Official Title: A Randomized, Multicenter, Open-Label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Patients

NCT Number: NCT03315455

Document Date: Protocol Amendment Version 5: 22-April-2023

PROTOCOL

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS**
PROTOCOL NUMBER:	YO39309
VERSION NUMBER:	5
EUDRACT NUMBER:	Not Applicable
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TEST PRODUCT:	Emicizumab (RO5534262)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic *signature and* date stamp *on the final page of this document.*

PROTOCOL AMENDMENT APPROVAL

PROTOCOL HISTORY

Protocol		Associated Country Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
5	See electronic date stamp on the final page of this document	—	—	—
—	—	China	5	10 Feburary 2022 [a]
4	19 July 2019	—	—	—
3	30 October 2017	—	—	—
2	20 March 2017	—	—	—
1	1 June 2016	—	—	—

[a] Not distributed to sites o. heath authorities.

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol YO39309 has been primarily amended to extend the study. The study will end 3 years after the last Arm D patient completes 1 year treatment and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products (see Sections 3.1 and 4.3.4). The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier (see Section 3.2.1). Changes to the protocol, along with a rationale for each change, are summarized below:

- Language has been added to clarify that collection of pharmacokinetic (PK)/anti-drug antibody (ADA)/Biomarker samples from Arm D patients will stop when the patient completes the study or after Week 49, whichever occurs first (Section 3.1).
- Language has been added to clarify that patients who discontinue treatment prior to the end of study will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug (Section 3.2.1).
- The length of study has been extended to 88 months to include a study Extension Phase because the study had been extended for 3 years after last Arm D patient completes 1 year of treatment and patients still having clinical benefit are transferred to a post-trial continued access solution. This is to allow patients who are still benefiting from emicizumab to continue treatment and to collect their safety data during the extended treatment (Section 3.2.2 and Appendix 1-B).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during Investigational Medicinal Product (IMP) transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- Language has been added to clarify that the Bleed/Medication questionnaire devices will remain with the patient/caregiver for the duration of the study. Bleed and medication data will not be collected during the study extension phase, but emicizumab dosing data will continue to be collected (Section 4.5.7).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).

- The name of a Roche policy on data sharing has been corrected (Section 9.5).

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.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 11

PROTOCOL SYNOPSIS 12

1. BACKGROUND 24
- 1.1 Background on Hemophilia A 24
- 1.1.1 Management 24
- 1.2 Background on Emicizumab 29
- 1.2.1 Molecule and Nonclinical Data 29
- 1.2.2 Clinical Experience 30
- 1.2.2.1 Clinical Pharmacology 31
- 1.2.2.2 Efficacy 31
- 1.2.2.3 Safety 33
- 1.2.2.4 Immunogenicity 34
- 1.3 Study Rationale and Benefit-Risk Assessment 35

2. OBJECTIVES AND ENDPOINTS 36

3. STUDY DESIGN 39
- 3.1 Description of the Study 39
- 3.2 End of Study and Length of Study 44
- 3.2.1 End of Study 44
- 3.2.2 Length of Study 44
- 3.3 Rationale for Study Design 45
- 3.3.1 Rationale for Emicizumab Dose and Schedule 46
- 3.3.2 Rationale for Patient Population 49
- 3.3.3 Rationale for Control Group 50
- 3.3.4 Rationale for the Primary Efficacy Analysis 50
- 3.3.5 Rationale for Patient-Reported Outcome Assessments 51
- 3.3.6 Rationale for Biomarker Assessments 52
- 3.3.7 Rationale for Pharmacokinetic Sample Schedule 53

4. MATERIALS AND METHODS 53
- 4.1 Patients 53
- 4.1.1 Inclusion Criteria 53

4.1.1.1 Arms A, B, and C 53
4.1.1.2 Arm D 54
4.1.2 Exclusion Criteria 55
4.1.2.1 Arms A, B, and C 55
4.1.2.2 Arm D 56
4.2 Method of Treatment Assignment and Blinding 57
4.3 Study Treatment 57
4.3.1 Formulation, Packaging, and Handling 58
4.3.1.1 Emicizumab 58
4.3.2 Dosage, Dose Adjustment, and Administration 58
4.3.3 Investigational Medicinal Product Accountability 61
4.3.4 Post-Trial Access to Emicizumab 61
4.4 Concomitant and Rescue Therapy 62
4.4.1 Permitted Therapy 62
4.4.2 Prohibited Therapy 63
4.5 Study Assessments 64
4.5.1 Informed Consent Forms and Screening Log 64
4.5.2 Medical History and Demographic Data 64
4.5.3 Physical Examinations 65
4.5.4 Vital Signs 65
4.5.5 Laboratory, Biomarker, and Other Biological Samples 65
4.5.6 Electrocardiograms 67
4.5.7 Patient-Reported Outcomes 67
4.5.7.1 Health-Related Quality of Life 68
4.5.7.2 Health Status 68
4.5.7.3 Adapted Inhib-QoL, Including Aspects of Caregiver Burden 68
4.5.7.4 Daycare/School Absences and Hospitalizations 69
4.5.8 Definition of a Bleed 69
4.5.8.1 Bleed Sites 69
4.5.8.2 Bleed Types 70
4.6 Patient, Treatment, Study, and Site Discontinuation 71
4.6.1 Patient Discontinuation 71
4.6.2 Study Treatment Discontinuation 71

4.6.3 Study and Site Discontinuation 71
5. ASSESSMENT OF SAFETY 72
5.1 Safety Plan 72
5.1.1 Patient Selection 72
5.1.2 Risks Associated with Emicizumab 72
5.1.2.1 Identified Risks 72
5.1.2.2 Potential Risks 74
5.1.3 Management of Patients Who Experience Specific Adverse Events 76
5.1.4 Interpretation of Coagulation Assays for Patients Receiving Emicizumab 77
5.1.5 Procedure-Related Risks 78
5.2 Safety Parameters and Definitions 78
5.2.1 Adverse Events 78
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 79
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 80
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 80
5.3.1 Adverse Event Reporting Period 80
5.3.2 Eliciting Adverse Event Information 81
5.3.3 Assessment of Severity of Adverse Events 81
5.3.4 Assessment of Causality of Adverse Events 81
5.3.5 Procedures for Recording Adverse Events 82
5.3.5.1 Injection-Site Reactions 82
5.3.5.2 Diagnosis versus Signs and Symptoms 82
5.3.5.3 Adverse Events That Are Secondary to Other Events 83
5.3.5.4 Persistent or Recurrent Adverse Events 83
5.3.5.5 Abnormal Laboratory Values 83
5.3.5.6 Abnormal Vital Sign Values 84
5.3.5.7 Abnormal Liver Function Tests 85
5.3.5.8 Deaths 85
5.3.5.9 Preexisting Medical Conditions 86

5.3.5.10 Lack of Efficacy or Worsening of Hemophilic Bleeds 86
5.3.5.11 Hospitalization or Prolonged Hospitalization 86
5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration 87
5.3.5.13 Patient-Reported Outcome Data 87
5.4 Immediate Reporting Requirements from Investigator to Sponsor 87
5.4.1 Emergency Medical Contacts 88
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 88
5.4.2.1 Events That Occur prior to Randomization or Study Drug Initiation 88
5.4.2.2 Events That Occur after Randomization or Study Drug Initiation 88
5.4.3 Reporting Requirements for Pregnancies 89
5.4.3.1 Pregnancies in Female Patients 89
5.4.3.2 Pregnancies in Female Partners of Male Patients 89
5.4.3.3 Abortions 90
5.4.3.4 Congenital Anomalies/Birth Defects 90
5.5 Follow-Up of Patients after Adverse Events 90
5.5.1 Investigator Follow-Up 90
5.5.2 Sponsor Follow-Up 90
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 91
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 91
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 91
6.1 Determination of Sample Size 92
6.2 Summaries of Conduct of Study 93
6.3 Summaries of Treatment Group Comparability 93
6.4 Efficacy Analyses 93
6.4.1 Primary Efficacy Endpoint 93
6.4.2 Secondary Efficacy Endpoints 95
6.5 Safety Analyses 96
6.6 Pharmacokinetic Analyses 97

6.7 Exploratory Analyses 97
6.8 Interim Analysis 97
7. DATA COLLECTION AND MANAGEMENT 97
7.1 Data Quality Assurance 97
7.2 Electronic Case Report Forms 98
7.3 Electronic Patient-Reported Outcome Data 98
7.4 Source Data Documentation 98
7.5 Use of Computerized Systems 99
7.6 Retention of Records 99
8. ETHICAL CONSIDERATIONS 100
8.1 Compliance with Laws and Regulations 100
8.2 Informed Consent 100
8.3 Institutional Review Board or Ethics Committee 101
8.4 Confidentiality 102
8.5 Financial Disclosure 102
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 103
9.1 Study Documentation 103
9.2 Protocol Deviations 103
9.3 Site Inspections 103
9.4 Administrative Structure 103
9.5 Publication of Data and Protection of Trade Secrets 103
9.6 Protocol Amendments 104
10. REFERENCES 106

LIST OF TABLES

Table 1 Status of Clinical Studies for Emicizumab 30
Table 2 Objectives and Corresponding Endpoints 37
Table 3 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in Study ACE001JP/ACE002JP 47
Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events 76

Table 5 Coagulation Test Results Affected and Unaffected by Emicizumab 78
Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale 81

LIST OF FIGURES

Figure 1 Study Schema 41
Figure 2 Individual Pharmacokinetic Profile with Corresponding Bleeding Event 47
Figure 3 Simulated Plasma Emicizumab Concentration over Time (Q4W Dosing) 48

LIST OF APPENDICES

Appendix 1-A Schedule of Assessments 114
Appendix 1-B Schedule of Assessments - Extension Phase 121
Appendix 2-A Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm A, QW) [a] 123
Appendix 2-B Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm B, Q4W) 125
Appendix 2-C Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm C, at Time of Switch to Emicizumab) 127
Appendix 2-D Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm D, QW) 129
Appendix 3 Haem-A-QoL (United States/English) 131
Appendix 4 Haemo-QoL-SF (United States/English) 138
Appendix 5 EQ-5D-5L (United Kingdom/English) 140
Appendix 6 Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English) 142
Appendix 7 Clinical Criteria for Diagnosing Anaphylaxis 147
Appendix 8 WHO Toxicity Grading Scale for Determining the Severity of Adverse Events 148
Appendix 9 Guidelines for Dosing and Monitoring Bypassing Agents for Patients on Emicizumab 154

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS**
PROTOCOL NUMBER:	YO39309
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IND NUMBER:	Not Applicable
NCT NUMBER:	NCT03315455
TEST PRODUCT:	Emicizumab (RO5534262)
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 for your study files. Please return a copy of the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF PROPHYLACTIC EMICIZUMAB VERSUS NO PROPHYLAXIS IN HEMOPHILIA A PATIENTS**
PROTOCOL NUMBER:	YO39309
VERSION NUMBER:	5
NCT NUMBER:	*NCT03315455*
TEST PRODUCT:	Emicizumab (RO5534262)
PHASE:	Phase III
INDICATION:	Hemophilia A
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate (with no formal hypothesis testing for Arm D) the efficacy, safety, and pharmacokinetics of prophylactic emicizumab administered at 1.5 mg/kg weekly (QW) and 6 mg/kg every 4 weeks (Q4W) compared with no prophylaxis in patients with hemophilia A randomized to Arms A, B, and C. A total of approximately 85 patients are planned: approximately 70 patients aged ≥12 years in Arm A, B, and C, and approximately 15 pediatric patients aged <12 years in Arm D (1.5 mg/kg/QW). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objectives:	**Primary Efficacy Endpoint**
For Arms A, B, and C: • To evaluate the efficacy of prophylactic emicizumab (i.e., administered on a scheduled basis with the intent to prevent bleeds) compared with no prophylaxis in patients with hemophilia A The primary definition of a bleed is a bleed for which coagulation factors are administered (i.e., treated bleeds). For Arm D: • To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (using same bleed definition as above)	• The number of bleeds over time (i.e., bleed rate) The endpoint will be analyzed separately for Arms A and B in adolescents and adults: 1.5 mg/kg QW and 6 mg/kg Q4W, as well as for Arm D in pediatric patients: 1.5 mg/kg QW.
Secondary Efficacy Objectives:	**Secondary Efficacy Endpoints**
For Arms A, B, and C: • To evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis	For Arms A, B, C, and D: • To evaluate the efficacy in reducing the number of all bleeds over time

Objectives	Corresponding Endpoints
• Change over time compared with historical bleed rate prior to study entry will be conducted within each treatment arm (intra-patient comparison for patients who have previously participated in Study BH29768) For Arm D: • To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time	• Change in the number of treated bleeds and all bleeds over time compared with the patient's historical bleed rate • To evaluate the efficacy in reducing the number of spontaneous bleeds over time • To evaluate the efficacy in reducing the number of joint bleeds over time • To evaluate the efficacy in reducing the number of target joint bleeds over time For Arms A, B, and C: • Change in HRQoL of patients according to Haem-A-QoL (aged ≥ 18 years) or Haemo-QoL-Short Form (aged 12–17 years) scores after 24 weeks • Change in health status of patients according to European Quality of Life Five-Dimension-Five Levels (EQ-5D-5L) Questionnaire scores after 24 weeks For Arm D: • Change in HRQoL of patients according to Haemo-QoL-Short Form (aged 8–12 years) scores after 24 weeks (completed by patients) • To evaluate proxy-reported HRQoL-SF and aspects of caregiver burden using the Adapted Inhib-QoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)
Exploratory Objectives:	**Exploratory Endpoints**
For Arms A, B, C, and D: • To assess the number of days away from school/work • To assess the number of days hospitalized • To assess potential PD biomarkers of emicizumab	For Arms A, B, C, and D: • Changes in number of days away from school/work during treatment • Changes in number of hospitalization days during treatment • PD biomarkers of emicizumab, including, but not limited to, aPTT, thrombin generation, and FVIII activity

Objectives	Corresponding Endpoints
Safety Objectives:	**Safety Endpoints**
For Arms A, B, and C: • To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A For Arm D: • To evaluate the overall safety of prophylactic emicizumab treatment in pediatric patients with hemophilia A and inhibitors	For Arms A, B, C, and D: • The incidence and severity of adverse events • The incidence and severity of thromboembolic events • Incidence and severity of thrombotic microangiopathy • Changes in physical examination findings and vital signs • Incidence of laboratory abnormalities • Incidence and severity of injection-site reactions • Incidence of adverse events leading to drug discontinuation • The incidence of severe hypersensitivity, anaphylaxis, or anaphylactoid reactions • The incidence and clinical significance of anti-emicizumab antibodies
Pharmacokinetic Objective:	**Pharmacokinetic Endpoints**
For Arms A, B, C, and D: • To characterize the exposure (trough plasma concentration) of emicizumab in patients treated on QW or Q4W dosing	For Arms A and D: • Trough plasma concentration • The plasma samples will be collected at the scheduled timepoints below: For patients treated on weekly dosing schedule: – Every week during Weeks 1–4 on emicizumab – Every 2 weeks during Weeks 5–8 on emicizumab – Every 4 weeks during Weeks 9–24 on emicizumab – Every 8 weeks during Weeks 25–48 on emicizumab – Every 12 weeks thereafter while on emicizumab, until the end of the study or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first For Arms B and C: For patients treated on every 4 weeks dosing schedule: – Every week during Weeks 1–4 on emicizumab – Every 4 weeks during Weeks 5–24 on emicizumab – Every 12 weeks thereafter while on emicizumab, until the end of the study or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first

Adapted Inhib-QoL = Inhibitor-Specific Quality of Life (with Aspects of Caregiver Burden); FVIII = factor VIII; HRQoL = health-related quality of life; PD = pharmacodynamic; Q4W = every 4 weeks; QW = every week.

STUDY DESIGN

DESCRIPTION OF STUDY

Study YO39309 is a multicenter, open-label, Phase III clinical study with randomized and non-randomized arms designed to investigate the efficacy, safety, and pharmacokinetics of emicizumab in patients with hemophilia A regardless of factor VIII (FVIII) inhibitor status. Seventy patients aged ≥12 years who received episodic therapy with FVIII or bypassing agents prior to study entry and experienced at least 5 bleeds over the prior 24 weeks (annualized bleeding rate [ABR] ≥ 10) will be randomized in a 2:2:1 ratio to the following regimens:

- Arm A: Emicizumab prophylaxis at 3 mg/kg weekly (QW) subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously
- Arm B: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg every 4 weeks (Q4W) subcutaneously
- Arm C: No prophylaxis control arm

In addition, 15 pediatric patients with hemophilia A and inhibitors who received episodic therapy with bypassing agents prior to study entry will be enrolled to Arm D:

- Arm D: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously

NUMBER OF PATIENTS

A total of 70 patients with severe hemophilia A who previously received episodic therapy with either FVIII or bypassing agents will be enrolled in Arms A, B, and C.

A total of 15 pediactric patients with hemophilia A with inhibitors from China mainland who previously received episodic therapy with bypassing agents will be enrolled in Arm D.

TARGET POPULATION

Inclusion Criteria

Arms A, B, and C

Patients in Arms A, B, and C must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient or a legal guardian
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of patient-reported outcome (PRO) questionnaires and bleed and medication diary through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level <1%) or hemophilia A with FVIII inhibitors
- Patients without FVIII inhibitors (< 0.6 BU/mL) who completed successful immune tolerance induction (ITI) must have done so at least 5 years before screening and have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor > 0.6 BU/mL since ITI
- Documentation of the details of episodic therapy (FVIII or bypassing agents) and of number of bleeding episodes for at least the last 24 weeks
- ≥ 5 bleeds in the last 24 weeks prior to study entry
- Adequate hematologic function, defined as platelet count ≥ 100,000/μL and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (excluding Gilbert's syndrome) and AST and/or ALT ≤ 3 × ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine ≤ 2.5 × ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 1 year of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Arm D

Patients in Arm D must meet the following criteria for study entry:

- Written informed consent must be obtained from parent/legally acceptable representative and an assent from the child when applicable (latest approved version by the Independent Ethics Committee [IEC]/Institutional Review Board [IRB]) prior to any of the study-specific assessments and procedures being performed.
- Children < 12 years of age at time of informed consent
- Body weight > 3 kg at time of informed consent
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of applicable PRO questionnaires
- Caregivers of all children must have the willingness and ability to comply with all study procedures, including the completion of the bleed/medication questionnaire and applicable HRQoL questionnaires
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 BU/mL)
- Requires treatment with bypassing agents
- Adequate hematologic function, defined as platelet count of $\geq 100 \times 10^9$ cells/L and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ age-adapted ULN (excluding Gilbert's syndrome) and both AST and ALT $\leq 3 \times$ age-adapted ULN at the time of screening
- Adequate renal function: serum creatinine must be $\leq 1.5 \times$ ULN for age

  If serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Bedside Schwartz formula must be > 70 mL/min/1.73m^2.
- For female patients who are of childbearing potential, follow the same contraception criteria as listed above for Arms A, B, and C.

<u>Exclusion Criteria</u>

ARMS A, B, and C

Patients in Arms A, B, and C who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment

- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (within the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count $<$ 200 cells/μL within 24 weeks prior to screening. Patients with HIV infection who has CD4 $>$ 200 cells/μL and meet all other criteria are eligible
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or lactating, or intending to become pregnant during the study

  Women with positive serum pregnancy test result within 7 days prior to initiation of study drug.

ARM D

Patients in Arm D who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) ITI therapy or prophylaxis treatment with FVIII

  Patients awaiting initiation of ITI will be eligible.

  Patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration.
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other diseases (i.e., certain autoimmune diseases [e.g., systemic lupus erythematosus], cardiovascular disease) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known infection with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV)
- Patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment
- Use of systemic immunomodulators (e.g., interferon or corticosteroids) at enrollment or planned use during the study

- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Inability (or unwillingness by caregiver) to receive (allow receipt of) blood or blood products (or any standard-of-care treatment for a life-threatening condition)
- Receipt of:
  - An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration
  - A non–hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter
  - An investigational drug concurrently
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Pregnant or lactating, or intending to become pregnant during the study

  Female patients with a positive serum pregnancy test result within 7 days prior to initiation of study drug.

END OF STUDY

The primary analysis will take place at the earliest timepoint when all randomized patients (Arms A, B, and C) have either completed 24 weeks of treatment or discontinued from the study.

For Arm D, the primary efficacy analysis will be conducted after the last enrolled patient have completed 24 weeks in the study or discontinued from treatment.

Patients who discontinue stuidy treatment prior to end of study (with the exception where the reason of discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow up visit 24 weeks after the final dose of study drug.

The end of this study is defined as the date when the last remaining patient has completed the last visit (LPLV), as defined by any of the following criteria:

- Completion of at least 24 weeks of emicizumab treatment
- Completion of safety follow-up visit 24 weeks after discontinuing emicizumab
- *Completion of the study Extension Phase (3 years after the last Arm D patient completes 1 year treatment) and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products*
- Withdrawal of consent
- Lost to follow-up

The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier.

LENGTH OF STUDY

The approximate length of the entire study from screening of the first patient to the end of the study (including Arm D and study *e*xtension phase) will be approximately 88 months.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product for this study is emicizumab.

Each single-use vial contains 30 mg or 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, 20 mmol/L histidine–aspartic acid buffer (pH 6.0). Because emicizumab is administered on a weight-based dosing regimen, two vial strengths will be supplied for this study, differing from each other only in emicizumab concentration: nominal vial strength 150 mg (150 mg/mL, 1.0 mL); and nominal vial strength 30 mg (30 mg/mL, 1.0 mL). The more dilute 30-mg vials are intended for

1.5-mg/kg maintenance dosing for patients in Arm D with body weight $<$20 kg and will enable safe subcutaneous weight-based dosing of small children with sufficient precision. It is important to note that vials of different emicizumab concentrations must not be combined in the same syringe.

Each patient starting on prophylactic emicizumab will receive 3 mg/kg QW subcutaneously for 4 weeks as loading doses, followed by 1.5 mg/kg QW (Arm A) or 6 mg/kg Q4W (Arm B) subcutaneously, for a total of at least 24 weeks or as long as they continue to derive sufficient clinical benefit. After completion of 24 weeks observation in the study, patients in Arm C could switch to receive emicizumab prophylaxis at the Arm B dosing regimen (emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W).

After at least 24 weeks on prophylactic emicizumab, patients in Arms A, B, and C will have the opportunity to increase their emicizumab dose to 3 mg/kg QW if they meet the following criteria and after consulting with the Medical Monitor:

- $\geq$2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab, both of which occur after the end of the loading dose period
- At least one of the bleeds must be verified by a physician (e.g., with diagnostic imaging, photograph)

Patients in Arm D will receive 3 mg/kg QW for 4 weeks as loading doses, followed by 1.5 mg/kg QW as maintenance during the 24-week treatment period. Individual patients experiencing suboptimal bleeding control on emicizumab may also have their dose up-titrated if they meet the same criteria as required for patients in Arm A, B and C and after consulting with the Medical Monitor.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control bleeds, including FVIII products or bypassing agents as standard-of-care episodic treatment. Exact dosages will not be specified in the study but rather these agents should be administered according to the respective prescribing information or as previously used by each individual patient (for information on the formulation, packaging, and handling of FVIII or bypassing agents, refer to local prescribing information for the agent in question).
- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure
- Drugs to treat an existing medical condition ongoing at study entry that do not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections)
- Local anesthetic cream for emicizumab SC administration
- Vaccinations should be administered following national immunization schedules. As per the World Federation of Hemophilia recommendations for vaccinations (World Federation of Hemophilia 2012), patients with hemophilia should be vaccinated. Thus, vaccinations should be administered according to the World Federation of Hemophilia recommendations and local Hemophilia Treating Center practice and ideally during a period when the bleeding status of the child is well controlled and stable. Vaccinations should not be administered on the same day as an emicizumab administration but ideally at a timepoint between two emicizumab administrations ($>$48 hours after emicizumab administration). Children who receive vaccinations must be carefully followed for any adverse reactions in the subsequent days following vaccine administration.

STATISTICAL METHODS

A detailed description of the statistical methods for the primary and secondary efficacy analyses will be provided in the statistical analysis plan.

PRIMARY ANALYSIS

For the randomized arms (Arms A, B, and C), the primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient yet to complete 24 weeks in the study discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The separate comparison of the number of bleeds over time between each of the randomized emicizumab arms and control arm will be performed

using a negative binomial (NB) regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (< 9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t / λ_c., which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level. Of note, hierarchical testing is used to account for multiple testing and the first test to be included in the hierarchy is the emicizumab 1.5 mg/kg QW maintenance dose versus control. The second test will be 6 mg/kg Q4W maintenance dose versus control (or 3 mg/kg Q2W versus control, depending on global Study BO39182 data readout). The description below covers both hypotheses to be tested:

H_0 (null hypothesis): Rate Ratio=1 versus H_1 (alternative hypothesis): Rate Ratio ≠ 1.

