Official Title:	**A SINGLE-CENTER, OPEN-LABEL, SINGLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF EMICIZUMAB IN HEALTHY CHINESE VOLUNTEERS**
NCT Number:	**NCT03380780**
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PROTOCOL

TITLE:	**A SINGLE-CENTER, OPEN-LABEL, SINGLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF EMICIZUMAB IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER:	YP39308
VERSION:	4
TEST PRODUCT:	Emicizumab (RO5534262)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 31 May 2016
DATE AMENDED:	Version 2: 19 March 2017 Version 3: 10 October 2017 Version 4: See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	25-Jan-2018 18:07:18

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol YP39308 has been primarily amended to update the exclusion criteria and study assessments. Changes to the protocol, along with a rationale for each change, are summarized below:

- The exclusion criterion of a positive T-SPOT®.*TB* test result at screening has been updated. The positive result represents confirmed active tuberculosis (TB) disease or potentially latent TB infection in the population. There should not be an impact on subjects' safety based on the mechanism of action of emicizumab. Only subjects with a positive T-SPOT.*TB* test result and with a confirmed active TB infection in clinical at screening should be excluded (Section 4.2.2).
- Specific ECG assessment has been revised to clarify timing of the three consecutive 12-lead ECGs to within 5 minutes (Section 4.6.1.2 and Appendix 1).
- Specific laboratory assessments have been revised: C-reactive protein (CRP) has been modified as "high-sensitivity" CRP; in viral serology, HIV-1 and HIV-2 Ab have been amended to HIV antibody; and testing for TB with T-SPORT.*TB* test has been added (Section 4.6.1.5 and Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form in your study files. Please return a copy to your local study monitor.

PROTOCOL SYNOPSIS

TITLE	**A SINGLE-CENTER, OPEN-LABEL, SINGLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF EMICIZUMAB IN HEALTHY CHINESE VOLUNTEERS**
PROTOCOL NUMBER	YP39308
VERSION NUMBER:	4
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase I
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary

The primary objective of this study is:

- To assess the pharmacokinetics of emicizumab in healthy Chinese subjects following a single subcutaneous (SC) administration of emicizumab.

Secondary

The secondary objective for this study is:

- To assess the safety and tolerability of emicizumab in healthy Chinese subjects following a single SC administration of emicizumab.

Study Design

Description of Study

This will be a single-center and open-label study and will evaluate the pharmacokinetics, safety, and tolerability of emicizumab following a single SC administration to healthy Chinese subjects.

Number of Subjects

A total of 16 healthy Chinese male subjects will be enrolled in the study to obtain at least 12 evaluable subjects.

Target Population

Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Healthy Chinese male subjects, aged 20–45 years inclusive at the time of screening.
- Chinese subjects must have Chinese parents and grandparents, all of whom were born in China.
- Healthy status as defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, coagulation, viral serology, urinalysis, and immunology.
- A body mass index between 19 and 24 kg/m^2, inclusive.
- Able to participate and willing to give written informed consent and to comply with the study requirements.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

- Any history or presence of clinically significant gastrointestinal, respiratory, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, metabolic, malignant, or dermatological disorder.
- Major illness within 1 month prior to dosing, and/or any condition which could relapse during or immediately after the study.
- Use of any prescribed or over-the-counter medication or herbal medicine taken within 14 days prior to dosing or within 5 times the elimination half-life of the medication prior to dosing (whichever is longer), with some exceptions.
- Confirmed supine systolic blood pressure (SBP) $\geq$ 140 or $\leq$ 90 mmHg, and diastolic blood pressure (DBP) $\geq$ 90 or $\leq$ 50 mmHg.
- Confirmed resting supine heart rate (HR) greater than 100 or less than 50 beats per minute.
- History of drug abuse within the past 2 years or confirmed positive results for drugs of abuse at screening or Day -1.
- Alcohol dependence or a history of this within the past 2 years or positive results for alcohol breath test at screening or Day -1.
- Confirmed clinically relevant abnormal (as judged by the investigator) laboratory test results.
- Any significant donation/loss of blood or plasma ($>$ 450 mL) within the 3 months prior to dosing.
- Regular smoker with consumption of more than 10 cigarettes per day or the equivalent amount of tobacco.
- Any other condition or disease other than stated which, in the judgment of the investigator, would place the subject at undue risk; interfere with the absorption, distribution, metabolism, and excretion of emicizumab; or interfere with the ability of the subject to complete the study.
- Participation within a clinical study with an investigational drug or device within the last 3 months prior to dosing.
- Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration or exposure to foods or environmental agents.
- Previous or concomitant thromboembolic disease such as deep vein thrombosis (DVT) or signs of thromboembolic disease, or family history of thromboembolic disorder such as serious DVT.
- At high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment.
- Protein C activity, protein S activity, antithrombin III activity, factor IX (FIX) activity, factor X (FX) activity, lupus anticoagulant (T1/T2 ratio), or anti-cardiolipin-beta-2 glycoprotein I (GPI) complex antibody levels outside the reference range at screening, or factor VIII (FVIII) activity $\geq$ 120% at screening.
- Previous or concomitant autoimmune or connective tissue disease.
- History of tuberculosis or $active\ tuberculosis\ with$ positive $T\text{-}SPOT^{®}.TB\ test$ result at screening.
- Any other reason that, in the judgment of the investigator, would render the subject unsuitable for study participation.

Length of Study

The total duration of the study for each subject will be up to 20 weeks divided as follows:

Screening: Up to 4 weeks

In Clinic period: Days -1 to 4

Ambulatory Visits: Days 6, 8, 11, 15, 22, 29, 36, 43, 50, 57, 71, 85, and 113

End of Study

The end of the study is defined as the date when the last subject, last observation occurs and is expected 113 ± 3 days after the last subject dose administration unless a subject withdraws his consent.

Outcome Measures

Pharmacokinetic Outcome Measures

Plasma concentrations of emicizumab will be measured by a specific and validated method. PK parameters will be estimated using standard non-compartmental methods.

- Primary PK parameters: Maximum plasma concentration observed (C_{max}) and area under the plasma concentration-time curve (AUC) between time zero extrapolated to infinity ($AUC_{0-\infty}$) of emicizumab
- Secondary PK parameters: Area under the plasma concentration-time curve between time zero and the time of the last quantifiable concentration (AUC_{0-last}), time to maximum plasma concentration (t_{max}), terminal plasma half-life ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (Vz/F), mean residence time (MRT) of emicizumab

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events
- Incidence and clinical significance of anti-emicizumab antibodies
- Laboratory test data (hematology, blood chemistry, coagulation screening test, urinalysis, viral serology, and immunology), vital signs, 12-lead ECG.
- Coagulation tests

Vital Signs

Vital signs will include measurements of temperature (tympanic), respiratory rate, pulse rate, and SBP and DBP while the subject is in a supine position after the subject has been resting for at least 5 minutes at each visit (10 minutes for the screening visit). Vital signs should be measured prior to blood sampling. When possible, the same arm should be used for all blood pressure (BP) measurements.

BP, respiratory rate, pulse rate, and body temperature ($axillary$) will be recorded at the timepoints specified in the Schedule of Assessments (SoA).

BP, respiratory rate, and pulse rate measurements will be performed in triplicate (can be as short as ranging from 20-second to 1-minute intervals between measurements). The mean of three consecutive replicates will be used as the value for the defined timepoint.

Electrocardiograms

ECGs will be collected after the subject has been in a supine position for at least 10 minutes. At the specified timepoints, 12-lead ECGs will be obtained in triplicate (i.e., three consecutive interpretable 12-lead ECGs within $5\ minutes$ and recorded on the electronic Case Report Form [eCRF]). Triplicate recordings should be taken for any unscheduled ECG.

All ECG recordings must be performed using a standard digital high-quality, high-fidelity ECG machine equipped with computer-based interval measurements. Automated ECG intervals (PR [PQ], QRS duration, QT, and QT corrected for HR [QTc] using the Fridericia correction factor) and HR will be captured, and the changes in T-wave and U-wave morphology will be documented. T-wave information will be captured as normal or abnormal, and U-wave information will be captured in two categories: absent/normal or abnormal.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the subject's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

The following are requirements for ECG assessments:

- The absence of any environmental distractions (television, radio, and conversation) during the pre-ECG rest and the ECG recording in the clinic must be emphasized.
- Avoid ECG recordings within 3 hours after meals, if allowed per predefined schedule.
- If possible, the same machine, brand and model, should be used for the same subject throughout the study.
- ECGs should be 12-lead and recorded at 25 mm/sec for at least 10 seconds.
- ECG machines should have periodic calibration and service records (minimum of once a year).
- If any QT/QTc values $>$ 500 msec or increases from predose on Day 1 QTc $>$ 60 msec (as provided by the machine) are observed, the site should repeat the ECG within the next 5 minutes and notify the Sponsor. If confirmed, ECG recordings should be repeated at least hourly until two successive ECGs show QTc values below the threshold value that triggered the repeated measurement.

Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at timepoints specified in the SoA.

Additional blood or urine samples may be taken at the discretion of the investigator if the results of any test fall outside the reference ranges, or if clinical symptoms necessitate additional testing to monitor subject's safety. Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before admission to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory, if applicable.

