings will be presented for all medical conditions (Listing 6).

9.1.2. Concomitant Medications

All medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHODrug Global C3 September 1, 2021 version of the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be summarized by ATC 1 and ATC 2 (Table 17). Individual participant listings will be presented for all prior and concomitant medications (Listing 19).

9.2. Measurements of Treatment Compliance

Date and time of study product administration, along with information on whether the participant was dosed according to protocol will be included in Listing 7.

9.3. Adverse Events

The Safety Population will be used for all analyses of AEs. An overall summary of AEs, including solicited symptoms (both systemic and local reactogenicity events), unsolicited events, grade 2 or higher laboratory AEs, grade 3 or higher laboratory AEs, grade 3 or higher laboratory AEs which are probably or definitely related to the IP, SAEs, and AEs which led to IP or study discontinuation will be summarized in Table 9.

9.3.1. Solicited Events and Symptoms

Solicited AEs (both local and systemic reactogenicity symptoms) will be collected during in person visits as detailed in Appendix A of the study protocol, the Times of Events Schedule, up to Day 14 after IP administration. Any events reported or continuing after Day 14 would need to be reported as AEs. Reported events will be presented in Table 10. Denominators for proportions are the number of participants in the Safety Population in each group.

The following solicited parameters will be presented in order:

- Systemic reactogenicity symptoms: feverishness, chills, headache, nausea, vomiting, malaise, myalgia, and arthralgia;
- Local reactogenicity symptoms (occurring at the injection site): pain, tenderness, erythema, and induration.

The following summaries of solicited AEs will be presented:

- The number, percent, and 95% CI for the percent or participants who experienced any solicited reactogenicity symptom and each solicited reactogenicity symptom parameter will be tabulated (Table 10). The 95% CIs will be calculated using the Clopper-Pearson method.
- Maximum severity of systemic reactogenicity symptoms (Figure 2) and local reactogenicity symptoms (Figure 3) experienced per dose group.
- Solicited adverse events will be listed separately for systemic reactogenicity symptoms (Listing 8) and local reactogenicity symptoms (Listing 9).

9.3.2. Unsolicited Adverse Events

All AEs will be presented in Listing 10. The AE listing will include the relationship to the IP, action taken with the IP, and whether the participant discontinued due to the AE/SAE information as well.

Denominators for proportions are the number of participants in the Safety Population in each dose group. In summaries of AEs, participants who experienced an adverse event will only be counted once within the same MedDRA category for the worst severity recorded. The worst severity reported will be counted separately for related and unrelated AEs when both severity and relatedness are tabulated. Repeated AEs will be included in summaries of the number of AEs. The following summaries for unsolicited, non-serious, AEs will be presented:

- The number and percent of participants experiencing unsolicited AEs by MedDRA SOC/PT, and maximum severity grade of each SOC/PT, for each dose group (Table 11), related AEs will be summarized in
- Table 12.

- The proportion of participants experiencing related AEs (Figure 4) and the number of events reported (Figure 5) will be summarized by MedDRA SOC and maximum severity will be displayed in bar charts for each dose group.
- Details for each unsolicited AE reported, including AEs that occurred prior to IP administration as a result of study procedures will be listed (Listing 10), and will include, MedDRA SOC/PT, the number of days post IP administration that the AE occurred, its severity, whether the event was an AE, the relationship to the study treatment, the action taken with the study treatment, whether the participant was discontinued due to the AE, and the AE outcome.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

Individual data listings of DLTs will be provided (Listing 13). The listing will include dose group, the AE description, the number of days post dose that the event occurred and its duration, its severity, the event's relationship to the study treatment, the action taken with the IP, whether the participant discontinued due to the AE, the outcome, and MedDRA SOC/PT. Individual data listings of all SAEs, including deaths, will be provided (Listing 11). This listing will include all of the fields in the DLT listing, the reason the event was reported as an SAE, and the event outcome. Individual data listings of any deaths that occurred at any time will be provided (Listing 12).

9.5. Pregnancies

Individual data listings of pregnancy reports will be provided if a pregnancy occurs post dosing during the study:

- Maternal information will be presented in Listing 23.
- Gravida and para information will be presented in Listing 24.
- Live birth outcomes will be presented in Listing 25 and still birth outcomes will be presented in Listing 26.
- Spontaneous, elective, or therapeutic abortion outcomes will be presented in Listing 27.

9.6. Clinical Laboratory Evaluations

The most extreme clinical laboratory severity grades observed after dosing will be summarized (Maximum Severity Post Baseline) and will include results from unscheduled visits. Parameters will be displayed by event direction (increase or decrease). Unscheduled clinical laboratory evaluations will be included in listings of all clinical laboratory results, but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post baseline. Any pre-existing abnormal laboratory results at screening will be graded and presented in listings but will not be reported as AEs unless they are treatment-emergent (severity worsens after dosing). Clinical laboratory parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction.

The following laboratory parameters will be presented (in order):

- HEM: WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, hematocrit, platelets (monocytes and basophils will not be graded for toxicity);
- CHEM: creatinine, glucose, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT;
- UA: RBC, WBC, protein.

Clinical laboratory results will be summarized in tables and figures and listed in listings:

- Number, proportion, and 95% CI of participants with mild, moderate, severe, or potentially life threatening clinical laboratory results by parameter, direction, and dose group for the maximum severity reported post baseline will be reported for chemistry (Table 13), hematology (Table 14), and urinalysis (Table 15) parameters;
- Graphical presentation of change from baseline by parameter, dose group, and timepoint for chemistry (Figure 7, Figure 8, Figure 9, Figure 10, Figure 11, and Figure 12), and hematology (Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19, Figure 20, and Figure 21);
- All chemistry results will be listed in Listing 14. All hematology results will be listed in Listing 15. All urinalysis results will be listed in Listing 16.

9.7. Vital Signs and Physical Evaluations

The most extreme vital sign severity grades observed after dosing will be summarized (Maximum Severity Post Baseline) and will include results from unscheduled visits. Unscheduled VS evaluations will be included in listings of all VS results, but excluded from tabular and graphical summaries by timepoint, except when calculating the maximum severity post baseline. VS parameters that have grading criteria for both decreases (result lower than normal range) and increases (result higher than normal range) will be summarized separately by direction.

The following VS parameters will be presented (in order): pulse (decrease then increase) respiratory rate (increase), systolic blood pressure (decrease then increase), diastolic blood pressure (increase), and temperature (increase).

VS results will be summarized in tables, figures, and listings:

- Number, proportion, and 95% CI of participants with mild, moderate, severe, or potentially life threatening VS results by parameter, direction, and dose group at the maximum severity reported post baseline, including a summary of all VS parameters (Table 16);
- Graphical presentation of change from baseline by parameter, dose group, and timepoint for baseline through Day 1 timepoints (Figure 22, Figure 24, Figure 26, Figure 28, and Figure 30) and for all timepoints (Figure 23, Figure 25, Figure 27, Figure 29, and Figure 31);
- All VS measurements, including weight, and height will be presented in Listing 17.
- Abnormal physical exam findings will be presented in Listing 18.

9.8. Other Safety Measures

No additional safety measures are planned.

10. PHARMACOKINETICS

10.1. Graphical and Tabular Summaries of Pharmacokinetic Profiles

The PK Population will be used when summarizing serum PK concentrations. For both study drugs, concentrations less than the lower limit of quantification (LLOQ) will be displayed as "<LLOQ" in listings and treated as missing in summary tables and figures. Pre-dose concentrations and concentrations collected before the first measurable PK concentration above the LLOQ will be treated as 0 for the purposes of calculating PK parameters. All other concentrations less than the LLOQ, for each study drug, observed after the first measurable concentration of the respective study drug will be considered missing when calculating PK parameters. There will be no imputation of missing concentrations. The geometric mean (GM) and coefficient of variation (CV)% of concentrations will be treated as missing for sets of data points containing a concentration below the limit of quantification (BQL). If sets of data points contain one BQL value at the majority of timepoints, this specification may be relaxed to treat GM and CV% as missing if 2 or more data points in the set contain a BQL value. If relaxed, this will be described in the CSR.

Collection of serum samples outside of the protocol defined time window for a timepoint will not result in exclusion of the sample result from the noncompartmental analysis (NCA). Results from PK serum samples that were collected substantially outside of the protocol defined time window will be excluded from concentration summary statistics by nominal timepoint and plots of mean concentration by nominal timepoint. Time interval windows for PK sample timepoints are defined as follows: + 15 minutes of the nominal timepoint for the samples taken after the C144-LS IV infusion (before C135-LS IV infusion) and after complete IP administration for the IV dose groups; ± 15 minutes of the nominal timepoint for the remaining post dose samples on Day 0; ± 1 day for the Day 1 and Day 3 samples; ± 3 days for the Day 7, Day 14, and Day 28 samples; ± 4 days for the Day 21 sample; ± 5 days for the Week 8 and Week 12 samples, and ± 7 days for the Week 18, Week 24, Week 36, and Week 48 samples. Pre-dose samples taken at any point before the first IP administration on the date of IP administration will be considered in-window; otherwise, they will be considered substantially out-of-window. For other time points, substantially out-of-window samples are defined to be twice the size of the sample timepoint windows described above.

If the exact time of serum PK sample collection is not recorded then the collection time will be imputed as the planned time for analysis, as long as it is not known that the sample was collected outside of the protocol defined window. If it is known that a sample was collected substantially outside of the protocol defined window then the sample will be excluded from concentration summaries in tables and figures. Rationale for excluding results from tables, figures, and NCA will be described in the CSR. Results from samples with imputed collection times will be indicated in listings of PK sample concentrations.

All participants who meet the criteria specified in Section 6.3.2 will be included in the PK population. The bioanalytical laboratory will report C144-LS and C135-LS concentrations in serum in units of µg/mL. Summary statistics for PK concentrations include n (the number of data points used to compute the summary statistics), mean, SD, min, max, GM, and CV%.

The definition of CV is described below.

For an independent identically distributed random sample $\{x_1, x_2, ..., x_n\}$ from a log-normal distribution, let s^2 be the sample variance statistic of the natural log-transformed values of the sample. The CV will be defined as:

$$CV = \sqrt{\exp(s^2) - 1}$$

PK concentrations will be presented in tables, figures, and listings:

- Mean and standard deviation for C144-LS and C135-LS concentrations by dose group and timepoint for the SC dose group (Table 18) and the IV dose group (Table 19);
- Individual concentrations in serum will be presented graphically for all sample timepoints from BL to 72 h post IP administration for each dose group on a linear and semi-log scale. Sample times include immediately after the C144-LS IV infusion (for the IV dose groups), immediately after C135-LS administration (for the IV dose groups), and 1 hour, 3 hours, 6 hours, 9 hours, 12 hours, and 72 hours post IP administration. C144-LS concentrations will be presented in Figure 32, Figure 34, Figure 36, Figure 38, and Figure 40 and C135-LS concentrations will be presented in Figure 42, Figure 44, Figure 46, Figure 48, and Figure 50;
- Individual concentrations in serum will be presented graphically over all sampling timepoints for each dose group separately on a linear and semi-log scale for C144-LS (Figure 33, Figure 35, Figure 37, Figure 39, Figure 41) and C135-LS (Figure 43, Figure 45, Figure 47, Figure 49, Figure 51);
- Plots of mean (± SD) concentration in serum profiles will be presented on linear and semi-log scales for both C144-LS (Figure 52 for baseline to 72 h post dose and Figure 53 for all post dose timepoints) and C135-LS (Figure 54 for baseline to 72 h post dose and Figure 55 for all post dose timepoints) by dose group.
- Participant specific serum PK concentrations of C144-LS and C135-LS will be listed in Listing 20, and will include nominal time, actual sample collection time, laboratory reported concentration, analysis concentration, and whether the sample was used in λ_z calculations.

The participant level PK concentration listing will include separate columns for concentrations reported by the lab and concentrations used for analysis. The lab reported concentrations may include codes, such as: “BQL” or “QNS” (Quantity not Sufficient), while the analysis concentrations will contain numeric data only, including imputed values such as 0 for pre-dose timepoints and BQL samples prior to the first quantifiable sample. The listing will also indicate the nominal time (i.e., the planned time) and actual post dose time in hours associated with the sample and will note sample times which were collected out of window, substantially out of window, or imputed.

10.2. Noncompartmental Analysis

PK parameters from serum PK data will be estimated through NCA using version 8.2 or higher of Phoenix WinNonlin®. Actual post dose time will be used for the estimation of serum PK parameters instead of nominal time. In the case of imputed sample collection times, the imputed time will be included in the NCA. Any outliers identified in the PK analysis will be discussed in the analysis report. Outliers will not be excluded from the PK analysis.

Phoenix WinNonlin® NCA will use the following settings to compute parameters from serum PK data:

- Linear Up Log Down calculation method
- Uniform weighting
- Oral dosing for SC dose groups, IV dosing for IV dose groups.
- Lambda Z Acceptance Criteria
  - Rsq_adjusted > 0.90
  - Includes at least 3 timepoints after Tmax

Only the PK parameters that meet the predefined criteria listed above will be included in summary tables and figures and statistical analyses. In the case that the Rsq_adjusted Lambda Z acceptance criteria is not met, the terminal phase PK parameters (λ_z, T-HALF, AUC (INF), CLT (or CLT/F), and Vz/F (or Vss)), defined below, will be excluded from summary presentations and statistical analyses. Regardless of whether the criteria was met, all PK parameters will be reported in listings (Listing 21 and Listing 22).

Cmax

Cmax is defined as the maximum drug or metabolite concentration observed in serum over all PK sample concentrations. It will be obtained from the **Cmax** parameter calculated by WinNonlin®. If there is no measurable concentration in the participant's PK profile, then Cmax will be missing for that participant. Cmax will be reported in units of µg/mL.

Tmax

Time of maximum concentration (Tmax) is defined as the time at which the Cmax occurs. It will be obtained from the **Tmax** parameter calculated by WinNonlin®. If there is no measurable Cmax in the participant's PK profile, then Tmax will be missing for that participant. Tmax will be reported in units of h.

λ_z

The terminal phase elimination rate constant (λ_z) is defined as the first-order rate constant describing the rate of decrease of drug or metabolite concentration in the terminal phase (defined as the terminal region of the PK curve where drug or metabolite concentration follows first-order elimination kinetics). λ_z will be computed as the slope of a terminal region consisting of ≥ 3 successive points in the plot of log-transformed concentration data versus time. λ_z will be estimated using uniform weighting.

Timepoints used in the estimation of λ_z will only be selected using the WinNonlin® automatic algorithm.

This parameter will be obtained from the **Lambda_z** parameter calculated by WinNonlin®. λ_z will be reported in units of 1/day.

T-HALF ($t_{1/2}$ as shown in protocol)

The T-HALF is defined as the time required for the drug or metabolite concentration to decrease by a factor of one-half in the terminal phase. The T-HALF can be estimated as ln(2)/ λ_z. It will be obtained from the **HL_Lambda_z** parameter calculated by WinNonlin®. Half-life will be reported in units of days.

AUC

AUC(0-T) is defined as the area under the concentration-time curve from the start of dosing (time 0) to the time of the last measured concentration. AUC(0-T) will be estimated using the Linear Up Log Down calculation method and obtained from the **AUClast** parameter calculated by WinNonlin®.

AUC(INF) is defined as the total area under the concentration-time curve from the start of dosing (time 0) taken to the limit as the end time becomes arbitrarily large. AUC(INF) can be calculated by adding AUC(0-T)to an extrapolated value equal to the last measured concentration greater than the lower limit of quantification (LLOQ) divided by λ_z:

$$\text{AUC(INF)} = \text{AUC(0-T)} + \frac{\text{C}_{\text{last}}}{\boldsymbol{\lambda_z}}$$

Where C_{last} is the last measured concentration ≥ LLOQ. AUC(INF) will be obtained from the **AUCINF_obs** parameter calculated by WinNonlin®.

