

Official Title: A MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO
EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS
OF SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN
HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS

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PROTOCOL

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MEDICAL MONITOR: [REDACTED] M.D., M.A.S.

SPONSOR: F. Hoffmann-La Roche Ltd and
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[REDACTED]	Company Signatory	01-Sep-2017 18:27:12

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Emicizumab—F. Hoffmann-La Roche Ltd
Protocol BH29992, Version 4

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BH29992 has been primarily amended to evaluate additional emicizumab dosing schedules and to update safety information. Changes to the protocol, along with a rationale for each change, are summarized below:

- Two cohorts (designated as Cohorts B and C; patients 2–11 years of age) have been added to the study to investigate additional less frequent emicizumab dosing schedules (every 2 weeks [Q2W] and every 4 weeks [Q4W]), which would allow the option to select a preferred schedule, while still delivering the same cumulative dose (Sections 1.3, 3.3.1, 3.3.1.1, and 6.9.1.1). The addition of these cohorts is reflected throughout the protocol (Sections 1–6).
- Recent safety findings of thrombotic microangiopathy (TMA) observed in Study BH29884 have been added (Sections 1.2, 3.1, and 5.1.1.4).
- Clarification regarding laboratory monitoring of coagulation status after any bypassing agent use has been added. Laboratory monitoring is to be done after any use of a bypassing agent, and not only after use of a bypassing agent to treat breakthrough bleeds (Section 5.1.2).
- An exclusion criterion has been added for patients who are unable to or unwilling to receive blood or blood products (or any standard-of-care treatment for a life-threatening condition). This criterion has been added in context of a fatal outcome from a life-threatening rectal hemorrhage in Study BH29884 in a patient who declined receipt of blood and blood products (Sections 4.3 and 5.1.1.4).
- The up-titration schema has been modified with removal of the 2.25-mg/kg once weekly (QW) dosing level. This is based on an interim data review characterizing exposure at 1.5 mg/kg QW in patients 2–12 years of age to be similar to adolescent/adult patients (Section 4.5.2). As such, the up-titration dose will be the same used in adolescent/adult patients (3 mg/kg QW).
- A new safety risk associated with emicizumab has been added as follows:
 - Life-threatening bleeding due to unreliable standard coagulation tests and inhibitors assays in the setting of emicizumab
 - Coagulation laboratory tests (including, but not limited to, aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable and are impacted by the presence of emicizumab and, therefore, are not reflecting the patient's underlying hemostatic status accurately (Section 5.1.1.5).
- The reporting of the term “sudden death” has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Event reporting for hospitalization has been clarified (Section 5.3.5.11).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).

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

PROTOCOL AMENDMENT, VERSION 4: SUMMARY OF CHANGES

PROTOCOL TITLE

The protocol title has been revised as follows:

A SINGLE-ARM, MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ONCE-WEEKLY SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2: BACKGROUND ON EMICIZUMAB

Clinical Studies

... Two severe adverse events were observed: appendicitis and mesenteric hematoma. Both events were considered to be serious adverse events and not related to emicizumab administration. In the Phase I/II Studies ACE001JP and ACE002JP, no *thrombotic microangiopathy (TMA)*, thromboembolic adverse events, or systemic hypersensitivity reactions have been reported in any dosing cohort thus far, including those patients who required concomitant FVIII concentrates or bypassing agent therapy to treat bleeds.

In the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), as of November-April 2017, TMA thrombotic microangiopathy (TMA; atypical hemolytic uremic syndrome [aHUS]) was observed in 32 patients receiving emicizumab and bypassing agents; and 32 cases of serious thromboembolic events were observed in 2 patients receiving emicizumab and bypassing agents. For more details refer to Sections 5.1.1.3 and 5.1.1.4.

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

... In these studies, no thromboembolic or systemic hypersensitivity adverse events were observed; however, in the ongoing Phase III Study BH29884, 32 cases of TMA (aHUS) and 2-3 serious thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Three-Four out of these 54 patients have fully recovered and the fourth patient's condition has improved, and 1 patient died due to severe rectal bleeding (see Sections 5.1.1.3 and 5.1.1.4).