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: ABR = (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25. If the NB model converges, van Elteren test to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the van Elteren test of ABR.

For Arm D, one efficacy objective is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time. This analysis will be performed separately as well as overall as appropriate.

DETERMINATION OF SAMPLE SIZE

For the randomized arms (Arms A, B, and C), the sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a NB distribution. With consideration of enrollment feasibility, a sample size of 70 patients, assuming an allocation ratio of 2:2:1 (28 patients in each randomized treatment group and 14 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 18 bleeds (with variances = mean $\times$ 10) for the emicizumab treatment and control arms, respectively, representing an expected 78% reduction in the ABR compared with the control arm. Initial sample size calculations were performed assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

However, the above approach to sample size calculation assumes similar follow up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of an NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 90% power at the 2-sided 0.05 level of significance.

Multiplicity will be accounted for by testing emicizumab QW arm versus no prophylaxis first, and upon successful testing, emicizumab Q4W (or Q2W, depending on global Study BO39182 data readout) versus no prophylaxis, each at 0.05 level.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) global data to date may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

The sample size for Arm D is based on favorable recruitment feasibility and clinical considerations rather than statistical considerations, taking into account the limited number of pediatric patients with hemophilia A inhibitors available for participation. Hence, approximately

15 children $<$12 years of age with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
aPCC	activated prothrombin complex concentrate
AUC	area under the plasma concentration–time curve
AUC_{τ}	area under the plasma concentration–time curve for a dosing interval
C_{max}	maximum plasma concentration
CCOD	clinical cutoff date
CVAD	central venous access device
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
FDA	(U.S.) Food and Drug Administration
FEIBA	factor eight inhibitor bypassing activity
FIX	factor IX
FVIII	factor VIII
FX	factor X
HCP	healthcare provider
HRQoL	health-related quality of life
ICH	International Conference for Harmonisation
IFU	Instructions For Use
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
Inhib-QoL	(Adapted) Inhibitor-Specific Quality of Life (with Aspects of Caregiver Burden)
IRB	Institutional Review Board
ITI	immune tolerance induction
IxRS	interactive voice or Web Response System
LPLV	last patient last visit
NB	negative binomial
NEC	necrotizing enterocolitis
PCC	prothrombin complex concentrate
PD	pharmacodynamic
PK	pharmacokinetic

Abbreviation	Definition
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QW	every week
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
SAP	Statistical Analysis Plan
ULN	upper limit of normal
VAS	visual analog scale

1. BACKGROUND

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 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 his sons and an abnormal X chromosome to all his daughters, his sons will not be affected and all of his daughters will be carriers. The offspring of a woman carrier have a 50% chance of receiving a mutated FVIII gene, thus hemophilia A will be transmitted to half the male infants and half of the female infants will be carriers. 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). Rarely, women can have more severe bleeding symptoms requiring treatment and may develop FVIII inhibitors. Approximately 30% of patients with hemophilia A do not have a family history of the disorder; these cases arise from spontaneous FVIII gene mutations.

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 $<5\%$ 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).

1.1.1 Management

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). Since the 1990s, recombinant FVIII (rFVIII) concentrates have been standard-of-care treatment options for patients with hemophilia A in many countries (Kingdon and Lundblad 2002). Since 2007, rFVIII concentrates have been standard-of-care treatment options for patients with hemophilia A in China. In children, the current standard-of-care is primary prophylaxis with regular FVIII infusions (starting from the first joint bleed onward or earlier; Valentino et al. 2012), focusing on joint preservation with, optimally, no bleeds and the

prevention of long-term consequences such as joint damage. The overall goal is to enable normal psychosocial development without overprotection (Coppola et al. 2010). Early prophylaxis has been shown to lead to better long-term outcomes (Kreuz et al. 1999; Manco-Johnson et al. 2007; Gouw et al. 2013). Adolescents and adult patients are more likely to have arthropathy with target joints (Gruppo et al. 2013) and the treatment goal of secondary prophylaxis (after the second joint bleed) or tertiary prophylaxis (after onset of joint disease) is to enable normal activities of daily life and physical exercise, as well as reduce progression of arthropathy and disability (Tagliaferri et al. 2008).

Treatment regimens to achieve optimal prevention of bleeding events vary between individuals; some patients tolerate trough FVIII levels of 1%, whereas, others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current prophylactic regimens commonly use infusion therapy administered 2–3 times weekly (Adynovate® U.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, as adequate prophylaxis requires a lifetime of self-administered IV infusion of FVIII 3–4 times each week. In addition to the obvious toll on the quality of patients' life (Teal et al. 2014), this burden results in suboptimal care for many who elect to avoid routine prophylaxis, despite its medical advantage (Geraghty et al. 2006; Lindvall et al. 2006; De Moerloose et al. 2008; Collins et al. 2014; Oldenburg 2015). Thus, episodic therapy is a standard-of-care for many patients with hemophilia in developed countries, where approximately one-third to one-half of the patients use FVIII on-demand and avoid continuous prophylaxis. For example, a recent analysis revealed that, in North America and Europe, only 44.3% of 1238 patients with severe hemophilia A are treated with routine FVIII prophylaxis (Oldenburg and Brackmann 2014). Similarly, prophylaxis was routinely offered to adults in only 18 of 35 European countries surveyed, and in 12 out of those 18 countries, 50% or fewer adults received FVIII prophylaxis (O'Mahony et al. 2013). 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.

Although patients on FVIII prophylaxis experience a low number of bleeds, magnetic resonance imaging scans demonstrate progressive arthropathy in up to two-thirds of patients who receive an adequate primary prophylaxis regimen. These changes begin within the first decade of life and involve clinically "bleed-free" joints (Kraft et al. 2012; Olivieri et al. 2012). Accordingly, 40% of men in the third decade of life reported the presence of a target joint, reduced mobility, or chronic pain (Fischer et al. 2013;

Noone et al. 2013). These findings indicate that FVIII prophylaxis delays, but does not completely prevent, long-term skeletal morbidity (Oldenburg 2015). This is in part due to the challenges of adherence and in part due to microbleeds associated with low FVIII trough levels (Ljung and Gretenkort-Andersson 2015). Due to the short half-life of FVIII, current prophylaxis regimens aim at maintaining FVIII levels at a trough of ≥1%, which restores hemostasis for only part of the time (Valentino et al. 2012). A study of patients with varying severities of hemophilia suggests that protection from joint bleeds occurs only at continuous levels over 12% (Den Uijl et al. 2011), and achieving higher FVIII activity, though difficult to accomplish with current regimens, has been recognized as a goal for optimal care in a position paper from the World Federation of Haemophilia (Skinner 2012).

Routine IV FVIII therapy relies on the venous cannulation skills of patients and their care providers (Hacker et al. 2001). In particular, this issue plagues the care of children with hemophilia, in whom central venous access devices (CVADs [i.e., Part-a-Cath®]) have been used regularly to overcome technical difficulties. Although CVADs make prophylaxis feasible in young children, they are associated with complications, including mechanical failure, dehiscence of the skin over the reservoir, infection, and thrombosis (Ewenstein et al. 2004). A recent prospective study reported that 183 lines were implanted in 99 patients and that 41% of patients had at least one infectious episode. The median time to line removal was 483 days (interquartile range: 143–1071; Rodriguez et al. 2015). A Finnish retrospective study similarly reported that 47% of 106 catheters implanted in 58 patients had to be removed due to a complication (Vepsalainen et al. 2015). In addition, significant health care provider efforts are required to manage optimal treatment solutions and to overcome identified issues (Schrijvers et al. 2013). Thus, both the disease and its treatment affect patients' health-related quality of life (HRQoL).

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. Because inhibitors can develop very early during the course of FVIII therapy (within 10–50 exposure days), with half of all cases occurring before the age of 5 years, pediatric patients represent the population at highest risk of developing inhibitors (Kreuz et al. 1995; Wight and Paisley 2003; Kempton and White 2009; Hay and DiMichele 2012). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy.

For patients who develop inhibitors against FVIII, immune tolerance induction (ITI) may help restore a patient's clinical response to FVIII concentrates. Permanent eradication of FVIII inhibitors is the ultimate goal of ITI, and it is successful in approximately 60%–80% of adults and children with inhibitors (Santagostino et al. 2009; Hay and DiMichele 2012). Most physicians delay the start of ITI for up to 1 year from the time the inhibitor is first diagnosed to allow very high titers of inhibitors to fall because a pre-ITI

inhibitor titer measuring <10 BU/mL is the most powerful predictor of ITI success (Mariani and Kroner 1999; DiMichele and Kroner 2002). Regimens that delay treatment until the inhibitor has fallen below 10 BU/mL positively affect both the likelihood of success (79%–87% success rate) and the time required to achieve tolerance (Mauser-Bunschoten et al. 1995; Kroner 1999; Rocino and de Biasi 1999; Smith et al. 1999). Furthermore, the rate of response to ITI does not decline until ITI has been delayed beyond 5 years from the time of diagnosis (Brackmann et al. 1996; Mauser-Bunschoten et al. 1995; Kroner 1999; DiMichele and Kroner 2002). However, an optimal regimen for ITI remains to be defined (although a recent study suggested superior safety outcomes using high-dose regimens administered daily [Hay and DiMichele 2012]), and the length of treatment is dictated by individual responses, ranging from months to years. Because uninterrupted and uncomplicated venous access is essential in children undergoing ITI, this process is particularly burdensome in the pediatric patient population, who require frequent visits to hemophilia centers for regular infusion of FVIII concentrate through CVADs.

Long-term CVAD use requires considerable commitment from caregivers and patients, and serious complications can occur, including thrombosis, bleeding, mechanical dysfunction, and most commonly, infection. A prospective study in pediatric hemophilia A patients with inhibitors reported that 183 lines were implanted in 99 patients, with 41% of patients having at least one documented infection. The median time to line removal was 483 days [interquartile range (143–1071; Rodriguez et al. 2015)]. A Finnish retrospective study similarly reported that 47% of 106 catheters implanted in 58 patients had to be removed because of a complication (Vepsalainen et al. 2015). CVAD-related bacteremia and sepsis pose potentially lethal problems for patients with hemophilia and result in a substantial proportion of emergency room visits for children. A retrospective study of pediatric emergency department management of children with hemophilia showed that of 536 visits from 84 male patients (median age 4 years), 12% were due to suspected CVAD infection (Ozgonenel et al. 2013). Indeed, infection occurs more frequently in hemophilia patients with inhibitors (Bollard et al. 2000; Valentino et al. 2004; van Dijk et al. 2004), with rates being highest among patients with inhibitors undergoing ITI, ranging from 50%–83% (van den Berg et al. 1998). If ITI is unsuccessful, inhibition of FVIII concentrate treatment may persist throughout the patient's life. Additionally, the use of ITI treatment is not viewed as a viable option for patient management in many countries, owing to its high cost, lack of availability of FVIII concentrates, and daily administrations. These disadvantages are compounded in the young pediatric population due to the necessity for central venous access and related complications, as well as the psychological stress of this treatment on patients and their families.

For patients with a history of a high-titer (≥ 5 BU/mL) inhibitor who are unable to eradicate their inhibitors or are not candidates for ITI, the only hemostatic options currently available are prothrombotic coagulation factors that augment other parts of the

coagulation cascade (i.e., “bypassing agents”). Bypassing products include factor eight inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be henceforth referred to as aPCC), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be henceforth referred to as rFVIIa; Srivastava et al. 2013). Unfortunately, the hemostatic effect of bypassing agents in patients with inhibitors is suboptimal, leading to a higher number of bleeds (annualized bleeding rate [ABR] of 8–10 with FEIBA [Leissinger et al. 2011; Antunes et al. 2014] and 2–3 bleeds per month with NovoSeven [Konkle et al. 2007] compared with that of FVIII concentrates in non-inhibitor patients who achieve a median ABR of approximately 0–2 with optimal prophylaxis (Manco-Johnson et al. 2013). In China, the available products are prothrombin complex concentrate (PCC) and rFVIIa; however, due to the high cost of the prophylaxis treatment, the majority of the patients with inhibitors can only afford on-demand treatment when there are bleeds, thus causing suboptimal bleeding control compared to those patients with prophylaxis treatment. In addition, as opposed to the 8- to 12-hour half-life and 15- to 20-minute infusion time of FVIII, NovoSeven® has a short half-life of only 2–3 hours, and FEIBA requires 25–50 minutes to infuse (with a half-life of 4–7 hours), requiring frequent and extended IV infusions, respectively.

Investigations into prophylactic therapy in adults and children with bypassing agents NovoSeven® (Konkle et al. 2007) and FEIBA (Leissinger et al. 2011; Antunes et al. 2014) have shown that these products lead to reductions in bleed rates compared with episodic treatment with these same products. However, as detailed above, this efficacy is suboptimal and does not approach the level of hemophilia control that can be achieved with FVIII concentrates in non-inhibitor patients.

Despite prophylactic regimens being standard-of-care for hemophilia patients without inhibitors in many countries, a large proportion of hemophilia patients with FVIII inhibitors currently are treated with episodic regimens, partly because of the treatment burden of these prophylaxis regimens. A survey of hemophilia centers across 14 countries suggested that 41% of pediatric hemophilia patients with inhibitors were on ITI alone, 17% were on both ITI and prophylactic bypassing agents, 16% were on prophylactic bypassing agents alone, and 26% were on neither ITI nor prophylactic bypassing agents (Carcao et al. 2015).

Of note, treatment of patients with congenital hemophilia A of any severity with high-titer inhibitors is similar, and their endogenous severity, as defined based on FVIII activity at diagnosis (mild, moderate, or severe), is no longer prognostic of their clinical phenotype and risk of bleeding. This is because the inhibitor would eventrally neutralize the residual endogenous FVIII, resulting in a severe bleeding phenotype in the end.

Both aPCC/PCC and rFVIIa are administered intravenously, with aPCC/PCC prophylaxis requiring every-other-day dosing and rFVIIa requiring daily (or more frequent) dosing. For years, the suboptimal bleeding control, the short half-life, and high cost of these

bypassing agents limit the use of prophylaxis treatment in inhibitor patients. Despite physician's efforts, joint disease ultimately occur.

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 effect of the disease on aspects of physical health and other areas of function. A study assessing the relationship between self-reported adherence to prophylaxis and health outcomes (HRQoL and bleeding episodes) showed that poorer adherence with prophylaxis was associated with a greater number of self-reported bleeding episodes, more days of work or school missed among pediatric patients, and lower physical health status scores among pediatric patients (Krishnan et al. 2015). Adherence to prophylaxis by patients with hemophilia A, defined as the extent to which a person's behavior corresponds to agreed recommendations by a healthcare provider (WHO 2003), ranges from 44% to 87% (Llewellyn et al. 2003; De Moerloose et al. 2008; Ho et al. 2014). In China, the adherence to prophylaxis by patients with hemophilia A is even worse, ranging from 5% to 15% for patients without FVIII inhibitors, and almost no patients with FVIII inhibitors receive prophylactic treatment (Xue et al, 2011; Xuan et al. 2014). In a Dutch study investigating patient behavior affecting adherence to prophylactic treatment, patients were asked about their experience with and adherence to administration of prophylaxis. Remarkably, some patients willingly chose non-adherence because they did not want to adapt their activities to hemophilia, and they were prepared to accept the consequences of their decision. Patients noted the difficulties of regular prophylaxis due to inadequate routine and the complexity of the needed self-management skills including planning, management of the treatment of bleeds, forgetfulness, stock management, and overruling activities in life (Schrijvers et al. 2015).

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

1.2.1 Molecule and Nonclinical Data

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, as emicizumab shares no sequence homology with FVIII. In addition, emicizumab offers the possibility of SC administration, removing the need for venous access. Finally, because the pharmacokinetic (PK) properties of this antibody are expected to enable marked extension of the dosing interval to once weekly (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W), 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 *add*burden prophylactic therapy.

See the RO5543262 (emicizumab) Investigator's Brochure for additional details on nonclinical studies with emicizumab.

1.2.2 Clinical Experience

Clinical data are currently available from *8* studies, which are listed below in Table 1. Please refer to Emicizumab's Investigator's Brochure for the complete, updated information.

Table 1 Status of Clinical Studies for Emicizumab

Study	Status
Study ACE001JP: A Phase I study investigating the tolerability, safety, pharmacokinetic, and pharmacodynamic response of subcutaneously administered emicizumab in healthy Japanese and Caucasian male subjects and in Japanese patients with hemophilia A	Completed
Study JP29574: A site of administration, relative and absolute bioavailability study in healthy adult male subjects	Completed
Study ACE002JP: A Phase I/II extension study investigating the safety and efficacy of long-term administration of emicizumab on bleeding control in a subset of patients with hemophilia A who participated in Study ACE001JP	Completed
Study BH29884 (HAVEN 1): A Phase III study investigating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis vs. no prophylaxis in patients with hemophilia A with FVIII inhibitors	*Completed*
Study BH29992 (HAVEN 2): A Phase III study investigating the efficacy, safety, and pharmacokinetics of subcutaneous administration of emicizumab in pediatric patients with hemophilia A with inhibitors	*Completed*
Study BH30071 (HAVEN 3): A Phase III study investigating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in patients with hemophilia A without inhibitors	*Completed*
Study BO39182 (HAVEN 4): A Phase III study investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of emicizumab given every 4 weeks in patients with hemophilia A	Completed
Study JO39881 ***(HOHOEMI)***: A Phase III study to evaluate the efficacy, safety, and pharmacokinetics of emicizumab given every 2 weeks and 4 weeks in hemophilia A pediatric patients aged less than 12 years without FVIII inhibitors	Completed

FVIII = factor VIII.

1.2.2.1 Clinical Pharmacology

Pharmacokinetics of emicizumab in hemophilia A patients were accurately described by a one-compartment disposition model with first-order absorption and first-order elimination. Emicizumab PK parameters were typical for a monoclonal antibody (Keizer et al. 2010). Emicizumab was well absorbed (absolute bioavailability of 80.4%–93.1% depending on the injection site location) following SC injection, with an absorption half-life of approximately 1.6 days. The volume of distribution at steady state following IV injection was 106 mL/kg. The apparent clearance and the elimination half-life were 0.271 L/day and 26.9 days, respectively. Emicizumab exhibited linear pharmacokinetics, with no indication for target-mediated drug disposition.

Similar emicizumab exposures were observed in children, adolescents, and adult patients. Inhibitor status or disease severity does not impact emicizumab exposure. Furthermore, similar PK profiles following SC injections in abdomen, upper arm, and thigh indicated that emicizumab can be interchangeably injected in these three locations.

In patients with hemophilia A, emicizumab shortened (normalized) aPTT, promoted the generation of thrombin, and increased the reported FVIII activity in a chromogenic assay containing human coagulation factors in a concentration dependent manner.

1.2.2.2 Efficacy

The efficacy of emicizumab in patients with hemophilia A has been evaluated in one Phase I/II study (ACE001JP [Part C]/ACE002JP) and four Phase III studies (HAVEN 1–4). After administration of emicizumab (0.3, 1, or 3 mg/kg/week QW, SC) to patients with hemophilia A in Studies ACE001JP (Part C)/ACE002JP, ABRs for treated bleeds were zero or decreased from the pre-dose period, regardless of the presence of inhibitors and/or prior use of prophylactic bypassing agents.

Emicizumab provides statistically significant and clinically meaningful prevention of bleeding in patients with hemophilia A. Results from Phase III clinical studies confirmed the adequacy of the selected dosing regimens. Overall, all three dosing regimens (loading doses of 3 mg/kg QW for 4 weeks followed by either 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W) using an equivalent cumulative dose, provided meaningful efficacy. This is supported by the primary analysis of pivotal studies BH29884 (clinical cutoff date [CCOD]: 8 September 2017), BH29992 (CCOD: 30 April 2018), BH30071 (CCOD: 15 September 2017), and BO39182 (CCOD: 15 December 2017).

At the primary analysis of Study BH29884, all primary and secondary efficacy endpoints related to bleed rates were statistically significant and clinically meaningful. Patients with hemophilia A on emicizumab prophylaxis compared with no prophylaxis showed a 87% and 80% reduction in rates of treated bleeds and all bleeds (treated and untreated), respectively. In addition, emicizumab improved HRQoL and health status in these

patients. Subgroup analyses were consistent with and further supported the clinical benefit of emicizumab to patients with hemophilia A.

The primary analysis results of Study BH29992 demonstrate a clinically meaningful effect of emicizumab prophylaxis in the prevention of bleeding events in children with hemophilia A with FVIII inhibitors. In total, 22 treated bleeds were reported in 15 of 65 participants during a median efficacy period of 58 weeks, while 90.9% (20/22) of treated bleeds were traumatic related. Importantly, the intra-patient analysis based on 18 patients previously treated with episodic or prophylactic bypassing agent showed a clinically meaningful 99% reduction in ABR (treated bleeds) with emicizumab 1.5 mg/kg QW treatment.

Study BH30071 met the primary endpoint of reduction of treated bleed rate and all of the bleed-related secondary endpoints. Emicizumab prophylaxis with the maintenance dose of 1.5 mg/kg QW or 3 mg/kg Q2W resulted in a statistically significant and clinically meaningful 96% and 97% reduction in rate of treated bleeds, respectively, compared with no prophylaxis. More than 55% of patients in all emicizumab treatment arms compared with no patients on no prophylaxis experienced zero treated bleeds and more than 90% of patients on emicizumab prophylaxis experienced fewer than four treated bleeds compared to approximately 6% of patients on no prophylaxis.

The primary analysis results of Study BO39182 support a clinically meaningful effect on bleed prevention of the emicizumab Q4W dosing regimen. In this study, the negative binomial model analysis of bleed rates showed that emicizumab Q4W prophylaxis provided adequate control of bleeds, with patients achieving ABR of 2.4 (95% CI: 1.38 to 4.28) for treated bleeds. More than half of the patients ($n = 23$, 56.1%) did not experience any treated bleeds while receiving emicizumab prophylaxis. The primary analysis report numerical improvements in HRQoL and health status endpoints.

Long-term efficacy data are available from Phase III Study BH29884, as well as ACE002JP. In the BH29884 study, where 1.5 mg/kg QW dosing of emicizumab prophylaxis was assessed, 82.3% patients have completed ≥ 48 weeks follow-up at the time of the clinical cutoff date. The median for the efficacy period is 60.29 weeks (range: 0.1–94.3 weeks, $n = 113$). The longest duration of emicizumab exposure to date is for patients ($n = 16$) in Study ACE002JP whose median exposure time is 3.4 years. The prevention of overall bleeding was maintained throughout Study ACE001JP and extension Study ACE002JP.

Long-term efficacy dataare available from Phase III StudBH29884as well as ACE002JP. Overall, the benefits of emicizumab prophylaxis were sustained and therapeutic effect was maintained over the long term as observed in Studies BH29884 and ACE002JP. These long-term effects are expected to be maintained with emicizumab treatment in patients with hemophilia A of all ages, regardless of the presence of FVIII inhibitors.

1.2.2.3 Safety

Safety in Healthy Subjects

Safety data from 108 healthy male subjects (Japanese and Caucasian) demonstrated a similar incidence of adverse events between placebo and emicizumab dosing groups, no racial differences, or dose-dependent increases in adverse events. Furthermore, there were no significant differences in the incidence of adverse events observed by formulation, injection site, or administration route. There were no serious adverse events, adverse events leading to discontinuation, or fatal outcomes in Study JP29574 or Study ACE001JP (Part A and Part B).

Safety in Patients with Hemophilia A

Safety data from 417 emicizumab-treated patients with hemophilia A (enrolled, n = 419) in Studies ACE001JP (Part C)/ACE002JP (n = 18) and Studies BH29884 (n = 113), BH29992 (n = 88), BH30071 (n = 152), and BO39182 (n = 48) have been pooled. Safety data are presented from patients who received emicizumab prophylaxis in Studies ACE001JP (Part C)/ACE002JP, BH29884, BH29992, BH30071, and BO39182. Study JO39881 (n = 13) is not included in the pooled safety data and is presented separately due to immaturity of the data.

A total of 2838 adverse events were reported in 384 patients (92.1%). Among the 417 patients overall, 71 patients (17.0%) experienced a serious adverse event, and 4 patients (1.0%) experienced a serious adverse event that led to withdrawal from treatment. In total, 142 patients (34.1%) experienced an adverse event assessed by the investigator as related to emicizumab.

Among patients in Study ACE001JP (Part C)/ACE002JP, the majority of the adverse events were mild or moderate in intensity, except for two adverse events of severe intensity (appendicitis and mesenteric hematoma), which were considered to be serious and unrelated to emicizumab. Similarly, most adverse events in the Phase III Studies BH29884, BH29992, BH30071, and BO39182 were of Grade 1 or 2 intensity, except for 63 adverse events of Grade ≥ 3 intensity. Most of the adverse events were unrelated to study drug and only 6 patients (1.4%) reported serious adverse events were related to treatment. Observed adverse events of special interest among patients with hemophilia A treated with emicizumab included thrombotic microangiopathy (3 patients [$< 1.0\%$]) and thromboembolic event (3 patients [$< 1.0\%$]). A total of 113 patients (27.1%) experienced a local injection site reactions. All were mild to moderate in intensity and only one leading to discontinuation in a patient in the Phase I study.