$\%AUC_{ex}$ is defined as percentage of AUC(INF) obtained by extrapolation from time of the last measured concentration to infinity. $\%AUC_{ex}$ can be calculated by dividing AUC from time of the last measured concentration to infinity by AUC(INF):

$$\%\text{AUC}_{ex} = \frac{AUC(INF) - \text{AUC}(0-\text{T})}{AUC(INF)},$$

If $\%AUC_{ex}$ is >20%, the estimated AUC(INF) will be excluded from statistical summaries of PK parameter estimates and downstream calculations. $\%AUC_{ex}$ will be obtained from the **AUC_%Extrap_obs** parameter calculated by WinNonlin®.

All AUCs will be reported in units of µg*day/mL.

CLT

Clearance (CLT) is defined as the volume of serum completely cleared of drug per unit time and is estimated in trials of an IV-administered drug as the actual dose divided by the AUC(INF). It will be obtained from the **Cl_obs** parameter calculated by WinNonlin® only for participants in the IV dose groups. If the amount extrapolated portion of AUC(INF) is >20%, the estimated CLT value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. CLT will be reported in units of mL/day.

CLT/F

Apparent oral clearance (CLT/F) will be calculated as Dose/AUC(INF). If $\%AUC_{ex}$ is >20%, the estimated CLT/F value will be excluded from statistical summaries of parameter estimates and downstream calculations. CLT/F will be obtained from the **CL_F_obs** parameter calculated by WinNonlin® only for participants in the SC dose groups. Clearance will be reported in units of mL/day.

Vss

Apparent volume of distribution at a steady state (Vss) is estimated in trials of an IV-administered drug and can be calculated using the AUC and area under the first moment curve (AUMC). It will be obtained from the **Vss_obs** parameter calculated by WinNonlin® only for participants in the IV dose groups. If the amount extrapolated portion of AUC(INF) is >20%, the estimated Vss value will be flagged when listed in the report and will be excluded from statistical summaries of parameter estimates and downstream calculations. Volume of distribution at steady state will be reported in units of L.

Vz/F

Apparent volume of distribution (Vz/F) will be calculated as $(CLT/F)/\lambda_z$. If $\%AUC_{ex}$ is >20%, the estimated Vz/F value will be excluded from statistical summaries of parameter estimates and downstream calculations. Vz/F will be obtained from **Vz_F_obs** calculated by WinNonlin® only for participants in the SC dose groups. Volume will be reported in units of L.

Serum PK parameters will be summarized and presented tabularly for C144-LS and C135-LS for the PK SC dose groups (Table 20) and the PK IV dose groups (Table 21);

- Participant specific serum PK parameters will be listed for C144-LS (Listing 21) and C135-LS (Listing 22).

10.3. Statistical Analysis

The PK Population will be used for statistical analyses of serum PK parameters described above. All individual PK parameters will be listed including any exclusions and reasons for exclusion. Summary statistics will be tabulated for each PK parameters by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(INF), CLT, CLT/F, Vss, and Vz/F. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for T-HALF.

10.3.1. Assessment of Dose Proportionality

The presence of dose proportionality in serum will firstly be assessed by comparing dose adjusted concentrations and exposure parameters graphically and using descriptive statistics. Dose adjusted exposure parameters will be calculated by dividing each exposure parameter (AUC(0-T), AUC(INF), and Cmax) by the corresponding dose for each dose group.

Comparison of dose adjusted exposure parameters will be presented tabularly and graphically:

- Summary statistics of dose adjusted exposure parameters will be presented tabularly for C144-LS and C135-LS for the SC PK groups (Table 22**)** and for the IV PK groups (Table 23) separately;

- Dose adjusted exposure parameters will be compared graphically in boxplots for each dose group for both C144-LS and C135-LS (Figure 56 and Figure 57).

Pairwise comparisons of exposure parameters (AUC(0-T), AUC(INF), and Cmax) will be conducted between dose groups using the PK Population. The pairwise comparison ratios will be displayed as follows:

- SC 2,3 / SC 1
- IV2 / IV 1
- IV3 / IV 1
- IV3 / IV 2

Results of the 90% confidence interval for the ratio of each exposure parameter compared between dose groups will be presented in Table 24. The estimated ratio of exposure parameters between doses will be graphically compared to the expected ratio given dose proportionality (dose ratio), along with the estimated CI for each pairwise comparison in a forest plot for both C144-LS and C135-LS (Figure 58 and Figure 59).

Since the confidence intervals will be for the ratio of each exposure parameter compared between dose groups, the values will be log transformed before using PROC ANOVA, and the resulting confidence intervals will be exponentiated to present the final results. The expected ratio for each comparison will be the ratio of the doses in the dose groups that are compared.

Pseudo code to estimate pairwise comparisons of the ratio of exposure parameters between dose groups is presented below. Variables used in the model are also detailed below:

- AVAL = log transformed value of the exposure parameter value for each exposure parameter (ex, AUC(0-T), AUC(INF), or Cmax)
- TRT = dose group indicator

Pseudo code for estimating the ratio of exposure parameters between each dose group using Tukey's correction for multiple hypotheses is below:

```
PROC ANOVA data= ADPP;
        class TRT;
        model AVAL=TRT;
        means TRT / tukey alpha = 0.10;
run;
```

The resulting confidence limit values and parameter estimates will then be exponentiated to give the estimate of the ratio of the exposure parameters and associated confidence limit on the linear scale. This analysis will be conducted for all exposure parameters (AUC(0-T), AUC(INF), and Cmax), for both C144-LS and C135-LS.

A power model of each exposure parameter will be used to further assess dose proportionality in the IV dose groups.

$$Y = \alpha + \beta ln(dose) + \varepsilon$$

Where Y is the log transformed value of the exposure parameter being assessed. Coefficient estimates and 95% confidence intervals for the dose coefficient will be provided in Table 25. A β power coefficient estimate of approximately 1 is consistent with dose proportionality. A comparison of each model fit versus the exposure parameter values for each dose level will be presented in Figure 60 for C144-LS and Figure 61 for C135-LS.

11. IMMUNOGENICITY

All immunogenicity results and analyses will be presented using the C144-LS and C135-LS immunogenicity populations by individual dose group. The denominators for proportions will be indicated within the table or table header. Immunogenicity serum samples will be collected at the times specified in Appendix A of the Study Protocol (Times of Events Schedule).

11.1.1. Assessment of Anti-Drug Antibody (ADA) Responses

The occurrence of ADA responses will be evaluated by a three-tiered approach using validated screening and confirmatory assays, followed by titering of responses to determine if the responses were treatment-induced or treatment-boosted. Confirmatory assays will only be conducted for samples with positive screening results. Response titrations will only be conducted for confirmed positive samples. An ADA response will be considered to have occurred if both the screening and confirmatory results are positive. An ADA response will be considered to not have occurred if either the screening or confirmatory result is negative. Serum ADA results will be summarized by the number of participants with available samples for testing. Refer to Section 6.5 for how samples negative or inconclusive for the presence of ADA, and positive but unquantifiable will be handled in summary tables and figures.

Sample ADA status will be defined as follows:

- Baseline ADA-positive sample: ADA is detected in the Day 0 sample, before IP administration.
- Baseline ADA-negative sample: ADA is not detected in the Day 0 sample, before IP administration.
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive seroconversion) sample in a participant for whom ADA is not detected at baseline, or (2) an ADA detected sample with an increase of at least 4-fold in ADA titer from baseline.
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline.

Sample ADA status will be used to define participant ADA status:

- Baseline ADA-positive participant: A participant with baseline ADA-positive sample.
- ADA-positive participant: A participant with at least one ADA positive-sample relative to baseline at any time after IP administration.
  - *Persistent Positive (PP):* ADA-positive sample at 2 or more consecutive timepoints where the first and last consecutive ADA-positive samples are at least 16 weeks apart.
  - *Not PP-Last Sample Positive:* Not persistent positive with ADA-positive sample at the participant's last sampling timepoint.
  - *Other Positive:* Not persistent positive but with some ADA-positive sample and with ADA-negative sample at the participant's last sampling timepoint.
- ADA-negative participant: A participant with no ADA-positive sample after IP administration.

The following summaries of ADA sample and participant results will be presented:

- Summary of confirmed positive ADA sample results will be presented by sample timepoint in Table 26 for the C144-LS Immunogenicity Population and Table 27 for the C135-LS Immunogenicity Population.
- Summary of ADA participant results over the entire study period will be presented in Table 28 for the C144-LS Immunogenicity Population and Table 29 for the C135-LS Immunogenicity Population.
- Summary statistics (number with results, Geometric Mean Titer (GMT), and 95% CI for the GMT) of all ADA titer levels will be presented by sample timepoint in Table 30 for the C144-LS Immunogenicity Population and Table 31 for the C135-LS Immunogenicity Population.
- ADA titration results will be presented graphically in boxplots by dose group and time point in Figure 62 and Figure 63 for the C144-LS Immunogenicity Population (SC and IV dose groups, respectively) and Figure 64 and Figure 65 for the C135-LS Immunogenicity Population (SC and IV dose groups, respectively).
- All ADA screening, confirmation, and titer results will be listed by dose group for the C144-LS and C135-LS immunogenicity populations in Listing 28 and Listing 29, respectively.

All ADA samples will be summarized in tables, figures, and listings, regardless of whether the sample was collected within the protocol defined window or not. ADA samples collected outside of the protocol defined window will be noted in Listing 28 and Listing 29.

12. REPORTING CONVENTIONS

The mean, median, SD, and any other statistics (other than quantiles), will be reported to one decimal place greater than the original data. Order statistics, such as the min and max values, will be reported to the same number of decimal places as the original data. Proportions and percentages will be presented as 2 decimal places; values <0.01 will be presented as "<0.01". Estimated parameters not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

Cmax will be reported with the same number of significant digits as the measurement. Other PK parameters will be reported using 3 significant digits.

Listings of individual participant data will include a Participant ID column. The participant identifiers assigned by site staff are replaced throughout this report with the SDTM variable USUBJID to protect the confidentiality of those who participated to participate in this protocol. USUBJID has been created as a composite of the platform code followed by a numeric identifier assigned chronologically to enrolled participants as well as screening failures across all sites and protocols in the EDC platforms. Any data sharing activities will include the USUBJID and not the participant identifiers assigned at the study site.

13. TECHNICAL DETAILS

SAS version 9.4 or above and R version 4.1 or above will be used to generate tables, figures, and listings. PK parameters will be estimated through NCA using Phoenix® WinNonlin® version 8.2 or later.

14. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The interim analysis per SAP Version 1.0, covering follow-up through Week 24 timepoint was conducted for timely dissemination of results for the planned Emergency Use Authorization application.

15. REFERENCES

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5. A phase 1 study of the safety and pharmacokinetics of a combination of two anti-SARS-CoV-2 mAbs (C144-LS and C135-LS) in healthy volunteers v2.1. Protocol Number: RUCOV1. The Rockefeller University; February 2021.

16. APPENDICES: LIST OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3, respectively.

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 1: Participant Disposition of Enrolled Participants by Dose Group – Safety Population

Participant Disposition	[Safety Group 1] (N=X) n (%)	[Safety Group 2] (N=X) n (%)	[Safety Group 3] (N=X) n (%)	[Safety Group 4] (N=X) n (%)	[Safety Group 5] (N=X) n (%)	[Safety Group 6] (N=X) n (%)	All Participants (N=X) n (%)
Received IP [a]	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
Received all assigned IP injections/ infusions, uninterrupted							
Completed all Safety Blood Draws							
Completed all PK Blood Draws							
Completed all Immunogenicity (ADA) Blood Draws							
Completed Follow-up							
Discontinued/Interrupted IP[b]							
Reason for Discontinuation/Interruption							
[Reason 1]							
[Reason 2]							
Early Termination[b]							
Reason for Early Termination							
[Reason 1]							
[Reason 2]							

Notes: N = Number of participants in the safety analysis population.
[a] Participants in study Part A were not randomized. Enrolled refers to participants in study Part A who were assigned study product. Only participants in study Part B were randomized.
[b] Refer to Listing for detailed reasons participants discontinued or terminated early. Discontinued is defined as partial dosing that was started and stopped without being restarted, or full dosing of only one mAB. Interruption is defined as stopped and restarted infusion, or a change in infusion location/IV site.

Table 2: Distribution of Protocol Deviations on Enrolled Participants by Category, Type, and Dose Group

Category	Deviation Type	Number of Participants (Number of Deviations)						
		[Safety Group 1] (N=X)	[Safety Group 2] (N=X)	[Safety Group 3] (N=X)	[Safety Group 4] (N=X)	[Safety Group 5] (N=X)	[Safety Group 6] (N=X)	All Participants (N=X)
Eligibility/enrollment	Any type	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)	x (x)
	Did not meet inclusion criterion							
	Met exclusion criterion							
	ICF not signed prior to study procedures							
	Other							
IP administration schedule	Any type							
	Out of window visit							
	Missed visit/visit not conducted							
	Missed IP administration							
	Delayed IP administration							
	Required procedure done incorrectly							
	Study product temperature excursion							
	Other							
Follow-up visit schedule	Any type							
	Out of window visit							
	Missed visit/visit not conducted							
	Other							

Table 2: Distribution of Protocol Deviations by Category, Type, and Dose Group (continued)

Category	Deviation Type	Number of Participants (Number of Deviations)						
		[Safety Group 1] (N=X)	[Safety Group 2] (N=X)	[Safety Group 3] (N=X)	[Safety Group 4] (N=X)	[Safety Group 5] (N=X)	[Safety Group 6] (N=X)	All Participants (N=X)
Protocol procedure/assessment	Any type							
	Incorrect version of ICF signed							
	Blood not collected							
	Urine not collected							
	Swab not collected							
	Other specimen not collected							
	Specimen result not obtained							
	Required procedure not conducted							
	Required procedure done incorrectly							
	Required procedure out of window							
	Study product temperature excursion							
	Specimen temperature excursion							
	Sponsor halted IP administration							
	Other							

Note: N=Number of participants in the safety analysis population.

Table 3: Analysis Populations by Dose Group – All Enrolled Participants

Analysis Populations	[Safety Group 1] (N=X)	[Safety Group 2] (N=X)	[Safety Group 3] (N=X)	[Safety Group 4] (N=X)	[Safety Group 5] (N=X)	[Safety Group 6] (N=X)	[All Participants] (N=X)
	n	n	n	n	n	n	n
Safety Population	x	x	x	x	x	x	x
PK Population	x	x	x	x	x	x	x
Immunogenicity Population (ADA)	x	x	x	x	x	x	x

Programming note: If C144-LS and C135-LS Immunogenicity Populations are different, they will be presented in separate rows in the table.

Table 4: Analysis Population Exclusions by Dose Group – All Enrolled Participants

Analysis Population Exclusions	Reason for Inclusion/Exclusion	[Safety Group 1] (N=X) n (%)	[Safety Group 2] (N=X) n (%)	[Safety Group 3] (N=X) n (%)	[Safety Group 4] (N=X) n (%)	[Safety Group 5] (N=X) n (%)	[Safety Group 6] (N=X) n (%)	[All Participants] (N=X) n (%)
Reasons for Exclusion								
Safety Population	Did not receive any amount of the IP[a]	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
PK Population	Any reason	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (100)	x (x.x)
	Received placebo						x (100)	
	No post dose serum sample with a measurable concentration of C144-LS or C135-LS							
	Protocol deviation(s) with potential to impact PK							
Immunogenicity Population (ADA)	Any reason	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	No post dose sample with a valid result							
	No pre dose sample with a valid result							

Notes:
N = Number of enrolled participants.
The order that reasons were considered for exclusion from analysis populations follows the order that reasons are presented in the table.
[a] Includes placebo.

Programming note: If C144-LS and C135-LS Immunogenicity Populations are different, they will be presented in separate rows in the table.