This current study is designed to evaluate the efficacy, safety, and pharmacokinetics of emicizumab administered subcutaneously initially once weekly (QW) in pediatric patients with hemophilia A with FVIII inhibitors. Following review of data in adult and adolescent patients with hemophilia A from two ongoing Phase III studies

evaluating emicizumab at 3 mg/kg every 2 weeks (Q2W; BH30071) and 6 mg/kg every 4 weeks (Q4W; BO39182), this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients (see Section 3.3.1).

SECTION 2: OBJECTIVES AND ENDPOINTS

The objectives of the study are to investigate (with no formal hypothesis testing) the efficacy, safety, and pharmacokinetics of ~~once-weekly SC administration of emicizumab administered at 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W~~ in pediatric patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents. *A total of approximately 80 patients are planned: approximately 60 patients in Cohort A (1.5 mg/kg QW) and approximately 10 patients each in Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W). At least 20 patients younger than 12 years old of age and up to 60 patients are planned for enrollment, with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent to further evaluate dosing of emicizumab in patients <40 kg. Of note, enrollment in Cohort A may be left open exclusively for patients <2 years of age until approximately 5 such patients have been enrolled.*

SECTION 2.1: EFFICACY OBJECTIVES

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The efficacy objectives for this study are as follows:

- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate) *
- To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate (intra-patient comparison, *Cohort A only, as patients enrolled in Cohorts B and C will not have previously participated in the non-interventional study*) *
- To characterize the efficacy of up-titration on ~~an both an intra-patient and population-level, also-based~~ on the basis of the number of bleeds over time *
- To evaluate the HRQoL of children 8–17 years of age according to Haemo-QoL-Short Form (SF) (completed by patients)
- To evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)
- To assess the number of days missed from daycare/school and days hospitalized

* Analyses will be performed for: treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

SECTION 2.2: SAFETY OBJECTIVE

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

SECTION 2.3: PHARMACOKINETIC OBJECTIVE

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W).

The PK objective for this study is to characterize the exposure (C_{trough}) of emicizumab in patients receiving 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W prior to drug administration on Day 1 and at the following timepoints: ...

SECTION 3.1: DESCRIPTION OF THE STUDY

This ~~single-arm, non-randomized~~, multicenter, open-label, Phase III clinical study will enroll children with hemophilia A who have inhibitors against FVIII. Children with hemophilia A and documented historical FVIII inhibitor titer (≥ 5 BU) must currently be receiving treatment with bypassing agents. At least ~~2040~~ patients younger than 12 years of age and up to ~~approximately 8060~~ patients are planned for enrollment, with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent. Patients will receive ~~weekly~~ SC doses of emicizumab *at 1.5 mg/kg QW (Cohort A)* for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see Figure 1). After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study.

Because of the uncertainty of the dosing regimen needed in patients < 12 years of age or < 40 kg to achieve similar exposure as in adults and adolescents, this study will *first* evaluate the appropriate dosing regimen in children by starting with the same *weekly* dosing regimen (1.5 mg/kg QW) being evaluated in the Phase III study (BH29884) in adult/adolescent patients with hemophilia A with inhibitors (see Section 3.3.1 for details). Emicizumab will be administered with a ~~weekly~~ loading dose of 3-0 mg/kg QW for the first 4 weeks ~~(Day 1 of each week)~~ followed by a maintenance dose of 1.5 mg/kg ~~week (Day 1 of each week) QW (Cohort A) for the remainder of the treatment period.~~ During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab. ~~Investigators will monitor patients regularly with the guidance of an up-titration algorithm (see Section 4.5.2). Should patients meet protocol-defined criteria for efficacy-guided up-titration, the investigator will contact the Medical Monitor to initiate a discussion about possible up-titration (see Section 4.5.2).~~

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg ~~QW/week~~) after the first 3–5 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks. ...

Furthermore, should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose (Cohort A). After the JMC recommendations are released following both interim data reviews, the study will continue to enroll in Cohort A up to a maximum of approximately 60 patients.

Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Recruitment to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via IxRS, for a total of approximately 10 patients per cohort. Of note, enrollment to Cohorts B and C will be limited to patients 2–11 years of age. Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 3 mg/kg Q2W (Cohort B) and 6mg/kg Q4W (Cohort C) for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see Figure 1). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab.

The entire study will enroll up to approximately 80 patients with allowance for additional patients <2 years of age in Cohort A.

A patient who fulfills the inclusion and exclusion criteria should be enrolled at the Week 1 visit. Prophylactic use of bypassing agents should be discontinued ~~by the time~~ the day before the first dose of emicizumab is given.