Samples for the following blood and urine laboratory tests will be collected and sent to the local laboratory for analysis at timepoints indicated in the SoA:

- Hematology: hemoglobin, hematocrit, total WBC count, differential WBC count (basophils, eosinophils, lymphocytes, monocytes and neutrophils), platelet count, RBC, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Blood Chemistry: albumin/globulin ratio, AST, ALT, LDH, total and indirect bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, CK, BUN, total protein, serum albumin, serum creatinine, uric acid, total cholesterol, triglycerides, fasting glucose, sodium, chloride, potassium, $high\text{-}sensitivity$ C-reactive protein.
- Screening Coagulation Test: Protein C activity, Protein S activity, antithrombin III activity, FVIII activity, FIX activity, FX activity, lupus anti-coagulant (T1/T2 ratio).
- Coagulation test 1: Prothrombin time (PT), PT/International Normalized Ratio (INR), aPTT, fibrinogen, D- dimer. Starting on Day 1 onward, blood samples will be drawn to conduct biomarker assays at the central laboratory ([redacted] in the United States). The same assays will be also conducted locally at screening, and on Day -1, Day 2, Day 11, Day 29, Day 57, and Day 113.
- Coagulation test 2: Prothrombin fragments 1+2, FVIII activity. The samples will be run centrally on frozen plasma ([redacted]).
- Coagulation test 3: FVIII inhibitors. The samples will be run centrally on frozen plasma ([redacted]).

- Urinalysis: A mid-stream, clean catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocytes, specific gravity and pH. If there is a clinically significant positive result (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick result, it should be recorded, and there is no need to perform microscopy. Urine color may be evaluated from urinalysis if considered necessary.
- Viral serology: hepatitis B surface antigen, hepatitis C virus (HCV) RNA or HCV antibodies, and *HIV antibody*.
- Immunology: non-specific IgG E antibodies and anti-cardiolipin-beta-2 GPI complex antibody levels.
- Drugs of abuse (urine): cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates.
- Alcohol: alcohol breath test.
- *Tuberculosis: T-SPOT.TB test*

Anti-Emicizumab Antibodies

Blood samples will be collected as indicated in the SoA for the detection of anti-emicizumab antibodies.

Investigational Medicinal Product(s)

Emicizumab is a recombinant humanized bispecific monoclonal antibody that binds to activated blood coagulation FIX and blood coagulation FX, and has cofactor activity that substitutes for that of blood coagulation FVIII. Emicizumab will be injected SC into the abdomen at a single dose of 1 mg/kg on Day 1.

Procedures

Screening

Written informed consent for participation in the study must be obtained before performing any study‑specific screening tests or evaluations. Informed Consent Forms for enrolled subject and for subjects who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator and kept at the investigational site.

A screening examination should be performed from Day −28 to Day −2 for healthy subjects. Subjects must fulfill all entry criteria to be accepted into the study. Assessments as detailed in the SoA (Appendix 1) will be conducted.

Treatment

Subjects will be admitted to the clinical research unit on Day −1. On the morning of Day 1, subjects will receive a single 1 mg/kg SC dose of study medication (emicizumab). The study medication will be administered after fasting from midnight for at least 8 hours. A standard lunch will be provided 4 hours after dosing. Subjects will leave the unit after 72 hours after dose assessments are completed and will return to the unit for the collection of PK samples and for remaining assessments. Subjects will receive standard meals while in the unit.

All assessments must be performed as per SoA.

Withdrawal Criteria

The investigator has the right to withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent at any time
- The subject develops a treatment-related serious adverse event.

- Any medical condition that the investigator or Sponsor determines may jeopardize the subject's safety if he continues in the study
- Investigator or Sponsor determines it is in the best interest of the subject
- Subject non-compliance

Subjects who withdraw from the study for non-safety reasons may be replaced. Subjects who withdraw from the study due to poor tolerability to study drug will not be replaced. Early termination blood samples for emicizumab PK and safety laboratory assessment will be collected at the time of discontinuation.

Statistical Methods

Pharmacokinetic Analyses

Individual plasma concentrations at each sampling timepoint for emicizumab will be presented by listings and appropriate descriptive summary statistics, including arithmetic means, geometric means, medians, minimums-maximums, SDs, and coefficients of variation. Individual and mean plasma concentration versus time data will be plotted on semi-logarithmic scales.

All PK parameters will be presented by individual listings and summary statistics including arithmetic means, geometric means, medians, minimums-maximums, SDs, and coefficients of variation.

The primary emicizumab PK study parameters will be the C_{max} and the AUC ($AUC_{0-\infty}$ if it can be derived, otherwise truncated as appropriate). All other PK parameters will be regarded as secondary.

Non-compartmental analysis will be employed for estimation of the following PK parameters:

- t_{max}: Time to maximum observed plasma concentration
- C_{max}: Maximum observed plasma concentration
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve between time zero extrapolated to infinity
- AUC_{0-last}: Area under the plasma concentration-time curve between time zero and the time of the last quantifiable concentration
- $t_{1/2}$: Apparent terminal half-life, computed as ($\ln 2/\lambda_z$)
- CL/F: Apparent clearance
- Vz/F: Apparent volume of distribution
- MRT: Mean residence time

Safety Analyses

All safety analyses will be based on the safety analysis population.

Sample Size Justification

The number of subjects (12 evaluable subjects) is chosen based on practical clinical judgment (AUC and C_{max} variability of emicizumab in Caucasian and Japanese healthy subjects) and China regulatory requirement.

Prohibited Therapy

As a general rule, no concomitant medications (including herbal products and vitamins) will be permitted, with the exception of medications to treat adverse events unless the rationale for exception is discussed and clearly documented between the investigator, the Medical and Safety Monitors, and the Roche clinical pharmacologist. All concomitant medications throughout the duration of the study should be recorded on the Concomitant Medications eCRF.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab	antibody
ADA	anti-drug antibody
A/G	albumin/globulin
ALP	alkaline phosphatase
aPCC	activated prothrombin complex concentrate
AUC	area under the plasma–concentration curve
$AUC_{0-\infty}$	area under the plasma concentration–time curve between time zero extrapolated to infinity
AUC_{0-last}	area under the plasma concentration–time curve between time zero and the time of the last quantifiable concentration
BA	bioavailability
BMI	body mass index
BP	blood pressure
CK	creatine kinase
C_{max}	maximum plasma concentration observed
CL/F	apparent clearance
CRO	contract research organization
CRP	C-reactive protein
DBP	diastolic blood pressure
DVT	deep vein thrombosis
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	(U.S.) Food and Drug Administration
FIX	factor IX
FIXa	activated factor IX
FVIII	factor VIII
FVIIIa	activated factor VIII
FX	factor X
GCP	Good Clinical Practice
GPI	glycoprotein I
HbsAg	hepatitis B surface antigen
HCP	healthcare provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Definition
IB	Investigator's Brochure
ICH	International $Council$ for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
MAD	multiple ascending doses
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRT	mean residence time
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
PT	prothrombin time
QRS	QRS complex
QTc	QT corrected for heart rate
rFVIIa	recombinant activated factor VII
SBP	systolic blood pressure
SC	subcutaneous
SoA	schedule of assessments
t_{max}	time to maximum plasma concentration
$t_{1/2}$	terminal plasma half-life
ULN	upper limit of normal
Vz/F	apparent volume of distribution
γ-GTP	γ-Glutamyltranspeptidase

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON HEMOPHILIA A

Hemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with hemophilia A have a deficiency in or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013).

Hemophilia A is most commonly caused by an inherited FVIII gene mutation within the Xq28 region of the X chromosome. It occurs almost exclusively in males having one defective copy of the relevant gene on their X chromosome. Because an affected man will transmit a normal Y chromosome to all of his sons and an abnormal X chromosome to all of his daughters, his sons will not be affected and all of his daughters will be carriers. The offspring of a female carrier have a 50% chance of receiving a mutated FVIII gene, thus half of the male infants will have hemophilia A, and half of the female infants will be carriers of the mutated gene. Females who are carriers of hemophilia A may experience bleeding symptoms similar to those seen in men with mild hemophilia A, as approximately 10% of carriers have a FVIII activity that is less than 35% (Plug et al. 2006).

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of hemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial hemorrhage. The severity of the disease roughly correlates with the residual endogenous level of FVIII activity. Approximately 68% of people with hemophilia A have moderate (25%) or severe (43%) forms, characterized by FVIII activity levels of $<5\%$ or $<1\%$, respectively, leading to frequent bleeding events with the sequelae of musculoskeletal complications (e.g., arthropathy), local functional deficits, hemorrhagic shock, neurocognitive defects, or even death (World Federation of Hemophilia 2013).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimize bleeding events and complications (Manco-Johnson et al. 2007). Current prophylactic regimens commonly use infusion therapy administered 2–3 times weekly (Adynovat® eU.S. Package Insert; Kovaltry® U.S. Package Insert); other regimens use every other day administration (Shapiro 2013). Prophylactic FVIII replacement therapy has been recognized as superior to episodic therapy of symptomatic bleeds for several decades (Khawaji et al. 2012) and was adopted by national and international organizations as the desired treatment approach. However, the burden of treatment (Eton et al. 2013, Mair and May 2014) is extraordinarily onerous because adequate prophylaxis requires a lifetime of self-administered intravenous (IV) infusion of FVIII 3–4 times each week. In addition to treatment burden, other reasons, including venous access and cost concerns, underlie

this problem (Gringeri et al. 2012), which contributes to hemophilia-associated long-term morbidity.