One fatal outcome due to rectal hemorrhage which is unrelated to emicizumab was reported in Study BH29884. No fatal outcomes have occurred in the other studies.

Study JO39881 in Japanese pediatric patients is ongoing. In this study, 13 patients with severe hemophilia A without FVIII inhibitors were enrolled in 2 cohorts (6 patients in the Q2W cohort and 7 patients in the Q4W cohort). As of the data cutoff date

(14 March 2018), all 13 patients were continuing treatment, and no patients had a dose up-titration.

There were no adverse events that were Grade 3 or higher, serious, led to withdrawal from treatment, or resulted in dose modification or interruption. No injection site reactions, thromboembolic events, thrombotic microangiopathy, or systemic hypersensitivity reactions were observed. For all the adverse events, a causal relationship with emicizumab was ruled out by investigators.

Study ML39356 (Expanded Access Program) was designed to provide access to emicizumab for patients with hemophilia A with FVIII inhibitors prior to its approval in the United States. The study is now completed; All remaining patients were transferred to commercial emicizumab once United States Food and Drug Administration (FDA) approval was granted for patients with FVIII inhibitors. The study collected safety data and no significant safety signals were observed.

MO39129 (STASEY) is an ongoing multi-center, open-label Phase IIIb study in patients with hemophilia A with FVIII inhibitors is ongoing with the first official safety assessment by the Independent Data Monitoring Committee scheduled to occur in February 2019. One serious adverse event of “abscess at sick of Hickman line removal” assessed as related to emicizumab by the investigator was observed in this study. At the time of the report, therapy with emicizumab was not altered in response to the abscess at the site of the Hickman line removal. No thromboembolic or thrombotic microangiopathy events were observed in the study.

Please refer to the Emicizumab Investigator's Brochure for a complete summary of safety information.

1.2.2.4 Immunogenicity

Of the 108 healthy adult male subjects in Studies ACE001JP (Part A and Part B) and JP29574, who received a single SC or IV dose of emicizumab, 6 subjects tested positive for plasma anti-drug antibodies (ADAs; non-IgE). Four of these subjects presented with treatment-induced ADA. In all 4 subjects, emicizumab was eliminated faster, and the pharmacodynamic (PD) effect (shortening of aPTT and promotion of thrombin generation in FVIII depleted plasma) dissipated earlier than in the subjects who tested negative. No adverse events occurred in these subjects.

In patients with hemophilia A participating in Studies ACE001JP (Part C)/ACE002JP, 4 of 18 patients tested positive for ADA. Three patients presented with treatment-induced ADA, and 1 patient presented with treatment-boosted response. No clinically relevant changes in the PK and PD profiles of emicizumab were detected, and there were no clear differences in bleeding reduction or the safety of emicizumab compared with other patients. Therefore, none of the ADAs were considered to have neutralizing potential.

The incidence of ADA in the HAVEN clinical trials is 3.5% (14/398). The rate of ADAs with neutralizing potential (based on declining PK) is 0.75% (3/398). The presence of ADAs with neutralizing potential may be associated with loss of efficacy. The patients who tested ADA-positive did not have a safety profile that differed from that of the overall population.

No patients in any of the studies developed de novo FVIII inhibitors, as is expected based on the fact that emicizumab does not share sequence or structural homology with FVIII.

See the Emicizumab Investigator's Brochure for additional details on clinical studies with emicizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This current study is designed to evaluate the efficacy and safety of emicizumab given QW or Q4W SC in adolescent and adult patients with hemophilia A irrespective of FVIII inhibitor status The inclusion of inhibitor and non-inhibitor patients is supported by the mode of action of emicizumab and the observation from Phase I/II and Phase III studies of similar pharmacokinetics, efficacy, and safety between the inhibitor and non-inhibitor populations.

Because the PK properties of this antibody are expected to enable extended dosing intervals of QW, Q2W, or Q4W, 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W regimens have been investigated in Phase III studies. The dosing regimens investigated in this study (3 mg/kg QW $\times$ 4 followed by 1.5 mg/kg QW or 6 mg/kg Q4W) are being investigated to provide an option for patients to receive emicizumab QW or Q4W, while delivering the same cumulative dose. The Q4W regimen of 6 mg/kg has resulted in a similar exposure (average steady-state concentration [$C_{avg,ss}$]) as the 1.5 mg/kg QW and 3 mg/kg Q2W regimens despite higher maximum plasma concentration (C_{max}) and lower trough concentration (C_{trough}) levels at steady state (see Section 3.3).

Safety data from 417 emicizumab treated patients with hemophilia A has demonstrated that emicizumab was well tolerated. Most adverse events were of Grade 1 or 2 intensity, and most of the adverse events were unrelated to study drug; only 6 patients reported serious adverse events that were related to treatment. Observed adverse events of special interest among patients with hemophilia A treated with emicizumab included thrombotic microangiopathy (3 patients [$<$1.0%]) and thromboembolic event (3 patients [$<$1.0%]); see Section 5.1.2 for details. A total of 113 patients (27.1%) experienced local injection site reactions. All were mild to moderate in intensity, with only one leading to discontinuation of a patient in the Phase I study. However, in Study BH29884, three cases of thrombotic microangiopathy was observed in 3 patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds; and three thromboembolic events were observed in 2 patients on emicizuamb who received

bypassing agents for the treatment of breakthrough bleeds, and one device occlusion in one patient assessed by the investigator as being unrelated to emicizumab.

Five of these 6 patients have fully recovered, while one patient's thrombotic microangiopathy has improved but that patient has died because of severe rectal bleeding (see Section 5.1.2.1). The safety is additionally supported by a no observed adverse effect level of up to 30 mg/kg QW in cynomolgus monkeys. The data from this nonclinical study estimate the maximum dose of 3 mg/kg QW used in the Phase I/II study was associated with a 10.3-fold and 11.2-fold safety margin based on C_{max} and area under the plasma concentration time-curve for a dosing interval ($AUC\tau$), respectively, while the dose of 6 mg/kg Q4W investigated in the present study is predicted to be associated with corresponding 17.4- and 22.5-fold safety margins, respectively.

In conclusion, the management challenges of adults and children with hemophilia A highlight the unmet need for therapeutics that have reliable efficacy, long half-life, and reduced treatment burden to prevent bleeding for patients with hemophilia A. Given this significant unmet medical need and the positive benefit-risk assessment, initiation of a larger, confirmatory Phase III study is indicated.

Following conditional approval of emicizumab prophylaxis treatment in pediatric patients with hemophilia A with inhibitor in China, and review of data from the ongoing Phase III HAVEN 2 study (BH29992), among 10 Asian pediactric patients enrolled out of total 63 patients, there was no difference in terms of PK, safety or efficacy based on ethnicity comparision, thus no difference is expected. However, this study will open one additional non-randomized arm to investigate a QW regimen in Chinese pediatric patients to further confirm the assumption.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate (with no formal hypothesis testing for Arm D) the efficacy, safety, and pharmacokinetics of prophylactic emicizumab administered at 1.5 mg/kg QW and 6 mg/kg Q4W compared with no prophylaxis in patients with hemophilia A randomized to Arms A, B, and C. A total of approximately 85 patients are planned: approximately 70 patients aged $\geq$12 years in Arm A, B, and C, and approximately 15 pediatric patients aged $<$12 years in Arm D (1.5 mg/kg QW). Specific objectives and corresponding endpoints for the study are outlined below (see Table 2).

Table 2 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objectives:	**Primary Efficacy Endpoint**
For Arms A, B, and C: • To evaluate the efficacy of prophylactic emicizumab (i.e., administered on a scheduled basis with the intent to prevent bleeds) compared with no prophylaxis in patients with hemophilia A The primary definition of a bleed is a bleed for which coagulation factors are administered (i.e., treated bleeds; see Section 4.5.8). For Arm D: • To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (using same bleed definition as above)	• The number of bleeds over time (i.e., bleed rate) The endpoint will be analyzed separately for Arms A and B in adolescents and adults: 1.5 mg/kg QW and 6 mg/kg Q4W, as well as for Arm D in pediatric patients: 1.5 mg/kg QW.
Secondary Efficacy Objectives:	**Secondary Efficacy Endpoints**
For Arms A, B, and C: • To evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis • Change over time compared with historical bleed rate prior to study entry will be conducted within each treatment arm (intra-patient comparison for patients who have previously participated in Study BH29768) For Arm D: • To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time	For Arms A, B, C, and D: • To evaluate the efficacy in reducing the number of all bleeds over time • Change in the number of treated bleeds and all bleeds over time compared with the patient's historical bleed rate • To evaluate the efficacy in reducing the number of spontaneous bleeds over time • To evaluate the efficacy in reducing the number of joint bleeds over time • To evaluate the efficacy in reducing the number of target joint bleeds over time For Arms A, B, and C: • Change in HRQoL of patients according to Haem-A-QoL (aged ≥ 18 years) or Haemo-QoL-Short Form (aged 12–17 years) scores after 24 weeks • Change in health status of patients according to European Quality of Life Five-Dimension-Five Levels (EQ-5D-5L) Questionnaire scores after 24 weeks For Arm D: • Change in HRQoL of patients according to Haemo-QoL-Short Form (aged 8–12 years) scores after 24 weeks (completed by patients) • To evaluate proxy-reported HRQoL-SF and aspects of caregiver burden using the Adapted Inhib-QoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)

Table 2 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Exploratory Objectives:	**Exploratory Endpoints**
For Arms A, B, C, and D: • To assess the number of days away from school/work • To assess the number of days hospitalized • To assess potential PD biomarkers of emicizumab	For Arms A, B, C, and D: • Changes in number of days away from school/work during treatment • Changes in number of hospitalization days during treatment • PD Biomarkers of emicizumab, including but not limited to aPTT, thrombin generation, and FVIII activity
Safety Objectives:	**Safety Endpoints**
For Arms A, B, and C: • To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A For Arm D: • To evaluate the overall safety of prophylactic emicizumab treatment in pediatric patients with hemophilia A and inhibitors	For Arms A, B, C, and D: • The incidence and severity of adverse events • The incidence and severity of thromboembolic events • Incidence and severity of thrombotic microangiopathy • Changes in physical examination findings and vital signs • Incidence of laboratory abnormalities • Incidence and severity of injection-site reactions • Incidence of adverse events leading to drug discontinuation • The incidence of severe hypersensitivity, anaphylaxis, or anaphylactoid reactions • The incidence and clinical significance of anti-emicizumab antibodies

Table 2 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Pharmacokinetic Objective:	**Pharmacokinetic Endpoints**
For Arms A, B, C, and D: • To characterize the exposure (trough plasma concentration) of emicizumab in patients treated on QW or Q4W dosing	For Arms A and D: • Trough plasma concentration • The plasma samples will be collected at the scheduled timepoints below: For patients treated on weekly dosing schedule: – Every week during Weeks 1–4 on emicizumab – Every 2 weeks during Weeks 5–8 on emicizumab – Every 4 weeks during Weeks 9–24 on emicizumab – Every 8 weeks during Weeks 25–48 on emicizumab – Every 12 weeks thereafter while on emicizumab, until the end of the study or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first For Arms B and C: For patients treated on every 4 weeks dosing schedule: – Every week during Weeks 1–4 on emicizumab – Every 4 weeks during Weeks 5–24 on emicizumab – Every 12 weeks thereafter while on emicizumab, until the end of the study or after the last patient completes 24 weeks treatment of emicizumab, whichever occurs first

Adapted Inhib-QoL = Inhibitor-Specific Quality of Life (with Aspects of Caregiver Burden); FVIII = factor VIII; HRQoL = health-related quality of life; PD = pharmacodynamic; Q4W = every 4 weeks; QW = every week.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study YO39309 is a multicenter, open-label, Phase III clinical study with randomized and non-randomized arms designed to investigate the efficacy, safety, and pharmacokinetics of emicizumab in patients with hemophilia A regardless of FVIII inhibitor status.
Seventy patients aged ≥ 12 years who received episodic therapy with FVIII or bypassing agents prior to study entry and experienced at least 5 bleeds over the prior 24 weeks will be randomized in a 2:2:1 ratio (see Figure 1) to the following regimens:

- Arm A: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously
- Arm B: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W subcutaneously

- Arm C: No prophylaxis (control arm)

In addition, 15 pediatric patients with hemophilia A and inhibitors who received episodic therapy with bypassing agents prior to study entry will be enrolled to Arm D:

- Arm D: Emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously

The endpoints will be analyzed separately for the two randomized emicizumab arms (Arms A and B): 1.5 mg/kg QW and 6 mg/kg Q4W, as well as for the additional arm in pediatric patients (Arm D): 1.5 mg/kg QW.

Randomized patients will be stratified according to the number of bleeds the patient experienced over the 24 weeks prior to study entry—less than versus greater than or equal to 9—to ensure a balance of patients with lower versus higher number of bleeds in all arms.

To ensure a representative variety of patients with hemophilia A enrolled in this study to investigate the efficacy and safety profile of emicizumab in both inhibitor and non-inhibitor adolescent and adult populations, enrollment of up to 55 non-inhibitor patients will be permitted.

Emicizumab is intended for prophylactic use only (i.e., not to treat bleeds that have already occurred). The primary efficacy analysis, defined as comparing the number of bleeds over time for patients randomized to receive prophylactic emicizumab versus no prophylaxis will be conducted at the earliest timepoint when all randomized patients (Arms A, B, and C) have either completed 24 weeks in the study or discontinued from treatment. For Arm D, the primary efficacy analysis will be conducted after the last enrolled patient has completed 24 weeks in the study or discontinued from treatment. Therefore, there will be a range of observation periods from 6 to approximately 12 months, or longer. Randomized patients will be enrolled globally from China and other countries. At least 60 patients will be enrolled from China.

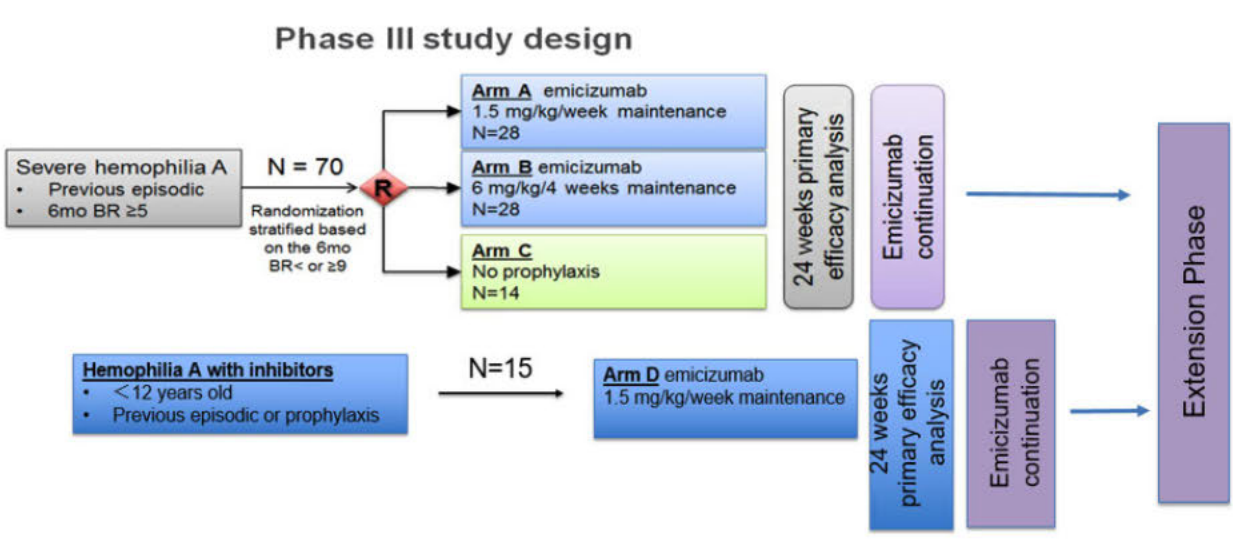
Arm D will only enroll patients from mainland China.

To obtain additional safety and efficacy data on emicizumab, patients who are randomized to Arm C (control arm with no prophylaxis) will have the opportunity after 24 weeks to switch to receive emicizumab prophylaxis at the 6 mg/kg Q4W dosing regimen (emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W). This regimen was chosen to enhance the safety and efficacy data obtained on this dosing regimen because there will be less data available on this regimen from the global studies than from the 1.5 mg/kg QW regimen.

After completing at least 24 weeks of treatment with prophylactic emicizumab, patients who receive emicizumab prophylaxis (Arms A, B, or C after treatment switch and Arm D)

and derive clinical benefit will be allowed to continue emicizumab as part of this study as long as they continue to derive clinical benefit and emicizumab is still in clinical development (see Section 4.3.4). There will be an extension phase in this study for all patients who complete at least 52 weeks of treatment with prophylactic emicizumab and still deriving clinical benefit. The study will be extending for 3 years after the last Arm D patient completes 1 year of treatment *and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 4.3.4). The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier.* Those who are well controlled after 24 weeks on emicizumab (<2 spontaneous and clinically significant bleeds) will continue treatment on their assigned emicizumab regimen; whereas, those who experience suboptimal control (≥2 spontaneous and clinically significant bleeds) will have the option to escalate to 3 mg/kg QW per investigator's judgement after consulting with the Medical Monitor.

Figure 1 Study Schema



BR=bleed rate; mo=month.

During the study, individual bleeds will be captured as they occur, while HRQoL, health status, patient safety, and days of school or work missed will be assessed as outlined in the schedule of assessments (Appendix 1-A and Appendix 1-B). Patients (or their caregiver) will be asked via an electronic, handheld device to report their bleeds (i.e., start date and time, reason, type, location, and associated symptoms for joint and muscle bleeds) and hemophilia-related medication use (i.e., start date and time, reason, type and dose of injection). The bleed/medication questionnaire should be completed whenever a bleed or medication use occurs. In the event of no bleed or medication use, the patient should complete the questionnaire at least once a week to serve as

confirmation that no bleed or medication use occurred. In addition, health status information will be collected whenever a bleed is reported.

Throughout the study, biomarkers related to thromboembolism (e.g., D-dimer, prothrombin $1+2$ fragment) and emicizumab trough concentrations will be collected as per the schedule of assessments. Immunologic biomarkers (i.e., anti-emicizumab antibodies and anti-FVIII antibodies) will also be measured (see Appendix 2).

Exploratory PD biomarkers (e.g., aPTT, FVIII activity, thrombin generation assay) will be collected as per the schedule of assessments. As values for some of these tests are normalized by low plasma concentrations of emicizumab, a variety of assay formats (one stage, chromogenic) and modifications (pre-dilution of patient plasma) will be investigated for assessment of PD response at higher emicizumab plasma concentrations. However, it is not expected that these biomarkers will be used to guide dosing or the selection of patients to be treated with emicizumab. Rather, these biomarkers may be used to identify a future assay for the monitoring of emicizumab activity. In addition,factor IX (FIX) and FX antigen levels will be measured.

Physical examinations, vital signs assessments, ECGs, and laboratory assessments will be collected as per the schedule of assessments and will be the same for all patients, with the exception that emicizumab PK and ADAs will not be measured in patients in Arm C prior to switch to emicizumab treatment. Adverse events will be captured as they occur for the duration of the study.

All patients who receive emicizumab in the study will undergo PK assessments. Based on clinical experience in the ongoing Phase I/II clinical studies with the treatment of over 80 breakthrough bleeds in patients receiving emicizumab with either FVIII or bypassing agents, FVIII, aPCC, or rFVIIa do not interfere with emicizumab PK assessments and no safety signals have been observed when breakthrough bleeds were treated with standard-of-care regimens during Phase I and Phase I/II studies. Therefore, no washout period is required prior to first emicizumab dose in this study, with the exception of patients who were previously receiving ITI in whom a 72-hour washout period is required prior to the first emicizumab administration.

However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), three thrombotic microangiopathy and three thromboembolic events were observed in 5 patients on emicizumab who concomitantly used on average, cumulative doses of >100 units/kg/24 hr for 24 hours of aPCC for the treatment of breakthrough bleeds. There was an additional thromboembolic event, which was a device occulation without concomitant aPCC and assessed by the investigator as being unrelated to emicizumab (see Section 1.2, Section 1.3, Section 5.1.2.1 , and Section 5.1.3). Although FVIII and aPCC are fundamentally different in their potential interaction with emicizumab, investigators should keep in mind

that circulating emicizumab increases patients' coagulation potential. Therefore, it is recommended that:

- Breakthrough bleeds should be treated with the lowest FVIII or rFVIIa dose expected to achieve hemostasis, which may be lower than the patients' prior dose. Investigators should review with patients the dose to be used to treat breakthrough bleeds.
- The use of aPCC/PCC or other bypassing agents should be avoided or limited (see Section 4.4.1).
- Investigators and patients should consider objective verification of bleeds.

Also, local laboratory assessments are required to monitor the risk for thromboembolic events or thrombotic microangiopathy as per the schedule of assessments (see Section 4.5.5 and Appendix 1-A).

Patients might require dosing with FVIII or bypassing agents for the treatment of potential breakthrough bleeds, especially for the time period until steady-state concentrations of emicizum

ab have been reached. The reason for the use of coagulation products will be documented (e.g., bleeding, prophylaxis). The number of infusions needed to treat the bleed will be derived from the medication log.

Of note, a non-interventional study (Study BH29768) has been initiated to document the number and types of bleeds and current treatment with episodic or prophylactic bypassing agents, as well as collect information on HRQoL, health status, and safety in patients with hemophilia A (including children $<$12 years of age). The assessments in the non-interventional study will mitigate the risk of inaccurate reporting of bleeds that may occur with historical data collection and may provide data collected prospectively for over 24 weeks. Patients who are enrolled in the non-interventional Study BH29768 are eligible to enroll in this study, provided they meet the eligibility criteria and are able to enroll at a participating site while the study is open for enrollment.

Investigators will contact the Medical Monitor in the event of suspected lack or loss of efficacy of emicizumab in order to discuss potential laboratory evaluations (e.g., anti-emicizumab antibodies, coagulation tests) to be performed as well as to re-evaluate their patient's benefit-risk of continued treatment.

Collection of PK/ADA/Biomarker samples from Arm D patients will stop when the patient completes the study or after *Week 49*, whichever occurs first.

A schedule of assessments is provided in Appendix 1 A, Appendix 1 B, Appendix 2 A, Appendix 2 B, Appendix 2 C , and Appendix 2 D.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 End of Study

The primary analysis will take place at the earliest timepoint when all randomized patients (Arms A, B, and C) have either completed at least 24 weeks of treatment or discontinued from the study. For Arm D, the primary efficacy analysis will be conducted after the last enrolled patient have completed at least 24 weeks in the study or discontinued from treatment.

Patients who discontinue study treatment prior to end of study (with the exception where the reason for discontinuation is the patient switching to commercial emicizumab product) will return to the clinic for a safety follow-up visit 24 weeks after the final dose of study drug.

The end of this study is defined as the date when the last remaining patient has completed the last visit (LPLV), as defined by any of the following criteria:

- Completion of at least 24 weeks of emicizumab treatment
- Completion of safety follow-up visit 24 weeks after discontinuing emicizumab
- Completion of the study Extension Phase *(3 years after the last Arm D patient completes 1 year treatment) and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products* [*see* Section 4.3.4]*)*
- Withdrawal of consent
- Lost to follow-up

The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier.

3.2.2 Length of Study

The length of the study for an individual patient will be:

- Screening period up to 4 weeks
- Treatment and observation period at least 24 weeks
- Safety follow-up visit 24 weeks after discontinuing emicizumab
- An extension phase in this study for all patients who complete at least 52 weeks of treatment with prophylactic emicizumab and still deriving clinical benefit for 3 years after last Arm D patient completes 1 year of treatment. *Extension phase may end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should a post-trial continued access solution be available earlier.*

The approximate length of the entire study from screening of the first patient to the end of the study (including Arm D and study Extension Phase) will be approximately 88 months.