FIGURE 1: Study Schema

Figure 1 has been revised to reflect changes made to the study design.

The primary analysis ~~for all cohorts~~ will be performed 52 weeks after ~~the last~~ all patients in the primary ~~cohort~~ population of Cohort A ~~has~~ have been enrolled or withdrawn prematurely, whichever occurs first. The primary population of eCohort A consists of all patients enrolled prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis of Cohorts A, B, and C. If no patients <2 years of age are included in the primary population of eCohort A, the primary analysis will still occur at the specified time; however, enrollment ~~in the study~~ to Cohort A may be left open exclusively for patients <2 years of age in order to enroll up to approximately 5 such patients. Note that these patients will be included in the primary analysis of eCohort A regardless of their follow-up time. Additionally, all available data from patients enrolled in Cohorts B and C (efficacy period approximately 6 months) will be included in the primary analysis of

Cohort A. Additionally, the protocol may be amended at a future date in order to study alternative dosing regimens (e.g., every 2 weeks, every 4 weeks) in pediatric patients.

During the study, caregivers will be asked to enter any individual bleeds, hemophilia-related medications, and emicizumab treatments that occur on an electronic, handheld device. Entries should be made at least weekly ~~to document emicizumab dosing, or~~ and also at any time a bleed occurs or a hemophilia medication, *including emicizumab*, is administered. ...

Emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred). Therefore, in this study all patients ~~may~~ will continue to receive episodic treatment for breakthrough bleeds as needed. ...

... However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 32 events of TMA and 32 *serious* thromboembolic events were observed in patients who concomitantly used ~~repeated doses of aPCC~~ *> 100 U/kg/day of aPCC on average for ≥ 24 hours* for the treatment of breakthrough bleeds (see Sections 1.2, 1.3, 5.1.1.3, and 5.1.1.4). ...

... Pediatric patients who are enrolled in the non-interventional Study BH29768 are eligible to enroll in this study, as long as they meet the inclusion and exclusion criteria and are able to enroll at a participating site while the study is open for enrollment. *All patients who participated in the non-interventional study will be enrolled in Cohort A.*

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

LENGTH OF STUDY

The length of the entire study from screening of the first patient to the last patient completing 52 weeks in the study and/or the end of study follow-up visit (24 weeks after discontinuing emicizumab) will be approximately ~~428~~152 weeks.

END OF STUDY

The primary analysis will take place at the same time for Cohorts A, B, and C. It will occur after all patients in the primary population of Cohort A have completed 52 weeks of treatment, or have withdrawn prematurely, whichever occurs first. All data from patients enrolled in Cohorts B and C will be included regardless of follow-up time.

SECTION 3.3: RATIONALE FOR STUDY DESIGN

... The Sponsor has chosen a similar approach utilizing a ~~single-arm, non-randomized~~, descriptive study to investigate the pharmacokinetics, safety, and efficacy of emicizumab in pediatric hemophilia A patients with FVIII inhibitors. ...

... The proposed study, BH29992, will *therefore* evaluate the use of prophylactic emicizumab, in children with inhibitors to FVIII previously treated with bypassing agents in a *non-randomized, single-arm, multicenter, open-label* study.

SECTION 3.3.1: Rationale for Emicizumab Dose and Schedule

~~Once weekly~~ Loading doses of 3 mg/kg QW emicizumab for 4 weeks ~~will be~~, followed by a maintenance dose of 1.5 mg/kg ~~once weekly~~ QW ~~will be the initial dosing regimen in pediatric~~ for patients enrolled in Cohort A. Subsequent dose adaptation will be made as required based on efficacy and exposure, as detailed below.

... In light of the opposing effect of body weight and clearance maturation on the emicizumab exposure, and the uncertainty associated with the effect of clearance maturation, there is a possibility that the same dosing regimen in adolescent/adult and pediatric patients (i.e., ~~once weekly~~ loading doses of 3 mg/kg QW for 4 weeks, followed by a maintenance dose of 1.5 mg/kg QW ~~once weekly~~) provides the same efficacy trough of 45 µg/mL. Thus, Study BH29992 will evaluate the appropriate dosing regimen in children by starting with the same dosing regimen as the adult and adolescent study, BH29884.