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%–30% of patients with severe hemophilia A and in 3%–13% of those with moderate or mild disease (Franchini and Mannucci 2013). In China, the development of inhibitors occurs in approximately 9%–15% of patients with hemophilia A (Wang et al. 2010). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titer (≥ 5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only hemostatic options currently available are prothrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”).

The development of effective prophylactic treatment options with decreased immunogenicity and less frequent dosing requirements is important to reduce the time and burden associated with frequent IV dosing and the impact of the disease on aspects of physical health and other areas of function. Given the incomplete efficacy and the significant management challenges in adults and children with hemophilia, there is a true need for therapeutics that have reliable efficacy, a long half-life, low treatment burden, and ease of administration to prevent bleeding in and minimize long-term morbidity of individuals with hemophilia A.

1.2 BACKGROUND ON EMICIZUMAB

Emicizumab (also known as ACE910 and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX), mimicking the co-factor function of activated FVIII (FVIIIa). In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors because emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because the pharmacokinetic properties of this antibody are expected to enable marked extension of the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with hemophilia A with and without FVIII inhibitors who are in need of effective, safe, and low-burden prophylactic therapy.

1.2.1 Previous Non-Clinical Studies

Binding studies of emicizumab to cynomolgus monkey factor IX (FIX) and FX showed similar affinities as those to the human factors. Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay-testing systems, which revealed that emicizumab shortened aPTT and promoted thrombin generation. Emicizumab bound to human Fcγ receptor, cynomolgus monkey Fcγ receptor, human neonatal Fc receptor, and

cynomolgus monkey neonatal Fc receptor with similar affinities as a human IgG4 antibody, natalizumab.

In vivo pharmacology experiments in cynomolgus monkeys were conducted in a hemophilia A model where endogenous FVIII levels were neutralized by a FVIII-specific monoclonal antibody. This model mimics essential characteristics of patients with hemophilia A and was used to test in vivo pharmacodynamics and efficacy under spontaneous or local trauma-induced bleeding conditions. In summary, emicizumab demonstrated the ability to significantly reduce bleeding tendency under both sets of conditions.

Potential prothrombotic risks associated with emicizumab-induced FVIII mimetic activity were further explored in an in vivo cynomolgus monkey venous stasis model. In this model, thrombus formation in the presence of emicizumab was compared with that in the presence of FVIII or bypassing agents recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC). Thrombus formation with emicizumab did not markedly exceed formation observed with rFVIIa, aPCC, or FVIII.

The pharmacokinetics/toxicokinetics of emicizumab were assessed in cynomolgus monkeys after single and multiple doses were administered intravenously and via the intended clinical SC route. After a single IV dose of 6 mg/kg of emicizumab in male cynomolgus monkeys, the plasma clearance was 3.62 mL/day/kg and the terminal plasma half-life ($t_{1/2}$) of emicizumab was 19.4 days. The single SC administration study (dose levels: 0.06, 0.6, and 6 mg/kg) indicated slow (time to maximum plasma concentration [t_{max}]: 3.00–5.33 days) and complete absorption (bioavailability [BA]: 102% at 6 mg/kg). The IV and SC multiple dosing studies (toxicokinetic monitoring) revealed a $t_{1/2}$ in the range of 14.9–30.8 days. Overall, exposures in terms of maximum plasma concentration observed (C_{max}) and area under the plasma-concentration curve (AUC) increased in an approximately dose-proportional manner.

A subfraction of the cynomolgus monkeys treated with repeated doses of emicizumab showed the formation of anti-emicizumab antibodies (which is expected with humanized monoclonal antibodies), with few animals also showing neutralizing antibodies.

Aspects of acute as well as repeated-dose toxicity including local tolerance assessment were evaluated in cynomolgus monkeys in 4-, 13-, and 26-week SC dose toxicity studies (at doses up to 30 mg/kg weekly), and a 4-week IV dose toxicity study (at doses up to 100 mg/kg weekly). No toxicologically relevant changes attributable to SC or IV administration of emicizumab were observed; the no observed adverse effect level was the highest tested dose in each toxicity study.

See the Emicizumab (RO5534262) Investigator's Brochure (IB) for additional details on nonclinical studies with emicizumab.

1.2.2 Previous Clinical Studies

Currently available experience with emicizumab in humans includes data from one completed Phase I study (ACE001JP) and its ongoing extension Phase I/II study (ACE002JP) and one completed BA study conducted in healthy volunteers (JP29574). ACE001JP was a single study conducted in three parts, including both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objectives of Parts A and B in healthy subjects were to investigate the tolerability, safety, and pharmacokinetic (PK), and pharmacodynamic (PD) response of SC-administered emicizumab in adult Japanese and Caucasian men and to evaluate the racial differences, if any, in their PK and PD response. Healthy men aged 20–44 years were eligible for enrollment. A total of 64 healthy subjects were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC-administered emicizumab in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age, ≥40 kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and/or treatment with coagulation factor in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

Parts A and B of Study ACE001JP consisted of a randomized, placebo-controlled, single-ascending dose study, which was conducted in Japanese (n=40; Part A) and Caucasian (n=24; Part B) healthy men; 48 subjects received a single SC injection of 0.001 to 1 mg/kg of emicizumab, and 16 subjects received a single SC injection of placebo. Part C of Study ACE001JP was an open-label, multiple ascending dose (MAD) study in 18 Japanese patients with hemophilia A, both with and without inhibitors. Of the 18 patients in Part C of Study ACE001JP, 6 patients were dosed with 0.3 mg/kg/wk SC following a single loading dose of 1 mg/kg SC, 6 patients were dosed with 1 mg/kg/wk SC following a single loading dose of 3 mg/kg, and 6 patients received 3 mg/kg/wk of emicizumab without a loading dose.

Study ACE002JP is an extension study that allows patients enrolled in Part C of Study ACE001JP to continue treatment with emicizumab. All continuing patients in Study ACE002JP have been observed for at least 96, 72, or 48 weeks in the 0.3, 1, and 3 mg/kg/wk dosing groups, respectively, except for 1 patient in the 3 mg/kg/wk group who has only been followed for 44 weeks.

Study JP29574 was a single-dose study in healthy Japanese male subjects. The objective was to investigate (1) the relative bioavailability (BA) of the new emicizumab material (G2.1) among different sites of SC administration (abdominal, upper arm, and thigh), (2) the absolute bioavailability of the new emicizumab material (G2.1), and (3) the relative bioavailability of the new emicizumab material (G2.1, 150 mg/mL) versus the previous emicizumab material (G1, 80 mg/mL). A total of 60 healthy male subjects were enrolled in five groups (12 subjects in each group) [Group A: G 1 SC injection 1 mg/kg in the abdomen; Group B: G2.1 SC injection 1 mg/kg in the abdomen; Group C: G2.1 SC

injection 1 mg/kg in the upper arm; Group D: G2.1 SC injection 1 mg/kg in the thigh; Group E: G2.1 IV infusion 0.25 mg/kg].

From Study ACE001JP in healthy subjects, all adverse events were of mild intensity, except for one moderate adverse event (nasopharyngitis in 1 subject on the 0.1 mg/kg dose). No racial differences were detected, and there were no dose-dependent increases in the incidence of adverse events. A causal relationship to emicizumab could not be ruled out for two adverse events (both in 1 volunteer) reported in the 1 mg/kg group (blood bilirubin increased and bilirubin conjugated increased). There were no serious adverse events, adverse events leading to discontinuation, or deaths in this study. From Study JP29574 in healthy subjects, all adverse events were mild to moderate in severity, and there were no severe adverse events, adverse events resulting in study discontinuation, or serious adverse events. A total of 27 adverse events in 22 out of 60 subjects have been observed after single SC or IV administration of emicizumab. Three adverse events (abdominal pain, oropharyngeal pain, and hot flush) have been considered to be related to emicizumab.

Emicizumab was safe and well tolerated in patients with hemophilia A in the Phase I/II studies (see Emicizumab IB). The majority of adverse events were of mild intensity, except for 5 moderate adverse events (upper respiratory tract infection, bipolar I disorder, hemophilia [i.e., left hip joint bleeding due to hemophilia], headache, and asthma) and 2 severe adverse events (appendicitis and mesenteric hematoma). Both severe events were considered to be serious adverse events and not related to emicizumab administration. A total of 7 patients reported injection-site reactions (including erythema, hematoma, rash, pain, discomfort, and pruritus). All injection-site reactions were of mild intensity. Besides injection-site reactions, the most frequently reported adverse events (reported in $\geq$4 patients) were nasopharyngitis, pharyngitis, dental caries, excoriation, and headache. There were no dose dependent increases in adverse events, and the majority of the adverse events were not considered related to emicizumab. Treatment was discontinued for 1 patient with injection-site erythema in the 1 mg/kg weekly group; the event was mild in intensity and resolved. This same patient also reported one non-related serious adverse event (hemophilia [i.e., left hip joint bleeding due to hemophilia]) approximately 22 weeks after the last dose of study drug. No thromboembolic adverse events have been reported when emicizumab has been administered alone or concomitantly with FVIII products or bypassing agents as episodic therapy.