3.3 RATIONALE FOR STUDY DESIGN

This is a multicenter, open-label, Phase III clinical study with randomized and non-randomized arms. Patients aged 12 years or older with hemophilia A with or without inhibitors against FVIII will be randomized to receive one of the following regimens:

- Emicizumab prophylaxis at 3 mg/kg QW for 4 weeks, followed by 1.5 mg/kg QW subcutaneously (Arm A)
- Emicizumab prophylaxis at 3 mg/kg QW for 4 weeks, followed by 6 mg/kg Q4W subcutaneously (Arm B)
- No prophylaxis control arm (Arm C)

Patients aged <12 years with hemophilia A with inhibitors against FVIII will be enrolled to receive the following regimen:

- Emicizumab prophylaxis at 3 mg/kg QW for 4 weeks, followed by 1.5 mg/kg QW subcutaneously (Arm D)

This prospective, randomized design (Arms A, B, and C) allows uniform collection of bleed data, medication use, and patient-reported outcomes (PROs) through the use of patient-validated measurement tools in all groups, enabling analysis of the effect of prophylactic emicizumab versus episodic therapy on these important measures. Reporting of bleeds by patients to their providers (e.g., doctors, nurses) is not standardized and can be incomplete in routine clinical care. In addition, the recording of bleeds by providers in medical records may be inconsistent. Therefore, testing the primary endpoint using a prospective randomized design is superior to comparison to historical control in patients who were not on prophylaxis prior to enrollment.

Given the proven efficacy of prophylaxis, it can be expected that standard-of-care may evolve towards more widespread treatment of patients with prophylaxis regimens. However, for myriad reasons, currently only about half the patients in developed countries and less than 20% patients in China are managed with routine prophylaxis, making the episodic approach a commonly used standard care (Richards et al. 2007; Xue et al. 2011; Gringeri et al. 2012; Zappa et al. 2012; Jackson et al. 2014; Oldenburg and Brackmann 2014; Jackson et al. 2015; Oldenburg 2015). Thus, for the primary efficacy endpoint, patients with no prophylactic therapy will be compared with patients treated with prophylactic emicizumab. This study will only enroll patients who previously received episodic therapy; this approach will reduce heterogeneity in the study population, which is appropriate since the bleed rates for patients receiving therapy on an episodic versus prophylactic basis are significantly different (Valentino et al. 2012; Manco-Johnson et al. 2013; Powell et al. 2013; Antunes et al. 2014; Mahlangu et al. 2014; Windyga et al. 2014). To help balance measured and unmeasured covariates between the groups with prophylactic emicizumab and the control group with no prophylactic therapy, randomized patients will be stratified according to the number of bleeds they had over the 24 weeks prior to study entry (less than versus greater than or equal to 9 bleeds).

The primary efficacy analysis to assess the effect of emicizumab on bleed rate reduction will be performed at the earliest timepoint when all randomized patients have either completed 24 weeks of study treatment or discontinued from the study. Indeed, a similar follow-up period was used in recent studies that investigated the safety and efficacy of novel FVIII formulations and in the emicizumab global studies (Mahlangu et al. 2014; Kavakli et al. 2015; Konkle et al. 2015). Further, patients who experience frequent bleeds may not find it acceptable to be randomized to their usual episodic therapy for longer than 24 weeks prior to receiving emicizumab. For this reason, individual patients in the control arm will be offered the opportunity to switch to emicizumab after 24 weeks in the study.

With available PK, efficacy, and safety data of emicizumab prophylaxis treatment in pediatric inhibitor patients, the effect of bleeding control is regardless of age, prior treatmet choice, and bleeding history. Thus, Arm D has been added to enroll pediatric patients with no limitation in terms of the minimal age; patients with both prior episodic and prophylaxis treatment with bypassing agents are allowed.

3.3.1 Rationale for Emicizumab Dose and Schedule

Emicizumab prophylaxis has been administered subcutaneously in 18 Japanese patients with hemophilia A (with and without FVIII inhibitors) in Study ACE001JP and in its extension Phase I/II Study ACE002JP. Three dose groups (of 6 patients each) received the following treatment (administration period of 12 weeks):

- A loading dose of 1 mg/kg followed by weekly doses of 0.3 mg/kg
- A loading dose of 3 mg/kg followed by weekly doses of 1 mg/kg
- Weekly doses of 3 mg/kg

Emicizumab was safe and well tolerated in these patients (see Section 1.2.2 and the Emicizumab Investigator's Brochure). The maximum clinical dose of 3 mg/kg/week is associated with a 10.3-fold and 11.2-fold safety margin based on C_{max} and $AUC\tau$, respectively. No clear difference in the plasma concentrations of emicizumab was observed between adolescents (12–18 years) and adult (aged 19–58 years) patients.

A substantial reduction in bleeding events has been observed with prophylactic emicizumab treatment, especially at doses ≥1 mg/kg/week (see Table 3, based on data cutoff of 17 April 2015). ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors.

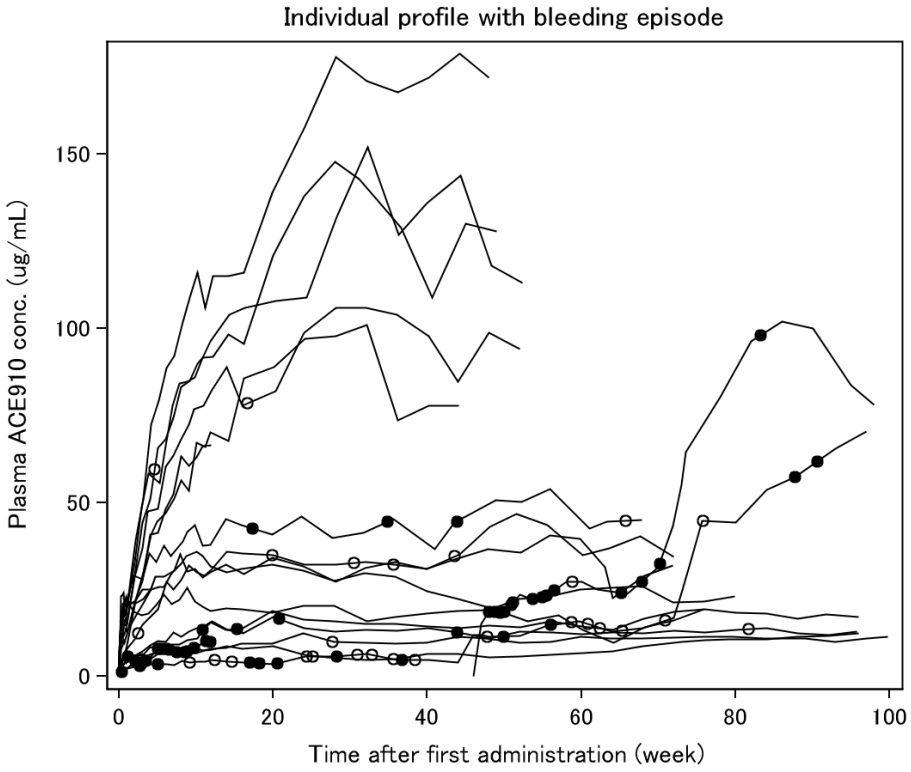
Table 3 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in Study ACE001JP/ACE002JP

Emicizumab Dose	0.3 mg/kg/wk	1 mg/kg/wk	3 mg/kg/wk
ABR reduction	74.5%	95.3%	96.4%

ABR = annualized bleeding rate; wk = week.

A median ABR of 0 was achieved with weekly maintenance doses of 1 and 3 mg/kg. The number of bleeding events decreased with increased emicizumab plasma concentrations (see Figure 2).

Figure 2 Individual Pharmacokinetic Profile with Corresponding Bleeding Event



ACE910 = emicizumab (also known as RO5534262)

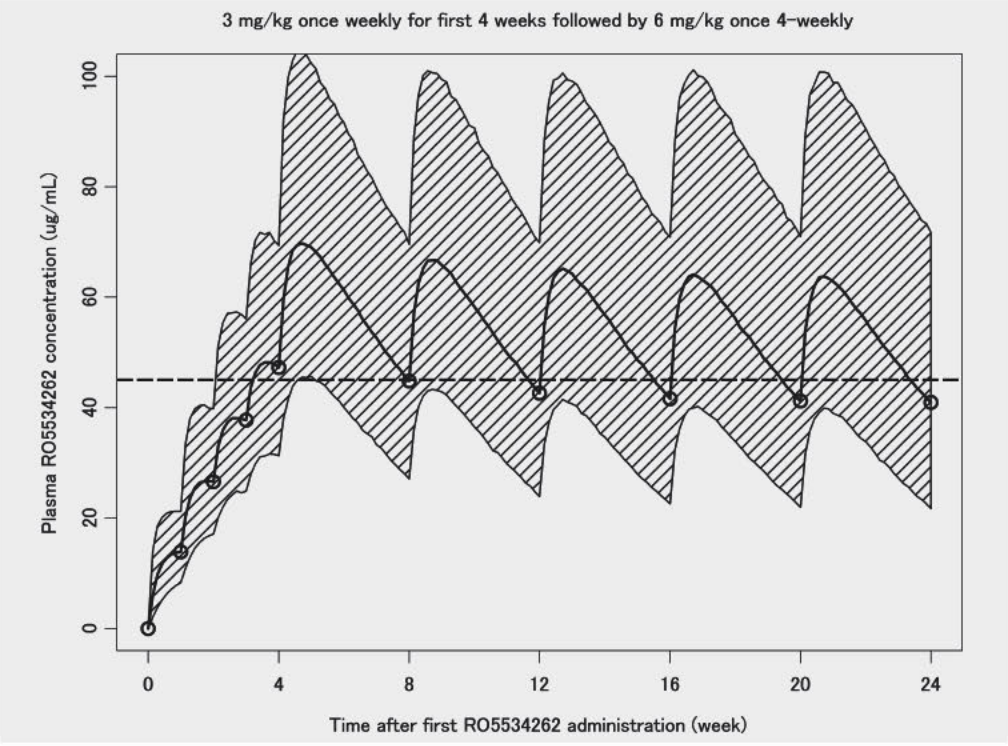
● Joint bleed

O Non-joint bleed

The exposure-response relationship of emicizumab was quantitatively characterized and simulations suggested that a median ABR of 0 is achieved for emicizumab trough plasma ≥45 μg/mL. On the basis of population PK modeling, a median trough plasma concentration of 45 μg/mL is predicted to be achieved after one month of treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with either weekly doses of 1.5 mg/kg or biweekly doses of 3 mg/kg.

A dose of 6 mg/kg Q4W is equivalent in terms of cumulative dose to the dose levels of 1.5 mg QW or 3 mg/kg Q2W that are being evaluated in the other Phase III studies. Assuming linear pharmacokinetics up to 6 mg/kg, model-based simulations were used to explore whether a Q4W dosing regimen could provide sufficient efficacy. Simulations showed that a once-weekly loading dose of 3 mg/kg for the first 4 weeks, followed by an every 4-week maintenance dose of 6 mg/kg would provide a steady-state C_{max} and AUC_{τ} of 78.1±20.9 μg/mL and 1570±447 day·μg/mL, respectively (see Figure 3). While more than half of the patients would not be expected to have a trough level of ≥45 μg/mL at steady state, the simulated ABR distribution was similar to the planned dosing regimens of other Phase III studies. Therefore, this Q4W dosing regimen is expected to maintain similar efficacy to the QW and Q2W dosing regimens.

Figure 3 Simulated Plasma Emicizumab Concentration over Time (Q4W Dosing)



Q4W = every 4 weeks; RO5534262 = emicizumab.
Dots and solid line = simulated median plotted at each trough sampling timepoint.
Shaded area = simulated 5- to 95-percentile range.

Broken line = target exposure level of 45 μg/mL.
NOTE: Once-weekly loading dose of 3 mg/kg for first 4 weeks followed by every 4 weeks maintenance dose of 6 mg/kg was applied.

Overall, a Q4W dosing regimen with 6 mg/kg is expected to provide favorable safety and efficacy in patients with hemophilia A with or without inhibitors. A global Study BO39182 is planned to investigate the efficacy, safety, and pharmacokinetics of Q4W SC administration of emicizumab. It is estimated that the study results of BO39182 will be available before the initiation of Study YO39309. A re-assessment of Q4W dosing schedule based on the results of BO39182 will be performed.

The loading doses of 3 mg/kg QW for 4 weeks were chosen in order to rapidly achieve the effective trough concentration of 45 μg/mL without exceeding the maximum dose of 3 mg/kg QW investigated in the Phase I and Phase I/II studies. The two maintenance dosing regimens will offer flexibility of dosing frequency to patients. Therefore, these prophylaxis regimens (i.e., 3 mg/kg QW for 4 weeks followed by 1.5 mg/kg QW or 6 mg/kg Q4W) will be investigated in this study.

Due to the similarity of the disease between adults/adolescents and children, as well as the availability of a physiologically functioning coagulation system from 6 months onwards (including the targets of emicizumab, FIX and FX), there are no anticipated differences in the action of emicizumab in pediatric patients compared with adults. Indeed, pediatric and adult patients with hemophilia A have shown a similar response to treatment with FVIII compounds (Mahlangu et al. 2014; Young et al. 2015) and bypassing agents (Young et al. 2012). In the Japanese Phase I/II clinical studies with emicizumab, adolescent patients (aged 12–18 years) with hemophilia A have demonstrated similar safety and efficacy results to those observed in adults. Furthermore, in the Phase III HAVEN 2 study, enrolling pediatric (<12 years of age) hemophilia A patients with inhibitors, no effects of age on PK parameters were found. Given emicizumab PK characteristics and analysis of patient characteristics, no dose adjustment appears to be required for specific patient populations (i.e., children, adolescents, the elderly, or patients with renal or hepatic impairment). Therefore, the dosing regimen to be investigated in the present study in patients <12 years of age is to be selected to target a similar plasma emicizumab concentration trough level as the one being targeted in adolescents and adults (i.e., 45 μg/mL).

3.3.2 Rationale for Patient Population

This study will include patients with hemophilia A, irrespective of the presence of FVIII inhibitors. The mode of action of emicizumab is identical in the presence or absence of FVIII inhibitors, and data from the Phase I and Phase I/II studies did not show a difference in the pharmacokinetics, safety, or efficacy between patients with or without inhibitors against FVIII. There are four global pivotal studies to investigate the efficacy and safety profile of emicizumab in patients with hemophilia A, with or without inhibitors. The results from these studies provided more data for further assessment of the patient

population. To ensure a representative variety of patients with hemophilia A enrolled in this study, for the randomized part of Arms A, B, and C, enrollment of up to 55 non-inhibitor patients will be permitted. Although the severity of a patient's hemophilia A is directly related to the FVIII activity, interpatient variability may exist based on level of physical activity, bleeding history, and other features. Therefore, patients previously treated with episodic FVIII or bypassing agents will be required to have had at least five bleeds in the 24 weeks prior to study entry to be eligible for enrollment into the study. This requirement is intended to select a group of patients with hemophilia A who have a high, unmet medical need and to enable evaluation of adequate control of bleeding in this population. In order to exclude patients who might have a higher chance of showing an immune response to foreign protein regimens (e.g., FVIII), patients without FVIII inhibitors ($<$0.6 BU/mL) who completed successful ITI at least five years before screening must have no evidence of inhibitor recurrence (permanent or temporary), indicated by detection of an inhibitor, FVIII half-life $<$6 hours, or FVIII recovery $<$66% since ITI (Antun et al. 2015).

3.3.3 Rationale for Control Group

The control group for the primary efficacy endpoint will be a concurrent, no prophylaxis "usual care" arm, in which patients who were on episodic therapy prior to study entry will be randomized (2:2:1 prophylactic emicizumab 1.5 mg/kg QW:prophylactic emicizumab 6 mg/kg Q4W:no prophylaxis), which will enable an inter-patient comparison of the treatment and control groups.

A second comparison will be a comparison to an individual patient's bleed rate calculated over the 24 weeks prior to study entry, from the medical record. This will enable intrapatient analyses of bleed rates to be performed.

All patients, whether assigned to receive prophylactic emicizumab or no prophylaxis, will continue to receive FVIII or rFVIIa on an episodic basis for the treatment of breakthrough bleeds during the study. Specific doses of FVIII or rFVIIa will not be mandated in the study but investigators should review with patients and approve the appropriate dose to be used to treat breakthrough bleeds. For patients receiving emicizumab, breakthrough bleeds should be treated with the lowest FVIII or rFVIIa dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII or rFVIIa dose.

3.3.4 Rationale for the Primary Efficacy Analysis

For Arms A, B, and C, the objective of the primary efficacy analysis is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis based on the number of bleeds over time (i.e., bleed rate). As mentioned in Section 3.1, the primary analysis will take place at the earliest timepoint when all randomized patients have either completed 24 weeks of treatment or discontinued from the study. This will lead to a range of observation periods from 6 to 12 months or longer in the prophylactic

emicizumab arm and is deemed to be sufficient to reliably assess the effect of prophylactic emicizumab on bleed rate reduction.

Primary efficacy analyses for Arm D will occur at the time of the last enrolled patient have completed 24 weeks in the study.

Additional efficacy analyses may be performed at the end of the study and as needed to support regulatory interactions.

In the multiple ascending dose (MAD) Phase I study (ACE001JP) involving Japanese patients with hemophilia A, a reduction in median ABR to 0 after 12 weeks of treatment (approximately 3 months) in the 1 and 3 mg/kg/wk emicizumab dose cohorts was demonstrated. In the Japanese Phase I/II extension study (ACE002JP), the median ABR of the 1 and 3 mg/kg/wk dose cohorts continued to remain zero in patients who continued to receive prophylactic emicizumab after a minimum of 24 weeks, which is consistent with evidence suggesting longer duration of prophylactic therapy is associated with maintenance of ABR reduction (Antunes et al. 2014). Patients in the 1 and 3 mg/kg/wk cohorts in Study ACE001JP/Study ACE002JP have been observed for at least 72 and 48 weeks, respectively, except for 1 patient in the 3 mg/kg/wk group who has only been followed for 44 weeks as of the cutoff date (17 April 2015).

3.3.5 Rationale for Patient-Reported Outcome Assessments

The study design uses the electronic capture of HRQoL, health status, and days of work/school missed using an electronic, handheld device. HRQoL is an important outcome in the care of patients with hemophilia (Brown et al. 2009). HRQoL in hemophilic patients is multifaceted and impacted by disease symptoms (e.g., pain, bleeding), treatment (prophylactic, on demand, side effects), limitations on daily functioning, anxiety/depression, and time spent in hospital.

The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective. Previous studies that have used the Haemo-QoL, a measure of dimensions of HRQoL affected by hemophilia in children and adolescents, have reported improvements in physical health, feelings, view of self, family relations, friend relations, perceived support, relation with others, participation in sports, dealing with hemophilia, views of treatment, views of the future, and relationships (Santagostino et al. 2014). Improvements in physical health, feelings, view of self, and participation in work and school have also been observed on the adult version of the measure, the Haem-A-QoL (Stasyshyn et al. 2014).

Managing a serious chronic diease like hemophilia in children, which is further complicated by inhibitors, has direct impact on the family. Therefore, it is equally important to assess the potential burden and impact on HRQoL that this may have on caregivers. In a study of caregivers of hemophilic children with inhibitors, an increased burden and higher impact of the disease on the family was reported (Lindvall

et al. 2014). This burden was reported in a variety of areas including financial, emotional, general strain, isolation, and activities.

The inclusion of HRQoL measures for Arms A, B, and C will allow for the assessment of the effect of prophylactic treatment with emicizumab in adolescents and adults with hemophilia A and evaluate the changes in HRQoL in patients receiving prophylaxis with emicizumab compared with patients receiving only episodic treatment for breakthrough bleeds.

For Arm D, the inclusion of HRQoL measures will allow for the assessment of the impact of prophylactic treatment with emicizumab in children with hemophilia A and their caregivers, and an evaluation of the changes in HRQoL in patients prior to and following treatment with emicizumab.

3.3.6 Rationale for Biomarker Assessments

Some biomarkers to measure the PD effect of emicizumab on hemostasis have not been fully validated to date and require further testing to determine which assays and technical conditions are most suitable for use with emicizumab treatment. See Section 5.1.4 for more information about the effects of emicizumab on existing laboratory assays. Plasma samples will be collected for PD biomarker assessment in parallel with PK samples at all clinic visits to demonstrate evidence of biologic activity of emicizumab in patients. These PD biomarkers include, but are not limited to, coagulation assays such as aPTT, thrombin generation, and FVIII activity assays. All of these assays were previously shown in the Phase I/II study to exhibit a dose-response relationship to emicizumab concentration (for more information, see the Emicizumab Investigator's Brochure). In addition, clot waveform analysis may be run as an exploratory PD coagulation assay. Exploratory plasma biomarkers will include FVIII antigen, FIX antigen, and FX antigen to assess whether drug treatment causes a change in the circulating levels of these coagulation factors, which are the binding targets of emicizumab, and may include measurement of other coagulation or hemophilia-related factors as well. Finally, residual blood from collected samples may be stored for 5 years and used for additional emicizumab-related research.

Assessments that require blood draws should be monitored closely to ensure that institutional mandates regarding total sample blood volumes are followed. In situations where no institutional guidance is available, the following limits should be utilized and have been included in the design of the sampling program: no more than 1% of the total blood volume should be taken at one time and no more than 3% of the total blood volume should be taken over a 30-day period (total blood volume is defined as 80–90 mL/kg [European Union 2008]). Thus, blood sampling timepoints and volumes follow the ethical considerations for clinical trials on medicinal products with the paediatric population. In situations where the total volume of blood drawn might exceed the limits stated above, clinical (safety) laboratory assessments should be prioritized. Any remaining permitted blood volume should be collected for PK and immunogenicity

samples, followed by biomarker and PD samples. See the laboratory manual for detailed weight-based blood sampling guidelines.

3.3.7 Rationale for Pharmacokinetic Sample Schedule

One of the aims of this study is to provide dosing recommendations for Chinese hemophilia A patients. A median ABR of 0 has been predicted to be achieved for an emicizumab trough plasma concentration of ≥ 45 μg/mL based on data in adolescent and adult patients with hemophilia A (Study ACE001JP/ACE002JP).

Plasma samples will be collected weekly during the loading dose period and at subsequently less frequent intervals while at steady state in order to document the exposure. This will ultimately allow for optimization of the dosing regimen of emicizumab in Chinese patients.

4. MATERIALS AND METHODS

4.1 PATIENTS

A total of 70 patients with severe hemophilia A who previously received episodic therapy with either FVIII or bypassing agents will be enrolled in Arms A, B, and C.

A total of 15 pediactric patients with hemophilia A with inhibitors from China mainland who previously received episodic therapy with bypassing agents will be enrolled in Arm D.

4.1.1 Inclusion Criteria

4.1.1.1 Arms A, B, and C

Patients in Arms A, B, and C must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient or a legal guardian
- Able to comply with the study protocol, in the investigator's judgment
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires and bleed and medication diary through the use of an electronic device
- Aged 12 years or older at the time of informed consent
- Body weight ≥ 40 kg at the time of screening
- Diagnosis of severe congenital hemophilia A (intrinsic FVIII level $< 1\%$) or hemophilia A with FVIII inhibitors
- Patients without FVIII inhibitors (< 0.6 BU/mL) who completed successful ITI must have done so at least 5 years before screening and have no evidence of inhibitor recurrence (permanent or temporary) indicated by detection of an inhibitor > 0.6 BU/mL since ITI (Antun et al. 2015)
- Documentation of the details of episodic therapy (FVIII or bypassing agents) and of number of bleeding episodes for at least the last 24 weeks

- ≥ 5 bleeds in the last 24 weeks prior to study entry
- Adequate hematologic function, defined as platelet count $\geq 100{,}000/\mu L$ and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN; excluding Gilbert's syndrome) and AST and ALT $\leq 3 \times$ ULN at the time of screening; no clinical signs or known laboratory/radiographic evidence consistent with cirrhosis
- Adequate renal function, defined as serum creatinine $\leq 2.5 \times$ ULN and creatinine clearance by Cockcroft-Gault formula ≥ 30 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 1 year of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include proper use of combined oral or injected hormonal contraceptives, bilateral tubal ligation, male sterilization, hormone-releasing intrauterine devices, and copper intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of $< 1\%$ per year. Barrier methods must always be supplemented with the use of a non-lipid-based spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.1.2 Arm D

Patients in Arm D must meet the following criteria for study entry:

- Written informed consent must be obtained from parent/legally acceptable representative and an assent from the child when applicable (latest approved version by the Independent Ethics Committee [IEC]/Institutional Review Board [IRB]) prior to any of the study-specific assessments and procedures being performed.
- Children < 12 years of age at time of informed consent
- Body weight > 3 kg at time of informed consent
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of applicable PRO questionnaires

- Caregivers of all children must have the willingness and ability to comply with all study procedures, including the completion of the bleed/medication questionnaire and applicable HRQoL questionnaires
- Diagnosis of congenital hemophilia A of any severity and documented history of high-titer inhibitor (i.e., ≥ 5 BU/mL)
- Requires treatment with bypassing agents
- Adequate hematologic function, defined as platelet count of $\geq 100 \times 10^9$ cells/L and hemoglobin ≥ 8 g/dL (4.97 mmol/L) at the time of screening
- Adequate hepatic function, defined as total bilirubin $\leq 1.5 \times$ age-adapted ULN (excluding Gilbert's syndrome) and both AST and ALT $\leq 3 \times$ age-adapted ULN at the time of screening
- Adequate renal function: serum creatinine must be $\leq 1.5 \times$ ULN for age

  If serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Bedside Schwartz formula must be > 70 mL/min/1.73m^2.
- For female patients who are of childbearing potential, follow the same contraception criteria as listed above for Arms A, B, and C.