Individual pediatric patients may have their dose up-titrated ~~after 12 weeks~~ if they experience suboptimal control of bleeding on emicizumab (see Section 4.5.2). ...

SECTION 3.3.1.1: Interim Analysis, JMC Recommendations, and Rationale for Enrollment of Q2W/Q4W in Pediatric Patients

The initial maintenance dose of 1.5 mg/kg QW was evaluated by the Study BH29992 JMC during an interim data review (clinical cutoff date: 28 October 2016). As enrollment occurred faster than anticipated, the two planned data review meetings were combined into one. All available data (including safety, efficacy, and pharmacokinetics) from the first 20 patients enrolled in Cohort A was assessed by the JMC to determine the appropriateness of the starting maintenance dose, as well as to decide whether the study could begin enrolling patients <2 years of age. On 7 December 2016, the JMC recommended continuing enrollment of patients in Cohort A at the maintenance dose of 1.5 mg/kg QW, as well as to open enrollment to patients < 2 years of age at that same maintenance dose. Since exposure at 1.5 mg/kg QW was similar between patients 3–12 years of age and adolescent/adult patients, the up-titration scheme for children has been modified to be the same as the one used in adolescent/adult patients, that is, individual up-titration to 3 mg/kg QW should they experience suboptimal control of bleeding on emicizumab (see Section 4.5.2).

Furthermore, two Phase III studies investigating 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) have been initiated in adolescent/adult patients with hemophilia A without inhibitors (BH30071) and with and without inhibitors (BO39182). All three dosing regimens are predicted to achieve similar exposure (in terms of steady-state average concentration, $C_{avg,ss}$; see Table 2), and despite higher peak concentrations and lower trough concentrations with less frequent dosing regimens, all are expected to result in similar treatment response (all three dosing regimens provide similar predicted ABR distribution) and safety profiles. Of note, the exposures achieved with these three dosing regimens remain well below the safe and well-tolerated

one achieved with the highest dose of 3 mg/kg QW (observed trough concentration of $120 \pm 26.8 \mu\text{g/mL}$). Ultimately, these three dosing regimens will provide the option for patients to receive emicizumab at different scheduled intervals, while still delivering the same cumulative dose.

TABLE 2: Simulated Median Pharmacokinetic Parameters

Table 2 has been added. Subsequent tables have been renumbered accordingly.

An independent Data Monitoring Committee (iDMC) conducted a scheduled review of the safety data in Study BH30071, which detected no unforeseen safety signals in adult/adolescent patients treated with emicizumab at 3 mg/kg Q2W. Meanwhile, an interim analysis of 6 mg/kg Q4W in a run-in cohort of 7 adolescent/adult patients in Study BO39182 indicated that observed PK parameters at 6 mg/kg Q4W were as expected, in line with earlier simulations. This study is ongoing with no safety concerns raised by the iDMC to date. Therefore in this current study, following completion of accrual to Cohort A (1.5mg/kg QW), enrollment to Cohorts B (3 mg/kg Q2W) and C (6 mg/kg Q4W) can commence.

The emicizumab regimens to be evaluated in this study consist of a loading dose of 3 mg/kg weekly for 4 weeks, followed by a maintenance dose administered either 1.5 mg/kg QW, 3 mg/kg every Q2W, or 6 mg/kg Q4W. Of note, a maintenance dose of 3 mg/kg QW may also be evaluated in the setting of patients who have their dose up-titrated.

SECTION 3.3.2: Rationale for Patient Population

... However, due to the current uncertainty of dosing in patients <40 kg (with some patients >12 years of age falling into this category), patients 12–17 years of age who weigh <40 kg will also be allowed to enroll (*in Cohort A*).

... Finally, pediatric patients <2 years of age with inhibitors treated with bypassing agents, and determined by investigator to be at high risk of bleed, will also be allowed to enroll (*in Cohort A*).