In Study BH29884, as of April 2017, thrombotic microangiopathy had been observed in 3 patients receiving emicizumab and bypassing agents, and thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. For more details refer to Section 5.2.1.3 and Section 5.2.1.4.

Emicizumab exhibited linear pharmacokinetics after single SC administration. Following single SC injection, its mean elimination $t_{1/2}$ (4–5 weeks) was similar to that of other

human immunoglobulin G antibodies. Furthermore, comparison of PK profiles between Japanese and Caucasian healthy subjects did not reveal racial differences. Similar PK profiles were observed in healthy Japanese subjects following abdominal SC injection of 1 mg/kg with two different emicizumab formulations (G1 [80 mg/mL] and G2.1 [150 mg/mL]). Also, similar PK profiles were observed following SC injections in abdomen, upper arm, and thigh, which suggest that emicizumab can be interchangeably injected in each of these three locations. In addition, emicizumab was almost completely absorbed following SC injection, with an absolute bioavailability of 80.4%–93.1%, depending on the injection site. In patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-proportional manner with weekly dosing to achieve a plateau after approximately 12 weeks in the first two dosing groups, in which a loading dose was administered, and after approximately 24 weeks in the highest dose group, in which no initial loading dose was administered.

In the Phase I/II studies ACE001JP, ACE002JP, and JP29574, emicizumab has been administered to 108 healthy subjects and 18 patients with hemophilia A. A total of 10 subjects/patients tested positive for anti-drug antibodies (ADAs) on at least one occasion. Seven subjects/patients developed an ADA after exposure, and in 3 other patients, ADA was detected before first exposure to emicizumab. No clinically relevant changes in the pharmacokinetics and pharmacodynamics of emicizumab have been detected in any of the hemophilia A patients who tested positive for ADA (i.e., none of the ADA have been neutralizing), and the presence of ADA did not have an effect on the annualized bleeding rate reduction in these patients.

Based on these compelling Phase I/II data, a clinical development program in adult and pediatric patients with hemophilia A (both with and without FVIII inhibitors) has been initiated. See the IB for additional details on clinical studies with emicizumab.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study is designed to evaluate the pharmacokinetics, safety, and tolerability of emicizumab following single SC administration to healthy Chinese male subjects.

As this is a Phase I study in healthy subjects, no therapeutic benefit is anticipated for these subjects. Under a controlled setting, this study should provide a better understanding of pharmacokinetics, safety, and tolerability to guide future clinical studies and optimize the benefit-risk in Chinese hemophilia A patients.

The target exposure-range of emicizumab has been shown to be safe and well tolerated in previous clinical studies and no ethnic difference in pharmacokinetics is observed between Asian (Japanese) and Caucasian healthy subjects. The investigated dosing regimen in this study (1 mg/kg, single dose) is associated with a safety margin (compared with corresponding exposure values achieved at NOAEL in the GLP cynomolgus monkey study after subcutaneous administration) of 228-fold and 244-fold based on C_{max} in Japanese and Caucasian healthy subjects, respectively, and of

33.7-fold and 30.0-fold based on AUC_{last}, respectively. The risks for an individual subject due to a single dose of emicizumab or study-related procedures are considered to be minimal.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is:

- To assess the pharmacokinetics of emicizumab in healthy Chinese subjects following a single SC administration of emicizumab.

2.2 SECONDARY OBJECTIVE

The secondary objective for this study is:

- To assess the safety and tolerability of emicizumab in healthy Chinese subjects following a single SC administration of emicizumab.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This will be a single-center and open-label study and will evaluate the pharmacokinetics, safety, and tolerability of emicizumab following a single SC administration to healthy Chinese subjects.

Figure 1 Overview of Study Design

<table>
<tr><th>Screening</th><th colspan="2">In Clinic Period</th><th>Ambulatory Visits</th></tr>
<tr><td>Days −28 to −2</td><td colspan="2">Days −1 to 4
(Discharge: the morning of Day 4)</td><td>Days 6 to 113</td></tr>
<tr><td></td><td>Admission to Clinic
Day −1</td><td>Study Drug Administration
Day 1</td><td></td></tr>
</table>

The total duration of the study for each subject will be up to 20 weeks divided as follows:

- Screening: Up to 4 weeks
- In Clinic period: Days −1 to 4
- Ambulatory visits: Days 6, 8, 11, 15, 22, 29, 36, 43, 50, 57, 71, 85, and 113

Subjects will be admitted to the clinical research unit on Day −1. On the morning of Day 1, subjects will receive a single 1 mg/kg SC dose of study medication (emicizumab). The study medication will be administered after fasting from midnight for at least 8 hours. A standard lunch will be provided 4 hours after dosing. Subjects will leave the unit after 72 hours after dose assessments are completed and will return to the unit for the

collection of PK samples and for remaining assessments. Subjects will receive standard meals while in the unit.

A total of 16 healthy Chinese male subjects will be enrolled in the study to obtain at least 12 evaluable subjects.

3.2 END OF STUDY

The end of the study is defined as the date when the last subject, last observation occurs and is expected 113 ± 3 days after the last subject dose administration unless a subject withdraws his consent.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Dosage Selection

In the healthy subject studies (ACE001JP and JP29574), single doses of up to 1 mg/kg emicizumab were well tolerated. Emicizumab exposure in Japanese healthy subjects was comparable to that in Caucasians. These data and emicizumab PK properties did not reveal or support the likelihood of ethnicity differences in emicizumab pharmacokinetics. In the MAD patient study (ACE001JP Part C and its extension ACE002JP), emicizumab exhibited linear pharmacokinetics over the dose range from 0.3 mg/kg to 3 mg/kg. To evaluate the pharmacokinetics in Chinese healthy subjects, the maximal tested dose in healthy subjects (1 mg/kg) has been selected for this study. This is considered to be adequate to assess the emicizumab PK profile in a Chinese healthy population and to compare the results with those from Caucasian and Japanese populations.

3.3.2 Rationale for Study Population

Healthy Chinese subjects have been chosen in this study as the absence of confounding disease processes in healthy subjects leads to a clear and more consistent assessment of drug disposition, and healthy subjects are unlikely to require concomitant treatments which could interfere with the study drug. In addition, the safety, tolerability, and pharmacokinetic profiles of emicizumab have been well evaluated and established in healthy Caucasian and Japanese subjects. The drug was safe and well tolerated in healthy subjects as evidenced by studies ACE001JP and JP29574.

3.4 OUTCOME MEASURES

3.4.1 Pharmacokinetic Outcome Measures

Plasma concentrations of emicizumab will be measured by a specific and validated method. PK parameters will be estimated using standard non-compartmental methods.

- Primary PK parameters: C_{max} and area under the plasma concentration-time curve between time zero extrapolated to infinity ($AUC_{0-\infty}$) of emicizumab

- Secondary PK parameters: Area under the plasma concentration–time curve between time zero and the time of the last quantifiable concentration ($AUC_{0\text{-last}}$), t_{max}, $t_{1/2}$, apparent clearance (CL/F), apparent volume of distribution (Vz/F), mean residence time (MRT) of emicizumab

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events
- Incidence and clinical significance of anti-emicizumab antibodies
- Laboratory test data (hematology, blood chemistry, coagulation screening test, urinalysis, viral serology, and immunology), vital signs, 12-lead ECG
- Coagulation tests

4. MATERIALS AND METHODS

4.1 CENTER

This is a single-center study. An additional site(s) may be included for back-up purposes and may be activated if needed.

Administrative and contact information and the list of investigators are provided separately.

4.2 STUDY POPULATION

This study will enroll 16 healthy male subjects.

Subjects who drop out of the study for non-safety reasons may be replaced to ensure sufficient data to characterize the PK and safety profile. Subjects who withdraw from the study due to poor tolerability to a study drug-related adverse event will not be replaced.

4.2.1 Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Healthy Chinese male subjects, aged 20–45 years inclusive at the time of screening.
- Chinese subjects must have Chinese parents and grandparents, all of whom were born in China.
- Healthy status as defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, coagulation, viral serology, urinalysis, and immunology.
- A body mass index (BMI) between 19 and 24 kg/m^2, inclusive.
- Able to participate and willing to give written informed consent and to comply with the study requirements.