4.1.2 Exclusion Criteria

4.1.2.1 Arms A, B, and C

Patients in Arms A, B, and C who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment
- History of illicit drug or alcohol abuse within 48 weeks prior to screening, in the investigator's judgment
- Previous (within the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other conditions (e.g., certain autoimmune diseases) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known HIV infection with CD4 count < 200 cells/μL within 24 weeks prior to screening. Patients with HIV infection who has CD4 > 200 cells/μL and meet all other criteria are eligible
- Use of systemic immunomodulators (e.g., interferon) at enrollment or planned use during the study, with the exception of anti-retroviral therapy

- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose additional risk, or would, in the opinion of the investigator, preclude the patient's safe participation in and completion of the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Receipt of:

  Emicizumab in a prior investigational study

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non-hemophilia-related investigational drug concurrently, within last 30 days or 5 half-lives, whichever is shorter
- Inability to comply with the study protocol in the opinion of the investigator
- Pregnant or lactating, or intending to become pregnant during the study

  Women with positive serum pregnancy test result within 7 days prior to initiation of study drug.

4.1.2.2 Arm D

Patients in Arm D who meet any of the following criteria will be excluded from study entry:

- Inherited or acquired bleeding disorder other than hemophilia A
- Ongoing (or plan to receive during the study) ITI therapy or prophylaxis treatment with FVIII

  Patients awaiting initiation of ITI will be eligible.

  Patients in whom ITI has failed will be eligible with a 72-hour washout period prior to the first emicizumab administration.
- Previous (in the past 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
- Other diseases (i.e., certain autoimmune diseases [e.g., systemic lupus erythematosus], cardiovascular disease) that may increase risk of bleeding or thrombosis
- History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
- Known infection with HIV, hepatitis B virus (HBV), hepatitis C virus (HCV)
- Patients who are at high risk for thrombotic microangiopathy (e.g., have a previous medical or family history of thrombotic microangiopathy), in the investigator's judgment

- Use of systemic immunomodulators (e.g., interferon or corticosteroids) at enrollment or planned use during the study
- Planned surgery (excluding minor procedures such as tooth extraction or incision and drainage) during the study
- Inability (or unwillingness by caregiver) to receive (allow receipt of) blood or blood products (or any standard-of-care treatment for a life-threatening condition)
- Receipt of:

  An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration

  A non–hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter

  An investigational drug concurrently
- Concurrent disease, treatment, or abnormality in clinical laboratory tests that could interfere with the conduct of the study or that would, in the opinion of the investigator or Sponsor, preclude the patient's safe participation in and completion of the study or interpretation of the study results
- Pregnant or lactating, or intending to become pregnant during the study

  Female patients with a positive serum pregnancy test result within seven days prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study with randomized and non-randomized arms. Adolescents and adult patients who received episodic therapy with FVIII or bypassing agents prior to study entry will be randomized in a 2:2:1 ratio to receive either prophylactic emicizumab at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW (Arm A) or 6 mg/kg Q4W (Arm B) subcutaneously, or to the control arm (no prophylaxis; Arm C). A central randomization procedure will be used for all patients who fulfill the entry criteria at screening. A block-based randomization method will be used, stratified by the number of bleeds in the last 24 weeks (<9 or ≥ 9). The proposed randomization method is designed to balance treatment group assignment within the prognostic stratification factor.

This study will open one additional non-randomized arm (Arm D) to investigate the 1.5 mg/kg QW regimen in pediatric patients aged ≤ 12 years with inhibitors. All patients will be recruited to Arm D.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Emicizumab

Emicizumab Drug Product 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 30 mg or 150 mg (nominal) of emicizumab at pH 6.0. The Drug Product is formulated in 150 mmol/L arginine, 0.5 mg/mL poloxamer 188, 20 mmol/L histidine–aspartic acid buffer (pH 6.0). Because emicizumab is administered on a weight-based dosing regimen, two vial strengths will be supplied for this study, differing from each other only in emicizumab concentration: nominal vial strength 150 mg (150 mg/mL, 1.0 mL); and nominal vial strength 30 mg (30 mg/mL, 1.0 mL). The more dilute 30-mg vials are intended for 1.5-mg/kg maintenance dosing for patients in Arm D with body weight < 20 kg and will enable safe subcutaneous weight-based dosing of small children with sufficient precision. It is important to note that vials of different emicizumab concentrations must not be combined in the same syringe. For information on the formulation and handling of emicizumab, see the Emicizumab Investigator's Brochure.

4.3.2 Dosage, Dose Adjustment, and Administration

As discussed in Section 3.3.1, each patient starting on prophylactic emicizumab will receive 3 mg/kg QW for 4 weeks as loading doses, followed by 1.5 mg/kg QW (Arm A) or 6 mg/kg Q4W (Arm B), for a total of at least 24 weeks or as long as they continue to derive sufficient clinical benefit. After completion of 24 weeks observation in the study, patients in Arm C could switch to receive emicizumab prophylaxis at the Arm B dosing regimen (emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W).

After at least 24 weeks on prophylactic emicizumab, patients in Arms A, B, and C will have the opportunity to increase their emicizumab dose to 3 mg/kg QW if they meet the following criteria and after consulting with the Medical Monitor:

- ≥ 2 spontaneous and clinically significant bleeds in the last 24 weeks on emicizumab, both of which occur after the end of the loading dose period
- At least one of the bleeds must be verified by a physician (e.g., with diagnostic imaging, photograph)

Patients in Arm D will receive 3 mg/kg QW for 4 weeks as loading doses, followed by 1.5 mg/kg QW as maintenance during the 24-week treatment period. Individual patients experiencing suboptimal bleeding control on emicizumab may also have their dose up-titrated if they meet the same criteria as required for patients in Arm A, B and C and after consulting with the Medical Monitor.

If the investigator believes that a specific patient warrants dose up-titration based on a different reason (e.g., traumatic bleed out of proportion to the degree of injury), they must discuss the case with the Medical Monitor for consideration.

In order to minimize the number of injections for patients in certain weight categories, the administration per single injection of up to 2 mL drug product solution may be permitted, pending approval from the Sponsor, individual countries, and participating sites. This will require combining emicizumab drug product solution from more than 1 vial (i.e., vial pooling) into a single syringe, using a new transfer needle for each vial. Upon Sponsor approval, the detailed procedure for vial pooling will be described in the Instructions for Use. Vials of different emicizumab concentrations must not be combined.

If a patient has a systemic hypersensitivity reaction or severe adverse reaction that may be attributable to emicizumab, subsequent doses should be held until the situation is discussed with the Medical Monitor. Should certain, unanticipated events occur during the study that require treatment with multiple daily administrations of FVIII concentrates or bypassing agents, such as non-elective surgery or severe/life-threatening bleeds, the investigator should contact the Medical Monitor immediately to discuss such cases and the management of future emicizumab doses. Due to emicizumab's unique mechanism of action and the characteristics of its binding to FIX and FX, co-administration of FVIII or bypassing agents and emicizumab is believed to be safe and in general should be continued without withholding emicizumab; however, an individualized decision should be made in consultation with the Medical Monitor. Any other emicizumab dose adjustment request will require discussion of the clinical case with the Medical Monitor.

Study site healthcare providers (HCPs) will be trained on how to properly prepare the study medication and administer the correct calculated dose subcutaneously as described in the "Instructions for Use" (IFU) document. Patients will, in turn, be trained by an HCP on study medication preparation and self-administration at the recommended sites of injection, as detailed in the IFU. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver will be trained. The HCP will inform the patient/caregiver of the volumetric dose to be administered and dosing frequency. Note that during the course of the study, should the patient's body weight change to affect the dose (e.g., ±10%), the new volumetric dose to be administered must be communicated to the patient/caregiver.

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

Emicizumab will be administered as a SC injection in the home setting, with one dose every week or every 4 weeks, after a period of in-clinic administration and training. The first five drug administrations must be performed in a monitored setting, such as an infusion center, clinic, or hospital, with a 60-minute observation period following each of the first three doses. The observation period for the fourth and fifth doses will be at the investigator's discretion. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions as described in Section 5.1.2.2 should be considered. At that time, the patient/caregiver will also have the opportunity to ask any questions of the HCP before the scheduled start of home administration. The

patient (≥ 7 years of age)/caregiver will observe at least one SC injection performed by the HCP and successfully administer at least one SC injection while being observed by a HCP prior to starting home administration. Each site will have the discretion to provide additional training if deemed appropriate. If, despite additional training, the investigator determines that the patient/caregiver is unable to inject emicizumab correctly, arrangements may be made to identify an alternative trained caregiver or HCP to administer the SC injections. At the investigator's discretion, study drug may be administered by a trained mobile nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in mobile nurse visits.

Patients/caregivers will be provided with the clinic contact information, to use in case they have questions related to self-administration between visits.

Medication administration errors during training will be documented in the electronic Case Report Form (eCRF). If necessary, patients or their HCP may choose to continue administration of study drug in the clinic. Compliance in the home setting is to be monitored by reviewing reported emicizumab use and recording collected used and unused vials at each site visit.

Patients shall administer study medication on the schedule dosing days. On days when trough plasma samples are to be collected, patients will be dosed after samples are drawn, potentially at the clinic (self-administration). On the other days, for patients on once weekly dosing, if the patient forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 3 days from the scheduled dosing date. If more than 3 days has passed, the missed dose should be skipped, and the patient should take his or her next dose at the next scheduled time with the study medication dosing resumed in accordance to the original dosing schedule. For patients on once every 4 weeks dosing, if the patient forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 14 days from the scheduled dosing date. If more than 14 days has passed, the patient should take his or her next dose at the next scheduled time with the study medication dosing resumed in accordance with the original dosing schedule.

Patients and/or the caregiver will be provided with *patient* cards, which they will be requested to carry at all times. These will include guidance on recognizing signs/symptoms of thromboembolic events or allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care. In addition, *patient* cards are designed to notify an external health care provider that emicizumab will interfere with certain coagulation laboratory tests (see Section 3.1) and the investigator should be contacted for assistance.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

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

4.3.3 Investigational Medicinal Product Accountability

Emicizumab, the only IMP in Study YO39309, is required for completion of this study and will be provided by the Sponsor, and accountability for each vial is required throughout the study. The study site will acknowledge receipt of IMPs using the interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMP received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Used and unused IMP vials will be returned by study patients to the site and appropriately accounted for. Used vials will then be disposed of at the study site according to the study site's institutional standard operating procedure. Instructions regarding how to handle unused vials should be obtained from the Sponsor. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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.

4.3.4 Post-Trial Access to Emicizumab

The Sponsor will offer post-trial access to the study drug (emicizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The patient is eligible and has access to a study providing access to the drug
- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for hemophilia A
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for hemophilia A
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT AND RESCUE THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/discontinuation visit. In addition, use of long-acting medications taken infrequently (e.g., zoledronic acid, denosumab) will be recorded as well. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Concomitant use of the following drugs and therapies will be permitted:

- Drugs intended to control bleeds, including FVIII products or bypassing agents as standard-of-care episodic treatment. Exact dosages will not be specified in the study; however, investigators should consider that circulating emicizumab may increase patients' coagulation potential. Investigators should review with patients the dose to be used to treat breakthrough bleeds. Breakthrough bleeds should be treated with the lowest FVIII or rFVIIa dose expected to achieve hemostasis, which may be lower than the patients' prior FVIII or rFVIIa dose.

  Caution should be taken for patients who are using rFVIIa (e.g., consideration of using no more than 90 μg/kg of rFVIIa as an initial dose).

  Use of aPCC/PCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC/PCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than 50 units/kg of aPCC/PCC to be administered as an initial dose.

Other bypassing agents (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 μg/kg of Byclot®).

Exact dose and schedule of bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC/PCC, or other bypassing agents should be performed only under medical supervision, which includes laboratory monitoring by additional local laboratory assessments (see Appendix 1-A), and consideration should be given to verifying bleeds prior to repeated dosing.

Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab.

- Drugs and therapies to treat adverse events and use of topical antiseptics, anesthetics, eye drops, etc., that are not considered to result in systemic exposure
- Drugs to treat an existing medical condition ongoing at study entry that do not violate the eligibility criteria (e.g., anti-retroviral therapy for HIV infections)
- Local anesthetic cream for emicizumab SC administration
- Vaccinations should be administered following national immunization schedules. As per the World Federation of Hemophilia recommendations for vaccinations (World Federation of Hemophilia 2012), patients with hemophilia should be vaccinated. Thus, vaccinations should be administered according to the World Federation of Hemophilia recommendations and local Hemophilia Treating Center practice and ideally during a period when the bleeding status of the child is well controlled and stable. Vaccinations should not be administered on the same day as an emicizumab administration but ideally at a timepoint between two emicizumab administrations (>48 hours after emicizumab administration). Children who receive vaccinations must be carefully followed for any adverse reactions in the subsequent days following vaccine administration.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 4 weeks prior to initiation of study treatment:

- Drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential cyclooxygenase-2 inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a venous access device]) but excluding drugs intended to control bleeding episodes or used in the context of minor surgery (e.g., tooth extraction) or injuries (e.g., concussion) to prevent deterioration
- Systemic immunomodulators (e.g., rituximab, interferon) other than anti-retroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction, CVAD removal, or incision and drainage as well as emergency surgeries)

- Use of aPCC/PCC for short-term prophylaxis

  Note: This criterion does not apply to the 4 weeks prior to initiation of study treatment.

- Use of other investigational drugs
- Use of anti-fibrinolytics in conjunction with aPCC/PCC or other bypassing agents (e.g., Byclot®)
- Use of concomitant prophylactic regimen with FVIII or rFVIIa

  Note: This criterion does not apply to the 4 weeks prior to initiation of study treatment.

  Intermittent, prophylactic doses or short-term prophylaxis (e.g., around the time of surgery), however, are permitted

If prohibited therapy is administered for any reason, it should be recorded on the eCRF. If prohibited treatment is prescribed or considered medically necessary, the Medical Monitor should be consulted to discuss any changes in the benefit/risk and determine whether the patient should continue on the study.

4.5 STUDY ASSESSMENTS

See Appendix 1-A for the schedule of assessments to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the parent/legally acceptable representative and an Assent from the child when applicable before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not enrolled will be maintained at the study site. For adolescents (i.e., 12–17 years of age), an Informed Assent Form will be completed instead. Parents or legally authorized representatives of pediatric patients and adolescents will also complete an Informed Consent Form.

All screening evaluations must be completed within 4 weeks prior to the first dose and reviewed to confirm that patients meet all eligibility criteria before enrollment and randomization. The investigator will maintain a *detailed* record of all patients screened and to *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, procedures, abuse of alcohol and drugs within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior immune tolerance induction, anaphylaxis, or known thrombophilia. It should also include all medications taken within the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies), or in the 24 weeks prior to screening for medications intended to treat osteopenia or osteoporosis. If the interval between screening and Week 1 is

longer than 2 weeks, all medications taken during this period should be reviewed and recorded. If imaging tests of bone health (e.g., densitometry, dual energy X-ray absorptiometry [DEXA] scan) were performed in the year prior to screening, the results should be recorded.

Additionally, the number of bleeds during the 24 weeks prior to study enrollment should be documented, as well as the number of school/work days missed and number of days hospitalized during the 24 weeks prior to study entry.

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

4.5.3 Physical Examinations

A complete physical examination should include but not necessarily be limited to the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. Subsequently, a targeted (i.e., musculoskeletal, dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated. New or worsened abnormalities from screening should be recorded as adverse events. A complete physical examination will be performed at screening and at least targeted physical examinations will be performed at subsequent visits.

4.5.4 Vital Signs

Vital signs will include measurement of pulse and respiratory rate, temperature (oral or tympanic), systolic and diastolic blood pressure, height, and weight and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments but may also be taken anytime as unscheduled assessments as judged by the investigator.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments. When study drug administration is scheduled on days of clinic visit, laboratory samples should be drawn before the administration of study drug. Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, and basophils], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries (sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase)

- In patients who receive bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator may monitor for potential thromboembolic events and thrombotic microangiopathy:
  - Platelet count
  - Serum creatinine
  - Lactate dehydrogenase (LDH)
  - Peripheral blood smear analysis to evaluate for schistocytes

  A plasma sample should also be provided for laboratory monitoring of:
  - Fibrinogen
  - D-dimer

For patients who require multiple doses of bypassing agents, local laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded on the Unscheduled Visit eCRFs.

- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and within 7 days prior to initiation of study medication, if applicable.

  Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

The following samples will be sent to the Sponsor or a designee for centralized analysis:

- Plasma samples for PK analysis
- Plasma samples for immunogenicity assessment (ADA)
- Serum and plasma for PD and exploratory PD biomarker assessments (aPTT, PT, FVIII activity, and others as listed in Appendix 2)
- Plasma samples for anti-FVIII antibody measurement (inhibitor titer) will be sent to the Sponsor throughout the study, with the exception of the test needed at screening for patients who do not have a documented negative inhibitor test (<0.6 BU) within 6 weeks prior to enrollment.

Please see the schedule of assessments, Appendix 1-A , for detailed information. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

4.5.6 Electrocardiograms

ECG recordings will be obtained at study sites at specified timepoints, as outlined in the schedule of assessments (see Appendix 1-A) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. The following parameters will be obtained: heart rate, QT, respiratory rate, QT interval corrected using Bazett's formula, QT interval corrected using Fridericia's formula, PR and QRS, and T-and U-wave morphology. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g.,vital sign measurements, blood draws) and should ideally not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Any ECG changes that are deemed clinically significant by the investigator (e.g.,associated with symptoms or lead to a change in study treatment or concomitant treatment, or discontinuation from study treatment), must be reported as an adverse event on the adverse event eCRF. The investigator or designee must review, sign, and date all ECG tracings. The ECG may be repeated if investigator deems it appropriate. Paper copies will be kept as part of the patient's permanent study file at the site.

4.5.7 Patient-Reported Outcomes

To capture bleed and hemophilia medication use data, as well as HRQoL and health status data during study treatment, patients/caregivers will complete the Bleed/Medication questionnaires on an electronic, handheld device that will be provided to them during their Week 1 visit at the site. This device will remain with the patients/caregiver for the duration of the study to enter bleed and medication data on a weekly basis at minimum *before the study extension phase. After the start of the extension phase, bleed and medication data will not be collected.* Patients and/or caregivers will complete HRQoL, proxy HRQoL-SF, and aspects of caregiver burden questionnaires at designated timepoints during clinic visits on a separate electronic, handheld device (tablet) that will remain at sites. The electronic, handheld device and instructions for completing the questionnaires will be provided by the investigator staff. The questionnaires should be completed by the patient or their caregivers at the site at the start of the visit and prior to all other study assessments.

After bleed, medication, HRQoL, proxy HRQoL, and aspects of caregiver burden entries have been saved, the data will be transmitted automatically from the respective devices to a centralized vendor database. Bleed and medication use data entered since the

patient's previous clinic visit will be reviewed at subsequent clinic visits, as per the schedule of assessments, for completeness and accuracy. Investigators will review the bleed and bleed medication data as per the schedule of assessments (see Appendix 1) and have the ability to correct or complete entries once verified with the patient/ caregiver using a Data Change Request Form process or via a Web-based portal, once implemented.

4.5.7.1 Health-Related Quality of Life

The Haem-A-QoL and the Haemo-QoL-SF (only for patients aged 8–17 years) will be used to measure HRQoL in adults and adolescents/pediatric patients, respectively (see Appendix 2, Appendix 3 , and Appendix 4, respectively). The Haem-A-QoL was designed for adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, view, sport and leisure time, work and school, dealing, treatment, future, family planning, and relationships/partners) and a scale representing total score. Items are rated along 5 response options, although for some items there is also a "not applicable" option (von Mackensen and Gringeri 2005; 2010).

The Haemo-QoL-SF was developed as a series of age-related questionnaires to measure HRQoL in children and adolescents with hemophilia (Bullinger et al. 2002; von Mackensen and Bullinger 2004; Pollak et al. 2006). These versions include a 77-item long form, a 35-item as well as a 16-item short form, and an 8-item index form. The short version for older children containing 35 items was selected for this study. This version covers nine dimensions considered relevant for the children's HRQoL (physical health, feelings, view of yourself, family, friends, other people, sports and school, dealing with hemophilia and treatment). Items are rated with five respective response options: never, seldom, sometimes, often, and always. Higher scores for both HRQoL measures are indicative of poorer HRQoL.

4.5.7.2 Health Status

The EQ-5D-5L (see Appendix 5) is a generic, preference-based health utility measure that assesses health status and is used to inform pharmacoeconomic evaluations, which will only be assessed for patients from Arms A, B, and C. The EQ-5D-5L consists of two parts. The first part, health state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). Published weights are available that allow for the creation of a single summary score. Overall scores typically range from 0 to 1, although a score below 0 is theoretically possible representing a state worse than death, with low scores representing a higher level of dysfunction. The second part is a 0 to 100-point visual analog scale (VAS) that assesses current health status; higher scores are reflective of better health.

4.5.7.3 Adapted Inhib-QoL, Including Aspects of Caregiver Burden

Proxy assessment of HRQoL-SF and aspects of caregiver burden for all children, regardless of age, will be collected using the Adapted Inhibitor-Specific Quality of Life

(Inhib-QoL) with Aspects of Caregiver Burden questionnaire (see Appendix 6). This will be completed by caregivers as per the schedule of assessments during clinic visits (see Appendix 1).

4.5.7.4 Daycare/School Absences and Hospitalizations

All patients or their caregivers will be asked to report on an electronic, handheld device the number of days of daycare/school that were missed (if applicable). The number of days the child was hospitalized (if applicable) will be derived from data collected on eCRF.

4.5.8 Definition of a Bleed

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis and similar to that used in a recent clinical study, will be used in this study (Blanchette et al. 2014; Mahlangu et al. 2014), which includes the following additional criteria:

- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are $\leq$72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken $>$72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

An additional definition of all bleeds (i.e., both treated and not treated with coagulation factors) will be applied for certain secondary efficacy analyses.

4.5.8.1 Bleed Sites

- Target joints: defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of $\geq$3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds: having an unusual sensation (“aura”) in the joint in combination with any of the following:

  Increasing swelling or warmth of the skin over the joint

  Increasing pain

  Progressive loss of range of motion or difficulty in using the limb as compared with baseline
- Muscle bleeds (sites as per the Bleed and Medications Questionnaire)
- Other bleeds (sites as per the Bleed and Medications Questionnaire)

4.5.8.2 Bleed Types

In addition, the assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of hemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (i.e., hemorrhage occurring secondary to an event such as trauma, "strenuous" activity, or "overuse") will be collected.

- Spontaneous bleeds: Bleeds will be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity, "overuse," or procedure/surgery. The determination of what constitutes "strenuous" or "overuse" will be at the discretion of the patient. For example, light jogging may be considered "non-strenuous" while sprinting may be considered "strenuous," lifting of weights for a short period of time may be considered "moderate use" while repetitive weightlifting may be considered "overuse."
- Traumatic bleeds: Bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient were to exercise "strenuously" and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent "strenuous" activity. Bleeds subsequent to injuries would certainly be classified as traumatic.
- Bleeds related to procedure/surgery: such as hematomas resulting from any surgeries or invasive procedures (e.g., tooth extractions, venipuncture, or SC drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) would not be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients (or patient's legally authorized representative) or their caregivers will complete an electronic Bleed and Medication Questionnaire whenever a bleed occurs, or at least weekly to confirm all bleeds have been recorded until the patient starts the study extension phase. *After the start of the extension phase, bleed and medication data will not be collected.* For each bleeding episode, they will provide information on the above topics as well as on the medication used to treat the bleed. Hemophilia medications that were taken will also be collected through the Bleed and Medication Questionnaire. In the event that the electronic Bleed and Medication Questionnaire is not available, a paper version of the Bleed and Medication Questionnaire may be used. The data will be reviewed by sites during site visits.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient's inability or unwillingness to comply with protocol requirements, non-compliance despite appropriate education measures taken by the clinical site

Patients may elect to withdraw from the activity monitoring but continue participation in the remainder of the study. If a patient decides to withdraw only from the activity monitoring prematurely, the patient will continue treatment and follow-up as per the study protocol. The primary reason for withdrawal from activity monitoring should be documented on the appropriate eCRF.

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

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients who become pregnant should immediately stop treatment and be managed as per local guidelines.

If the patient discontinues study treatment, bleed, hemophilia medication, HRQoL, health status, and missed days of school or work should be recorded by the patient on the electronic, handheld device until the safety follow-up visit (i.e., 24 weeks after the last study drug administration).