SECTION 3.3.3: Rationale for the Efficacy Analyses

The objective of the efficacy analysis is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate). Another efficacy analysis will also characterize the efficacy of up-titration on an intra-patient ~~and population~~ level. As mentioned in Section 3.1, the *primary* efficacy analysis will be performed 52 weeks after the last patient from the primary *population of Cohort A* has been enrolled or withdrawn prematurely, whichever occurs first. *Primary efficacy analyses for Cohorts B and C will occur at the time of the primary analysis for Cohort A. Additional efficacy analyses will be performed at the end of the study and as needed to support regulatory interactions.*

SECTION 4.1: PATIENTS

Approximately 80 The target population will be children < 12 years of age with hemophilia A and with FVIII inhibitors who have been previously treated with bypassing agents to control or prevent bleeds will be enrolled in the study (approximately 60 patients in Cohort A, 10 patients in Cohort B, and 10 patients in Cohort C). In addition to this primary population of children < 12 years of age, patients 12–17 years of age who weigh < 40 kg at the time of informed consent will also be eligible to enroll. These patients, as well as those < 2 years of age at the time of informed consent, will only be eligible to enroll in Cohort A. Of note, enrollment in Cohort A may be left open exclusively for patients < 2 years of age until approximately 5–10 such patients have been enrolled prior to the closure of Cohorts B and C, whichever occurs first.

SECTION 4.2: INCLUSION CRITERIA

- Children < 12 years of age at time of informed consent with allowance for the following:
 - Patients 12–17 years of age and who weigh < 40 kg at the time of informed consent (*Cohort A only*)
 - Patients < 2 years of age will be allowed to participate only after the protocol-defined interim data review criteria are met (*Cohort A only*)
- For patients < 2 years of age (*Cohort A only*): determined by investigator to be in high unmet medical need

SECTION 4.3: EXCLUSION CRITERIA

- 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)

SECTION 4.4: METHOD OF TREATMENT ASSIGNMENT

The study is ~~an~~ a non-randomized, open-label, Phase III, multicenter, ~~single-arm~~ study of emicizumab in pediatric patients < 12 years of age and 12–17 years of age who weigh < 40 kg with hemophilia A with inhibitors.

The study consists of three cohorts. Patients will receive an initial loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of either 1.5 mg/kg QW (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg Q4W (Cohort C). The study will begin by recruiting patients in Cohort A. Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Recruitment to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via IxRS.

The time between screening and enrollment of eligible patients should be ≤ 28 days; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria. ~~Emicizumab will be administered with a weekly loading dose of 3.0 mg/kg for the first 4 weeks (Day 1 of each week) followed by a maintenance dose of 1.5 mg/kg/week (Day 1 of each week). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see Section 4.5.2).~~

SECTION 4.5.2: Dosage, Administration, and Compliance

~~Emicizumab treatment will begin with~~ ~~will be administered subcutaneously at a weekly~~ a loading dose of 3.0 mg/kg QW for the first 4 weeks (Day 1 of each week) followed on Week 5 by a ~~starting~~ maintenance dose of either 1.5 mg/kg QW/week (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg/kg Q4W (Cohort C). Note that the cumulative dose studied in all three cohorts is identical, but the dose administration schedule differs between cohorts. ~~(Day 1 of each week).~~ Patients will receive weekly SC doses of prophylactic emicizumab for a minimum of 52 weeks, or until unacceptable toxicity or discontinuation from the study due to any cause. ~~The initial dosing regimen may be adapted if the maintenance dose of 1.5 mg/kg/week in the first few 3–5 patients ≥ 2 to < 12 years of age fails to achieve optimal control of bleeds after the first 12 weeks of treatment. This decision will be determined following a first interim data review of all available data (e.g., safety, efficacy, and pharmacokinetics) by the JMC (as detailed in the JMC Agreement). All patients enrolled following the first interim data review will receive the starting maintenance dose selected by the JMC. In a second interim data review, all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated by the JMC to provide recommendations for enrollment of children < 2 years of age, as well as on any additional adaptations of the maintenance dose if necessary. Should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose. After the JMC recommendations are released following both interim data reviews, the study will continue to enroll up to a maximum of approximately 60 patients (to maximize the safety database).~~

On 7 December 2016, the JMC recommended continued enrollment to Cohort A at the original starting maintenance dose of 1.5 mg/kg QW, and to open enrollment to patients < 2 years of age at that same maintenance dose. Moreover, review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) has identified no safety concerns to date. See Section 3.3.1.1 for details.