Table 5: Summary of Screen Failures and Eligible Non-Enrollments

Category	Screen Failure or Eligible Non-Enrollment Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of participants failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx.x
	Aged 18 to <65	x	xx.x
	If sexually active male or female and participating in sexual activity that could lead to pregnancy, agrees to use one effective method of contraception from 10 days prior to the antibody administration until 6 months after IP administration	x	xx.x
Exclusion	Any exclusion criterion	x	xx.x
	Weight > 110 kg (groups S1 and S2 only)		
	History of prior positive SARS-CoV-2 RT-PCR or SARS- CoV-2 serology		
	Active respiratory or non-respiratory systems consistent with COVID-19		
	Medically attended acute illness or hospitalization (i.e., >24 hours) for any reason within 30 days prior to screening		
	Acute exacerbation of a chronic pulmonary condition (e.g., chronic obstructive pulmonary disease [COPD], asthma exacerbations, or uncontrolled hypertension, as defined by a systolic blood pressure > 180 and or diastolic blood pressure > 120, in the presence or absence of antihypertensive medications) in the past 6 months.		
	Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.		
	Other clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation.	x	xx.x
	Are eligible for COVID-19 vaccination prior to your entry in the study according to local guidelines (e.g., healthcare professionals, non-healthcare professionals such as teachers, firefighters, public transit workers).	x	xx.x
	Laboratory abnormalities in the parameters listed: • Absolute neutrophil count ≤ 1,500 K/mcL • Hemoglobin ≤ 10.5 gm/dL if female; 11 gm/dL if male; • Platelet count ≤ 125,000 K/mcL; • ALT ≥ 1.25 x ULN; AST ≥ 1.25 X ULN; • Total bilirubin ≥ 1.25 x ULN; • Creatinine ≥ 1.1 x ULN	x	xx.x
	Pregnancy or lactation		
	Any vaccination within 14 days prior to SARS-CoV-2 mAbs administration (except influenza vaccine).		
	History of prior therapy with any SARS-CoV-2 vaccine or antibodies, including convalescent plasma.		
	Known allergy/sensitivity or any hypersensitivity to components of the investigational agents.		
	History of severe reaction to a vaccine or monoclonal antibody administration or history of severe allergic reactions.		
	Participation in another clinical study of an investigational product currently or within the past 12 weeks, or expected participation during this study.		
Eligible but Not Enrolled	Any reason for being eligible but not enrolled		
	[Reason 1]		
	[Reason 2]		

[a] More than one criterion may be marked per participant.
[b] Denominator for percentages is the total number of screen failures.

Table 6: Summary of Categorical Demographic and Baseline Characteristics by Dose Group – Safety Population

This table will be repeated for the pooled safety dose groups, excluding the "all participants" column.

Variable	Characteristic	[Safety Group 1] (N=X) n (%)	[Safety Group 2] (N=X) n (%)	[Safety Group 3] (N=X) n (%)	[Safety Group 4] (N=X) n (%)	[Safety Group 5] (N=X) n (%)	[Safety Group 6] (N=X) n (%)	All Participants (N=X) n (%)
Sex	Male	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
	Female							
Ethnicity	Not Hispanic or Latino							
	Hispanic or Latino							
	Not Reported							
	Unknown							
Race	American Indian or Alaska Native							
	Asian							
	Black or African American							
	Native Hawaiian or Other Pacific Islander							
	White							
	Multi-Racial							
	Not Reported							
	Other/Unknown/Refused to specify							
Notes: N = Number of participants in the safety analysis population.								

Table 7: Summary of Continuous Demographic and Baseline Characteristics by Dose Group – Safety Population

This table will be repeated for the pooled safety dose groups, excluding the "all participants" column.

Variable	Statistic	[Safety Group 1] (N=X)	[Safety Group 2] (N=X)	[Safety Group 3] (N=X)	[Safety Group 4] (N=X)	[Safety Group 5] (N=X)	[Safety Group 6] (N=X)	All Participants (N=X)
Age	Mean	xx	xx	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x
Height	Mean	xx	xx	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x
Weight	Mean	xx	xx	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x
BMI	Mean	xx	xx	xx	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx	xx	xx	xx
	Median	xx	xx	xx	xx	xx	xx	xx
	Minimum	x	x	x	x	x	x	x
	Maximum	x	x	x	x	x	x	x

Note: N = Number of participants in the safety analysis population.

Table 8: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Dose Group – Safety Population

MedDRA System Organ Class	[Safety Group 1] (N=X)	[Safety Group 2] (N=X)	[Safety Group 3] (N=X)	[Safety Group 4] (N=X)	[Safety Group 5] (N=X)	[Safety Group 6] (N=X)	All Participants (N=X)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any SOC	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
[SOC 1]							
[SOC 2]							

Note: N = Number of participants in the safety analysis population; n = Number of participants reporting medical history within the specified SOC. Each participant is only counted once per SOC.

Safety Tables

Table 9: Overall Summary of Adverse Events – Safety Population

This table will be repeated for the pooled safety dose groups.

	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any AE[1,2,4]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Any Solicited Symptom[2,3]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Systemic Symptoms (All Grades)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Local Symptoms (All Grades)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Any Unsolicited AE within 4 weeks of IP[4]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5] and Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5] and Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Any Unsolicited AE during the study follow-up[4]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5] and Grade 2 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5] and Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Any Grade 2 or Higher Laboratory Result[6]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Any Grade 3 or Higher Laboratory Result[6]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Probably or Definitely Related[5] Grade 3 or Higher	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Any SAE[7]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
Related[5]	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
AE Leading to Treatment Discontinuation	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)
AE Leading to Study Discontinuation	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)	xx (xx.x)	(xx.x, xx.x)

N = Number of participants in the safety analysis population
n = Number of participants who experienced at least one event (participants with >1 reported event are counted only once in each category).
% = Percentage of participants who experienced events in each category relative to the total number within each dose group.
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
[1] Includes solicited AEs and unsolicited AEs.
[2] Solicited symptoms are reported through 14 days post-vaccination (i.e., 15-day follow-up period).
[3] By definition, solicited symptoms (local and systemic) are considered related to IP.
[4] Includes SAEs..
[5] "Related" is defined as possibly, probably, or definitely related to the IP.
[6] Chemistry or hematology laboratory results post-IP administration and through 28 days after each vaccination. Only Grade 3 or higher laboratory results were assessed for relationship to IP.
[7] SAE: Serious Adverse Event reported at any time during the study, including death.

Table 10: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, and Dose Group – Safety Population

This table will be repeated for the pooled safety dose groups.

Symptom	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Solicited Symptom												
Any	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x
Grade 1												
Grade 2												
Grade 3												
Grade 4												
Grade 5												
Repeat For:												
Any Systemic Symptom												
Feverishness												
Chills												
Headache												
Nausea												
Vomiting												
Malaise												
Arthralgia												
Any Local Symptom												
Pain[1]												
Tenderness[1]												
Erythema[1]												
Induration[1]												

Notes: N = Total number of participants in the safety analysis population.
n (%) = Number and percent of participants with an event (% of N).
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
Solicited symptoms are reported through 2 weeks following IP administration. The maximum severity experienced over the 2-week period is summarized.
[1] Occurring at injection or infusion site.

Table 11: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, and Dose Group – Safety Population

This table will be repeated for the pooled safety dose groups.

MedDRA SOC/PT	Severity Grade	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
		n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
Any AE													
Any SOC/PT	Any	x (xx.x)	x	x (xx.x)	x	x (xx.x)	x	x (xx.x)	x	x (xx.x)	x	x (xx.x)	x
	Grade 1												
	Grade 2												
	Grade 3												
	Grade 4												
	Grade 5												
SOC 1													
Any PT	Any												
	Grade 1												
	Grade 2												
	Grade 3												
	Grade 4												
	Grade 5												
PT 1	Any												
	Grade 1												
	Grade 2												
	Grade 3												
	Grade 4												
	Grade 5												

Notes: N = Number of participants in the safety analysis population.
n = Number of participants who experienced at least one event (participants with >1 reported event are counted only once for each SOC/PT for the highest severity reported).
% = Percentage of participants who experienced events in each SOC/PT relative to the total number within each dose group.
Number of Events = The total number of AEs reported in each SOC/PT combination for the specified grade.

Table 12: Related Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity and Dose Group – Safety Population

This table will repeat Table 11 for related unsolicited adverse events.

Table 13: Laboratory Results Maximum Severity Post-Baseline by Dose Group, Chemistry – Safety Population

This table will be repeated for the pooled safety dose groups.

Parameter/ Maximum Severity Post-Baseline[1]	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Chemistry Parameter												
None[2]	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x
Grade 1												
Grade 2												
Grade 3												
Grade 4												
Missing												
Repeat for:												
Creatinine, Increase												
Glucose, Decrease												
Glucose, Increase												
Total Bilirubin, Increase												
Direct Bilirubin, Increase												
Alkaline Phosphatase, Increase												
AST, Increase												
ALT, Increase												

Notes: N = Number of participants in the safety analysis population with available results.
n (%) = Number and percent of participants with a reported event (% of N).
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
[1] "Maximum Post Baseline" indicates the maximum severity experienced by each participant at any timepoint post baseline, including unscheduled assessments.
[2] Severity grade of "None" refers to results within the site reference range, or results outside of the site reference range that do not meet the Grade 1 criteria as defined by the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

Table 14: Laboratory Results Maximum Severity Post-Baseline by Dose Group, Hematology – Safety Population

This table will be repeated for the pooled safety dose groups.

Parameter/ Maximum Severity Post-Baseline[1]	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Hematology Parameter												
None[2]	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x
Grade 1												
Grade 2												
Grade 3												
Grade 4												
Missing												
Repeat for:												
White Blood Cells, Decrease												
White Blood Cells, Increase												
Neutrophils, Decrease												
Lymphocytes, Decrease												
Eosinophils, Increase												
Hemoglobin, Decrease												
Hematocrit, Decrease												
Platelets, Decrease												

Notes: N = Number of participants in the safety analysis population with available results.
n (%) = Number and percent of participants with a reported event (% of N).
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
[1] "Maximum Post Baseline" indicates the maximum severity experienced by each participant at any timepoint post baseline, including unscheduled assessments.
[2] Severity grade of "None" refers to results within the site reference range, or results outside of the site reference range that do not meet the Grade 1 criteria as defined by the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

Table 15: Laboratory Results Maximum Severity Post-Baseline by Dose Group, Urinalysis – Safety Population

Parameter/ Maximum Severity Post-Baseline[1]	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Urinalysis Parameter												
None	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x
Grade 1												
Grade 2												
Grade 3												
Grade 4												
Missing												
Repeat for:												
Red Blood Cells, Increase												
Protein, Increase												

Notes: N = Number of participants in the safety analysis population with available results.
n (%) = Number and percent of participants with a reported event (% of N).
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
[1] "Maximum Post Baseline" indicates the maximum severity experienced by each participant at any timepoint post baseline, including unscheduled assessments.

Table 16: Vital Sign Results Maximum Severity Post-Baseline by Dose Group – Safety Population

This table will be repeated for the pooled safety dose groups.

Parameter/ Maximum Severity Post-Baseline[1]	[Safety Group 1] (N=X)		[Safety Group 2] (N=X)		[Safety Group 3] (N=X)		[Safety Group 4] (N=X)		[Safety Group 5] (N=X)		[Safety Group 6] (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any VS Parameter												
None	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x	x (xx.x)	xx.x, xx.x
Grade 1												
Grade 2												
Grade 3												
Grade 4												
Missing												
Repeat for:												
Pulse, Decrease												
Pulse, Increase												
Respiratory Rate, Increase												
Systolic Blood Pressure, Decrease												
Systolic Blood Pressure, Increase												
Diastolic Blood Pressure, Increase												
Temperature, Increase												

Notes: N = Number of participants in the safety analysis population with available results.
n (%) = Number and percent of participants with a reported event (% of N).
95% CI = Exact Clopper-Pearson 95% confidence interval for the percent.
[1] "Maximum Post Baseline" indicates the maximum severity experienced by each participant at any timepoint post baseline, including unscheduled assessments.

Table 17: Summary of Participants with Concurrent Medications by WHO Drug Classification – Safety Population

WHO Drug Code Level 1, Anatomic Group / Level 2, Therapeutic Subgroup	[Safety Group 1] (N=X) n (%)	[Safety Group 2] (N=X) n (%)	[Safety Group 3] (N=X) n (%)	[Safety Group 4] (N=X) n (%)	[Safety Group 5] (N=X) n (%)	[Safety Group 6] (N=X) n (%)	All Participants (N=X) n (%)
Any Level 1 Codes							
Any Level 2 Codes	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
[ATC Level 1 - 1]							
Any [ATC 1 - 1]							
ATC [2 -1]							
ATC [2 -2]							
ATC [2 -3]							
[ATC Level 1 - 2]							
ATC [2 -1]							
ATC [2 -2]							
ATC [2 -3]							

Note: N = Number of participants in the Safety Population.

Pharmacokinetics

Table 18: Summary of C144-LS and C135-LS Concentrations in Serum by Dose Group: All Timepoints, PK Population – SC Dose Groups

Nominal Time[a] (h)	Mean (SD)			
	C144-LS		C135-LS	
	[PK SC Group 1] (N=X)	[PK SC Group 2] (N=X)	[PK SC Group 1] (N=X)	[PK SC Group 2] (N=X)
D0 - prior to IP Administration	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]
D0 - 1 h post end of IP Administration				
D0 - 3 h post end of IP Administration				
D0 - 6 h post end of IP Administration				
D0 - 9 h post end of IP Administration				
D0 - 12 h post end of IP Administration				
D1				
D3				
D7				
D14				
D21				
D28				
W8				
W12				
W18				
W24				
W36				
W48				

Notes:
N = Number of participants in the PK population in each dose group.
Mean concentration at each timepoint is reported in units of µg/mL. SD is reported in parentheses next to the mean. The number of data points used to compute summary statistics at each time point are included in brackets. All BQL values were treated as missing.
[a] Times are relative to time of dosing.

Table 19: Summary of C144-LS and C135-LS Concentrations in Serum by Dose Group: All Timepoints, PK Population – IV Dose Groups

Nominal Time[a] (h)	Mean (SD)					
	C144-LS			C135-LS		
	[PK IV Group 1] (N=X)	[PK IV Group 2] (N=X)	[PK IV Group 3] (N=X)	[PK IV Group 1] (N=X)	[PK IV Group 2] (N=X)	[PK IV Group 3] (N=X)
D0 - prior to C144-LS Infusion	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]	x (x.x) [n]
D0 - end of C144-LS Infusion (prior to C135-LS Infusion)						
D0 - end of C135-LS Infusion						
D0 - 1 h post end of IP Administration						
D0 - 3 h post end of IP Administration						
D0 - 6 h post end of IP Administration						
D0 - 9 h post end of IP Administration						
D0 - 12 h post end of IP Administration						
D1						
D3						
D7						
D14						
D21						
D28						
W8						
W12						
W18						
W24						
W36						
W48						

Notes:
N = Number of participants in the PK population in each dose group.
Mean concentration at each timepoint is reported in units of µg/mL. SD is reported in parentheses next to the mean. The number of data points used to compute summary statistics at each time point are included in brackets. All BQL values were treated as missing.
[a] Times are relative to time of dosing.

Table 20: Summary Statistics of Serum PK Parameters by Dose Group, PK Population – SC Dose Groups

PK Parameter (Units)	C144-LS		C135-LS	
	PK SC Group 1 (N=X)	PK SC Group 2 (N=X)	PK SC Group 1 (N=X)	PK SC Group 2 (N=X)
Cmax, (µg/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
Tmax, (h)	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]
AUC(0-T), (µg*day/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
AUC(INF), (µg*day/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
λ_z, (1/day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
T-HALF, (day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
CLT/F, (mL/day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
Vz/F, (L)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]

Notes: N = Number of participants included in the PK analysis population for each group.
Values of GM (CV %) [n] are shown, except for Tmax for which values of median (min-max) are shown and T-HALF for which values of mean (SD) are shown. n represents the number of data points used to compute the summary statistics.
Terminal phase parameters were excluded from summary statistics if the R squared adjusted was < 0.9. AUC(INF), clearance, and volume parameters were excluded if the percentage of AUC(INF) obtained by extrapolation was > 20%.