4.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

- Any history or presence of clinically significant gastrointestinal, respiratory, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, metabolic, malignant, or dermatological disorder.
- Major illness within 1 month prior to dosing, and/or any condition which could relapse during or immediately after the study.
- Use of any prescribed or over-the-counter (OTC) medication or herbal medicine taken within 14 days prior to dosing or within 5 times the elimination half-life of the medication prior to dosing (whichever is longer), with some exceptions (see Section 4.5.2).
- Confirmed supine systolic blood pressure (SBP) $\geq$140 or $\leq$ 90 mmHg, and diastolic blood pressure (DBP) $\geq$90 or $\leq$ 50 mmHg.
- Confirmed resting supine heart rate (HR) greater than 100 or less than 50 beats per minute.
- History of drug abuse within the past 2 years or confirmed positive results for drugs of abuse at screening or Day -1.
- Alcohol dependence or a history of this within the past 2 years or positive results for alcohol breath test at screening or Day -1.
- Confirmed clinically relevant abnormal (as judged by the investigator) laboratory test results.
- Any significant donation/loss of blood or plasma ($>$450 mL) within the 3 months prior to dosing.
- Regular smoker with consumption of more than 10 cigarettes per day or the equivalent amount of tobacco.
- Any other condition or disease other than stated which, in the judgment of the investigator, would place the subject at undue risk; interfere with the absorption, distribution, metabolism, and excretion of emicizumab; or interfere with the ability of the subject to complete the study.
- Participation within a clinical study with an investigational drug or device within the last 3 months prior to dosing.
- Any clinically relevant history of hypersensitivity or allergic reactions, either spontaneous or following drug administration or exposure to foods or environmental agents.
- Previous or concomitant thromboembolic disease such as deep vein thrombosis (DVT) or signs of thromboembolic disease, or family history of thromboembolic disorder such as serious DVT.
- At high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment.

- Protein C activity, protein S activity, antithrombin III activity, FIX activity, FX activity, lupus anticoagulant (T1/T2 ratio), or anti-cardiolipin-beta-2 glycoprotein I (GPI) complex antibody levels outside the reference range at screening, or FVIII activity $\geq$ 120% at screening.
- Previous or concomitant autoimmune or connective tissue disease.
- History of tuberculosis or *active tuberculosis with* positive T-SPOT®.*TB* test result at screening.
- Any other reason that, in the judgment of the investigator, would render the subject unsuitable for study participation.

4.3 METHOD OF TREATMENT ASSIGNMENT

This study is open-label and consists of one cohort. A total of 16 healthy male subjects will be enrolled in the study in order to obtain at least 12 evaluable subjects. Each subject will be assigned to receive a 1 mg/kg single SC dose of emicizumab. Subject number will be allocated sequentially in the order in which the subjects are enrolled.

4.4 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is emicizumab (RO5534262).

4.4.1 Formulation, Packaging, and Handling

Emicizumab (RO5534262) will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2°C–8°C (do not freeze and protect from light). Each single-use vial contains 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated as 150 mg/mL emicizumab in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, and 20 mmol/L histidine-aspartic acid buffer (pH 6.0). For further information on the formulation and handling of emicizumab, see the IB.

4.4.2 Dosage, Administration, and Compliance

4.4.2.1 Emicizumab

Each subject will receive a single abdominal SC injection of 1 mg/kg emicizumab under fasting conditions.

Details on the devices to be used for study medication withdrawal from vial and SC injection are provided in the Pharmacy Manual.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF).

Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Subjects will be observed for a minimum of 60 minutes after the administration.

4.4.3 Investigational Medicinal Product Accountability

Emicizumab, the only IMP in this study, will be provided by the Sponsor. Accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

The investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the subject to whom the study drug was dispensed (e.g., subject initials and date of birth).
- All records and drug supplies must be available for inspection by the Roche Monitor (at every monitoring visit).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, or destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person (or company) who destroyed investigational products(s)

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.5 CONCOMITANT THERAPY AND FOOD

Concomitant therapy consists of any medication (e.g., prescription drugs, OTC, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 4 weeks prior to initiation of study drug to the study

completion/discontinuation visit All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF).

4.5.1 Permitted Therapy

Acetaminophen/paracetamol is allowed up to a maximum dose of 1 g/day up to 48 hours prior to dosing, not to exceed 4 g total during the week prior to dosing.

4.5.2 Prohibited Therapy

As a general rule, no concomitant medications (including herbal products and vitamins) will be permitted, with the exception of medications to treat adverse events unless the rationale for exception is discussed and clearly documented between the investigator, the Medical and Safety Monitors, and the Roche clinical pharmacologist. All concomitant medications throughout the duration of the study should be recorded on the Concomitant Medications eCRF.

4.5.3 Prohibited Food

- The consumption of foods and beverages containing caffeine or methylxanthine (e.g., tea, coffee, cola, and, chocolate) will not be permitted during the in-house periods. During the non-resident period, subjects will be asked to consume $\leq$6 cups of coffee or tea per day and $\leq$1 L per day of methylxanthine-containing drinks.
- Alcohol will not be allowed 48 hours before the dose and whilst staying in the study center. During the periods that subjects are not a resident in the unit, alcohol consumption has to be less than 2 drinks per day of alcohol (1 drink equates to approximately 330 mL of beer, 125 mL of wine, or 25 mL of spirits).
- The use of tobacco is not permitted during the in-house period.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the schedule of assessments (SoA) outlined in Appendix 1.

At timepoints when several assessments coincide, the following sequence should be followed with the PK blood sample to be taken as close as possible to the nominal timepoint:

- ECG recordings
- Vital signs
- Physical examination
- Blood draws, taken in standard order of collection:
  - Coagulation blood samples (citrate plasma)
  - Serum or EDTA plasma for safety, PK, and ADA samples
- Urine collection
- Study drug administration

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, and nutritional supplements) used by the subject within 30 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.6.1.2 Electrocardiograms

ECGs will be collected after the subject has been in a supine position for at least 10 minutes. At the specified timepoints, 12-lead ECGs will be obtained in triplicate (i.e., three consecutive interpretable 12-lead ECGs within 5 minutes and recorded on the eCRF). Triplicate recordings should be taken for any unscheduled ECG.

All ECG recordings must be performed using a standard digital high-quality, high-fidelity ECG machine equipped with computer-based interval measurements. Automated ECG intervals (PR [PQ], QRS duration, QT, and QT corrected for HR (QTc) using the Fridericia correction factor) and HR will be captured, and the changes in T-wave and U-wave morphology will be documented. T-wave information will be captured as normal or abnormal, and U-wave information will be captured in two categories: absent/normal or abnormal.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the subject's permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

The following are requirements for ECG assessments:

- The absence of any environmental distractions (television, radio, and conversation) during the pre-ECG rest and the ECG recording in the clinic must be emphasized.
- Avoid ECG recordings within 3 hours after meals, if allowed per predefined schedule.
- If possible, the same machine, brand and model, should be used for the same subject throughout the study.
- ECGs should be 12-lead and recorded at 25 mm/sec for at least 10 seconds.
- ECG machines should have periodic calibration and service records (minimum of once a year).
- If any QT/QTc values $>$ 500 msec or increases from predose on Day 1 QTc $>$ 60 msec (as provided by the machine) are observed, the site should repeat the ECG within the next 5 minutes and notify the Sponsor. If confirmed, ECG recordings should be repeated at least hourly until two successive ECGs show QTc values below the threshold value that triggered the repeated measurement.

4.6.1.3 Vital Signs

Vital signs will include measurements of temperature (axillary), respiratory rate, pulse rate, and systolic and diastolic blood pressure (BP) while the subject is in a supine position after the subject has been resting for at least 5 minutes at each visit (10 minutes for the screening visit). Vital signs should be measured prior to blood sampling. When possible, the same arm should be used for all BP measurements.

BP, respiratory rate, pulse rate, and body temperature (axillary) will be recorded at the timepoints specified in the SoA (see Appendix 1).

BP, respiratory rate, and pulse rate measurements will be performed in triplicate (can be as short as from 20-second to 1-minute intervals between measurements). The mean of three consecutive replicates will be used as the value for the defined timepoint.

4.6.1.4 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck, and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. A genitourinary examination may be performed in the case of evocative symptoms at the investigator's discretion.

Any abnormality identified at screening or at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), abbreviated, symptom-directed physical examinations should be performed at the discretion of the investigator. Changes from baseline abnormalities should be recorded in subject's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Body weight will be recorded at screening and Day 1. Height will only be recorded at screening. BMI will be calculated at screening in accordance with the formula provided in Appendix 2.

4.6.1.5 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at timepoints specified in the SoA (Appendix 1).

Additional blood or urine samples may be taken at the discretion of the investigator if the results of any test fall outside the reference ranges, or if clinical symptoms necessitate additional testing to monitor subject's safety. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before admission to confirm eligibility. If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food

containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory, if applicable.