During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab. Patients in Cohorts A, B, or C with ≥ 2 qualifying bleeds within a 12-week interval may have the opportunity to have their maintenance emicizumab dose increased to 3 mg/kg QW starting on Week 17, if they receive approval from the Medical Monitor. Of note, for patients from Cohorts

B or C who have a dose up-titration, their dosing regimen will change from Q2W or Q4W to QW. Qualifying bleeds are defined as spontaneous and clinically significant, physician verified (e.g., with diagnostic imaging, clinical examination, photograph), and occurring while on prophylactic emicizumab at steady-state on the maintenance dose (after Week 5). Investigators will monitor patients regularly with the guidance of an up-titration algorithm (see Figure 3 and Table 2). Should patients meet protocol-defined criteria for efficacy-guided up-titration, the investigator will contact the Medical Monitor to initiate a discussion about possible up-titration. Ultimately, the decision for up-titration will be based on meeting protocol-defined criteria and approval from the Medical Monitor. In the case of Upon up-titration to *a new maintenance dose of 3 mg/kg QW, the patient's schedule of assessments will reset to Week 1, and the next five weekly up-titrated doses* visits must be administered at the take place at the site during a patient's visit.

On the basis of three predefined maintenance doses (1.5, 2.25, and 3.0 mg/kg/week; see Section 3.3.1), efficacy-guided up-titration will be possible from 1.5 to 2.25 mg/kg/week and subsequently to 3.0 mg/kg/week (see Figure 3 and Table 2). An individual patient is eligible for up-titration after a minimum of 12 weeks of treatment on a respective dose following protocol-defined criteria as described below. Bleeding events qualifying for up-titration must be spontaneous and clinically significant, with a minimum of two being physician verified (e.g., with diagnostic imaging, clinical examination, photograph). Following the initial 12 weeks of treatment at a specific dose, patients should be assessed regularly for bleeds meeting criteria for up-titration. Of note, all available cumulative data for the individual patient (i.e., including safety and pharmacokinetics) may also be considered in the decision making process for efficacy-guided up-titration.

- After completing the first 12 weeks (i.e., week +13), including 8 weeks at 1.5 mg/kg/week, up-titration to 2.25 mg/kg/week may occur if the patient has developed ≥ 2 bleeds in the last 8 weeks. From 12 weeks onward, a patient may be eligible for up-titration to 2.25 mg/kg/week if the patient has developed ≥ 2 bleeds in any given period of 12 weeks starting from week +5 at the 1.5 mg/kg dose level.
- After completing 12 weeks (i.e., up-titration 1, week +13) at 2.25 mg/kg/week, up-titration to 3.0 mg/kg/week may occur if the patient has developed ≥ 2 bleeds in the last 4 weeks. From 12 weeks onward at 2.25 mg/kg/week, a patient may be eligible for up-titration to 3.0 mg/kg/week if the patient develops ≥ 2 bleeds in any given period of 12 weeks starting from week +9 at the 2.25 mg/kg dose level.
- After completing 12 weeks (i.e., up-titration 2, week +13) at 3.0 mg/kg/week, further up-titration may be considered if the patient has developed ≥ 2 bleeds in the last 4 weeks. From 12 weeks onward at 3.0 mg/kg/week, further up-titration may be considered if the patient has developed ≥ 2 bleeds in any given period of 12 weeks starting from week +9 at the 3.0 mg/kg dose level.

- If the investigator believes that a specific patient warrants dose up-titration based on a different reason, they must discuss the case with the Medical Monitor for consideration and potential approval.

Based on ongoing evaluation of efficacy, safety, and PK data, including interim analyses, the Sponsor and/or the JMC may recommend a dose higher than 3.0 mg/kg QW~~week~~ for a patient or a patient population. Dosing above 3.0 mg/kg QW~~week~~ (not higher than 6.0 mg/kg QW~~week~~) may, therefore, occur while ensuring that the exposure will not exceed the exposure achieved with the safe and well tolerated highest dosing regimen tested in clinic.

~~FIGURE 3: Efficacy-Guided Up-Titration Algorithm~~

Figure 3 (previous version) has been removed.

~~TABLE 2: Efficacy-Guided Up-Titration~~

Table 2 (previous version) has been removed. Subsequent tables have been renumbered accordingly.

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 IFU document. Patients/caregivers will in turn be trained by an HCP on study medication preparation and self-administration/administration at the recommended sites of injection as detailed in the IFU. The HCP is to 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., $\pm 10\%$), the new volumetric dose to be administered must be communicated to the patient/caregiver.*

In order to minimize the number of injections for pediatric patients in certain high weight categories, the administration per single injection of up to 2 mL of 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 *of a given concentration* (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 IFU. Vials of different emicizumab concentrations must not be combined.*

Details on the devices to be used for study medication withdrawal from the 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,~~ after a period of in-clinic administration and training. ...