Table 21: Summary Statistics of Serum PK Parameters by Dose Group, PK Population – IV Dose Groups

PK Parameter (Units)	C144-LS			C135-LS		
	PK IV Group 1 (N=X)	PK IV Group 2 (N=X)	PK IV Group 3 (N=X)	PK IV Group 1 (N=X)	PK IV Group 2 (N=X)	PK IV Group 3 (N=X)
Cmax, (µg/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
Tmax, (h)	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]	x (x - x) [n]
AUC(0-T), (µg*day/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
AUC(INF), (µg*day/mL)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
λ_z, (1/day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
T-HALF, (day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
CLT (mL/day)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]
Vss (L)	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]	x (x) [n]

Notes: N = Number of participants included in the PK analysis population for each group.
Values of GM (CV %) [n] are shown, except for Tmax for which values of median (min-max) are shown and T-HALF for which values of mean (SD) are shown. n represents the number of data points used to compute the summary statistics.
Terminal phase parameters were excluded from summary statistics if the R squared adjusted was < 0.9. AUC(INF), clearance, and volume parameters were excluded if the percentage of AUC(INF) obtained by extrapolation was > 20%.

Table 22: Summary Statistics for Dose Adjusted Exposure Parameters, PK Population – SC Dose Groups

mAb/Dose Adjusted Exposure Parameter	Dose Group	N	Mean	SD	Median	Min	Max	GM	CV %
C144-LS									
AUC(0-T)/Dose, (µg*day/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x
AUC(INF)/Dose, (µg*day/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x
Cmax/Dose, (µg/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x
C135-LS									
AUC(0-T)/Dose, (µg*day/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x
AUC(INF)/Dose, (µg*day/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x
Cmax/Dose, (µg/mg*mL)	SC1	x	x.x	x.x	x.x	x	x	x.x	x.x
	SC2	x	x.x	x.x	x.x	x	x	x.x	x.x

Notes:
N = Number of data points used to compute the summary statistics.
GM=geometric mean, CV=coefficient of variation.

Table 23: Summary Statistics for Dose Adjusted Exposure Parameters, PK Population – IV Dose Groups

mAb/Dose Adjusted Exposure Parameter	Dose Group	N	Mean	SD	Median	Min	Max	GM	CV %
C144-LS									
AUC(0-T)/Dose, (µg*day/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x
AUC(INF)/Dose, (µg*day/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x
Cmax/Dose, (µg/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x
C135-LS									
AUC(0-T)/Dose, (µg*day/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x
AUC(INF)/Dose, (µg*day/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x
Cmax/Dose, (µg/mg*mL/kg)	IV1	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV2	x	x.x	x.x	x.x	x	x	x.x	x.x
	IV3	x	x.x	x.x	x.x	x	x	x.x	x.x

Notes:
N = Number of data points used to compute the summary statistics.
GM=geometric mean, CV=coefficient of variation.

Table 24: Comparison of Exposure Parameters Between Dose Groups, Pairwise Comparisons, PK Population – All PK Dose Groups

Exposure Parameter/Comparison	Dose Ratio	C144-LS		C135-LS	
		Estimate	90% CI[1]	Estimate	90% CI[1]
AUC(0-T)					
SC2/SC1	x.xx	x.xx	(x.xx, x.xx)	x.xx	(x.xx, x.xx)
IV2/IV1					
IV3/IV1					
IV3/IV2					
AUC(INF)					
SC2/SC1					
IV2/IV1					
IV3/IV1					
IV3/IV2					
Cmax					
SC2/SC1					
IV2/IV1					
IV3/IV1					
IV3/IV2					

Notes:
n = Number of participants in the PK analysis group subset with results included in the ANOVA test comparison.
[1] Student's t-distribution was used to estimate 90% confidence intervals for the SC dose group comparisons. ANOVA pairwise comparisons using Tukey's correction for multiple hypotheses was used to estimate the 90% confidence intervals for the IV dose group comparisons.

Table 25: Power Model Coefficient Estimates from Dose Proportionality Assessment Among IV Dose Groups – PK Population

Exposure Parameter	C144-LS		C135-LS	
	Estimate	95% CI	Estimate	95% CI
AUC(0-T)	x	x.xx, x.xx	x	x.xx, x.xx
AUC(INF)				
Cmax				
Note: A β power coefficient estimate of 1 is consistent with dose proportionality.				

Immunogenicity

Table 26: Summary of Confirmed Positive Anti-Drug Antibody Results, C144-LS - Immunogenicity Population

Study Day	[Immunogenicity Group 1] 100 mg, SC (S1) (N=X)	[Immunogenicity Group 2] 200 mg, SC (S2 + S3 Active) (N=X)	[Immunogenicity Group 3] 1.5 mg/kg, IV (V1) (N=X)	[Immunogenicity Group 4] 5 mg/kg, IV (V2) (N=X)	[Immunogenicity Group 5] 15 mg/kg, IV (V3) (N=X)	[Immunogenicity Group 6] Placebo (N=X)
D0 (Baseline)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)
D28						
W12						
W24						
W48						
Any Post-Baseline Timepoint	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)

N=the number of participants in the C144-LS Immunogenicity Population in each dose group.
Result numerators displayed represent the number of confirmed positive anti-C144-LS antibody samples within each dose group at each study day. Denominators represent the total number of samples tested for ADA within each dose group at each study day. The corresponding percentage is displayed in parentheses for each dose group and study day.
An ADA positive sample at baseline is defined as: ADA detected in the Day 0 sample, before IP administration.
An ADA positive sample post-baseline is defined as: (1) an ADA detected (positive seroconversion) sample in a participant for whom ADA is not detected at baseline, or (2) an ADA detected sample with an increase of at least 4-fold in ADA titer from baseline.

Table 27: Summary of Confirmed Positive Anti-Drug Antibody Results, C135-LS - Immunogenicity Population

This table will repeat the above table for C135-LS.

Table 28: Summary of Anti-Drug Antibody Participant Results, C144-LS - Immunogenicity Population

ADA Result	Participant ADA Response Type	[Immunogenicity Group 1] 100 mg, SC (S1) (N=X)	[Immunogenicity Group 2] 200 mg, SC (S2 + S3 Active) (N=X)	[Immunogenicity Group 3] 1.5 mg/kg, IV (V1) (N=X)	[Immunogenicity Group 4] 5 mg/kg, IV (V2) (N=X)	[Immunogenicity Group 5] 15 mg/kg, IV (V3) (N=X)	[Immunogenicity Group 6] Placebo (N=X)
Baseline ADA Positive	-	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)	x (xx.x)
ADA Positive	Persistent Positive						
	Not PP-Last Sample Positive						
	Other Positive						
ADA Negative	-						

N=the number of participants in the C144-LS Immunogenicity Population in each dose group.
Result numbers displayed represent the number of participants contributing each ADA response type. N was used as the percent denominator. The corresponding percentage is displayed in parentheses for each dose group.
Persistent Positive (PP): A participant with an ADA-positive sample at 2 or more consecutive timepoints where the first and last consecutive ADA-positive samples are at least 16 weeks apart.
Not PP-Last Sample Positive: A participant who is not persistent positive with ADA-positive sample at the last sampling timepoint.
Other Positive: A participant who is not persistent positive but with some ADA-positive sample and with the last sample being ADA negative.

Table 29: Summary of Anti-Drug Antibody Participant Results, C135-LS - Immunogenicity Population

This table will repeat the above table for C135-LS.

Table 30: Summary of Anti-Drug Antibody Titration Results and Fold Rise from Baseline, C144-LS - Immunogenicity Population

Study Day	Statistic	[Immunogenicity Group 1] 100 mg, SC (S1) (N=X)	[Immunogenicity Group 2] 200 mg, SC (S2 + S3 Active) (N=X)	[Immunogenicity Group 3] 1.5 mg/kg, IV (V1) (N=X)	[Immunogenicity Group 4] 5 mg/kg, IV (V2) (N=X)	[Immunogenicity Group 5] 15 mg/kg, IV (V3) (N=X)	[Immunogenicity Group 6] Placebo (N=X)
D0 (Baseline)	n	x					
	GMT	xxx.x					
	95% CI	(xxx.x, xxx.x)					
D28	n	x					
	GMT	xxx.x					
	95% CI	(xxx.x, xxx.x)					
W12	…						
W24	…						
W48	…						
Peak Titer Post-Baseline	…						

GMT=Geometric Mean Titer
N=the number of participants in the C144-LS Immunogenicity Population in each dose group.
n=the number of samples with quantifiable titration results in each dose group at each sample timepoint.
Titration results which were positive for ADA but have titers below the minimum required dilution (100) were analyzed as 50. Titration results which were negative for the presence of ADA were analyzed as 1.

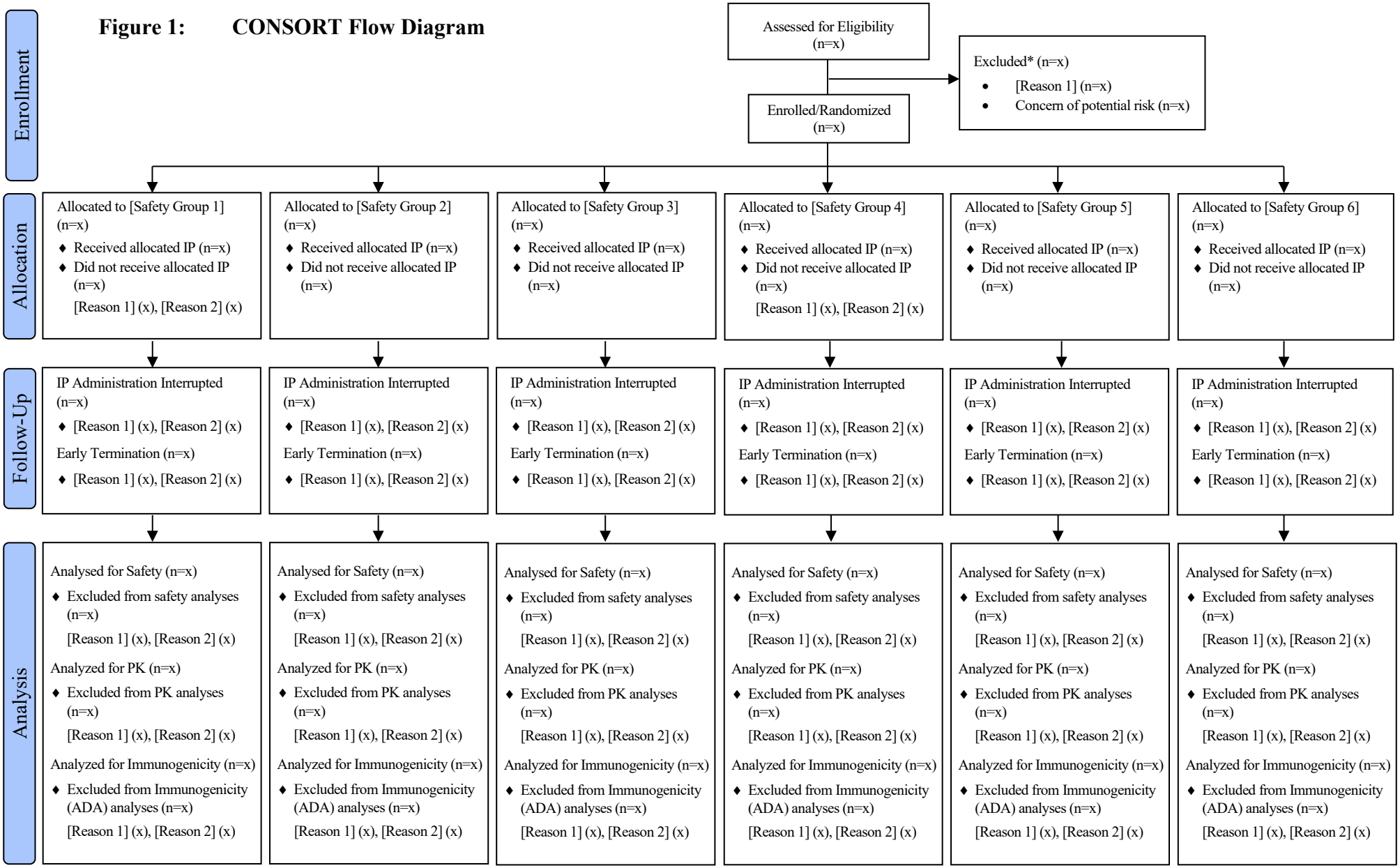
Table 31: Summary of Anti-Drug Antibody Titration Results and Fold Rise from Baseline, C135-LS - Immunogenicity Population

This table will repeat the above table for C135-LS.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

Figure 1: CONSORT Flow Diagram



Safety Figures

Figure 2: Maximum Severity of Solicited Systemic Symptoms per Dose Group by Day Post IP Administration