Samples for the following blood and urine laboratory tests will be collected and sent to the local laboratory for analysis at timepoints indicated in the SoA (Appendix 1):

- Hematology: hemoglobin, hematocrit, total WBC count, differential WBC count (basophils, eosinophils, lymphocytes, monocytes and neutrophils), platelet count, RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).
- Blood Chemistry: albumin/globulin (A/G) ratio, AST, ALT, LDH, total and indirect bilirubin, alkaline phosphatase (ALP), gamma glutamyl transpeptidase (γ-GTP), CK, BUN, total protein, serum albumin, serum creatinine, uric acid, total cholesterol, triglycerides, fasting glucose, sodium, chloride, potassium, *high-sensitivity* C-reactive protein (CRP).
- Screening Coagulation Test: Protein C activity , Protein S activity, antithrombin III activity, factor VIII activity, factor IX activity, factor X activity, lupus anti-coagulant (T1/T2 ratio).
- Coagulation test 1: Prothrombin time (PT), PT/International Normalized Ratio (INR), aPTT, fibrinogen, D- dimer. Starting on Day 1 onward, blood samples will be drawn to conduct biomarker assays at the central laboratory ([redacted] in the United States). The same assays will be also conducted locally at screening, and on Day −1, Day 2, Day 11, Day 29, Day 57, and Day 113.
- Coagulation test 2: Prothrombin fragments 1+2, FVIII activity. The samples will be run centrally on frozen plasma ([redacted]).
- Coagulation test 3: FVIII inhibitors. The samples will be run centrally on frozen plasma ([redacted]).
- Urinalysis: A mid-stream, clean catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocytes, specific gravity and pH. If there is a clinically significant positive result (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick result, it should be recorded, and there is no need to perform microscopy. Urine color may be evaluated from urinalysis if considered necessary.
- Viral serology: hepatitis B surface antigen (HBsAg), HCV RNA or HCV antibodies, and human immunodeficiency virus (*HIV antibody*).

- Immunology: non-specific immunoglobulin E (IgE) antibodies and anti-cardiolipin-beta-2 GPI complex antibody levels.
- Drugs of abuse (urine): cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates.
- Alcohol: alcohol breath test.
- *Tuberculosis: T-SPOT.TB test*

4.6.1.6 Pharmacokinetic Samples

Blood samples for the determination of plasma concentrations of emicizumab will be collected as specified in the SoA (see Appendix 1) and will be sent to the Sponsor or a designee for centralized analysis.

The actual date and time of each blood sample collection will be recorded on the PK Sampling Information eCRF.

Emicizumab plasma concentrations will be measured by a specific and validated enzyme-linked immunosorbent assay method. For blood draws, when the PK assessment is scheduled for the same nominal time as another scheduled assessment, the PK sample will take precedence.

Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual.

PK parameters will be estimated using standard non-compartmental methods for emicizumab:

- Primary PK parameters: C_{max} and $AUC_{0-\infty}$ of emicizumab
- Secondary PK parameters: AUC_{0-last}, t_{max}, $t_{1/2}$, CL/F, Vz/F, and MRT of emicizumab

4.6.1.7 Additional Coagulation Samples

Blood samples for determination of additional coagulation parameters will be collected as specified in the SoA (see Appendix 1) and will be sent to the Sponsor or a designee for centralized analysis. Please consult the laboratory manual for details on sample collection and processing.

The actual date and time of each blood sample collection will be recorded on the Coagulation Sampling Information eCRF.

4.6.1.8 Anti-Emicizumab Antibody Samples

Blood samples will be collected as indicated in the SoA (Appendix 1) for the detection of anti-emicizumab antibodies, and the samples will be run centrally on frozen plasma ([redacted] in the Netherlands).

4.6.1.9 Total Blood Loss

A total of approximately 300 mL of blood over the 113 days (for comparison, a standard blood donation is 200–400 mL collected at one blood draw) will be drawn from each subject participating.

Blood samples will be used to perform pharmacokinetics, to assess anti-emicizumab antibodies, and to assess clinical laboratory measurements listed above.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled subject and for subjects who are not subsequently enrolled will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator and kept at the investigational site.

A screening examination should be performed from Day –28 to Day –2 for healthy subjects. Subjects must fulfill all entry criteria to be accepted into the study. Assessments as detailed in the SoA (Appendix 1) will be conducted.

4.6.2.2 Assessments during Treatment

All assessments must be performed as per SoA (see Appendix 1).

Under no circumstances will subjects who enroll in this study and have completed treatment as specified, be permitted to be allocated a new subject number and re-enroll in the study.

4.6.2.3 Assessments at Study Completion/Early Termination Visit

Subjects who complete the study or discontinue from the study early will be asked to return to the clinic 113±3 days after the dosing of study drug for a follow-up visit unless the subject withdraws his consent.

4.7 SUBJECT, STUDY, AND SITE DISCONTINUATION

4.7.1 Subject Discontinuation

The investigator has the right to withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily withdraw from the study at any time for

any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent at any time
- The subject develops a treatment-related serious adverse event.
- Any medical condition that the investigator or Sponsor determines may jeopardize the subject's safety if he continues in the study
- Investigator or Sponsor determines it is in the best interest of the subject
- Subject non-compliance

Subjects who withdraw from the study for non-safety reasons may be replaced. Subjects who withdraw from the study due to poor tolerability to study drug will not be replaced. Early termination blood samples for emicizumab PK and safety laboratory assessment will be collected at the time of discontinuation.

4.7.1.1 Withdrawal from Study

Every effort should be made to obtain information on subjects who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, subjects will not be followed for any reason after consent has been withdrawn.

When a subject voluntarily withdraws from the study, or is withdrawn by the investigator, samples collected until the date of withdrawal will be analyzed, unless subject specifically requests for these to be discarded or local laws require their immediate destruction.

4.7.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.

The Sponsor will notify the investigator, Ethics Committee (EC) and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International *Council* for Harmonisation (ICH) guideline for Good Clinical Practice (GCP)

5. ASSESSMENT OF SAFETY

Emicizumab is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with emicizumab in completed and ongoing studies. The anticipated important safety risks for emicizumab are outlined below. Please refer to the Emicizumab IB for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.1.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions)
- Significant medical event in the investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to the WHO toxicity grading scale; [see Section 5.3.3]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). These may include suspected or confirmed cases. Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.7
- Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Appendix 3 and Appendix 4)
- Thromboembolic events

5.2 SAFETY PLAN

Emicizumab is currently in clinical development and is not approved. Thus, the complete safety profile is not known at this time. The safety plan for this study is designed to ensure subject safety and will include specific eligibility criteria and monitoring assessments as detailed below. Please refer to the Emicizumab IB for a complete summary of safety information.

5.2.1 Risks Associated with Emicizumab

5.2.1.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the IB.

Directions for emicizumab administration should be followed as outlined in Section 4.4.2.

5.2.1.2 Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as serious adverse events or adverse events of special interest as described in Sections 5.1.1 and 5.1.3, respectively.

Healthcare providers (HCPs) administering the study medication in the clinic must be trained in the appropriate administration procedures, be able to recognize the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions, and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 3 and Appendix 4).

Subjects will be observed for a minimum of 60 minutes after the administration.

5.2.1.3 Hypercoagulation and Thromboembolic Events

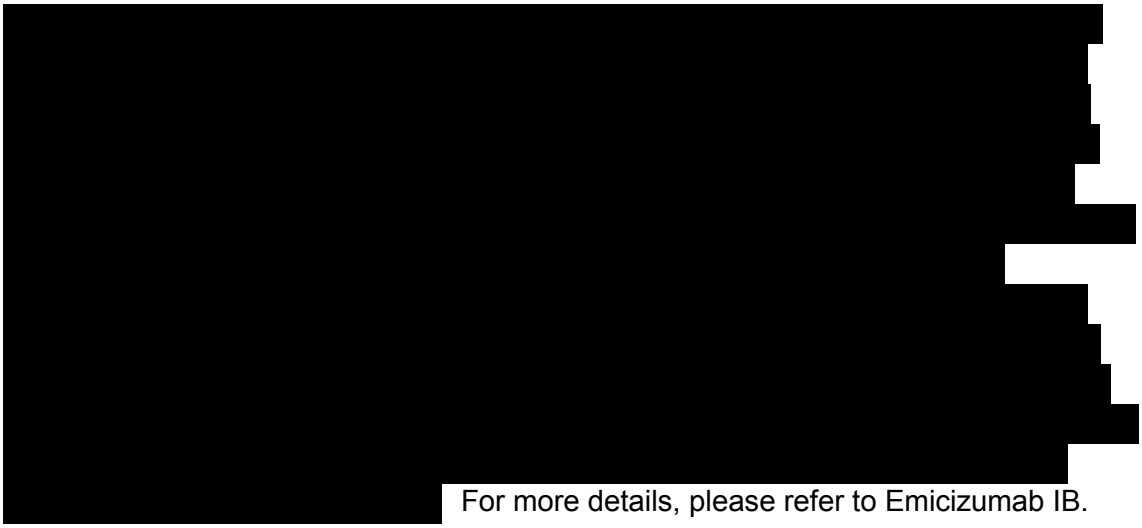
As of April 2017, thromboembolic events had been reported in 2 patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884. [redacted]

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.1.2 and Section 5.1.3, respectively.

5.2.1.4 Thrombotic Microangiopathy

Thrombotic microangiopathy is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, etc. As of April 2017, 3 cases of thrombotic microangiopathy had been observed in Study BH29884 involving patients with hemophilia A with inhibitors while receiving emicizumab.

[redacted]



For more details, please refer to Emicizumab IB.

Any thrombotic microangiopathy event should be reported as an adverse event of special interest and also as a serious adverse event, if it meets criteria for such (see Section 5.1.2 and Section 5.1.3).

5.2.1.5 Life-Threatening Bleeding because of Unreliable Standard Coagulation Tests and Inhibitor Assays in the Setting of Emicizumab

Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by the Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.2.1.4). Because of the long half-life of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose.

There is a risk of life-threatening bleeding due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab in the market setting by practitioners, particularly for emergency care practitioners.