Study medication should be administered on the scheduled dosing day. On days when trough plasma PK samples are to be collected, patients will be dosed after those samples are drawn.

- *For patients in Cohort A (QW dosing), if the patient/caregiver forgets or cannot administer study medication on the scheduled dosing day, the 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/caregiver should administer his or her next dose at the next scheduled time (with the study medication dosing resumed in accordance with the original dosing schedule).*
- *For patients in Cohort B (Q2W dosing), if the patient/caregiver forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 7 days from the scheduled dosing date. If more than 7 days have passed, the patient/caregiver 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.*
- *For patients in Cohort C (Q4W dosing), if the patient/caregiver 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 have passed, the patient/caregiver 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.*

SECTION 4.6.2: Prohibited Therapy

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

- Use of aPCC or Byclot® as concomitant prophylactic treatment, including for short-term prophylaxis (*note: this criterion does not apply to the 4 weeks prior to initiation of study treatment*)
- Use of anti-fibrinolytics in conjunction with aPCC or 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 doses or short-term prophylaxis (e.g., around the time of surgery), however, are permitted

...

SECTION 4.7.1: Informed Consent Forms and Screening Log

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization/enrollment. ...

SECTION 4.7.5: Laboratory, Biomarker, and Other Biological Samples

- In patients who receive bypassing agents, ...

If applicable, laboratory results should be recorded in the ~~unscheduled visit eCRFs~~
"Local Lab Following Treatment with Bypassing Agents" eCRF page.

SECTION 5.1.1.3: Hypercoagulation and Thromboembolic Events

As of ~~November 2016~~ April 2017, there have been ~~2-3~~ *serious* thromboembolic events reported in 2 patients ~~with hemophilia A with inhibitors~~ *who were treated with bypassing agents* while receiving emicizumab *prophylaxis* in Study BH29884. [REDACTED]

[REDACTED]

[REDACTED] *For more details please refer to the Emicizumab Investigator's Brochure.*

These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism *or thrombosis* (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; *or if in the skin, blackening and associated pain*) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

SECTION 5.1.1.4: Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, and so. As of ~~November 2016~~ April 2017, ~~32~~ cases of TMA, ~~diagnosed as aHUS~~, were observed in Study BH29884 involving patients with hemophilia A with inhibitors *who were treated with bypassing agents* while receiving emicizumab. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

For more details please refer to the Emicizumab Investigator's Brochure.

SECTION 5.1.1.5: 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 by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.3 and the Emicizumab Investigator's Brochure). Due to the long $t_{1/2}$ 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 a practitioner other than the emicizumab-prescribing practitioner in settings such as an emergency room or in an acute-care setting.

Emicizumab's 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 April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.

SECTION 5.1.2: Management of Specific Adverse Events

TABLE 3: Guidelines for Management of Specific Adverse Events

Table 3 has been revised to reflect the changes to the protocol.

SECTION 5.1.3: Interpretation of Coagulation Assays for Patients Receiving Emicizumab

... 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 4 summarizes the coagulation tests affected and unaffected by emicizumab. See the Emicizumab Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

TABLE 4: Coagulation Test Results Affected and Unaffected by Emicizumab

Table 4 has been added. Subsequent tables have been renumbered accordingly.

SECTION 5.3.5.8: Deaths

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. ~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ 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").*

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

~~The following hospitalization scenarios are not considered to be adverse events:~~ *An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*

- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for respite care

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

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

The patient has not experienced an adverse event

~~The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:~~ *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

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor: [REDACTED], M.D. (secondary)

Telephone No.: [REDACTED]

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No formal hypothesis testing is planned in the study. All the analyses will be descriptive and be performed for each cohort separately.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The sample size for this study 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 with inhibitors available for participation in this study. Hence, at least 2040 children younger than 12 years of age and up to 8060 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: *approximately 60 patients in Cohort A* with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent *and approximately 10 patients each in Cohort B and Cohort C.*

SECTION 6.2: SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study *in each cohort* will be summarized. ...

SECTION 6.3: SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, weight etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented ~~overall and by cohort dosing regimen~~ (i.e., Cohort A: 1.5 mg/kg QW; Cohort B: 3 mg/kg Q2W; Cohort C: 6 mg/kg Q4W) and overall as appropriate (maintenance dose 1.5, 2.25, or 3.0 mg/kg/week).