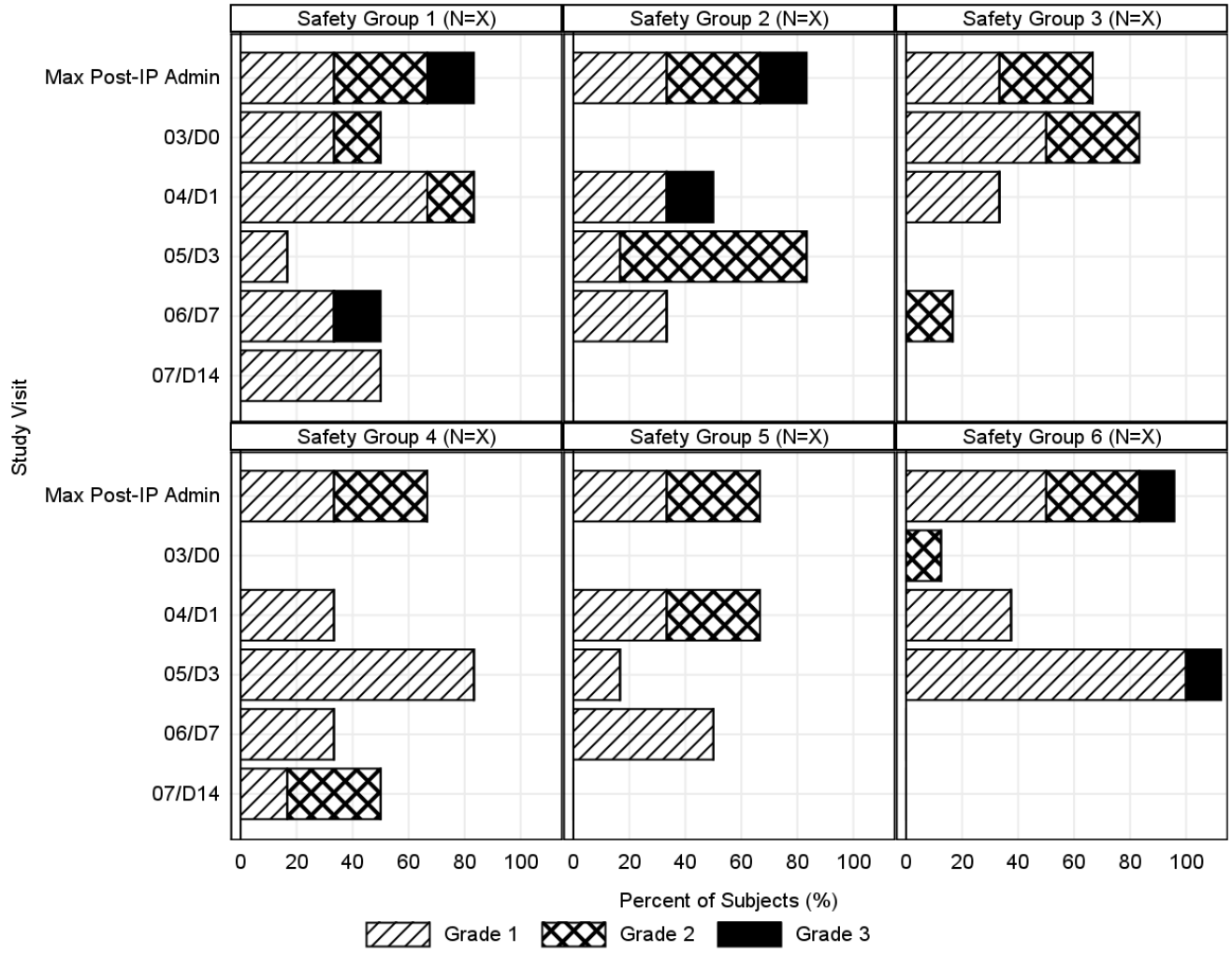
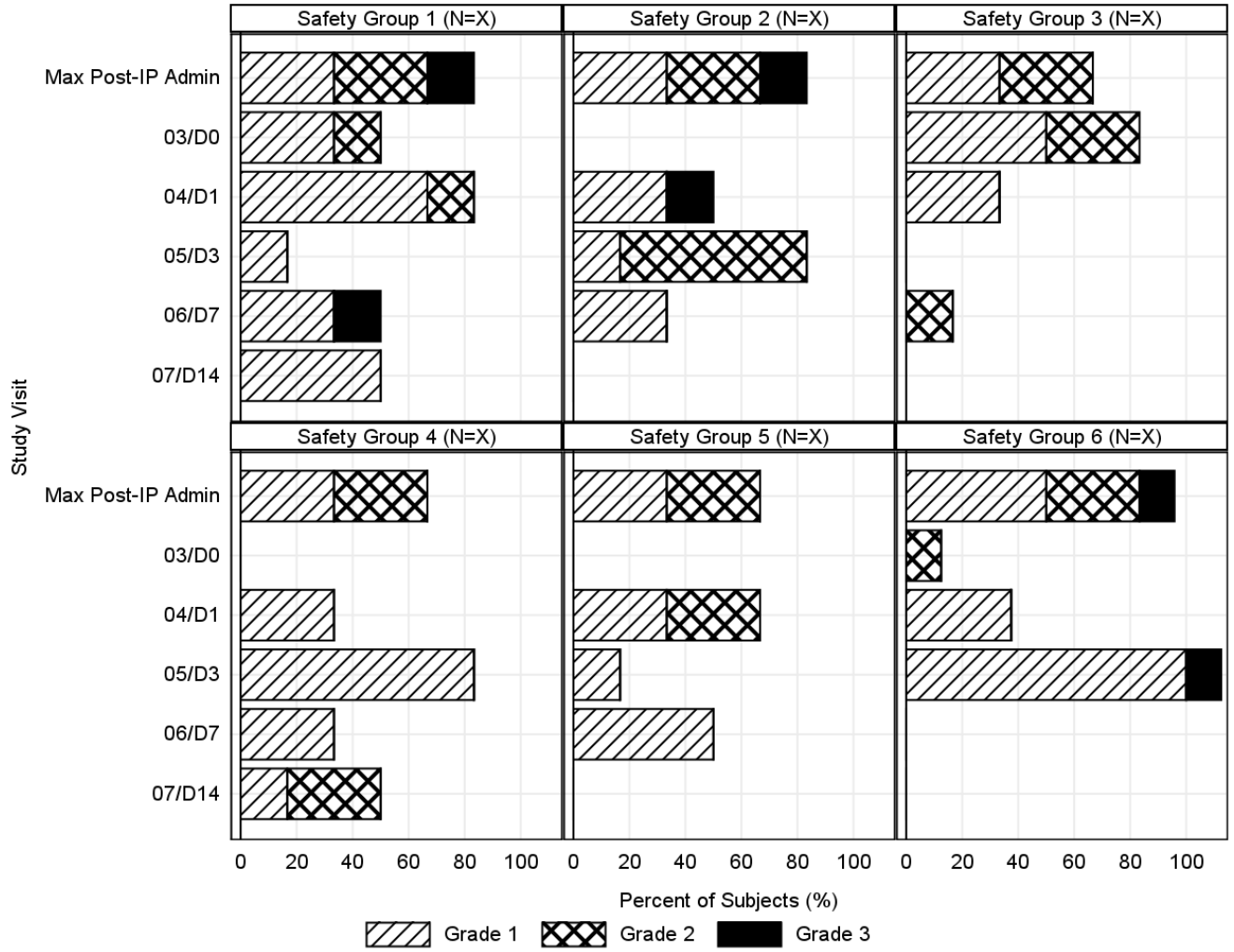


Figure 3: Maximum Severity of Solicited Local Symptoms per Dose Group by Day Post IP Administration



14.3.1.2 Unsolicited Adverse Events

Figure 4: Proportion of Participants with Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

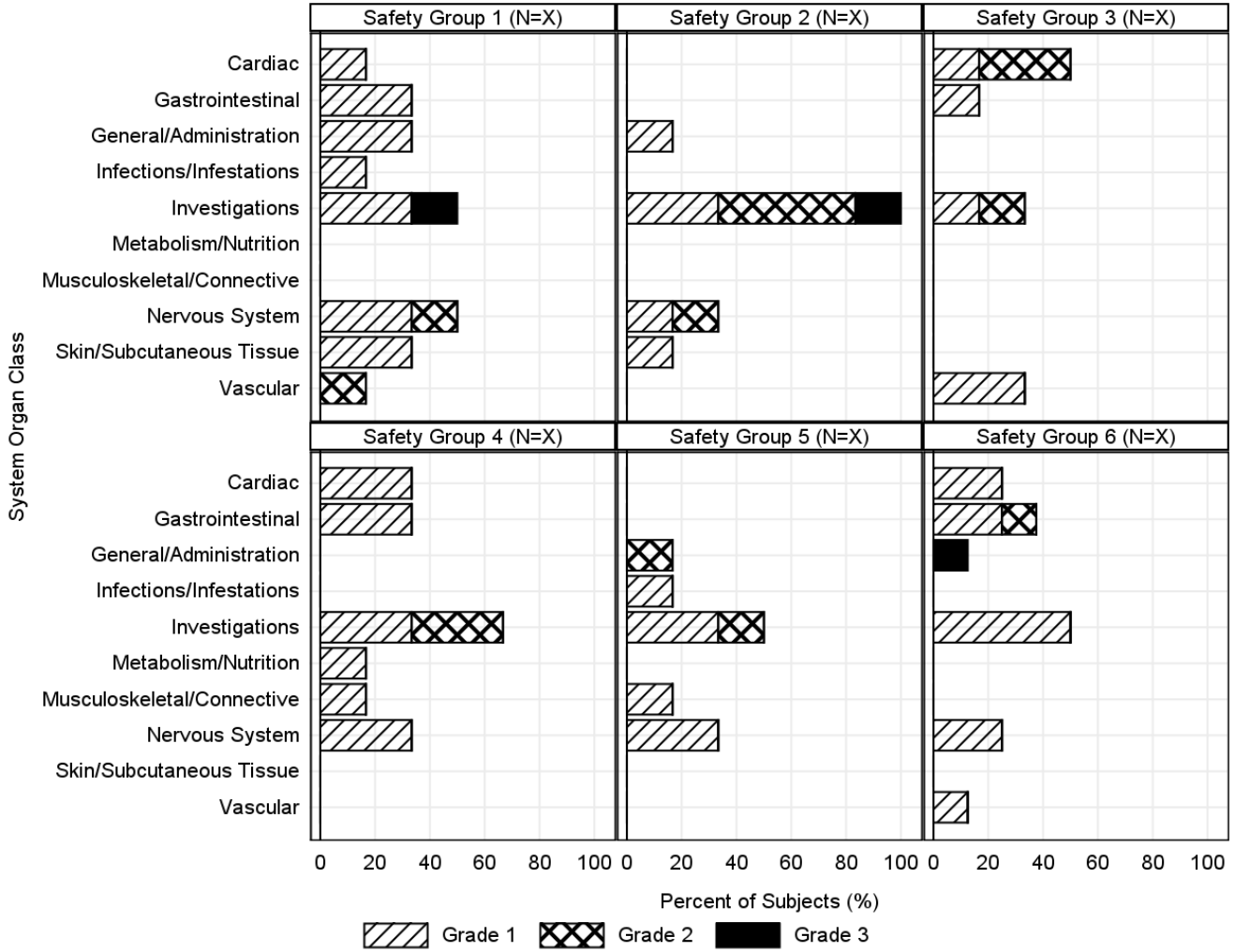


Figure 5: Frequency of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

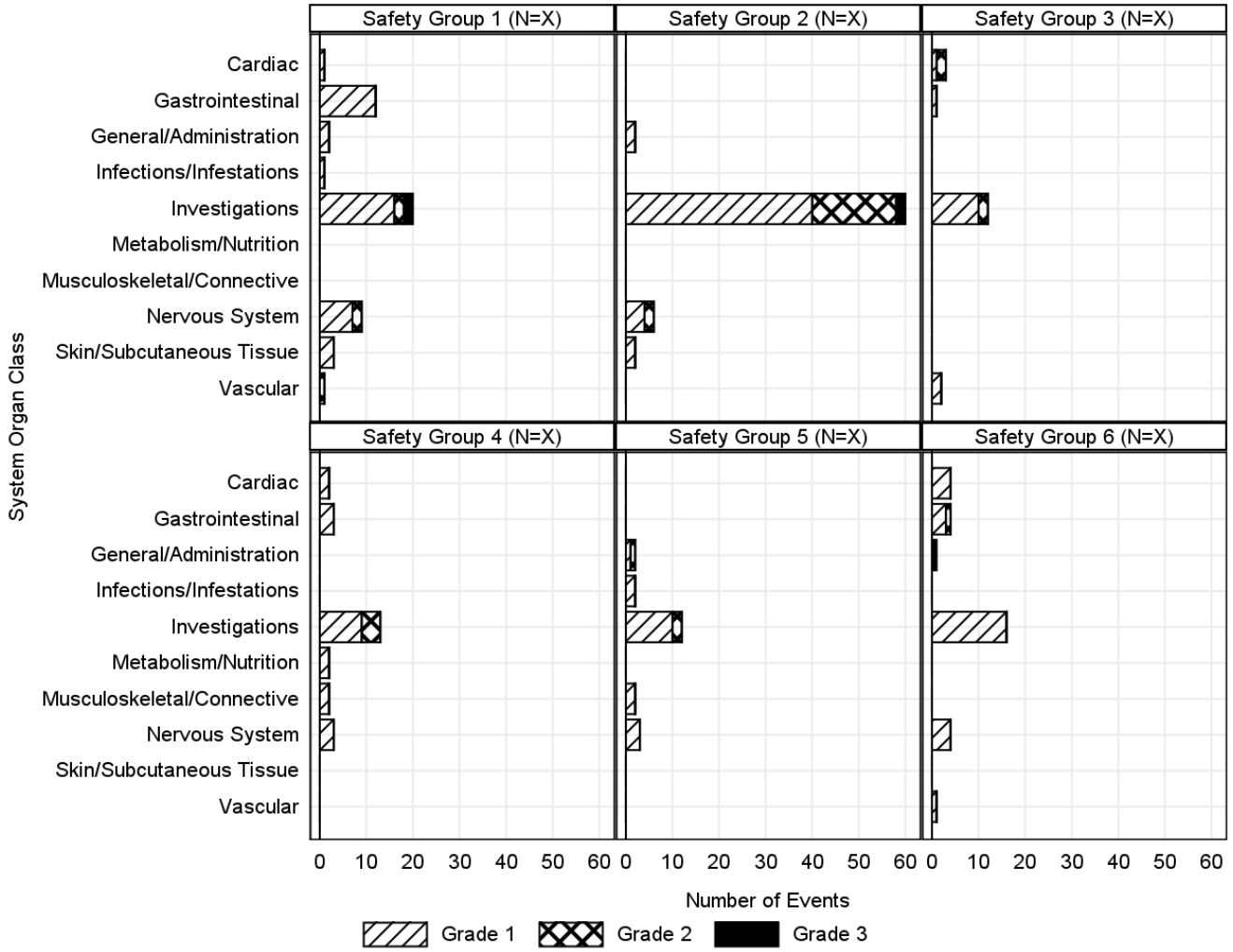
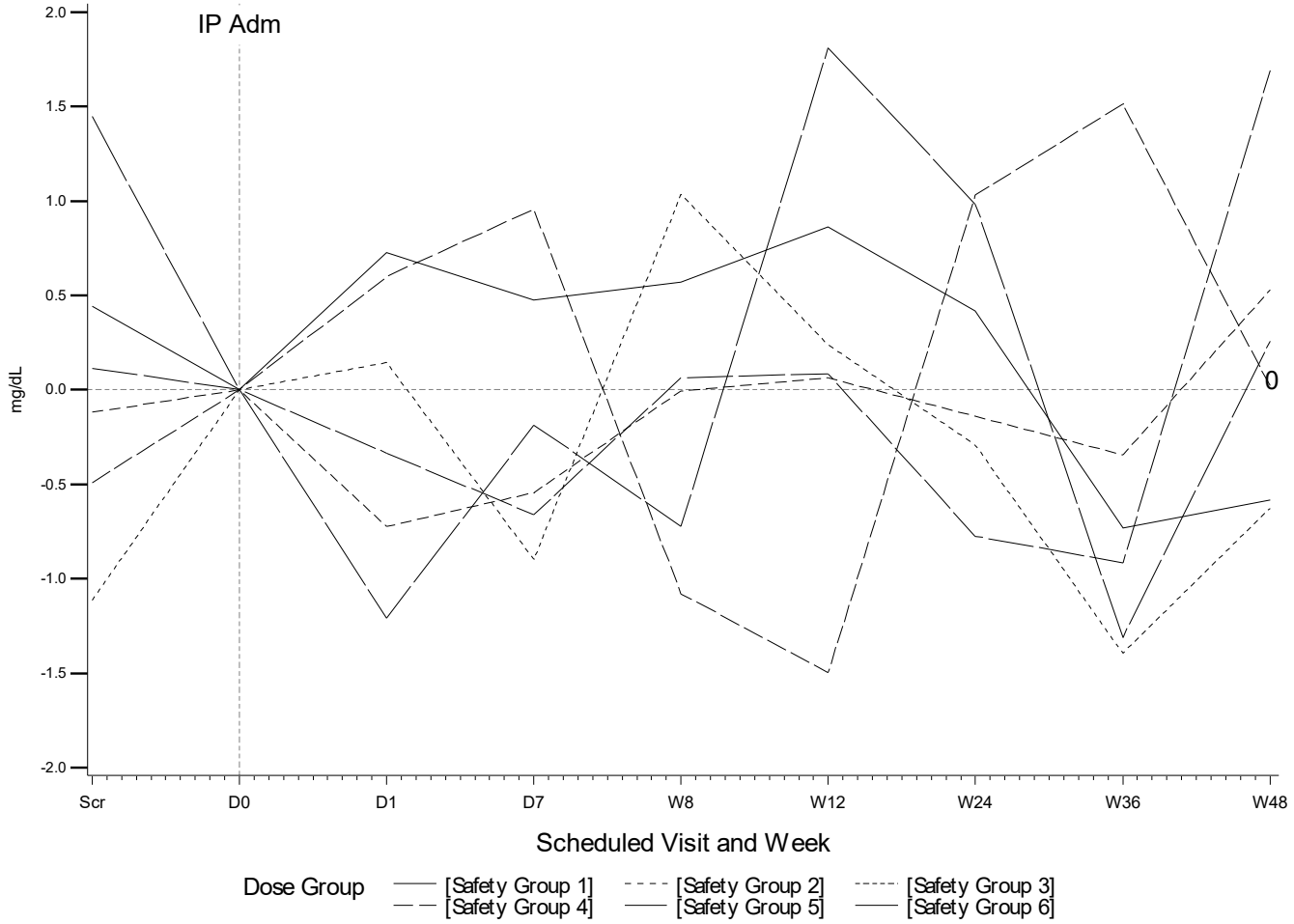


Figure 6: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group – Creatinine



*D0 timepoints represent the following visits, in order: post C144-LS, post IP Admin, 1 h post IP admin, 3 h post IP admin, 6 h post IP Admin, and 12 h post IP admin.

Figure 7: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Glucose

This figure will repeat Figure 6 for glucose.

Figure 8: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Total Bilirubin

This figure will repeat Figure 6 for total bilirubin.

Figure 9: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Direct Bilirubin

This figure will repeat Figure 6 for direct bilirubin.