Emicizumab mechanism of action and resulting interference was clearly demonstrated in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials also demonstrated the effects of emicizumab on laboratory tests. However, as of April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab had been observed.

5.2.2 Management of Specific Adverse Events

Table 1 Guidelines for Managing Specific Adverse Events

Event	Actions to Be Taken
Injection-Site Reaction	• Injection-site reactions should be treated as clinically indicated. • Emicizumab should not be injected into areas where the skin is red, bruised, tender, or hard or into areas where there are moles or scars. • In the clinic setting, subjects will be monitored for signs of injection-site reactions in the period immediately following injections.
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	• Suspected cases should be fully evaluated and treated as clinically indicated. • Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) and resuscitation equipment must be available for immediate use during the initial administrations in the infusion center, clinic, or hospital. • If a subject has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody in the event any of these reactions occur. • In the clinic setting, subjects will be monitored for signs of hypersensitivity reaction, anaphylaxis, anaphylactoid reaction for 60 minutes following injections.
Hypercoagulation and Thromboembolic Events	• HCPs should be vigilant for subjects who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines.
Thrombotic microangiopathy	• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thrombotic microangiopathy and immediately begin work-up and treatment, as per local guidelines.
Coagulation Disorder and Risk of Bleeding	• HCPs should be vigilant for abnormal or unusual bleeding tendencies. Coagulation tests or other work-up may be indicated if judged to be appropriate by the investigator. If bleeding is observed, appropriate action as per local guidelines must be taken immediately.

HCP = healthcare provider.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each subject contact. All adverse events, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the subject completes his last study visit. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all subject evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 3) will be used for assessing adverse event severity (WHO 2003). Table 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Severity	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Note: Developed by the Division of Microbiology and Infectious Diseases. Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

Local adverse events that occur within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as an “injection-site reaction” on the Adverse Event eCRF. Associated signs and symptoms (e.g.,

injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. If a subject experiences both a local and systemic reaction to the same administration of study drug, each reaction should be recorded separately on the Adverse Event eCRF with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF. Only for local injection-site reactions should the dedicated Injection-Site Reaction eCRF be used to capture the individual signs/symptoms.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, other than injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event

worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification or treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 times the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification or treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event of special interest the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.1.2 and 5.1.3).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The subject has not suffered an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Overdoses

An overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study subjects, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3), investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the Serious Adverse Event Responsible within 24 hours.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Partners of Male Subjects

Although embryo-fetal development studies are not available, condom use will not be required in male subjects enrolled in the study because the margin between the minimal anticipated biological effect level plasma concentration (7 ng/mL) and the estimated maternal C_{max} (at a single SC dose of 1 mg/kg) is greater than 10-fold (Banholzer et al. 2012). At this time, very little emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male subjects treated with emicizumab, so contraception use by male subjects is not required for participation in the study. Therefore, no proactive collection of pregnancy information for female partners of male subjects treated with emicizumab will be required.

5.5 FOLLOW-UP OF HEALTHY SUBJECTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the subject's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 16 weeks after the last subject dosing of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the electronic data capture (EDC) system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Emicizumab (RO5534262) IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objective of this study is to characterize the pharmacokinetic profile of emicizumab in healthy Chinese subjects following single SC administration of emicizumab. Statistical summaries will be descriptive in nature. All subjects who receive any amount of study medication and with at least one post-baseline safety assessment will be included in the safety analysis.

6.1 DETERMINATION OF SAMPLE SIZE

The number of subjects (12 evaluable subjects) is chosen based on practical clinical judgment (AUC and C_{max} variability of emicizumab in Caucasian and Japanese healthy subjects) and China regulatory requirement.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of subjects who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Protocol deviations will be listed and evaluated for their potential impact on interpretation of study results. Study drug administration will be summarized.

6.3 ANALYSIS POPULATIONS

6.3.1 Pharmacokinetic Analysis Population

Subjects will be excluded from the PK analysis population if they deviate significantly from the protocol or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.3.2 Safety Analysis Population

All subjects who have received any amount of study medication, whether prematurely withdrawn from the study or not, and with at least one post-baseline safety assessment, will be included in the safety analysis.

6.3.3 Immunogenicity Analysis Population

The immunogenicity analyses will include subjects with at least one predose and one postdose ADA assessment.

6.4 SUMMARIES OF TREATMENT GROUP

Demographic and baseline characteristics (including age, sex, etc.) will be summarized using means, SDs ranges for continuous variables and proportions for categorical variables, as appropriate.

6.5 PHARMACOKINETIC ANALYSES

Individual plasma concentrations at each sampling timepoint for emicizumab will be presented by listings and appropriate descriptive summary statistics, including arithmetic means, geometric means, medians, minimums-maximums, SDs, and coefficients of variation. Individual and mean plasma concentration versus time data will be plotted on semi-logarithmic scales.

All PK parameters will be presented by individual listings and summary statistics including arithmetic means, geometric means, medians, minimums-maximums, SDs and coefficients of variation.

The primary emicizumab PK study parameters will be the C_{max} and the AUC ($AUC_{0-\infty}$ if it can be derived, otherwise truncated as appropriate). All other PK parameters will be regarded as secondary.

Non-compartmental analysis will be employed for estimation of the following PK parameters:

- t_{max}: Time to maximum observed plasma concentration
- C_{max}: Maximum observed plasma concentration
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve between time zero extrapolated to infinity
- AUC_{0-last}: Area under the plasma concentration-time curve between time zero and the time of the last quantifiable concentration
- $t_{1/2}$: Apparent terminal half-life, computed as ($ln2/\lambda_z$)
- CL/F: Apparent clearance
- Vz/F: Apparent volume of distribution
- MRT: Mean residence time

6.6 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population.

6.6.1 Adverse Events

The original terms recorded on the eCRF by the investigator for adverse events will be standardized by the sponsor.

Adverse events will be summarized by mapped term and appropriate thesaurus level.

6.6.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Subjects listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

The proportion of subjects with laboratory abnormalities will be summarized. Additionally, the value and change from baseline for each laboratory test will be summarized by visit using descriptive statistics.

6.6.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of investigator ranges, e.g., enzyme tests that include AST, ALT, alkaline phosphatase, and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.6.2.2 Definition of Laboratory Abnormalities

For all laboratory parameters included, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in subject listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a subject, the midpoint of the standard reference range will be used as the subject's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the subject listings as "HH" for very high or "LL" for very low.

6.6.3 Vital Signs

Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.6.4 ECG Data Analysis

ECG data will be presented by individual listings with flagging of values outside the normal ranges and flagging of marked abnormalities. In addition, tabular summaries will be used, as appropriate.

6.6.5 Concomitant Medications

The original terms recorded on the subjects' eCRF by the investigator for concomitant medications will be standardized by the sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.7 IMMUNOGENICITY ANALYSES

The numbers and proportions of ADA-positive subjects and ADA-negative subjects will be summarized. Subjects are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Subjects are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety and PK results will be analyzed and reported descriptively via subgroup analyses.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the EDC system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the investigator.

The Sponsor will produce a Data Handling Manual that describes the quality checking to be performed on the data. Laboratory electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line EDC system. The data collected in the source documents will be entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made, reasons for change, time and date of entry, and user name of person authorizing entry or change. For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment‑related adverse event, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor or contract research organization (CRO) on the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

At the end of the study, the investigator will receive subject data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor with direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry

of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the subject or the subject's legally authorized representative before his participation in the study. The case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the subject to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Subjects must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Consent Forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the subject, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. This means that subject names are not included in data sets that are transmitted to any Sponsor location.

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last subject, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit an Development Safety Update Report once a year to the IEC and competent authorities according to local regulatory requirements and timelines of each country participating in the study.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the study management, data management, statistical analysis, and medical writing for the clinical study report.

The Sponsor is also responsible for managing CROs used in the study.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Assessments

	Screen	Treatment Period																
Week	–	–	0				1		2	3	4	5	6	7	8	10	12	16
Scheduled Time (Days)	(–28 to –2)	–1	1	2	4	6	8	11	15	22	29	36	43	50	57	71	85	113[a]
Informed consent	x																	
Inclusion/exclusion criteria	x	x																
Demography	x																	
Medical history	x																	
Physical examination [b]	x	x	x [c]	x [d]	x [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x [c]	x [d]	x [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG-12 lead [f]	x	x	x [c]	x [d]	x [d]	x	x		x		x		x		x	x	x	x
Hematology [g]	x	x		x [d]	x [d]		x		x		x		x		x	x	x	x
Clinical chemistry [h]	x	x		x [d]	x [d]		x		x		x		x		x	x	x	x
Urinalysis [i]	x	x		x [d]			x				x				x		x	x
Serology [j]	x																	
Immunology [k]	x																	
Tuberculosis T-SPOT®.TB test	*x*																	
Screening coagulation test [l]	x																	
Substance use testing [m]	x	x																
Admission		x																
Discharge					x													
Ambulatory visit [n]	x					x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

	Screen	Treatment Period																
Week	–	–	0				1		2	3	4	5	6	7	8	10	12	16
Scheduled Time (Days)	(–28 to –2)	–1	1	2	4	6	8	11	15	22	29	36	43	50	57	71	85	113[a]
Coagulation test 1 [o]	x	x	x [c]	x [d, o]	x [d]		x	x [o]	x		x [o]		x		x [o]	x	x	x [o]
Coagulation test 2 [p]			x [c]	x [d]	x [d]		x	x	x		x		x		x	x	x	x
Coagulation test 3 [q]			x [c]															x
PK blood Sampling (EDTA plasma)			x [c]	x [d]	x [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Anti-emicizumab antibodies (EDTA Plasma)			x [c]												x			x
Administration of study medication [r]			x															
Injection-site reaction			x				x											
Adverse events	x																	
Previous and concomitant treatments	x																	

Ab = antibody; ALP = alkaline phosphatase; A/G = albumin/globulin ratio; BMI = body mass index; BP = blood pressure; CK = creatine kinase; CRP = C-reactive protein; eCRF = electronic case report form; GPI = glycoprotein I; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus 1; HIV-2 = human immunodeficiency virus 2; IgE = immunoglobulin E; INR = International normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PK = pharmacokinetic; PT = prothrombin time; γ-GTP = gamma glutamyl transpeptidase.