4.6.3 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 patients.

- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

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 (e.g., bleed/medication questionnaire data not checked by investigator/co-investigator for >8 weeks)
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

5.1.1 Patient Selection

The inclusion and exclusion criteria in this study are designed to select patients who are not at increased risk based on the current understanding of the investigational medication. See Section 4.1.1 and Section 4.1.2 for full inclusion and exclusion criteria, respectively.

5.1.2 Risks Associated with Emicizumab

5.1.2.1 Identified Risks

Thrombotic Microangiopathy (Associated with Emicizumab and aPCC)

Thrombotic microangiopathy is a very rare, but serious condition whereby microvascular thrombosis leads to organ damage.

As of October 2018, among 417 patients in five studies (ACE002JP, BH29884, BH29992, BH30071, and BO39182), there were 3 patients (1.0%), all in Study BH29884, who experienced thrombotic microangiopathy while receiving emicizumab prophylaxis. These events are believed to be caused by an interaction between emicizumab and aPCC, as all 3 patients received cumulative doses of >100 U/kg/day on average of aPCC for ≥24 hours for the treatment of breakthrough bleeds just prior to developing symptoms. These events were reported as serious adverse events (two Grade 4 events and one Grade 3 event). One patient died due to a serious adverse event of Grade 4 rectal haemorrhage (assessed as unrelated to emicizumab). From additional analyses, including data on the thrombotic microangiopathy and thromboembolic events,

there is evidence to support a drug-drug interaction between aPCC and emicizumab. Please see the Emicizumab Investigator's Brochure for a complete summary of safetyinformation.

Specific guidance regarding the use of bypassing agents in combination with emicizumab is detailed in Section 4.4.1.

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 5.2.2 and Section 5.2.3).

Guidelines for management of patients who develop thrombotic microangiopathy are provided in Section 5.1.3.

Hypercoagulation and Risk of Thrombosis

As of October 2018, four thromboembolic events have been reported in 3 patients with hemophilia A with inhibitors while receiving emicizumab in Study BH29884.
Two patients who administered cumulative doses of $>$ 100 U/kg/day on average of aPCC for $\geq$ 24 hours while receiving emicizumab developed thromboembolic events. The thromboembolic events were reported as serious adverse events (Grade 3 cavernous sinus thrombosis, Grade 3 skin necrosis, and Grade 2 thrombophlebitis superficial); however, none were life-threatening or fatal. No anticoagulation was started and symptoms in both patients improved with supportive care. These adverse events are believed to be caused by a drug-drug interaction between emicizumab and aPCC.
There was 1 patient who experienced a thromboembolic event of Grade 1 device occlusion in Study BH29884 while receiving emicizumab. This patient was receiving emicizumab prophylaxis; however, this adverse event was assessed as being unrelated to emicizumab. Of note, this patient did not receive treatment with aPCC or other bypassing agents when he had this device occlusion.

No cases of thromboembolic events have been observed in patients who only received emicizumab, who only received emicizumab and rFVIIa alone, or who were treated with single doses of aPCC up to 100 U/kg/infusion.

Thromboembolic events have not been observed in any of the other completed (ACE001JP and JP29574) or ongoing clinical studies (ACE002JP, BH29992, BH30071, and BO39182). Please see the Emicizumab Investigator's Brochure for more details.

Specific guidance regarding the use of bypassing agents in combination with emicizumab is detailed in Section 4.4.1.

Thromboembolic events 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 5.2.2 and Section 5.2.3).

HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism (i.e., dyspnea, chest pain, leg pain or swelling, or if in the head, headache, numbness in the face, eye pain or swelling, or vision impairment) and ensure that they understand the importance of seeking appropriate medical attention. Patients/caregivers will also receive two *patient* cards to remind them of this information and these instructions should thromboembolism be suspected.

Guidelines for management of patients who develop hypercoagulation thromboembolic events are provided in Section 5.1.3.

Injection-Site Reactions

In the completed and ongoing clinical studies of emicizumab, injection-site reactions have been observed in some patients with hemophilia A. As of October 2018, among 417 patients, 113 patients (27.1%) developed injection-site reactions. All were assessed to be mild or moderate in intensity. Reported events include injection site erythema, injection site pruritus, injection site swelling, injection site haematoma, injection site bruising, injection site urticaria, injection site papule, injection site warmth, injection site induration, injection site pallor, injection site discomfort, injection site pain, injection site rash, general signs and symptoms of necrotizing enterocolitis (NEC), purpura and related conditions, and rash, eruptions and exanthems NEC. One patient reported non-site specific procedural complications. In Study ACE001JP, two episodes of injection site erythema in a [redacted] year-old patient resulted in discontinuation of emicizumab treatment.

Directions for emicizumab administration should be followed, as outlined in Section 3.3.1 , Section 4.3.2, and in the Instructions for Use. This includes alternating the site of injection, from one injection to the next, in the recommended injection-site locations listed in the IFU.

Guidelines for management of patients who develop injection-site reactions are provided in Section 5.1.3.

5.1.2.2 Potential Risks

Life-Threatening Bleeding Due to 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 on the Bethesda assay) are not reliable and do not accurately reflect a patient's underlying hemostatic status while receiving emicizumab prophylaxis. Owing to 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 if a patient is treated by practitioners

other than emicizumab-prescribing practitioners in settings such as an emergency room or in an acute care setting.

Emicizumab mechanism of action and resulting interference were 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 October 2018, 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.

See Section 5.1.4 for interpretation of coagulation assays for patients receiving emicizumab.

Anaphylaxis, Anaphylactoid, and Systemic Hypersensitivity Reactions

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 Section 5.2.3.

Patients with a history of hypersensitivity associated with monoclonal antibody therapies or to the components of the emicizumab injection will be excluded from study participation. 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 7).

HCPs should also instruct patients how to recognize the signs and symptoms of hypersensitivity, anaphylactic, and anaphylactoid reactions and to contact an HCP or seek emergency care in case of any such occurrence. Patients/caregivers will also receive two alert cards to remind them of this information and these instructions should any of these reactions occur.

For patients with a previous history of a clinically significant hypersensitivity reaction, after each of the first three doses, the site will call the patient 24 hours after each dose to assess the status of the patient. Additional precautions following each of these doses may also be considered including having an extended observation period or IV access prior to dosing, etc. The investigator may include these or other precautions, as deemed appropriate.

Guidelines for management of patients who develop anaphylaxis, anaphylactoid, and systemic hypersensitivity reactions are provided in Section 5.1.3.

Immunogenicity

As with administration of any exogenous protein, a potential exists for the development of ADAs. Such antibodies can be neutralizing and/or sensitizing, producing the potential for reduced efficacy and/or allergic reactions. As discussed in Section 1.2.2.4, patients with hemophilia were reported to have positive ADAs. There were 4 positive ADA patients with declining PK profiles (ADA with neutralizing potential) of which one discontinued due to lack of efficacy. For additional information please see the Emicizumab Investigator's Brochure.

5.1.3 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 4.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Thrombotic Microangiopathy	• Please see Section 3.1 and Section 3.3.3 for guidance on management of breakthrough bleeds, including required laboratory monitoring. • 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. • If a patient has a thrombotic microangiopathy event, further administration of study drug should be interrupted. The decision to resume emicizumab after an event of thrombotic microangiopathy must be discussed with the Medical Monitor.
Hypercoagulation and Thromboembolic Events	• Please see Section 3.1 and Section 3.3.3 for guidance on management of breakthrough bleeds, including required laboratory monitoring. • HCPs should be vigilant for patients who exhibit signs/symptoms consistent with thromboembolic events and immediately begin work-up and treatment, as per local guidelines. • If a patient has a thromboembolic event, administration of study drug should be interrupted. The decision to resume emicizumab after a thromboembolic event must be discussed with the Medical Monitor.
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, patients will be monitored for signs of injection-site reactions in the period immediately following injections. Patients will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.

Event	Action to Be Taken
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 patient has symptoms of anaphylaxis or severe hypersensitivity, administration of study drug must be immediately stopped and treatment of the reaction be initiated. • No re-challenge should be performed in patients who experience a severe hypersensitivity, anaphylactic, or anaphylactoid reaction unless, after careful discussion with the medical monitor, the clinical benefit clearly outweighs the risk. The investigator should contact the Medical Monitor to assess if the clinical benefit clearly outweighs the risk to determine if and when the patient should resume taking emicizumab and discuss the patient's continued study participation. If the patient continues in the study, the next two scheduled doses must be in a monitored setting with at least a 60-minute observation period and resuscitation treatment immediately available. After each of these two doses in the clinic, the site will call the patient 24 hours after each dose to assess status of the patient. • Investigators may order any pertinent laboratory tests, including an unscheduled anti-drug antibody, in the event any of these reactions occur.
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.

5.1.4 Interpretation of Coagulation Assays for Patients Receiving Emicizumab

Emicizumab interacts with standard laboratory assays used in the management of patients with hemophilia A. In one-stage assays, emicizumab is associated with a supra-physiologically short time to clot formation and thus normalization of aPTT at subtherapeutic levels and an overestimation of true FVIII activity. Emicizumab is not recognized or neutralized by FVIII inhibitors and, therefore, cannot be detected by a functional test such as Bethesda or Nijmegen-Bethesda assays, which use a one-stage clotting-based readout. Emicizumab activity cannot be detected by chromogenic assays using purified bovine coagulation proteins and can only be detected using an assay composed of human proteins. Table 5 summarizes the coagulation tests affected and unaffected by emicizumab. See the RO5543262 (Emicizumab) Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

Table 5 Coagulation Test Results Affected and Unaffected by Emicizumab

Results Affected by Emicizumab	Results Unaffected by Emicizumab
• aPTT • Activated clotting time (ACT) • One-stage, aPTT-based, single-factor assays • aPTT-based Activated Protein C Resistance (APC-R) • Bethesda assays (clotting-based) for FVIII inhibitor titers	• Thrombin time (TT) • One-stage, PT-based, single-factor assays • Chromogenic-based single-factor assays other than FVIIIa • Immuno-based assays (e.g., ELISA, turbidometric methods) • Bethesda assays (bovine chromogenic) for FVIII inhibitor titers • Genetic tests of coagulation factor mutations (e.g., Factor V Leiden, Prothrombin 20210)

FVIII = factor VIII.

[a] For important considerations regarding FVIII chromogenic activity assays, please see information provided above in Section 5.1.4.

5.1.5 Procedure-Related Risks

Emicizumab is administered subcutaneously. Patients should be properly instructed to handle and prepare the injection and understand the risk for injection site reactions. See Section 5.1.2.1 for more information.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting 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.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. Therefore, an adverse event can 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), except as described in Section 5.3.5.10
- 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)

Bleeds considered as serious adverse events should be reported as serious adverse events on the eCRF. New nonserious bleeds, consistent with patients' pre-study disease, will not be considered adverse events and will not be recorded on the eCRF (but should be captured on the bleed/medication questionnaire).

5.2.2 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 patient 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 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient 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 Grades 1–4, according to the WHO Toxicity Grading Scale for Determining The Severity of Adverse Events criteria; 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).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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 potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- 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 patient 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 Sampson's Criteria in Appendix 7)
- Thromboembolic events
- Microangiopathic hemolytic anemia or thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 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 5.2.2 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 patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to randomization (randomized arms) or initiation of study drug (non-randomized arm), only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After randomization (randomized arms) or initiation of study drug (non-randomized arm), all adverse events will be reported until the patient completes his or her 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 (see 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 patient 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 8) will be used for assessing adverse event severity (WHO 2003). Table 6 will be used for assessig severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	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

Notes: 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 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, 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, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as 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 patient 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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 in the investigator's opinion are judged to be related to study drug injection should be captured as an "injection-site reaction" on the Adverse Event eCRF. An injection-related reaction that is localized should be marked as a "local injection-site reaction." 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 patient 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. 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 That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event 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 consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both 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 patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. 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 patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event 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:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is 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., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) 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 whether 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

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, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is 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 blood pressure), 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$baseline value 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 5.3.5.2) 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 an adverse event of special interest (see Section 5.4.2).

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). This includes death attributed to progression of hemophilia.

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").

If the death is attributed to progression of hemophilia, "hemophilia progression" should be recorded on the Adverse Event eCRF.

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 Lack of Efficacy or Worsening of Hemophilic Bleeds

At any time during the study an unexpected worsening of hemophilia-related bleeding, as judged by the investigator, should be recorded as an adverse event. For example, increased severity (e.g., increased number of FVIII doses required to stop bleeds compared with before study entry) or frequency of bleeds. Hemophilia worsening should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia"). A clinically significant bleed (i.e., intracranial, retroperitoneal) does not by itself constitute loss of efficacy, unless it is associated with features indicating worsening of the underlying hemophilia phenotype. Events that are clearly consistent with the expected pattern of the underlying disease and do not indicate an unexpected worsening in severity or frequency should not be recorded as adverse events. These data will be reflected in efficacy assessment data only.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), 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
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for drug administration)
- 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 patient has not experienced 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 that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. 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 or qualifies as an adverse event of special interest, 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).

No safety data related to overdosing or drug administration error of emicizumab are available, as no such instances have been observed to date. To minimize the risk of errors associated with future home administration of emicizumab, data related to medication errors with observed patient/caregiver administration of emicizumab during the first 5 weeks at the site by the investigator and/or clinical staff will be recorded and corrected at the time of occurrence. In addition, the recording of medication and handling errors associated with home administration, as well as drug compliance, will be collected at each clinic visit.

5.3.5.13 Patient-Reported Outcome Data

The PRO measurements are described in Section 4.5.7. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. All adverse events will be reported by the investigator on the Adverse Event eCRF. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data, and will be included in the appropriate section of the final study report.

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 study. 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 (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

To ensure the safety of study *participants, access to* Medical *Monitors is available 24 hours per day, 7 days per week.* The Emergency Medical Call Center *will connect the investigator with an Emergency Medical Contact, provide medical translation services if nedessary, and track all calls. Contact information, including, toll*-free numbers for the *Emergency Medical Call Center*, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Randomization or Study Drug Initiation

After informed consent has been obtained but prior to randomization (randomized arms) or initiation of study drug (non-randomized arm), only serious adverse events caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Randomization or Study Drug Initiation

After randomization (randomized arms) or initiation of study drug (non-randomized arm), serious adverse events and adverse events of special interest will be reported until the last scheduled study visit (see Section 5.6). Investigators should record all case details

that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Although embryo-fetal development studies are not available, condom use will not be required in male patients 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 both 1.5 and 3 mg/kg QW dosing regimens) 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 patients treated with emicizumab. Therefore, contraception use by male patients is not required for participation in the study, and proactive collection of pregnancy information for female partners of male patients treated with emicizumab will not be required during the study.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS 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 patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-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 patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

At the time of pregnancy outcome, reporting instructions provided in Section 5.4.3.1 should be followed.

5.5.2 Sponsor Follow-Up

For serious adverse events, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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 LPLV), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Clinical Trial Adverse Event/ Special Situations 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 adverse events of special interest (see Section 5.2.3) 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 Investigator's Brochure

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

This section provides a general overview of the methods. If any of the items require a unique approach that differs from the general overview, it will be noted in the appropriate section.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

All summary tables will be structured with a column for each treatment arm and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

Efficacy analyses will follow the principle of intention-to-treat (i.e., based on randomized population).

For Arm D, no formal hypothesis testing is planned. All the analyses will be descriptive and performed separately.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for the randomized arms (including Arms A, B, and C) is based on clinical and statistical considerations, taking into account the limited number of patients with hemophilia A available for participation in clinical studies and in an effort to collect sufficient data to assess the safety and efficacy of emicizumab.

The sample size calculation is based on the evaluation of the primary efficacy endpoint, defined as the number of bleeds over time (i.e., bleed rate) with emicizumab (treatment group, λ_t) versus no prophylaxis (control group, λ_c), which are said to follow a negative binomial (NB) distribution. With consideration of enrollment feasibility, a sample size of 70 patients, assuming an allocation ratio of 2:2:1 (28 patients in each randomized treatment group and 14 patients in control group), will achieve a power of more than 90% assuming a mean ABR of 4 and 18 bleeds (with variances $=$ mean $\times$ 10) for the emicizumab treatment and control arms, respectively, representing an expected 78% reduction in the ABR compared with the control arm. Initial sample size calculations were performed with East®, Version 6 (Cytel, Cambridge, MA), assuming the patients from each treatment group are followed up to 0.5 units of time (i.e., 24 weeks).

However, the above approach to sample size calculation assumes similar follow up for each patient. Because this is unlikely to be seen in the study, power was also estimated by simulation to account for different follow-up times among patients. Conducting simulations on the basis of an NB regression model including an offset variable to account for variable follow-up times, with all other assumptions remaining the same as previously described, the sample size is projected to have greater than 90% power at the 2-sided 0.05 level of significance.

Multiplicity will be accounted for by testing emicizumab QW arm versus no prophylaxis first, and upon successful testing, emicizumab Q4W (or Q2W, depending on global Study BO39182 data readout) versus no prophylaxis, each at 0.05 level.

During the study, a re-assessment of the initially specified sample size based on aggregated (not by treatment arm) global data to date may be performed. This may result in an increase in sample size, if necessary, to maintain adequate power without

affecting the type 1 error rate. Study integrity will be upheld, as access to information via aggregated analyses and their results will be minimized to limit operational bias.

The sample size for Arm D is based on favorable recruitment feasibility and clinical considerations rather than statistical considerations, taking into account the limited number of pediatric patients with hemophilia A inhibitors available for participation. Hence, approximately 15 children < 12 years of age with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Flow of patients through the study will be displayed in a "CONSORT" diagram. A clear account of all patients who entered the study, who were enrolled and randomized, and who entered and completed each phase of the study will be displayed. In addition, reasons for premature discontinuations from study treatment and reasons for withdrawing from the study (e.g., during follow-up) will be described.

Variables from the eCRF used to establish how many patients reached the various stages of the study, how many dropped out and for what reasons will be described in the Statistical Analysis Plan (SAP).

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

For Arms A, B, and C, comparisons between the treatment arms of demographic data and baseline characteristics will be conducted to establish if any observed differences between the treatment arms are not due to imbalances in patient characteristics at baseline. Only descriptive analyses are planned, and no formal statistical tests will be applied.

For Arm D, a summary will be provided separately.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis will include all randomized patients (Arms A, B, and C), with patients grouped according to the treatment assigned at randomization.

The clinical effect of prophylactic emicizumab treatment in pediatric patients with inhibitors (Arm D) will be descriptive and analyzed separately.

6.4.1 Primary Efficacy Endpoint

For the randomized arms (Arms A, B, and C), the primary efficacy objective is to evaluate the clinical effect of prophylactic emicizumab compared with no prophylaxis on the number of bleeds over time. The definition of a bleed for the primary analysis is

described in Section 4.5.8, with the primary endpoint comparing bleeds requiring treatment.

The primary efficacy analysis will be conducted after all randomized patients have completed 24 weeks in the study or the last randomized patient, yet to complete 24 weeks in the study, discontinues study participation, whichever occurs first, and using an intent-to-treat principle. The separate comparison of the number of bleeds over time between each of the randomized emicizumab arms and control arm will be performed using an NB regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of randomization and the time that each patient stays in the study included as an offset in the model. The model also includes the number of bleeds (<9 or ≥ 9) in the last 24 weeks prior to study entry as a stratification factor in the randomization. This analytic model estimates the rate ratio, λ_t / λ_c., which quantifies the risk of bleeding associated with prophylactic emicizumab (λ_t) in comparison to no prophylaxis (λ_c). Statistical significance is controlled at the 2-sided, 0.05 alpha (α) level. Of note, hierarchical testing is used to account for multiple testing and the first test to be included in the hierarchy is the emicizumab 1.5 mg/kg QW maintenance dose versus control. The second test will be 6 mg/kg Q4W maintenance dose versus control (or 3 mg/kg Q2W versus control, depending on global Study BO39182 data readout). The description below covers both hypotheses to be tested:

H_0 (null hypothesis): Rate Ratio $= 1$ versus H_1 (alternative hypothesis): Rate Ratio $\neq 1$.

The treatment effect therein is based on a contrast statement in the model with use of the SAS GENMOD procedure. Statistical significance at the pre-specified alpha level will be based on a Wald testing procedure. Bleed rates for prophylactic emicizumab and no prophylaxis and the rate ratio will be presented and include 95% confidence intervals.

The number of bleeds can also be annualized for each patient using the following formula: ABR $=$ (Number of bleeds during the efficacy period/Total number of days during the efficacy period) $\times$ 365.25. If the NB model converges, van Elteren test to compare the mean ABR between the randomized arms will be provided only as a sensitivity analysis. However, if the convergence of the NB model is not achieved or is questionable, the primary efficacy analysis will be based on the van Elteren test of ABR.

For Arm D, one efficacy objective is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time. This analysis will be performed separately as well as overall as appropriate.

A detailed description of the statistical methods for the primary and secondary efficacy analyses will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

For Arms A, B, and C, the number of all bleeds (i.e., those treated and not treated with coagulation factors) spontaneous bleeds, joint bleeds, and target joint bleeds over time in patients who receive prophylactic emicizumab compared with no prophylaxis will be evaluated by the NB regression model as specified for the primary efficacy endpoint.

For patients in Arms A, B, and C, the number of treated bleeds and all bleeds will be compared with the patient's historical bleed rate recorded in the medical record prior to study entry, using an NB regression model similar to the one described for the primary efficacy endpoint.

In addition, the number of joint and target joint bleeds over time between the emicizumab prophylaxis and no prophylaxis arms will be evaluated by an NB regression model, as specified for the primary efficacy endpoint.

For Arm D, descriptive analyses of characterizing the effect of emicizumab on-study treatment period for bleed over time as well as analyses of up-titration will be performed separately.

The number of bleeds, sites of bleeds, and types of bleeds will be summarized for all patients and listed for each patient individually. Several exploratory analyses will be conducted to characterize the type, location, duration, frequency, and pattern of bleeds. For continuous endpoints, descriptive statistics will be calculated and categorical endpoints will be characterized through frequency tables.

Adherence with the HRQoL and health status measures will be summarized at the end of the study. HRQoL (using the Haem-A-QoL or the Haemo-QoL-SF) and health status (using the EQ-5D-5L) will be assessed on a regular basis, as per the schedule of assessments (Appendix 1-A).

Because different HRQoL measures (Haem-A-QoL and the Haemo-QoL-SF) are being used for the adult and adolescent/pediatric patients, all calculations and analyses will be conducted separately for adults and adolescents/pediatrics. Scale scores for the Haem-A-QoL and Haemo-QoL-SF will be calculated and summarized descriptively for all timepoints in the study. The HRQoL scale scores for all patients will be evaluated after 24 weeks in the study, a timepoint that is consistent with other recent registrational studies in hemophilia (Lentz et al. 2013; Powell et al. 2013; Mahlangu et al. 2014) and analyses of such data (Santagostino et al. 2014; Wyrwich et al. 2015). For Arms A, B, and C, an analysis of covariance model will be used to compare the 24-week and final assessments with the baseline scale scores for each HRQoL measure. Within-subject and between-group changes from baseline on the different HRQoL scale scores will also be calculated at 24 weeks, and a descriptive analysis including patients between 8 to 17 years old from Arms A, B, C and D will also be conducted. For Arm D, proxy-reported HRQoL and aspects of caregiver burden using the Adapted Inhib-QoL

with Aspects of Caregiver Burden questionnaire (completed by caregivers) will be summarized by timepoint.

For the assessments of the EQ-5D-5L, the number and percentage of patients in each of the five categories for each question for each group will be assessed. Changes in the EQ-5D-5L index utility score from baseline will also be compared between groups. In addition, summary statistics including mean, standard deviation, median, minimum, and maximum will be displayed for the patients' health state using the EQ-VAS both within and between groups. The proportion of patients who report changes in each group exceeding the clinically meaningful threshold on the EQ-5D-5L index and EQ-VAS scores in each group will be reported at 24 weeks.

6.5 SAFETY ANALYSES

The safety analyses population will be based on all enrolled patients grouped according to the actual treatment received. For Arm C patients, all safety data reported up to the day prior to switching will be included in the "control arm" safety summaries, and all safety data reported on or after the date of switching to active treatment will be reported separately.

Safety will be assessed for Arms A, B, and C and separately for Arm D through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology, including complete blood count with differential), ECGs, vital signs, and antibodies to emicizumab and FVIII.

To evaluate the overall safety of prophylactic emicizumab compared with no prophylaxis, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade for each treatment arm.

For clinical laboratory data, summary statistics will be presented by treatment arm. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale.

Data on the effect of immunogenicity (anti-emicizumab antibodies) on safety, efficacy, and/or clinical pharmacology and pharmacokinetics will be summarized adopting standard language/terminology (Shankar et al. 2014).