Figure 10: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Alkaline Phosphatase

This figure will repeat Figure 6 for alkaline phosphatase.

Figure 11: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –AST

This figure will repeat Figure 6 for AST.

Figure 12: Chemistry Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –ALT

This figure will repeat Figure 6 for ALT.

Figure 13: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –WBC

This figure will repeat Figure 6 for white blood cells.

Figure 14: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Neutrophils

This figure will repeat Figure 6 for neutrophils.

Figure 15: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group – Lymphocytes

This figure will repeat Figure 6 for lymphocytes.

Figure 16: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Monocytes

This figure will repeat Figure 6 for monocytes.

Figure 17: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Eosinophils

This figure will repeat Figure 6 for eosinophils.

Figure 18: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Basophils

This figure will repeat Figure 6 for basophils.

Figure 19: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group – Hemoglobin

This figure will repeat Figure 6 for hemoglobin.

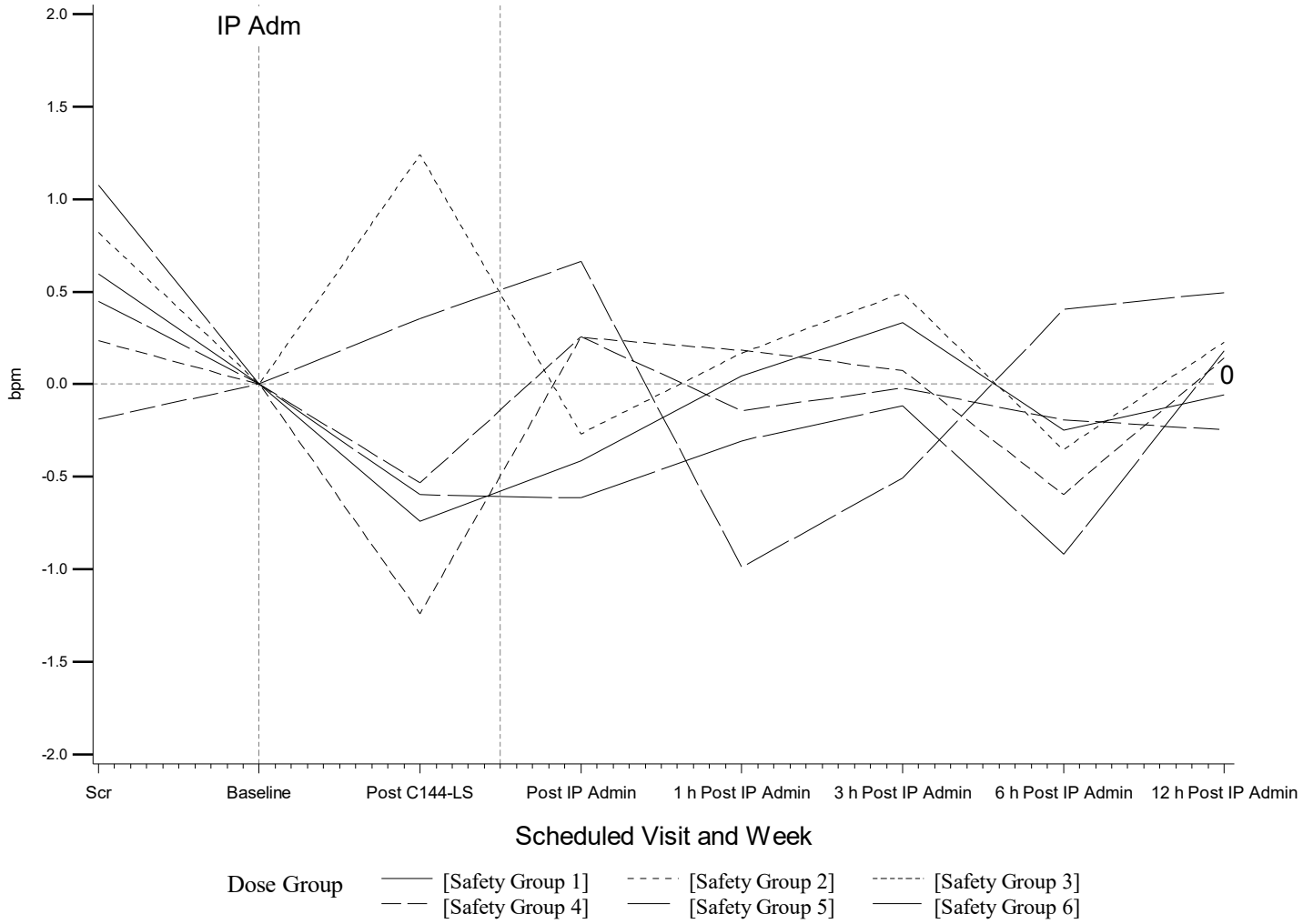
Figure 20: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Hematocrit

This figure will repeat Figure 6 for hematocrit.

Figure 21: Hematology Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Dose Group –Platelets

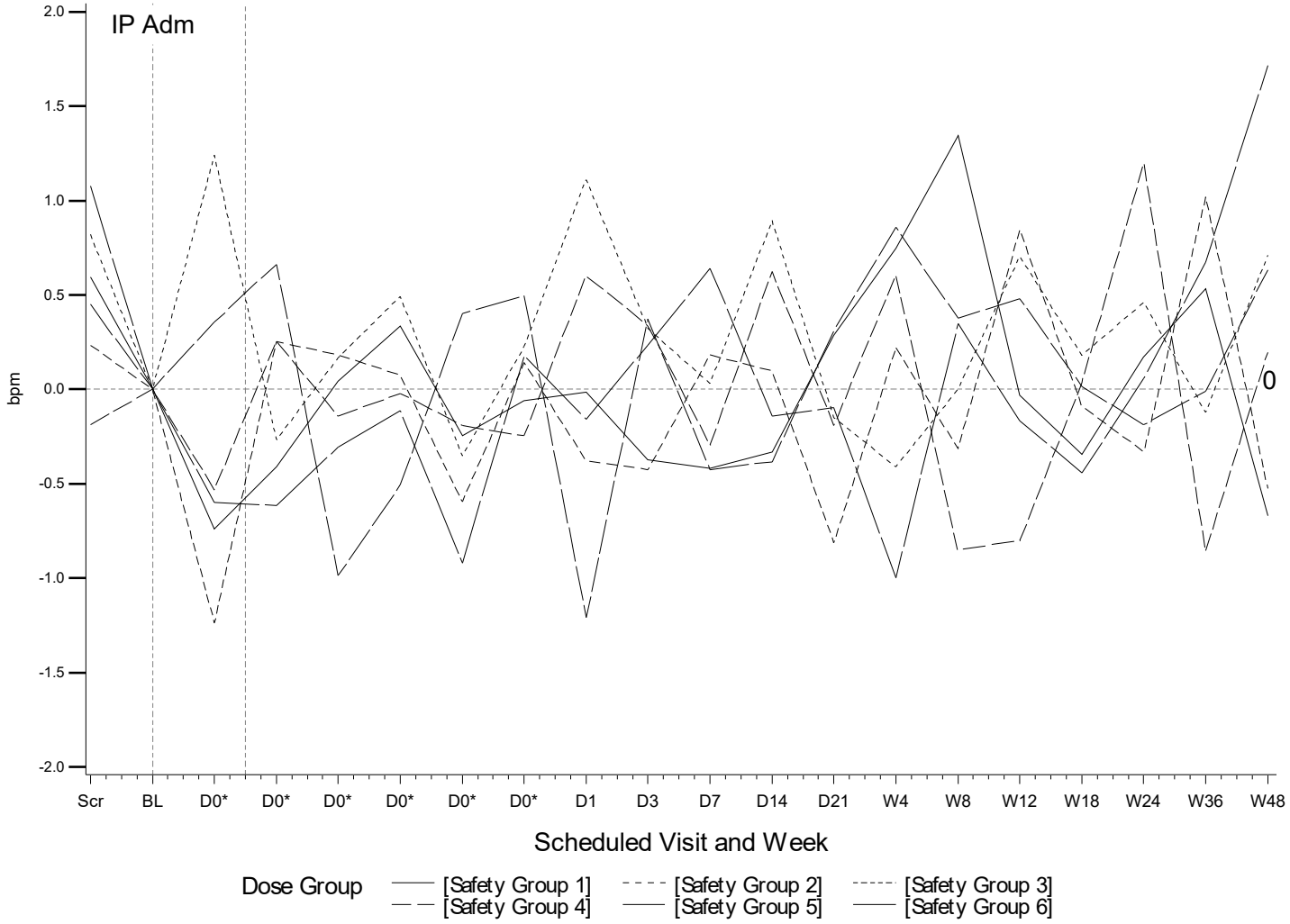
This figure will repeat Figure 6 for platelets.

Figure 22: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Pulse at Screening, Baseline to Day 1



*D0 timepoints represent the following visits, in order: post C144-LS, post IP Admin, 1 h post IP admin, 3 h post IP admin, 6 h post IP Admin, and 12 h post IP admin.

Figure 23: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Pulse, Entire Study Period



*D0 timepoints represent the following visits, in order: post C144-LS, post IP Admin, 1 h post IP admin, 3 h post IP admin, 6 h post IP Admin, and 12 h post IP admin.

Figure 24: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Respiration Rate at Screening, Baseline to Day 1

This figure will repeat Figure 22 for respiration rate.

Figure 25: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Respiration Rate, Entire Study Period

This figure will repeat Figure 23 for respiration rate.

Figure 26: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group – Systolic Blood Pressure at Screening, Baseline to Day 1

This figure will repeat Figure 22 for systolic blood pressure.

Figure 27: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group – Systolic Blood Pressure, Entire Study Period

This figure will repeat Figure 23 for systolic blood pressure.

Figure 28: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group – Diastolic Blood Pressure at Screening, Baseline to Day 1

This figure will repeat Figure 22 for diastolic blood pressure.

Figure 29: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group – Diastolic Blood Pressure, Entire Study Period

This figure will repeat Figure 23 for diastolic blood pressure.

Figure 30: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Temperature at Screening, Baseline to Day 1

This figure will repeat Figure 22 for Temperature.

Figure 31: Vital Sign Results by Scheduled Visits: Mean Change from Baseline by Dose Group –Temperature, Entire Study Period

This figure will repeat Figure 23 for Temperature.

Pharmacokinetics

Figure 32: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Administration – PK Population – SC Group 1

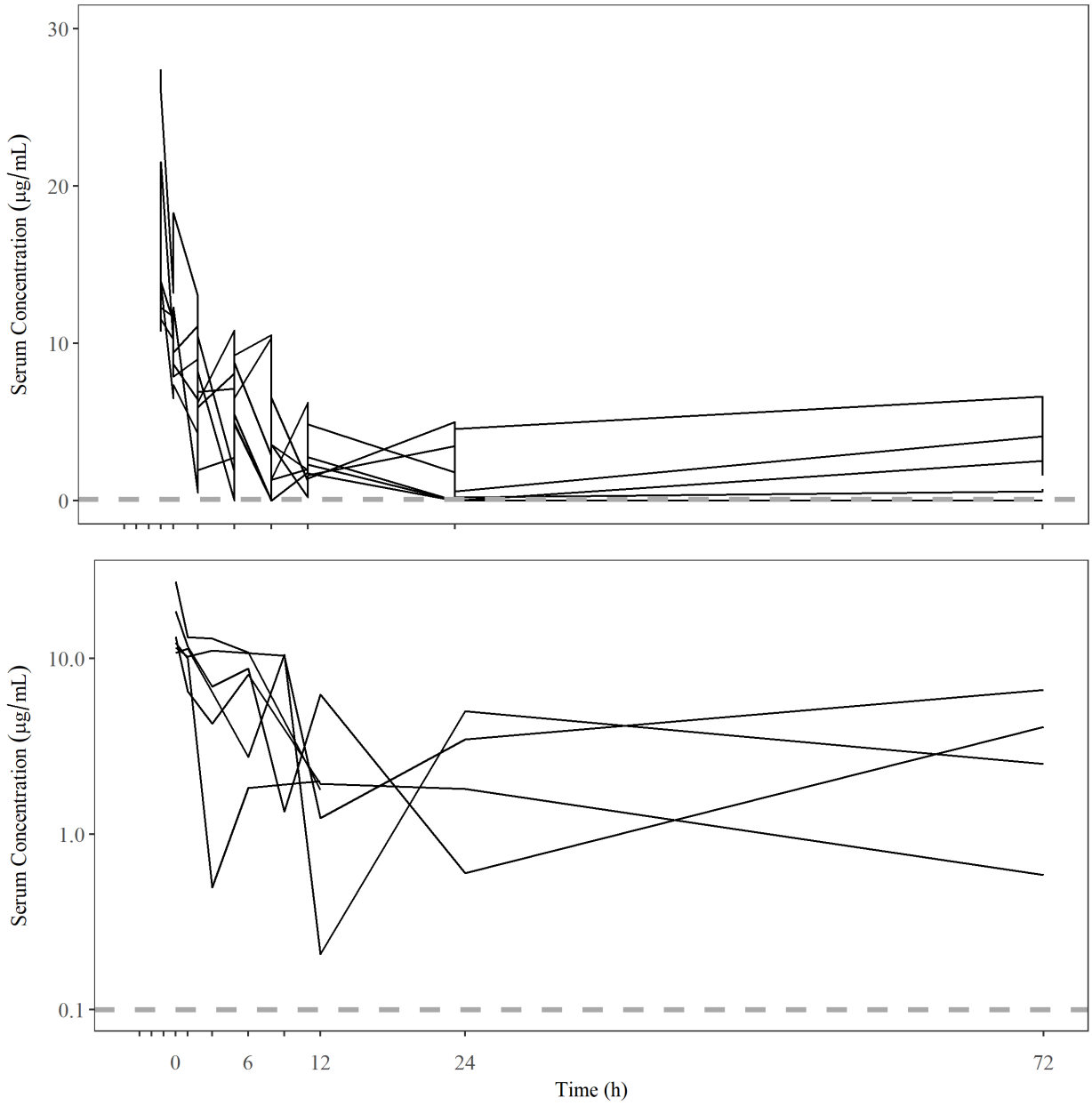


Figure 33: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – SC Group 1

This figure will repeat Figure 32 for all PK sample timepoints.

Figure 34: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – SC Group 2

This figure will repeat Figure 32 for PK SC Group 2.

Figure 35: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – SC Group 2

This figure will repeat Figure 32 for all PK sample timepoints for PK SC Group 2.

Figure 36: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 1

This figure will repeat Figure 32 for PK IV Group 1.

Figure 37: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK IV Group 1

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 1.

Figure 38: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 2

This figure will repeat Figure 32 for PK IV Group 2.

Figure 39: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – IV Group 2

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 2.

Figure 40: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 3

This figure will repeat Figure 32 for PK IV Group 3.

Figure 41: Overlay of Individual C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – IV Group 3

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 3.

Figure 42: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – SC Group 1

This figure will repeat Figure 32 for PK SC Group 1 for C135-LS.

Figure 43: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – SC Group 1

This figure will repeat Figure 32 for all PK sample timepoints for PK SC Group 1 for C135-LS.

Figure 44: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – SC Group 2

This figure will repeat Figure 32 for PK SC Group 2 for C135-LS.

Figure 45: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – SC Group 2

This figure will repeat Figure 32 for all PK sample timepoints for PK SC Group 2 for C135-LS.

Figure 46: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 1

This figure will repeat Figure 32 for PK IV Group 1 for C135-LS.

Figure 47: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – IV Group 1

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 1 for C135-LS.

Figure 48: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 2

This figure will repeat Figure 32 for PK IV Group 2 for C135-LS.

Figure 49: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – IV Group 2

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 2 for C135-LS.

Figure 50: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin – PK Population – IV Group 3

This figure will repeat Figure 32 for PK IV Group 3 for C135-LS.

Figure 51: Overlay of Individual C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints- PK Population – IV Group 3

This figure will repeat Figure 32 for all PK sample timepoints for PK IV Group 3 for C135-LS.