[a] In the event of early termination, all assessments indicated for Day 113 will be conducted.

[b] Body weight will only be recorded at screening and on Day 1. Height will only be recorded at screening. BMI will be calculated at screening in accordance with the formula provided in Appendix 2. At subsequent visits (or as clinically indicated), abbreviated, symptom-directed physical examinations should be performed at the discretion of the investigator.

[c] Activity will be conducted or samples will be collected before study drug administration.

Appendix 1
Schedule of Assessments (cont.)

[d] Time matching *dosing* on Day 1.

[e] Vital signs will include measurements of temperature (axillary), respiratory rate, pulse rate, and systolic and diastolic BP while the subject is in a supine position after the subject has been resting for at least 5 minutes at each visit (10 minutes for the screening visit). Vital signs should be measured prior to blood sampling. When possible, the same arm should be used for all BP measurements. BP, respiratory rate, and pulse rate measurements will be performed in triplicate (can be as short as ranging from 20-second to 1-minute intervals between measurements). The mean of three consecutive replicates will be used as the value for the defined timepoint.

[f] ECGs will be collected after the subject has been in a supine position for at least 10 minutes. At the specified timepoints, 12-lead ECGs will be obtained in triplicate (i.e., three consecutive interpretable 12-lead ECGs within 5 minutes and recorded on the eCRF). Triplicate recordings should be taken for any unscheduled ECG.

[g] Hematology will include analysis of the following: hemoglobin, hematocrit, total WBC count, differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, RBC, MCV, MCH, and MCHC.

[h] Blood chemistry will include analysis of the following: A/G ratio, AST, ALT, LDH, total and indirect bilirubin, ALP, γ-GTP, CK, BUN, total protein, serum albumin, serum creatinine, uric acid, total cholesterol, triglycerides, fasting glucose, sodium, chloride, potassium, and *high-sensitivity* CRP.

[i] A mid-stream, clean catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocytes, specific gravity, and pH. If there is a clinically significant positive result (i.e., confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick result, it should be recorded, and there is no need to perform microscopy. Urine color may be evaluated from urinalysis if considered necessary.

[j] Viral serology will include analysis of the following: HBsAg, HCV RNA or HCV Ab, and *HIV antibody*.

[k] Immunology will include analysis of the following: non-specific IgE antibodies and anti-cardiolipin-beta-2 GPI complex antibody levels.

[l] Protein C activity, Protein S activity, antithrombin III activity, factor VIII activity, factor IX activity, factor X activity, lupus anticoagulant (T1/T2 ratio). These tests will be run locally.

[m] Substance use testing will include analysis of the following: cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates in urine; and alcohol levels by an alcohol breath test.

[n] Permissible time windows for Days 6 and 8 is ± 2 hr of the time matching *dosing* on Day 1; for Days 11, 15, 22, and 29 is ± 1 day; for Days 36, 43, 50, and 57 is ± 2 days, and for Days 71, 85, and 113 is ± 3 days.

[o] Coagulation test 1 is aPTT, PT, PT/INR, fibrinogen, and D-dimer. Starting on Day 1 onward, blood samples will be drawn to conduct biomarker assays at the central laboratory ([redacted] in the United States). The same assays will be also conducted locally at screening, Day -1, Day 2, Day 11, Day 29, Day 57, and Day 113.

[p] Coagulation test 2 is Prothrombin fragments $1+2$ and FVIII activity. The samples are run centrally on frozen plasma ([redacted]).

[q] Coagulation test 3 is FVIII inhibitors. The samples are run centrally on frozen plasma ([redacted]).

[r] The study medication will be administered after fasting from midnight for at least 8 hours. A standard lunch will be provided 4 hours after dosing.

Appendix 2
Formula for Calculation of Body Mass Index

Formula for calculation of BMI

$$\text{BMI } (kg/m^2) = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

Unit Conversion: 1 kg = 2.2 lb

1 inch = 2.54 cm

Example: BMI of a subject being 1.70 m tall and weighing 80 kg:

$$\frac{80}{(1.70)^2} = 27.7 \text{ kg/m}^2$$

The subject's standing height will be measured in bare feet standing with his heels and back in contact with the vertical bar of a wall mounted measuring device. The head is held so the subject looks straight forward. A level will be placed on the subject's head to ensure that the subject is looking straight forward. The point at which the lower surface of the level intersects with the vertical measuring device will be the standing height.

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

HEMATOLOGY				
Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	$<$6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	$<$500/mm^3
Platelets	75000–99999/mm^3	50000–74999/mm^3	20000–49999/mm^3	$<$20000/mm^3
Prothrombin time (PT)	1.01–1.25 $\times$ ULN	1.26–1.5 $\times$ ULN	1.51–3.0 $\times$ ULN	$>$3 $\times$ ULN
Activated partial thromboplastin (APPT)	1.01–1.66 $\times$ ULN	1.67–2.33 $\times$ ULN	2.34–3 $\times$ ULN	$>$3 $\times$ ULN
Fibrinogen	0.75–0.99 $\times$ LLN	0.50–0.74 $\times$ LLN	0.25 - 0.49 $\times$ LLN	$<$0.25 x LLN
Fibrin split product	20–40 mcg/mL	41–50 mcg/mL	51–60 mcg/mL	$>$60 mcg/mL
Methemoglobin	5%–9.9%	10.0%–14.9%	15.0%–19.9%	$>$20%
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 $\times$ ULN	2.6–5 $\times$ ULN	5.1–10 $\times$ ULN	$>$10 $\times$ ULN
ALT (SGPT)	1.25–2.5 $\times$ ULN	2.6–5 $\times$ ULN	5.1–10 $\times$ ULN	$>$10 $\times$ ULN
GGT	1.25–2.5 $\times$ ULN	2.6–5 $\times$ ULN	5.1–10 $\times$ ULN	$>$10 $\times$ ULN
Alkaline phosphatase	1.25–2.5 $\times$ ULN	2.6–5 $\times$ ULN	5.1–10 $\times$ ULN	$>$10 $\times$ ULN
Amylase	1.1–1.5 $\times$ ULN	1.6–2.0 $\times$ ULN	2.1–5.0 $\times$ ULN	$>$5.0 $\times$ ULN

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required.	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	< 30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

CHEMISTRIES continued				
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or < 3g/L or 200 mg–1 g loss/day	2–3+ or 0.3–1.0% or 3–10 g/L 1–2 g loss/day	4+ or > 1.0% or > 10 g/L 2–3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
Hypertension	transient increase > 20 mm; no Rx required	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization required	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx required	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1–2 units transfused	massive blood loss; > 3 units transfused

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx $<$80%–70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50%–70% (or peak Flow)	no normalization with bronchodilator; FEV_1 25%–50% (or peak flow retractions)	cyanosis: FEV_1 $<$25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3–4 loose stools/day	5–7 loose stools/day	orthostatic hypotension or $>$7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

NEURO AND NEUROMUSCULAR				
Neuro-cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7°C –38.5°C or 100.0°F–101.5°F	38.6°C–39.5°C or 101.6°F–102.9°F	39.6°C–40.5°C or 103°F–105°F	> 40°C or > 105°F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25%–50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis

Appendix 3
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

OTHER PARAMETERS continued				
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

NOTE: For coding purposes, the following toxicity grades may be used interchangeably: 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening.

Appendix 4
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (Sampson et al. 2006). Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue/uvula) and at least one of the following:

   Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   Involvement of the skin-mucosal tissue (e.g., generalized hives, itching/flushing, swollen lips/tongue/uvula)

   Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   Reduced BP or associated symptoms (e.g., hypotonia, syncope, incontinence)

   Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   Infants and children: low systolic blood pressure (SBP, age specific) or greater than 30% decrease in SBP

      Low SBP for children is defined as <70 mmHg from 1 month to 1 year, $<(70\ \text{mmHg} + [2 \times \text{age}])$ from 1 to 10 years, and <90 mmHg from 11 to 17 years.

   Adults: SBP of ≤ 90 mmHg or $\geq 30\%$ decrease from that person's baseline

REFERENCE

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.