Although this is an open-label study, Sponsor personnel will not have access to safety summaries by treatment arm prior to the formal reporting of the study results. HCPs at participating study sites, as well as the Sponsor's drug safety and medical monitoring staff, will have access to the treatment assignments of patients for safety monitoring purposes only.

6.6 PHARMACOKINETIC ANALYSES

For all patients, predose (trough) plasma concentrations of emicizumab will be presented descriptively by treatment group, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling may be used to analyze the dose-concentration-time data of emicizumab following SC administration. Population PK parameters, such as clearance and volume of distribution, will be estimated, and the influence of various covariates, such as age, sex, and body weight, on these parameters will be investigated graphically. Secondary PK parameters, such as AUC, will be derived from individual post-hoc predictions. Data may be pooled with data from other studies. These analyses will be reported in a dedicated report.

6.7 EXPLORATORY ANALYSES

Summary statistics of the number of work/school days missed and days hospitalized will be presented by treatment arm.

PD parameters (e.g., aPTT, parameters derived from thrombin generation, FVIII activity) will be presented using summary statistics, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

6.8 INTERIM ANALYSIS

No interim analysis is planned for this study.

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. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient 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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient reported data will be collected electronically with use of electronic devices provided by a vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a centralized database at the vendor. The data from the electronic, handheld devices are available for view access only via secure access to a Web portal provided by the vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor. The Sponsor will receive all data entered by patients on the electronic, handheld devices and all relevant study documentation.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 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 patient 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, PROs, 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 study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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 7.6.

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

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

The Sponsor will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient 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 patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients 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 patient 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 patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Patients who are declared legally incompetent or who are physically or mentally incapable of providing informed consent but otherwise meet the qualifications for participation in Study YO39309 will be included, as emicizumab prophylaxis may directly benefit this population with high unmet medical need. In such cases, investigators will obtain informed consent from a guardian or legally authorized representative of the patient in accordance with applicable law. In addition, the investigator must also obtain the assent of the patient when they are able to give assent to decisions made on their behalf. Any indication on the part of the patient that they are not willing to participate in the study will be honored.

In cases where there is reason to question the competence of a patient who has not been declared incompetent (e.g., a patient in the early stages of Alzheimer's disease), a patient advocate will be involved in the consent process and throughout the duration of the patient's participation in the study.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, 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 patient 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 9.6).

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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

Patient 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 patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of the U.S. 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., LPLV).

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 patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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.

9.4 ADMINISTRATIVE STRUCTURE

This study will enroll approximately 85 patients: approximately 70 patients in Arms A, B, and C; and approximately 15 patients in Arm D.

Randomization and drug assignment will be performed by an IxRS, which will also manage emicizumab inventory for all sites globally.

PROs will be captured electronically using a device provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section 4.5.5.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the final analyses of the study to healthcare professionals and to the

public, both at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, see the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical studies 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 studies 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.

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.

9.6 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 patients or changes that involve logistical or administrative aspects only.

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Appendix 1-A
Schedule of Assessments

Schedule of Assessments–Arms A and B																		
	Screen-ing [a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Q8W from Wk 33	Wk 49	Q12W from Wk 61	Daily/ weekly [b]	Study Comp/ ET [c]	Early Disc. Safety F/U Visit before Study Comp [d]
Informed consent [e]	x																	
Inclusion/exclusion criteria	x																	
Medical history and demographics [f]	x																	
Physical examination (including weight) [g]	x	x				x						x		x			x	x
Height	x											x		x				
Vital signs [h]	x	x [h]	x	x	x	x	x	x	x	x	x	x [h]	x	x [h]	x		x [h]	x
Serum pregnancy test [i]	x	x																
Urine pregnancy test [i]		x				x		x	x	x	x	x	x	x	x		x	x
Concomitant medications [j]	x	x				x		x	x	x	x	x	x	x	x		x	x
ECG [k]	x	x [k]				x						x					x	
Safety laboratory assessments [i]	x [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Bleed/medication questionnaire [l]																x		
Bleed/medication data review [l]		x				x		x	x	x	x	x	x	x	x		x	x
Adverse events [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL and health status (EQ-5D-5L) [o]		x							x			x		x	x		x	
Emicizumab administration [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PK/PD/*ADA* assessment [q]	See Appendix 2-A for details																	
Following treatment with bypassing agents [r]	Monitoring for thromboembolic events and thrombotic microangiography [r]																	

Appendix 1-A (cont.)
Schedule of Assessments

Schedule of Assessments–Arm C (Screening to Switch to Emicizumab)								
	Screening [a]	Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Daily/weekly [b]
Informed consent [e]	x							
Inclusion/exclusion criteria	x							
Medical history and demographics [f]	x							
Physical examination (including weight) [g]	x	x						
Vital signs [h]	x	x [h]	x	x	x	x	x	
Height	x							
Serum pregnancy test [i]	x	x						
Urine pregnancy test [i]		x						
Concomitant medications [j]	x	x	x	x	x	x	x	
ECG [k]	x	x [k]						
Safety laboratory assessments [i]	x [i]	x						
Anti-FVIII antibodies	x							
Bleed medication questionnaire [l]								x
Bleed/injection data review [s]		x	x	x	x	x	x	
Adverse events [m]		x	x	x	x	x	x	
HRQoL and health status [o]		x			x			
PD biomarkers assessment [q]		x						

Appendix 1-A (cont.)
Schedule of Assessments

Schedule of Assessments–Arm C (Continued, at Time of Switch to Emicizumab)																	
	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Q12W from Wk 61	Wk 73	Wk 85	Daily/ weekly [b]	Study Comp/ ET [c]	Early Disc. Safety F/U Visit before Study Comp [d]
Physical examination (including weight) [g]	x				x						x		x			x	x
Vital signs [h]	x [h]	x	x	x	x		x	x	x	x	x [h]	x	x [h]	x		x [h]	x
Height	x										x		x				
Serum pregnancy test [i]	x																
Urine pregnancy test [i]	x				x		x	x	x	x	x	x	x	x		x	x
Concomitant medications [j]	x				x		x	x	x	x	x	x	x	x		x	x
ECG [k]	x				x [k]						x					x	
Safety laboratory assessments [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Bleed/medication questionnaire [l]															x		
Bleed/medication data review [s]	x				x		x	x	x	x	x	x	x	x		x	x
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
HRQoL and health status [o]	x							x			x		x	x		x	
Emicizumab administration [p]	x	x	x	x	x		x	x	x	x	x	x	x	x			
PK/PD/*ADA* assessment [q]	See Appendix 2-A for details																
Following treatment with bypassing agents [r]	Monitoring for thromboembolic events and thrombotic microangiopathy [r]																

Appendix 1-A (cont.)
Schedule of Assessments

Schedule of Assessments–Arm D																					
	Screen-ing [a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 49	Q12W from Wk 61	Daily/ weekly [b]	Study Comp/ ET [c]	Early Disc. Safety F/U Visit before Study Comp [d]
Informed consent [e]	x																				
Inclusion/exclusion criteria	x																				
Medical history and demographics [f]	x																				
Physical examination (including weight) [g]	x					x			x			x			x		x	x		x	x
Height	x											x					x				
Vital signs [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Serum pregnancy test [i]	x	x																			
Urine pregnancy test [i]		x				x		x	x	x	x	x	x	x	x	x	x	x		x	x
Concomitant medications [j]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
ECG [k]	x	x				x														x	
Safety laboratory assessments [i]	x		x		x			x	x	x	x	x	x	x	x	x	x	x		x	x
Bleed/medication questionnaire [l]																			x	x	x
Bleed/medication data review [s]		x				x		x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
IMP management [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Haemo-QoL-Short Form [o]		x							x			x			x		x			x	
Adapted Inhib-QoL [0]		x							x			x			x		x			x	
Emicizumab administration [p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
PK/PD/*ADA* assessment [q]	See Appendix 2-A for details.																				
Following treatment with bypassing agents [r]	Monitoring for thromboembolic events and thrombotic microangiopathy [r]																				

Appendix 1-A (cont.)
Schedule of Assessments

Disc=discontinuation; eCRF=electronic Case Report Form; ET=early termination; F/U=follow-up; FVIII=factor VIII; HRQoL=health-related Quality of Life; IMP=investigational medicinal product; Adapted Inhib-QoL=Inhibitor-Specific Quality of Life (with Aspects of Caregiver Burden); PD=pharmacodynamic; PK=pharmacokinetic; Q8W=every 8 weeks; Q12W=every 12 weeks; study comp.=study completion; Wk=week.

Notes: All assessments should be performed within ±2 days of the scheduled visit for the first 3 months, then ±7 days thereafter. PD and PK (trough) samples will be collected within ±2 days of the scheduled visit and linked to the timing from the dose. Clinic visits should coincide with the day of emicizumab dosing, and on those days the dose should be administered after blood draws and other assessments are conducted. Unscheduled assessments may be performed at the discretion of the investigator and as clinically indicated. Except for the bleed/injection questionnaire, HRQoL, and health status, all other patient data will be collected during office or nurse visits. Evaluation at Week 25 or 49 will occur after a full 24 or 48 weeks in the study, respectively. Study completion evaluation occurs when a patient discontinues emicizumab or transitions into another study.

[a] Screening may occur up to 4 weeks before Week 1 dosing.

[b] Patients will complete the bleed/medication questionnaire at least weekly and at the time of a bleed, or when they take a hemophilia-related medication (including emicizumab). Arm B patients should indicate at least weekly whether or not they had a bleed.

[c] There will be an Extension Phase in this study for all patients who have completed at least 52 weeks of treatment with prophylactic emicizumab and are still deriving clinical benefit. The study will be extending for 3 years after the last Arm D patient completes 1 year of treatment *and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 4.3.4). The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier.*

[d] In the event a patient discontinues emicizumab early before the study completion, an early discontinuation safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab. *If a patient enters extension phase, follow Appendix 1-B for study completion or early discontuation safety follow up.*

[e] Obtain written informed consent (or patient's assent and caregiver written informed consent if patient is an adolescent/pediatric) before distribution of electronic, handheld device and collection of any data. Patients will be enrolled and randomized after giving informed consent, and assent when appropriate.

[f] Collected from patient medical records and documented on the eCRF, including information on target joint(s).

[g] Calculation of dose based on weight is required. A complete physical examination will be performed at screening and at least a targeted physical examination will be performed at subsequent visits. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions) as clinically indicated and/or with report of new or worsening adverse event.

[h] Body temperature (oral or tympanic), blood pressure, pulse rate, and respiratory rate only to be used to monitor hypersensitivity reactions during and after injection and not to be entered on eCRF, except at Weeks 1, 25, 49, study completion/early termination, and at the Early Discontinuation Safety Follow-up visit before study completion (i.e., 24 weeks after discontinuing emicizumab for patients in Arms A and B and at Week 73 for patients in Arm C). Weight will be measured and recorded in the eCRF at each clinic visit prior to any injections (if applicable.) Height will be measured at screening and annually.

Appendix 1-A (cont.)
Schedule of Assessments

[i] Laboratory data (performed locally) include: complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count), serum chemistries (i.e., sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase). Laboratory assessments completed at the screening visit do not have to be repeated at Week 1, if the period between screening and Week 1 is 5 days or less and there has been no change in health status as assessed by the investigator. Patients with childbearing potential will be required to have a negative serum pregnancy test result at screening (and within 7 days of study drug initiation, if applicable) and urine pregnancy tests performed at every clinic visit, with the exception of Weeks 2–4 and 7. Patients on Arm C will have urine pregnancy test performed at screening and before starting emicizumab (Week 25).

[j] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at the time of the monthly assessment, excluding treatments for bleeds (i.e., FVIII and other medications to treat bleeds), which will be collected on the bleeding questionnaire.

[k] Performed locally. If screening ECG is abnormal, repeat at Week 1 (or Week 2 if screening and Week 1 occur on the same day), otherwise do not repeat. ECGs will also be performed 4–8 and 24 weeks after starting emicizumab or dose up-titration, as well as at study completion/early termination.

[l] Reported by the patient or their caregivers and includes: start date and time, reason, type, location, and associated symptoms for joint and muscle bleeds, as well as start date and time, reason, type, and dose of each injection, excluding emicizumab.

[m] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. If there is unexpected worsening of the patient's hemophilia in terms of severity (e.g., increased number of doses of FVIII to stop bleeds compared with before study entry), frequency of bleeds, or nature at any time during the study, this should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

[n] Drug accountability will not be performed at the first visit that includes emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit.

[o] Patient-reported outcomes will be captured on-site by a device and transmitted to the patient-reported outcome database. The questionnaires should be completed by the patient or their caregivers at the site at the start of the visit and prior to all other study assessments. For patients in Arms A, B and C, questionnaires include Haem-A-QoL questionnaire (age ≥18 years) and Haemo-QoL-Short Form (age 12–17 years), and health status questionnaire EQ-5D-5L. For patients from Arm D and their caregivers, questionnaires include Haemo-QoL-Short Form (age 8–12 years) and Adapted InhibQoL including Aspects of Caregiver Burden (completed by caregivers, regardless of age). Days of work/school missed will be captured, as applicable to each arm.

[p] For patients randomized to Arm A: emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously. For patients randomized to Arm B: emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W subcutaneously. For patients randomized to Arm C, following 24 weeks of no prophylaxis: emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 6 mg/kg Q4W subcutaneously. For patients in Arm D: emicizumab prophylaxis at 3 mg/kg QW subcutaneously for 4 weeks, followed by 1.5 mg/kg QW subcutaneously. There will be an extension phase in this study for all patients who complete at least 52 weeks of treatment with prophylactic emicizumab and still deriving clinical benefit. The study will be extending for 3 years after the last Arm D patient completes 1 year of treatment or until China's reimbursement of emicizumab is received, whichever comes first *and patients still having clinical benefit are transferred to a post-trial continued access solution per Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 4.3.4). The study will end earlier, before 3 years after the last Arm D patient completes 1 year treatment, should the post-trial continued access solution be available earlier.*

Appendix 1-A (cont.)
Schedule of Assessments

[q] See Appendix 2-A for detailed explanation of PD biomarker assessments (Sets 1 and 2). Blood samples will be banked for 5 years for future exploratory PD biomarker analyses. Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[r] Following bypassing agent treatment, patients should provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and peripheral blood smear analysis for schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local laboratory monitoring of fibrinogen and D-dimer. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded in the Unscheduled Visit eCRFs

[s] At the Week 1 visit, patients or their caregivers will be trained on how to use, and be provided with, their own electronic, handheld device. At subsequent visits, as marked, investigator review of patient-reported bleed/injection questionnaire information will be conducted. Information regarding trauma events in the preceding month will be collected in the eCRF by the investigator.

Appendix 1-B
Schedule of Assessments - Extension Phase

Extension Phase Schedule of Assessments — Arm A, B, C, and D				
	Extension Phase Day 1 [a]	*Every 24 Weeks* [a]	*Extension Phase Completion/Extension Phase Early Termination* [b]	*Extension Phase Early Disc. Safety F/U Visit*
Informed consent [c]	x			
Physical examination (including weight and height) [d]	x	x	x	x
Vital signs [e]	x	x	x	x
Concomitant medications [f]	x	x	x	x
Safety laboratory Assessments [g]	x	x	x	x
Adverse events [h]	x	x	x	x
IMP management [i]	x	x		
Emicizumab dispensing and administration [j]	x	x		
Following treatment with bypassing agents [k]	*Monitoring for thromboembolic events and thrombotic microangiopathy*			

Appendix 1-B (cont.)
Schedule of Assessments - Extension Phase

Disc = discontinuation; ET = early termination; eCRF = electronic case reporting form; F/U=follow-up.

[a] Assessments performed within ± *14* day of visit.

[b] In the event a patient discontinues emicizumab early before the study completion *(with the exception where the reason for discontinuation is the patient switching to commercial emicizumab product)*, an early discontinuation safety follow-up visit should be performed 24 weeks after discontinuation of emicizumab

[c] Obtain a separate written informed consent (or patient's assent and caregiver written informed consent if patient is an adolescent/pediatric) before transferred to extension phase.

[d] Calculation of dose based on weight is required. A complete physical examination will be performed at extension phase Day 1 and at least a targeted physical examination will be performed at subsequent visits. Targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, and injection-site reactions) as clinically indicated and/or with report of new or worsening adverse event. Height will be measured at extension phase Day 1 and annually.

[e] Body temperature (oral or tympanic), blood pressure, pulse rate, and respiratory rate only to be used to monitor hypersensitivity reactions during and after injection and not to be entered on eCRF, except at study completion/early termination. Weight will be measured and recorded in the eCRF at each visit prior to any injections (if applicable).

[f] Concomitant medications (e.g., extra pain medication with bleed) will be asked about at the time of the scheduled visit, excluding treatments for bleeds (i.e., FVIII and other medications to treat bleeds), which will *not be collected during the study extension phase*.

[g] *Safety* laboratory *assessments should* be performed *at least once every 12 months, including* complete blood count with differential (i.e., neutrophils, hemoglobin, platelet count) *and* serum chemistries (i.e., potassium, creatinine, total and direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase)*, PT, APTT, and INR. Investigators may choose to add any additional tests to be processed in the local lab at clinical* discretion.

[h] Injection-site reaction adverse events will be collected on a separate form from the adverse event form. If there is unexpected worsening of the patient's hemophilia in terms of severity (e.g., increased number of doses of FVIII to stop bleeds compared with before study entry), frequency of bleeds, or nature at any time during the study, this should be documented as an adverse event on the Adverse Event eCRF, conveying that the underlying condition has changed by including applicable descriptors (e.g., "increased clinical severity of hemophilia").

[i] Drug dispensation will not occur at the study completion/early termination visit.

[j] *For patients randomized to Arm A: emicizumab 1.5 mg/kg QW subcutaneously. For patients randomized to Arm B: emicizumab 6 mg/kg Q4W subcutaneously. For patients randomized to Arm C: 6 mg/kg Q4W subcutaneously. For patients in Arm D: 1.5 mg/kg QW subcutaneously. Patients should record their actual Emicizumab administer in their handheld device.*

[k] *Following bypassing agent treatment, patients are recommended to provide a sample for local laboratory monitoring of thromboembolic events and thrombotic microangiopathy for platelet count, serum creatinine, LDH, and peripheral blood smear analysis of schistocytes within 24−48 hours of initial bypassing agent use. A plasma sample can also be provided for local laboratory monitoring of fibrinogen and D-dimer. For patients who require multiple doses of bypassing agents, laboratory monitoring is recommended every 24−48 hours thereafter until 24−48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded in the Unscheduled Visit eCRFs.*

Appendix 2-A
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm A, QW) [a]

Schedule of Assessments–Arm A (QW)																		
	Screen-ing	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Q8W from Wk 33	Wk 49	Q12W from Wk 61	Daily/ weekly	Study Comp./ ET [b]	Safety F/U Visit [c]
PK assessment [d]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Anti-emicizumab antibodies [e]		x				x		x	x	x	x	x	x	x	x		x	x
PD biomarkers Set 1 [f, g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
PD biomarkers Set 2 [g, h]		x										x					x	x
Anti-FVIII antibodies [i]	x	x		x					x			x	x	x	x		x	x

ADA = anti-drug antibody; CWA = clot waveform analysis; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = factor XIII; PD = pharmacodynamic; PK = pharmacokinetic; Q2W = every 2 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; QW = every week; study comp = study completion; VWF = von Willebrand factor; Wk = week.

Note: Blood samples should always be drawn pre-dose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed within ±2 days of the scheduled visits.

[a] If Arm B is switched to a Q2W dosing schedule in the future (based on emerging global data), the schedule for a QW dosing schedule is also applicable to a Q2W dosing schedule.

[b] Study completion visit for PK, PD biomarker, and ADA sample collection is defined as when either the patient completed the study as defined in Section 3.2 or after the last patient completed 24 weeks of treatment with emicizumab, whichever occurs first. *Sample collection has stopped since March 2021.*

[c] Anti-emicizumab antibody blood samples may also be drawn if a hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[d] Emicizumab concentration. Plasma samples for this assessment should be taken prior to injection. Patients will be dosed at the clinics (self-administration) on days where trough plasma samples are to be collected.

[e] Anti-emicizumab antibody blood samples may also be drawn if a hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[f] Set 1: Standard aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, D-dimer, pro-thrombin fragment 1.2.

Appendix 2-A (cont.)
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm A, QW) [a]

[g] PD samples will be citrate plasma. Biomarker assays will include, but are not limited to, those listed. Additional samples will be frozen and banked for future exploratory research related to emicizumab, which may include coagulation tests such as CWA and others. Blood volumes and processing procedures will be specified in the Central Laboratory Services Manual. Unscheduled samples might be taken at the discretion of the investigator, while on emicizumab. Reasons for unscheduled samples may include evaluation or treatment for bleeds or hypersensitivity reactions.

[h] Set 2: FXIII activity (will only be run at baseline), VWF antigen, fibrinogen.

[i] Starting at Week 1, all anti-FVIII antibodies will be measured at a central laboratory using an aliquot of the citrate plasma collected for PD biomarker assessments. Local tests for anti-FVIII antibodies will not work after the first dose of study drug, as emicizumab interferes with all forms of the Bethesda assay. Please consult the Central Laboratory Services Manual for details.

Appendix 2-B
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm B, Q4W)

Schedule of Assessments: Arm B Q4W															
	Screen-ing	Treatment Period											From Wk 25 to Study Comp.	Study Comp./ET [a]	Safety F/U Visit
Week		1	2	3	4	5	7	9	13	17	21	25			
Emicizumab PK		x	x	x	x	x		x	x	x	x	x	Q12W	x	x
Anti-emicizumab antibody [b]		x				x		x	x	x	x	x	Q12W	x	x
PD biomarker set 1 [c, d]		x	x	x	x	x		x	x	x	x	x	Q12W	x	x
PD biomarker set 2 [d, e]		x										x		x	x
Anti-FVIII antibodies [f]	x	x						x		x		x	Q12W	x	x

ADA = anti-drug antibody; CWA = clot waveform analysis; ET = early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = Factor XIII; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q12W = every 12 weeks; study comp. = study completion; VWF = von Willebrand factor; Wk = week.

Note: Blood samples should always be drawn pre-dose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include, but are not limited to, those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed within ± 2 days of the scheduled visits.

[a] Study completion visit for PK, PD biomarker, and ADA sample collection is defined as when either the patient completed the study as defined in Section 3.2 or after the last patient completed 24 weeks of treatment with emicizumab, whichever occurs first. *Sample collection has stopped since March 2021.*

[b] Anti-emicizumab antibody blood samples may also be drawn if a hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[c] Set 1: Standard aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, D-dimer, pro-thrombin fragment 1.2.

Appendix 2-B (cont.)
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm B, Q4W)

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[d] PD samples will be citrate plasma. Biomarker assays will include, but are not limited to, those listed. Additional samples will be frozen and banked for future exploratory research related to emicizumab, which may include coagulation tests such as CWA and others. Blood volumes and processing procedures will be specified in the Central Laboratory Services Manual. Unscheduled samples might be taken at the discretion of the investigator, while on emicizumab. Reasons for unscheduled samples may include evaluation or treatment for bleeds or hypersensitivity reactions.

[e] Set 2: FXIII activity (will only be run at baseline), VWF antigen, fibrinogen.

[f] Starting at Week 1, all anti-FVIII antibodies will be measured at a central laboratory using an aliquot of the citrate plasma collected for PD biomarker assessments. Local tests for anti-FVIII antibodies will not work after the first dose of study drug, as emicizumab interferes with all forms of the Bethesda assay. Please consult the Central Laboratory Services Manual for details. Anti-FVIII antibodies will be collected for central analysis at Week 1, Week 25, every 12 weeks starting from Week 25, and at the completion visit for all patients. Testing at Week 9 and Week 17 for non-inhibitor patients only.

Appendix 2-C
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm C, at Time of Switch to Emicizumab)

Arm C, at Time of Switch to Emicizumab														
Week	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 31	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	From Wk 61	Study Comp./ET [a]	Safety F/U Visit
Emicizumab PK	x	x	x	x	x		x	x	x	x	x	Q12W	x	x
Anti-emicizumab antibody [b]	x				x		x	x	x	x	x	Q12W	x	x
PD biomarker Set 1 [c, d]	x	x	x	x	x		x	x	x	x	x	Q12W	x	x
PD biomarker Set 2 [d, e]	x										x		x	x
Anti-FVIII antibodies [f]	x						x		x		x	Q12W	x	x

ADA = anti-drug antibody; CWA = clot waveform analysis; ET=early termination; F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; FXIII = Factor XIII; PD = pharmacodynamic; PK = pharmacokinetic; Q12W = every 12 weeks; study comp.=study completion; VWF = von Willebrand factor; Wk = week.

Note: Blood samples should always be drawn pre-dose (if taken on days of emicizumab administration); consult the Sample Handling Manual for details. PD biomarker tests will include, but are not limited to those listed here. In order to characterize pharmacokinetics, it is mandatory that assessments are being performed within ± 2 days of the scheduled visits.