Figure 52: Mean (±SD) C144-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin, PK Population

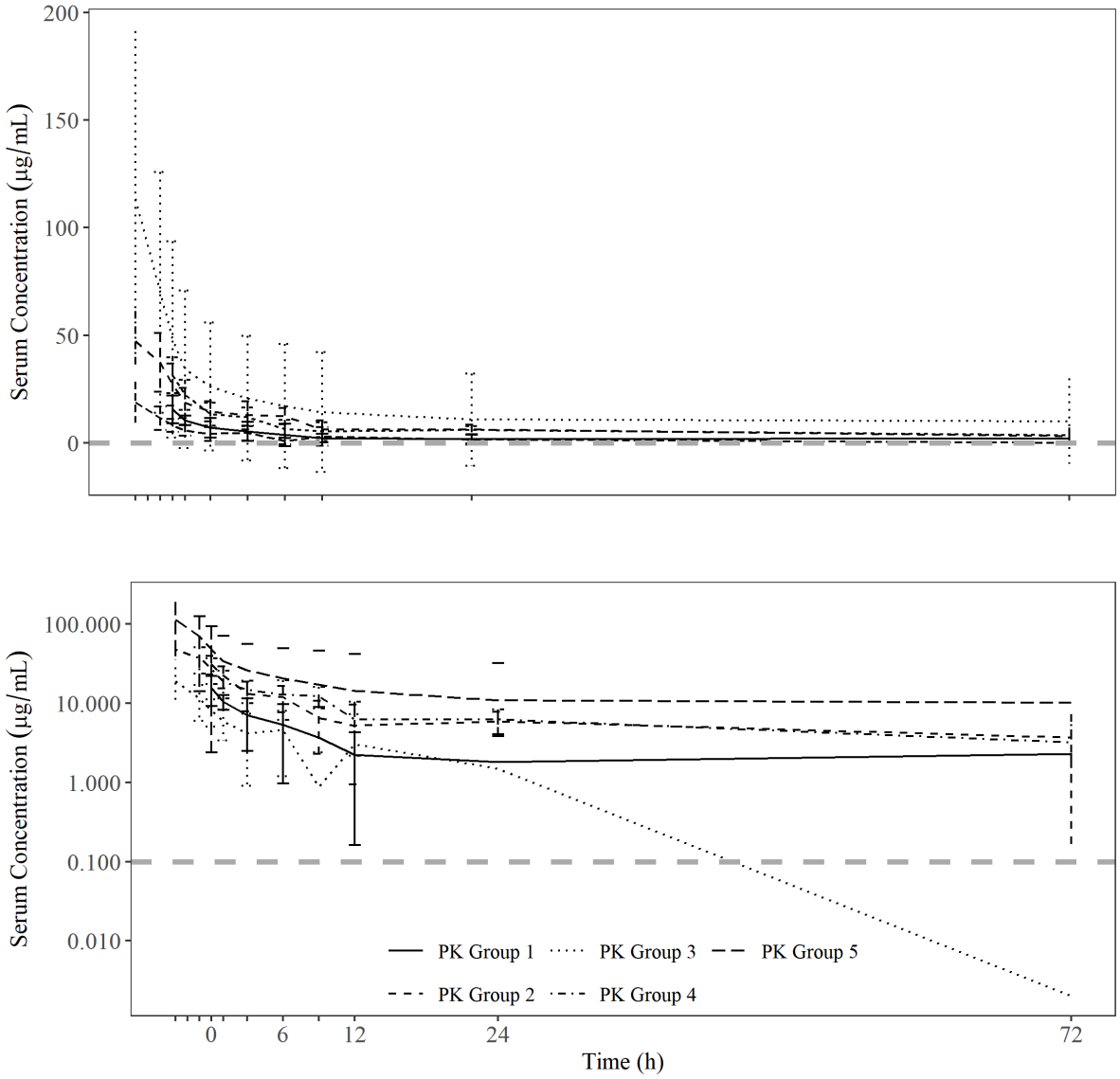


Figure 53: Mean C144-LS Concentration in Serum Profiles by Dose Group, All Timepoints, PK Population

This figure will repeat Figure 52 for all PK sample timepoints.

Figure 54: Mean C135-LS Concentration in Serum Profiles by Dose Group, Baseline to 72 h Post IP Admin, PK Population

This figure will repeat Figure 52 for all C135-LS concentrations.

Figure 55: Mean C135-LS Concentration in Serum Profiles by Dose Group, All Timepoints, PK Population

This figure will repeat Figure 52 for all C135-LS concentrations at all PK sample timepoints.

Figure 56: Comparisons of Dose Adjusted Exposure Parameters, C144-LS, PK Population

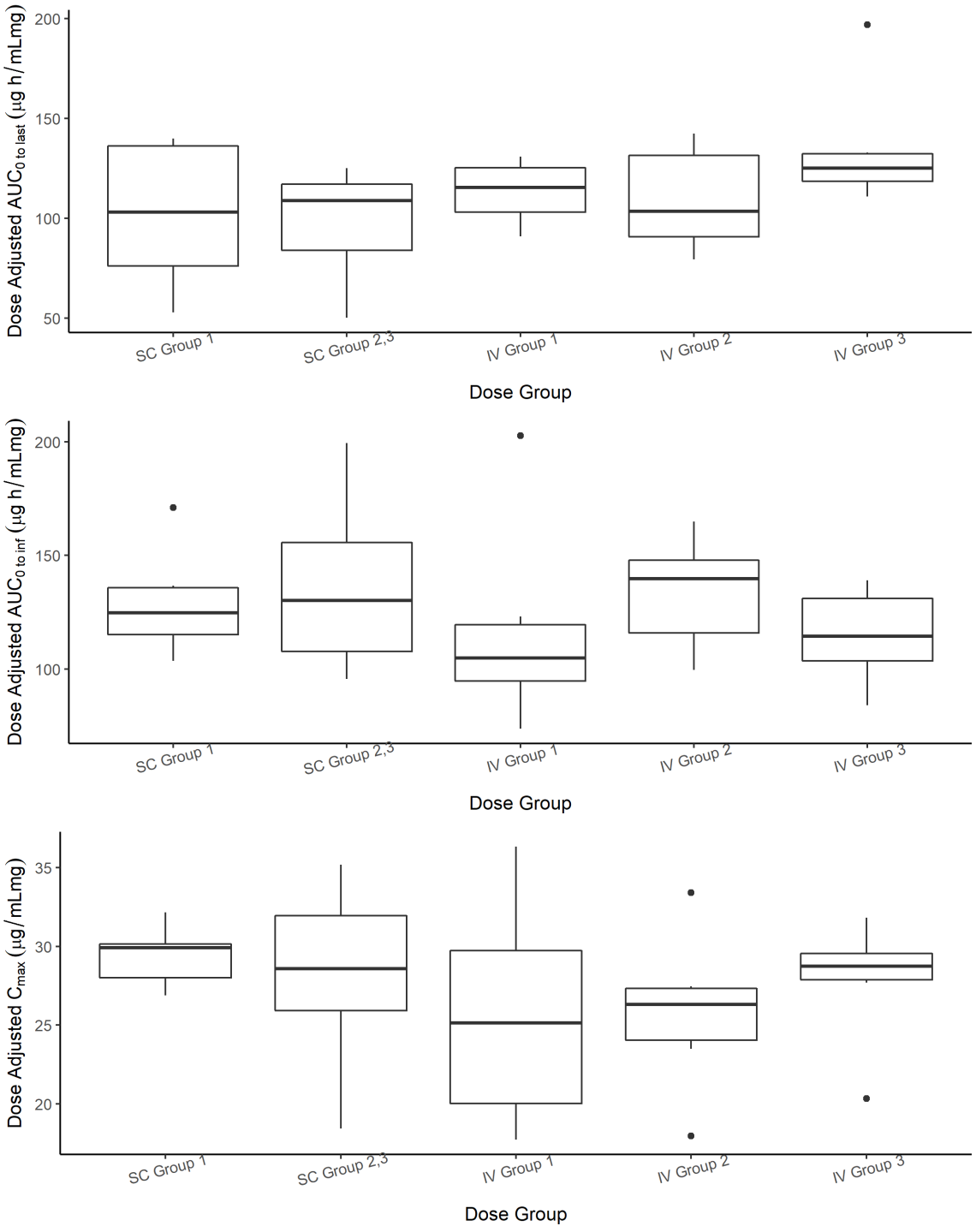


Figure 57: Comparisons of Dose Adjusted Exposure Parameters, C135-LS, PK Population

This figure will repeat Figure 56 for C135-LS.

Figure 58: Pairwise Comparison of PK Exposure Parameters, C144-LS, PK Population

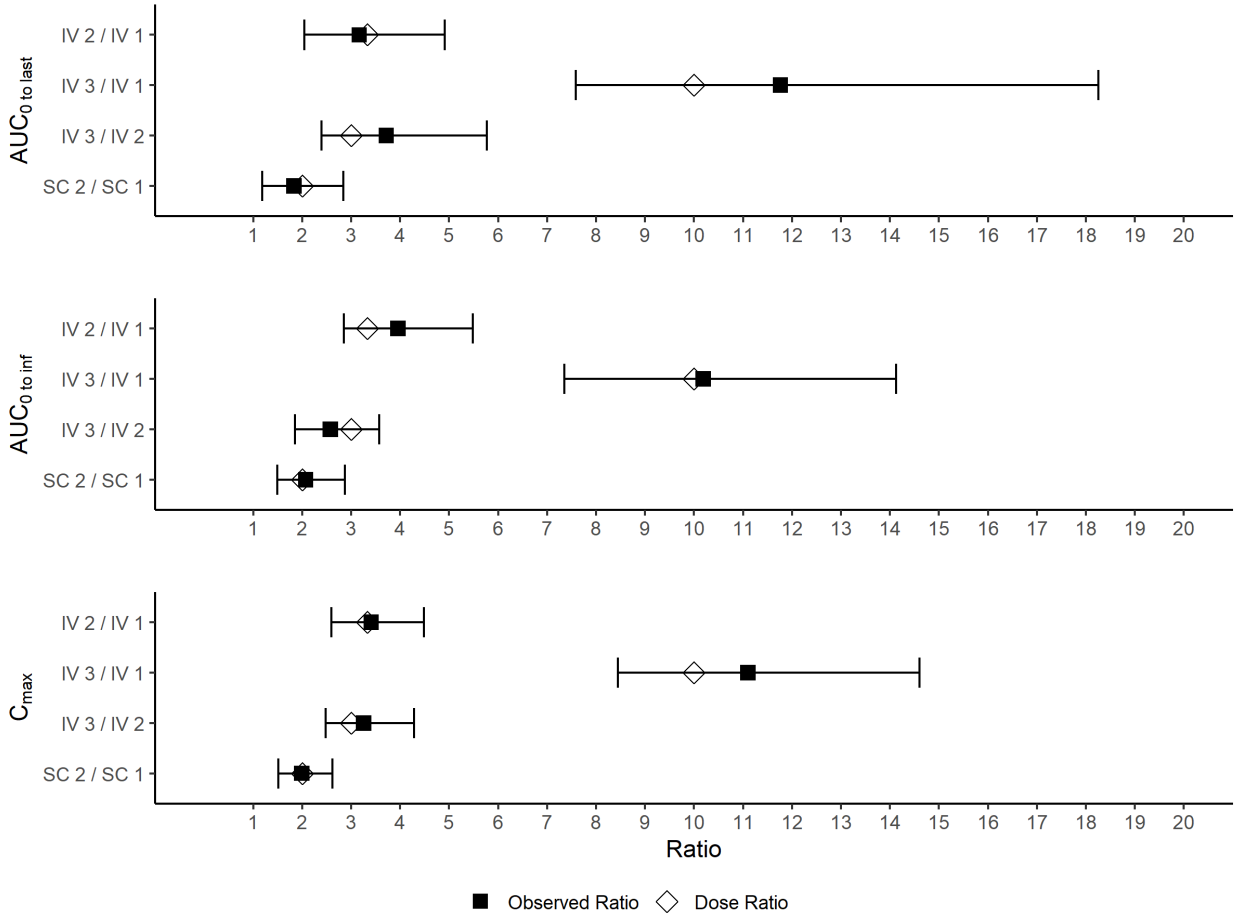


Figure 59: Pairwise Comparison of PK Exposure Parameters, C135-LS, PK Population

This figure will repeat Figure 58 for C135-LS.

Figure 60: Dose Proportionality Power Model Among IV Dose Groups, C144-LS, PK Population

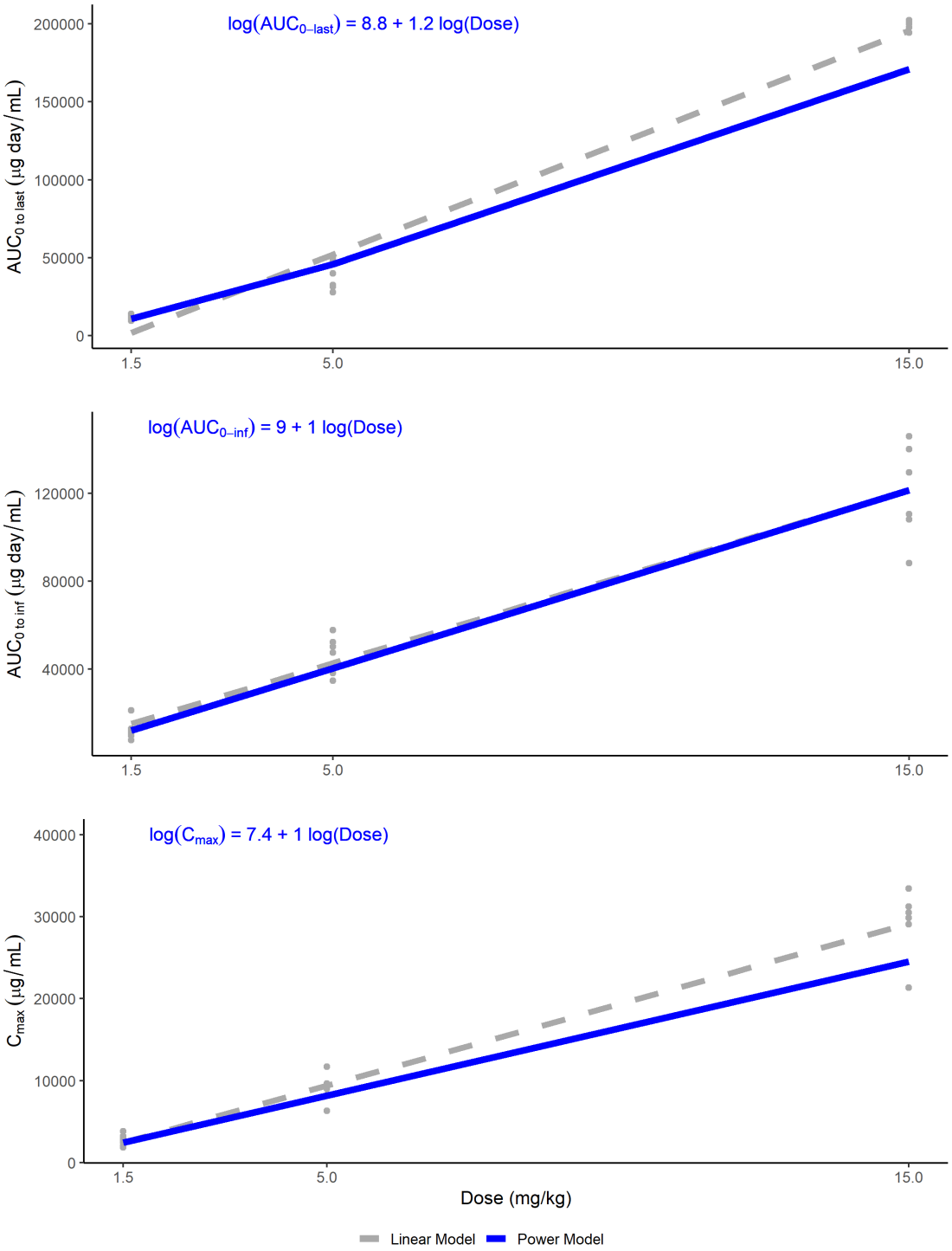


Figure 61: Dose Proportionality Power Model Among IV Dose Groups, C135-LS, PK Population

This figure will repeat Figure 60 for C135-LS.

Immunogenicity

Figure 62: Summary Boxplots of Anti-Drug Antibody Titration Results by Study Visit, C144-LS, Immunogenicity Population – SC Dose Groups

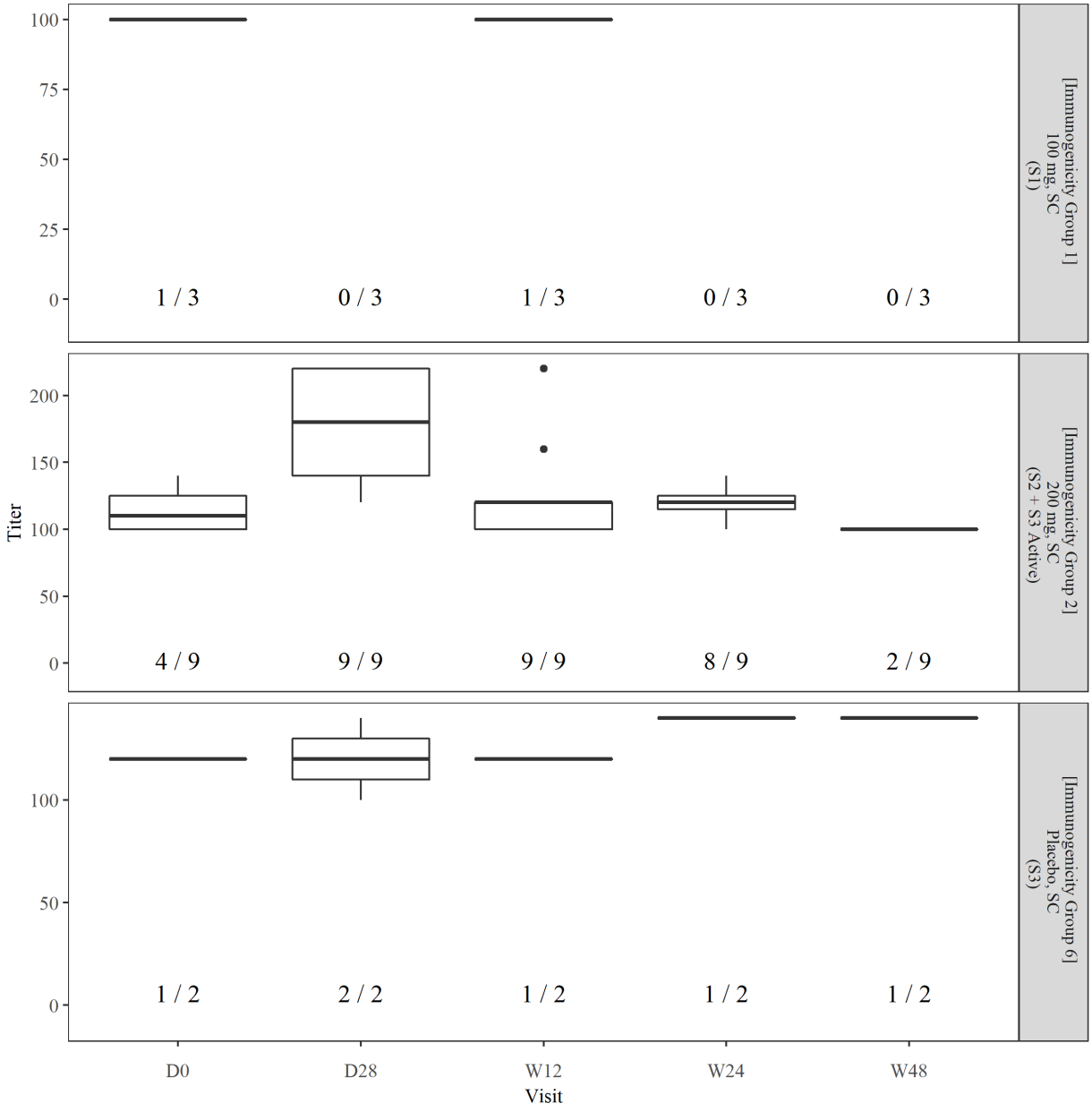


Figure 63: Summary Boxplots of Anti-Drug Antibody Titration Results by Study Visit, C144-LS, Immunogenicity Population – IV Dose Groups

Repeat Figure 62 for the IV dose groups.

Figure 64: Summary Boxplots of Anti-Drug Antibody Titration Results by Study Visit, C135-LS, Immunogenicity Population – SC Dose Groups

Repeat Figure 62 for the C135-LS.

Figure 65: Summary Boxplots of Anti-Drug Antibody Titration Results by Study Visit, C135-LS, Immunogenicity Population – IV Dose Groups

Repeat Figure 62 for the C135-LS and IV dose groups.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

16.2 Data Listings by Participant

16.2.1 Participant Disposition

Listing 1: Early Terminations or Discontinued Participants, All Enrolled Participants

Dose Group	Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
[Safety Group 1]				
[Safety Group 2] (S2)				

16.2.2 Protocol Deviations

Listing 2: Participant Specific Protocol Deviations, All Enrolled Participants

Dose Group	Participant ID	Sequence Number	Deviation	Deviation Category	Visit Number	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Resolution	Comments
[Safety Group 1]										
[Safety Group 2] (S2)										

Listing 3: Non-Participant -Specific Protocol Deviations, All Enrolled Participants

Site	Start Date	Deviation	Reason for Deviation	Deviation Resulted in Participant Termination?	Deviation Category	Deviation Resolution	Comments

16.2.3 Participants Excluded from the Analysis Populations

Listing 4: Participants Excluded from Analysis Populations, All Enrolled Participants

Dose Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Any Safety Results Available?	Any PK Results Available?	Any Immunogenicity (ADA) Results Available?	Reason Participant Excluded
[Safety Group 1]		[e.g., Safety, Enrolled, PK, Immunogenicity (ADA)]	[e.g., Safety, PK, Immunogenicity (ADA)]				
[Safety Group 2] (S2)							
[Safety Group 2] (S3 Active)							
Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.							

16.2.4 Demographic/Baseline Characteristics Data

Listing 5: Demographic Data, Safety Population

Dose Group	Participant ID	Sex	Age at Enrollment (Years)	Ethnicity	Race
[Safety Group 1]					
[Safety Group 2] (S2)					
[Safety Group 2] (S3 Active)					

Listing 6: Medical History, Safety Population

Dose Group	Participant ID	Sequence Number	Medical History Term	MedDRA System Organ Class	MedDRA Preferred Term	Condition Start Day	Ongoing at Enrollment?
[Safety Group 1]							
[Safety Group 2] (S2)							
[Safety Group 2] (S3 Active)							

16.2.5. Extent of Exposure Data

Listing 7: Treatment Compliance, Safety Population

Dose Group	Participant ID	mAB	Route	Dosed According to Protocol?	IP Administration Date	Start Time	End Time	Number of Injections	Location	Dose Interrupted (AE Description; Number)
[Safety Group 1]										
[Safety Group 2] (S2)										
[Safety Group 2] (S3 Active)										

16.2.7 Adverse Events

Listing 8: Solicited Events – Systemic Symptoms, Safety Population

Dose Group	Participant ID	Post Dose Day	Symptom	Severity	Relatedness	Associated with Cytokine Release Syndrome?
[Safety Group 1]						
[Safety Group 2] (S2)						
[Safety Group 2] (S3 Active)						

Listing 9: Solicited Events – Local Symptoms, Safety Population

Dose Group	Participant ID	Post Dose Day	Symptom	Severity	Relatedness	Associated with Cytokine Release Syndrome?
[Safety Group 1]						
[Safety Group 2] (S2)						
[Safety Group 2] (S3 Active)						

Listing 10: Unsolicited Adverse Events, Safety Population

Adverse Event	MedDRA System Organ Class	MedDRA Preferred Term	Day of Onset Post-IP	Duration (Days)	Severity	SAE?	Relationship to IP	Action Taken with IP	Participant Discontinued Due to AE	Outcome
Dose Group: Participant ID: AE Number:										
Dose Group: Participant ID: AE Number:										
Note: For additional details about SAEs, see Listing 11.										

Listing 11: Serious Adverse Events, Including Deaths

Serious Adverse Event	Day of Onset Post IP	Duration (Days)	No. of Days Post IP the Event Became Serious	Reason Reported as an SAE	Was the Event a DLT?	Severity	Relationship to Study Treatment	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Dose Group: Participant ID: AE Number:												
Comments:												
Dose Group: Participant ID: AE Number:												
Comments:												

Listing 12: Listing of Deaths

Serious Adverse Event	Day of Onset Post IP	Duration (Days)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Was the Event a DLT?	Severity	Relationship to IP	Action Taken with IP	Participant Discontinued Due to SAE	MedDRA System Organ Class	MedDRA Preferred Term
Dose Group: Participant ID: AE Number:											
Comments:											
Dose Group: Participant ID: AE Number:											
Comments:											

Listing 13: Dose Limiting Toxicities

Adverse Event	Day of Onset Post IP	Duration (Days)	SAE?	Severity	Relationship to IP	Action Taken with IP	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Dose Group: Participant ID: AE Number:										
Comments:										
Dose Group: Participant ID: AE Number:										
Comments:										

16.2.8 Individual Laboratory Data and Other Safety-Related Data

Listing 14: Clinical Laboratory Results – Chemistry, Safety Population

Dose Group	Participant ID	Planned Time Point	Actual Study Day	Sex	Age (Years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range Low	Reference Range High
[Safety Group 1]										
[Safety Group 2] (S2)										
[Safety Group 2] (S3 Active)										

Listing 15: Clinical Laboratory Results – Hematology, Safety Population

Dose Group	Participant ID	Planned Time Point	Actual Study Day	Sex	Age (Years)	Laboratory Parameter (Units)	Result (Severity Grade)	Change from Baseline	Reference Range Low	Reference Range High
[Safety Group 1]										
[Safety Group 2] (S2)										
[Safety Group 2] (S3 Active)										

Listing 16: Clinical Laboratory Results – Urinalysis, Safety Population

Dose Group	Participant ID	Planned Time Point	Actual Study Day	Sex	Age (Years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High
[Safety Group 1]									
[Safety Group 2] (S2)									
[Safety Group 2] (S3 Active)									

16.2.9 Vital Signs and Physical Exam Findings

Listing 17: Vital Signs, Safety Population

Dose Group	Participant ID	Planned Time Point	Actual Study Day	Pulse (beats/min)	Respiratory Rate (breaths/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Temperature (°C)	Weight (kg)	Height (cm)	BMI (kg/m^2)
[Safety Group 1]											
[Safety Group 2] (S2)											
[Safety Group 2] (S3 Active)											

Listing 18: Physical Exam Findings, Safety Population

Dose Group	Participant ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as a Reactogenicity Event? (Description; Number)	Reported as an AE? (AE Description; Number)
[Safety Group 1]							
[Safety Group 2] (S2)							
[Safety Group 2] (S3 Active)							

Listing 19: Concomitant Medications, Safety Population

Dose Group	Participant ID	CM Sequence Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
[Safety Group 1]									
[Safety Group 2] (S2)									

16.2.9. Pharmacokinetic Data

Listing 20: Participant Level C144-LS and C135-LS Concentrations in Serum, PK Population

Dose Group	mAB	Participant ID	Nominal Time[a]	Actual Time[a]	Laboratory Reported Concentration (µg/mL)	Analysis Concentrations (µg/mL)	Excluded from NCA	Used in λ_z Calculations
[Safety Group 1]								
[Safety Group 2] (S2)								

Notes: a Times are relative to time of dosing. For actual time, out of window times are indicated by an asterisk (*), substantially out of window times are indicated by two asterisks (**) and imputed times are indicated by three asterisks (***).

BQL = Below the Limit of Quantification.

Listing 21: Participant Specific C144-LS Serum PK Parameters, PK Population

Dose Group	Participant ID	Cmax (µ/mL)	Cmax/Dose ((µg/mL/mg) or ((µg/mL)/kg/mg)[1]	Tmax (h)	AUC(0-T) (µg* day/mL)	AUC(0-T)/Dose ((µg day/mL)/mg) or ((µg day/mL) kg/mg)[2]	AUC(INF) (µg*day/mL)	AUC(INF)/Dose ((µg day/mL)/mg) or ((µg day/mL) kg/mg)[2]	λ_z (1/day)	T-HALF (day)	CLT/F (mL/day) or CLT (mL/day)[3]	Vz/F (L) or Vss (L)[3]
[Safety Group 1]												
[Safety Group 2] (S2)												
[Safety Group 2] (S3 Active)												

[1]Dose adjustments were made by the assigned dose. Units of (µg/mL)/mg are for SC groups and units of (µg/mL)*kg/mg are for IV groups.

[2]Dose adjustments were made by the assigned dose. Units of (µg*day/mL)/mg are for SC groups and units of (µg*day/mL)*kg/mg are for IV groups.

[3]CLT/F and Vz/F are presented for participants in the SC dose groups. CLT and Vss are presented for participants in the IV dose groups.

Parameters values where the λ_z acceptance criteria were not met are indicated by an asterisk (*).
Terminal phase parameter values where the $\%AUC_{ex}$ criteria was not met are indicated by a circumflex (^).

Listing 22: Participant Specific C135-LS Serum PK Parameters, PK Population

This listing will repeat Listing 21 for C135-LS.

16.2.10 Pregnancy Reports

Listing 23: Pregnancy Reports – Maternal Information, Safety Population

Dose Group	Participant ID	Report Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
[Safety Group 1]									
[Safety Group 2] (S2)									
Note: Maternal Complications and medications taken during pregnancy are included in Listing 19.									

Listing 24: Pregnancy Reports – Gravida and Para, Safety Population

Dose Group	Participant ID	Pregnancy Number	Gravida	Birth Type	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?
[Safety Group 1]								
[Safety Group 2] (S2)								
Note: Gravida includes the current pregnancy, para events do not.								

Listing 25: Pregnancy Reports – Live Birth Outcomes, Safety Population

Participant ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
Note: Congenital anomalies are included in Listing 20.												

Listing 26: Pregnancy Reports – Still Birth Outcomes, Safety Population

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 27: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes, Safety Population

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Reason for Therapeutic Abortion

16.2.11 Immunogenicity

Listing 28: Anti-Drug Antibody Titration Results, C144-LS - Immunogenicity Population

Dose Group	Participant ID	Visit	Sample Collection Date [a]	Screening Result	Confirmation Result	Reported Titration Result	Analysis Titration Result [b]
[Immunogenicity Group 1]							
[Immunogenicity Group 2] (S2)							
[Immunogenicity Group 2] (S3 Active)							

Notes:

[a] Samples collected outside of the protocol defined visit window are indicated with an asterisk (*). The number of days before or after the protocol defined visit window that the sample was collected is included in parentheses next to the sample collection date.

[b] Results that were inconclusive for the presence of ADA were analyzed as ADA negative. Samples with positive results for ADA for which the ADA titration result was unquantifiable were reported as "<100" and analyzed as 50 in tables and figures. Samples which were negative for presence of ADA were analyzed as 1 in tables and figures.

Listing 29: Anti-Drug Antibody Titration Results, C135-LS - Immunogenicity Population

Dose Group	Participant ID	Visit	Sample Collection Date [a]	Screening Result	Confirmation Result	Reported Titration Result	Analysis Titration Result [b]
[Immunogenicity Group 1]							
[Immunogenicity Group 2] (S2)							
[Immunogenicity Group 2] (S3 Active)							

Notes:

a Samples collected outside of the protocol defined visit window are indicated with an asterisk (*). The number of days before or after the protocol defined visit window that the sample was collected is included in parentheses next to the sample collection date.

b Results that were inconclusive for the presence of ADA were analyzed as ADA negative. Samples with positive results for ADA for which the ADA titration result was unquantifiable were reported as "<100" and analyzed as 50 in tables and figures. Samples which were negative for presence of ADA were analyzed as 1 in tables and figures.