[a] Study completion visit for PK, PD biomarker, and ADA sample collection is defined as when either the patient completed the study as defined in Section 3.2 or after the last patient completed 24 weeks of treatment with emicizumab, whichever occurs first. *Sample collection has stopped since March 2021.*

[b] Anti-emicizumab antibody blood samples may also be drawn if a hypersensitivity event occurs or on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[c] Set 1: Standard aPTT, PT, FVIII activity, thrombin generation, FIX antigen, FX antigen, D-dimer, pro-thrombin fragment 1.2.

Appendix 2-C (cont.)
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples
(Arm C, at Time of Switch to Emicizumab)

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[d] PD samples will be citrate plasma, EDTA plasma, or serum. Biomarker assays will include, but are not limited to, those listed. Additional samples will be frozen and banked for future exploratory research related to emicizumab, which may include coagulation tests such as CWA and others. Blood volumes and processing procedures will be specified in the Central Laboratory Services Manual. Unscheduled samples might be taken at the discretion of the investigator, while on emicizumab. Reasons for unscheduled samples may include evaluation or treatment for bleeds or hypersensitivity reactions.

[e] Set 2: FXIII activity (will only be run at baseline), VWF antigen, fibrinogen.

[f] Starting at Week 1, all anti-FVIII antibodies will be measured at a central laboratory using an aliquot of the citrate plasma collected for PD biomarker assessments. Local tests for anti-FVIII antibodies will not work after the first dose of study drug, as emicizumab interferes with all forms of the Bethesda assay. Please consult the Central Laboratory Services Manual for details. Anti-FVIII antibodies will be collected for central analysis at Week 25, Week 49, every 12 weeks starting from Week 49, and at the completion visit for all patients. Testing at Week 33 and Week 41 for non-inhibitor patients only.

Appendix 2-D
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm D, QW)

Schedule of Assessments: [a] Arm D QW																	
	Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Q8W from Wk 33	Wk 49	Q12W from Wk 61	Study Comp/ ET [b]	Safety F/U Visit
Anti-FVIII antibodies [c, d]	x	x		x					x			x	x	x		x	
Anti-emicizumab antibodies [c, e, f]		x				x		x	x	x	x	x	x	x		x	
PK assessment [c, e, g]		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
PD biomarkers Set 1 [c, e, h, i]		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
PD biomarkers Set 2 [c, e, h, j, k]		x										x				x	

F/U = follow-up; FIX = factor IX; FVIII = factor VIII; FX = factor X; PD = pharmacodynamic; PK = pharmacokinetic; Q12W = every 12 weeks; study comp = study completion; Wk = Week.

Notes: On treatment days, pre-injection blood collection should be made 0–120 minutes before the injection.

[a] All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). All PD samples will be citrate plasma.

[b] *Collection of PK/ADA/Biomarker samples from Arm D patients will stop when the patient completes the study or after Week 49, whichever occurs first.*

[c] When blood is drawn via catheter or CVAD, a discard tube must be used prior to collection of samples for any laboratory assessment, due to the possibility of contamination by saline or anticoagulants used to flush the device. Please consult the study Laboratory Manual for details on sample collection and processing.

[d] Anti-FVIII antibodies will be measured at a central laboratory using citrate plasma. Anti-FVIII antibodies is the only biomarker sample taken at screening. In case a patient screen fails or does not enroll in the study for any reason, the sample should be destroyed and not sent to the central laboratory. Throughout the study, additional blood samples may also be drawn on an unscheduled basis (at the clinical judgment of the investigator) for analysis at a central laboratory. Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.

Appendix 2-D (cont.)
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (Arm D, QW)

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[e] In case of up-titration, additional assessments including PK, PD biomarkers, anti-emicizumab antibodies, safety laboratory samples, and ECG will be required, with the schedule of assessments resetting back to Week 1, including an ECG.

[f] Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab injection at Weeks 1, 5, 9, 13, 17, 21, 25, 33, 41, 49, and every 12 weeks starting from Week 61, study completion/early termination and at the 24-week safety follow-up visit. If patients continue on emicizumab past 49 weeks of treatment, anti-emicizumab antibodies will be collected every 12 weeks. If any of these samples are positive and/or if there is suboptimal clinical response or low pharmacokinetic exposure, additional samples may be collected and analyzed for anti-emicizumab antibodies. Anti-emicizumab antibodies should also be drawn at the time of systemic hypersensitivity events. For each additional anti-emicizumab sample, a PK sample should be concomitantly drawn.

[g] Emicizumab concentration. Plasma samples for this assessment should be taken prior to emicizumab injection.

[h] PD biomarkers will be measured at a central laboratory. Blood samples may also be drawn to conduct biomarker assays at the central laboratory on an unscheduled basis (at the clinical judgment of the investigator) at any time.

[i] PD set 1: PT/INR, D-Dimer, aPTT (Stago), fibrinogen.

[j] PD set 2: FVIII activity% (Biophen).

[k] These plasma samples will only be collected if the permitted blood volumes allow (based on patient body weight as described in Section 3.3.6). Please refer to the Laboratory Manual for details.

Appendix 3
Haem-A-QoL (United States/English)

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Trial ID: Page 1/7

VISIT X

Centre ID/No.: |_|_|_|

Subject No.: |_|_|_|_|_|_|

Visit Date: |_|_|_|_|_|_|_|_| D D M M M Y Y Y Y

HAEM-A- QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please be so kind as to answer the following questions in this questionnaire, designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- ⇨ Please read each question carefully.
- ⇨ Think about how things have been for you over the past weeks.
- ⇨ Put an "X" in the box corresponding to the answer that fits you best.
- ⇨ Only mark one box for each question.
- ⇨ There are no right or wrong answers.
- ⇨ It's what you think that matters.
- ⇨ There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: __ / __ / __ (month/ day/ year)

Trial ID: Page 2/7

VISIT X

Subject No.: ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋

1. Here we would like to find out about hemophilia and your PHYSICAL HEALTH

	In the past month...	never	rarely	sometimes	often	all the time
1.	... my swellings hurt	☐	☐	☐	☐	☐
2.	... I had pain in my joints	☐	☐	☐	☐	☐
3.	... it was painful for me to move	☐	☐	☐	☐	☐
4.	... I had difficulty walking as far as I wanted to	☐	☐	☐	☐	☐
5.	... I needed more time to get ready because of my condition	☐	☐	☐	☐	☐

2. and now about how you have been FEELING because of your hemophilia

	In the past month...	never	rarely	sometimes	often	all the time
1.	... my hemophilia was a burden for me	☐	☐	☐	☐	☐
2.	... my hemophilia made me angry	☐	☐	☐	☐	☐
3.	... I was worried because of my hemophilia	☐	☐	☐	☐	☐
4.	... I felt excluded	☐	☐	☐	☐	☐

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

Trial ID: Page 3/7

VISIT X

Subject No.: |_|_|_|_|_|_|

3. How does hemophilia affect your VIEW OF YOURSELF?

In the past month...	never	rarely	sometimes	often	all the time
1. ... I envied healthy people my age	☐	☐	☐	☐	☐
2. ... I felt comfortable with my body	☐	☐	☐	☐	☐
3. ... hemophilia made my life more difficult	☐	☐	☐	☐	☐
4. ... I felt different from others because of my hemophilia	☐	☐	☐	☐	☐
5. ... I was able not to think all the time about my hemophilia	☐	☐	☐	☐	☐

4. These questions are about SPORTS AND LEISURE

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I had to avoid sports like football	☐	☐	☐	☐	☐	☐
3. ... I played sports just as much as others	☐	☐	☐	☐	☐	☐
4. ... I didn't have the freedom to travel where I wanted	☐	☐	☐	☐	☐	☐
5. ... it was necessary for me to plan everything in advance	☐	☐	☐	☐	☐	☐

HAEM-A-QOL - USA/English - Final version - 29 Jun 07 -

Trial ID: Page 4/7

VISIT X

Subject No.: |_|_|_|_|_|_|

5. These questions are about WORK AND SCHOOL

In the past month...	never	rarely	some-times	often	all the time	not applicable
1. ... I was able to go to work/school regularly in spite of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I was able to work/study like healthy colleagues	☐	☐	☐	☐	☐	☐
3. ... my everyday work/school activities were jeopardized by my hemophilia	☐	☐	☐	☐	☐	☐
4. ... I found it difficult to pay attention at work/school because I was in pain	☐	☐	☐	☐	☐	☐

6. The next questions are about DEALING WITH HEMOPHILIA

In the past month...	never	rarely	sometimes	often	all the time
1. ... I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2. ... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
3. ... I was able to control my bleeds	☐	☐	☐	☐	☐

Trial ID: Page 5/7

VISIT X

Subject No.: |_|_|_|_|_|_|

7. and what about your TREATMENT?

In the past month...	never	rarely	sometimes	often	all the time
1. ... I was dependent on the factor concentrate because of my hemophilia	☐	☐	☐	☐	☐
2. ... I was dependent on physicians for the treatment of my hemophilia	☐	☐	☐	☐	☐
3. ... I was annoyed about the amount of time spent having the injections	☐	☐	☐	☐	☐
4. ... I felt the injections interrupted my daily activities	☐	☐	☐	☐	☐
5. ... I was afraid of complications	☐	☐	☐	☐	☐
6. ... I had problems with how my treatment was administered	☐	☐	☐	☐	☐
7. ... I was afraid that in case of emergency, other doctors wouldn't know how to treat hemophilia	☐	☐	☐	☐	☐
8. ... I was satisfied with the hemophilia center	☐	☐	☐	☐	☐

Trial ID: Page 6/7

VISIT X

Subject No.: |_|_|_|_|_|_|

8. What do you think about the FUTURE?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been thinking that it will be difficult for me to lead a normal life	☐	☐	☐	☐	☐
2. ... I have been expecting that things will get better in the future	☐	☐	☐	☐	☐
3. ... I have been worrying that my condition is worsening	☐	☐	☐	☐	☐
4. ... my life plans have been influenced by my hemophilia	☐	☐	☐	☐	☐
5. ... I have been afraid that I will need a wheelchair	☐	☐	☐	☐	☐

9. The next questions are about hemophilia and your FAMILY PLANNING

Recently...	never	rarely	some-times	often	all of the time	not applicable
1. ... I have had difficulties having children	☐	☐	☐	☐	☐	☐
2. ... I have been afraid that I cannot have children	☐	☐	☐	☐	☐	☐
3. ... I have been afraid that I will not be able to take care of my children	☐	☐	☐	☐	☐	☐
4. ... I have been worrying about not being able to raise a family	☐	☐	☐	☐	☐	☐

Trial ID:	Page 7/7
VISIT X	
Subject No.:	

10. What about PARTNERSHIP AND SEXUALITY?

Recently...	never	rarely	sometimes	often	all the time
1. ... I have been finding it difficult to date because of my hemophilia	☐	☐	☐	☐	☐
2 ... I have been insecure in my relationships with women because of my hemophilia	☐	☐	☐	☐	☐
3. ... I haven't been able to have a normal relationship because of my hemophilia	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

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Appendix 4
Haemo-QoL-SF (United States/English)

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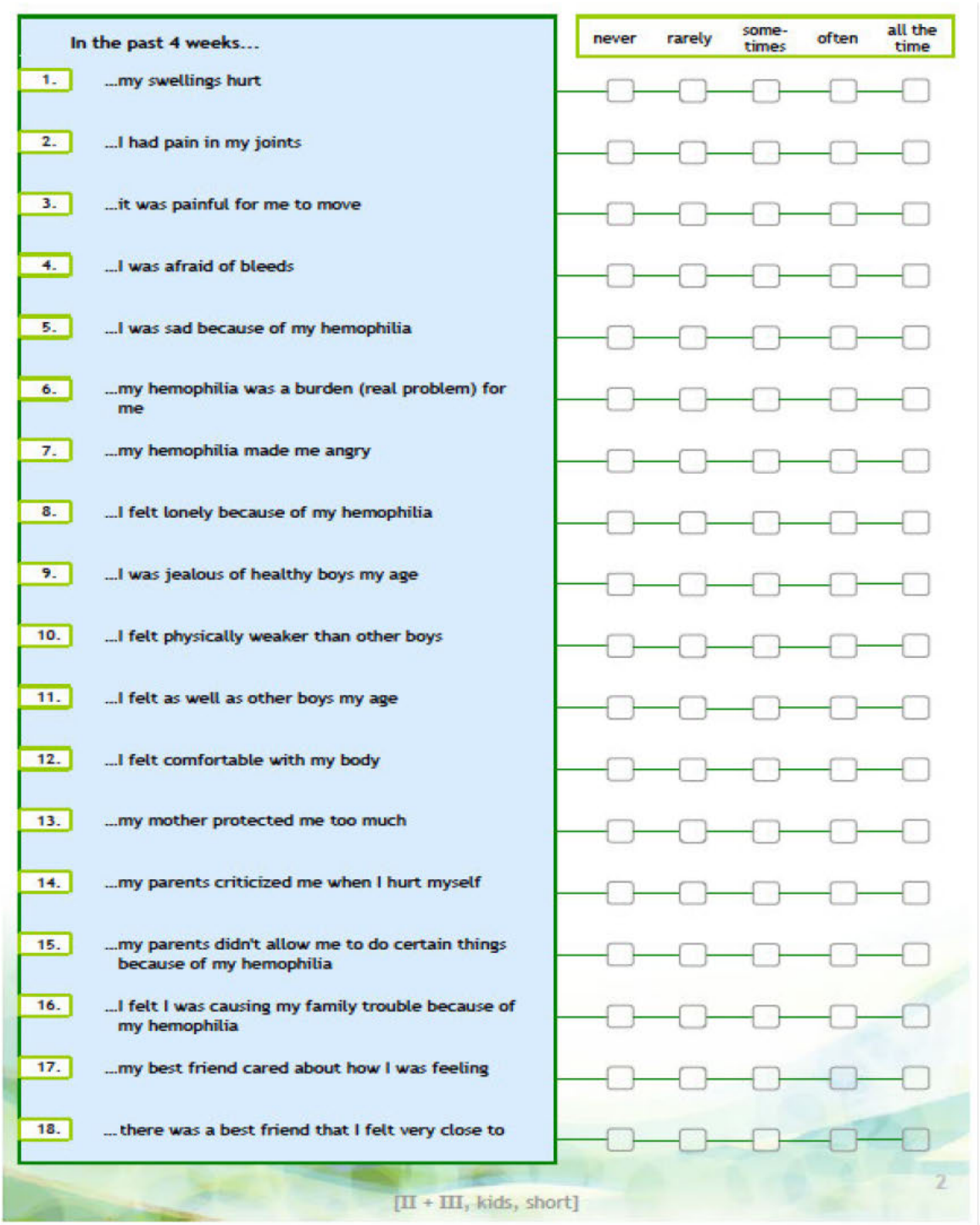

In the past 4 weeks...	never	rarely	some-times	often	all the time
19. ...my friends took care of me when I felt bad	☐	☐	☐	☐	☐
20. ...I felt different from others because of my hemophilia	☐	☐	☐	☐	☐
21. ...other kids teased me because of my hemophilia	☐	☐	☐	☐	☐
22. ...people behaved differently towards me because of my hemophilia	☐	☐	☐	☐	☐
23. ...I felt left out when others did things together	☐	☐	☐	☐	☐
24. ...I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐
25. ...I had to do indoor activities more than other kids because of my hemophilia	☐	☐	☐	☐	☐
26. ...I had to avoid sports like football or skateboarding	☐	☐	☐	☐	☐
27. ...I played sports just as much as any other kid	☐	☐	☐	☐	☐
28. ...I felt that my hemophilia problems were under control	☐	☐	☐	☐	☐
29. ...hemophilia was a normal part of my life	☐	☐	☐	☐	☐
30. ...I felt healthy even with my hemophilia	☐	☐	☐	☐	☐
31. ...I accepted having hemophilia	☐	☐	☐	☐	☐
32. ...the treatment I got was okay	☐	☐	☐	☐	☐
33. ...I disliked visiting the hemophilia center	☐	☐	☐	☐	☐
34. ...the injections bothered me	☐	☐	☐	☐	☐
35. ...I was annoyed about the amount of time spent having the injections	☐	☐	☐	☐	☐

3

[II + III, kids, short]

Appendix 5
EQ-5D-5L (United Kingdom/English)

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Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

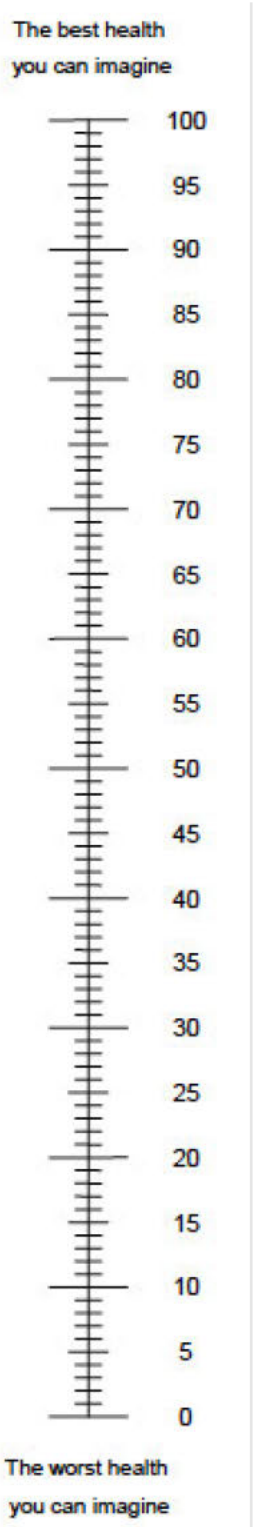
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6
Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English)

Adapted Inhib-QoL Questionnaire Screens

Dear Caregiver,

We have put together some questions, which we would like you to answer. The questionnaire was made for caregivers of hemophilic children with inhibitors.

We really appreciate you taking the time to complete this questionnaire. The questionnaire is divided into two parts; first, we would like to know your opinion on how your child's situation is; second, we want to ask you how your child's situation is for you.

We would like to understand more about the life of children with inhibitors and their families.

For the following questions please follow the instructions below:

- Read each question carefully.
- Check the box corresponding to the answer that best fits your child/you.

All your answers will be treated with the strictest confidence!

IN THE FIRST PART, WE WOULD LIKE TO KNOW HOW YOUR CHILD'S SITUATION IS.

Question Text	Response Values
About hemophilia and physical health	
In the past 4 weeks... my child's swellings hurt	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... my child had pain in his joints	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... it was painful for my child to move	0=never 1=seldom 2=sometimes 3=often 4=all the time

Appendix 6 (cont.): Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English)

Question Text	Response Values
In the past 4 weeks... my child's joints were stiff	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... my child had bleeds	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... my child had bruises	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... my child could not sleep during the night because of pain	0=never 1=seldom 2=sometimes 3=often 4=all the time
About your child's treatment	
In the past 4 weeks... my child had to go to the hospital	0=never 1=seldom 2=sometimes 3=often 4=all the time
In the past 4 weeks... my child was afraid of needles	0=never 1=seldom 2=sometimes 3=often 4=all the time

Appendix 6 (cont.): Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English)

IN THIS SECOND PART, WE WOULD LIKE TO ASK YOU HOW YOU PERCEIVE YOUR CHILD'S SITUATION.

Question Text	Response Values
In the past 4 weeks... my child's joints were stiff	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... my child had bleeds	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... my child had bruises	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... my child could not sleep during the night because of pain	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
About your child's treatment	
In the past 4 weeks... my child had to go to the hospital	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... my child was afraid of needles	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
Question Text	Response Values
In the past 4 weeks... I felt the need to supervise him when he was playing with others	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... I was scared when he played with others	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks...	0 = never

Appendix 6 (cont.): Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English)

I would have been grateful for psychological support from the hemophilia center	1 = seldom 2 = sometimes 3 = often 4 = all the time
Here we would like to know how you perceive your child's treatment.	
In the past 4 weeks... his treatment did not interfere with our everyday life	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... it was easy to prepare the injection	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... I was satisfied with the amount of time it takes to administer the medication	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... I was satisfied with how often my child must be treated	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... the medication did not cause my child any discomfort	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
Question Text	Response Values
In the past 4 weeks... my child did not worry about receiving his medication	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... I felt like my child was a guinea pig	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
Here we would like to know how your family life is, in your opinion.	
In the past 4 weeks... our life has been out of control due to his hemophilia	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time

Appendix 6 (cont.): Adapted Inhibitor-Specific Quality of Life (Inhib-QoL) with Aspects of Caregiver Burden (United States/English)

In the past 4 weeks... his hemophilia impacted family plans (e.g., travels, vacations	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... my child's relatives had the wrong attitude towards him	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... our family worried when he was afflicted	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
About hemophilia and your child's siblings	
Does your child have siblings?	1 = Yes 0 = No
In the past 4 weeks... my child's sibling/s were jealous of him	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
Question Text	**Response Values**
How is the contact with others?	
In the past 4 weeks... I avoided visiting other people because I was worried how they would react towards my child	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
In the past 4 weeks... I preferred to stay at home with my child to avoid problems	0 = never 1 = seldom 2 = sometimes 3 = often 4 = all the time
Missing school/daycare questions	
Did your child miss any days of daycare or school due to hemophilia in the past 4 weeks...?	1 = Yes 0 = No -1 = My child was not enrolled in daycare or school
How many days of daycare or school did your child miss due to hemophilia in the past 4 weeks...?	Range: 1–28
How many days of daycare or school was your child expected to attend in the past 4 weeks...?	Range: If SCHDAY1N is null then 1–28 else SCHDAY1N - 28

Appendix 7
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.[1] 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 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, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

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

   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure*
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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[1] 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.

* Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix 8
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	75,000–99,999/mm^3	5,0000–74,999/mm^3	20,000–49,999/mm^3	$<$20,000/mm^3
Prothrombin time	1.01–1.25 $\times$ ULN	1.26–1.5 $\times$ ULN	1.51–3.0 $\times$ ULN	$>$3 $\times$ ULN
Activated partial thromboplastin	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 8 (cont.): WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

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 8 (cont.): WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

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 inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization	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	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 8 (cont.): WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

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 8 (cont.): WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

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	37.7–38.5 C or 100.0–101.5 F	38.6–39.5 C or 101.6–102.9 F	39.6–40.5 C or 103–105 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 8 (cont.): WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

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

Appendix 9
Guidelines for Dosing and Monitoring Bypassing Agents for Patients on Emicizumab

The use of bypassing agents is not expected in hemophilia A patients without inhibitors. For completeness, this appendix includes guidelines provided for treatment of breakthrough bleeds in patients with inhibitors. Careful consideration of the risks and potential benefits is advised when combining emicizumab, factor VIII (FVIII), and bypassing agent.

Drugs intended to control bleeds, including bypassing agents, should be used at the lowest dose expected to achieve hemostasis. Given that circulating emicizumab may increase patients' coagulation potential, the doses required to achieve hemostasis may be lower than the FVIII or bypassing agent doses used prior to starting the study.

Caution should be taken for patients who are using recombinant activated factor VII (rFVIIa [e.g., consideration of using no more than 90 μg/kg of rFVIIa as an initial dose]).

Use of activated prothrombin complex concentrate (aPCC) or PCC in combination with emicizumab should be avoided completely in patients who have the option of using other bypassing agents to treat bleeds. In the event that aPCC/PCC is the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than 50 units/kg of aPCC/PCC to be administered as an initial dose.

Other bypassing agents (e.g., Byclot®) should be avoided. In cases where such agents are the only available bypassing agent, the lowest dose expected to achieve hemostasis should be prescribed, with no more than the lowest dose described in the prescribing information to be administered as an initial dose (e.g., no more than 60 μg/kg of Byclot®).

Exact dose and schedule of bypassing agents should be discussed with patients at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC/PCC, or other bypassing agents should be performed only under medical supervision, which includes laboratory monitoring by additional local and central laboratory assessments, and consideration should be given to verifying bleeds prior to repeated dosing. Caution should be taken if anti-fibrinolytics are used in conjunction with rFVIIa in patients receiving emicizumab. The use of anti-fibrinolytics in conjunction with aPCC/PCC or Byclot® is prohibited.

MONITORING

In the event of a bleed treated with bypassing agents, the following local laboratory tests will be performed within 24–48 hours of initial bypassing agent use so the investigator may monitor for of potential thromboembolic events and thrombotic microangiopathy: platelet count, serum creatinine, LDH, and peripheral blood smear analysis to evaluate

for schistocytes. A plasma sample should also be provided for local laboratory monitoring of fibrinogen and D-dimer. For patients who require multiple doses of bypassing agents, laboratory monitoring should be performed every 24–48 hours thereafter until 24–48 hours following the last dose of bypassing agents administered to treat a given bleed. If applicable, laboratory results should be recorded in the Unscheduled Visit electronic Case Report Forms (eCRFs).

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