SECTION 6.4: EFFICACY ANALYSES

The efficacy analyses are to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate), and to characterize the efficacy of up-titration on an intra-patient ~~and population~~ level. These analyses will be conducted using different bleed definitions such as treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

The primary analysis will be performed 52 weeks after the last patient in the primary ~~population of e~~Cohort A has been enrolled or withdrawn prematurely, whichever occurs first. The primary ~~population cohort~~ consists of all patients enrolled in Cohort A prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients), and is used to define the timing of the primary analysis. *The primary analysis will also include all available data from patients enrolled in Cohorts B and C, regardless of their follow-up time.* ~~If no patients < 2 years of age are included in the primary cohort, the primary analysis will still occur at the specified time; however, e~~Enrollment in the study Cohort A may be left open exclusively for patients < 2 years of age in order to enroll ~~up to approximately 5–10~~ such patients. Note that these patients will be included in the primary ~~population analysis cohort~~ regardless of their follow-up time. Further analyses ~~will may~~ be conducted while the study is ongoing (see Section 6.9).

SECTION 6.4.1: Efficacy Endpoints

One efficacy objective is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time. *This analysis will be performed for each cohort separately as well as overall as appropriate.* Another objective is to characterize the efficacy up-titration on an intra-patient ~~and population~~ level. The comparison between historical and on-study treatment period for bleeds over time will also be evaluated for patients who were previously enrolled in Study BH29768. *These patients will enroll exclusively in Cohort A, therefore this intra-patient analysis will be conducted only in patients receiving the 1.5 mg/kg QW maintenance dose.* The definition of a bleed is described in Section 4.7.8. All definitions (i.e., treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, treated target joint bleeds) will be evaluated for each of the efficacy objectives.

Characterizing the effect of emicizumab on-study treatment period for bleed over time as well as analyses of up-titration and the comparison between historical and on study treatment period for bleed over time will be performed *for Cohort A and for the overall analysis* using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of the time that each patient stays in the study included as an offset in the model.

The number of bleeds will be also annualized (Annualized Bleeding Rate—ABR) *for Cohorts B and C as well as* for each patient using the following formula:

...

Efficacy endpoints will be analyzed separately by cohort (i.e., Cohort A: 1.5 mg/kg QW; Cohort B: 3 mg/kg Q2W; Cohort C: 6 mg/kg Q4W) and overall as appropriate. Patients who require up-titration will be reported in their original maintenance dose group, and a listing based on their up-titration period will be provided. A detailed description of the statistical methods that will be used for the efficacy analyses will be provided in the SAP.

SECTION 6.4.2: Exploratory Efficacy Endpoints

Summary statistics of the number of daycare/school and days hospitalized will be presented for each cohort separately.

SECTION 6.5: SAFETY ANALYSES

Safety analyses will be performed for each cohort separately and overall as appropriate.

SECTION 6.6: PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by dose groups (1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W, 3 mg/kg QW in case of up-titration), including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

SECTION 6.7: PATIENT-REPORTED OUTCOME ANALYSES

Scale scores for the Haemo-QoL-SF and the Adapted InhibQoL Including Aspects of Caregiver Burden will be calculated for each assessment, with change scores being examined for the assessments over the course of the study. These will be summarized descriptively by cohort. A descriptive summary of the number of daycare/school days missed and days hospitalized will also be presented by cohort.

SECTION 6.8: PHARMACODYNAMIC BIOMARKER ANALYSES

PD parameters (e.g., aPTT, FVIII activity) will be presented using summary statistics by dose groups, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. These analyses will be presented by cohort.

SECTION 6.9.1.1: JMC Recommendations and Enrollment of Q2W/Q4W in Pediatric Patients

On 7 December 2016, based on a combined interim analysis of the first 20 patients enrolled, the JMC recommended to continue enrolling patients to Cohort A at the maintenance dose of 1.5 mg/kg QW, and to begin enrollment of patients <2 years of age. See Section 3.3.1.1 for details.

After the JMC recommendations ~~are~~^{were} released following ~~both interim data reviews~~^{this interim analysis}, the study ~~will~~^{was} continued to enroll ~~up to a maximum of approximately 60 patients (to maximize the safety database)~~^{up to approximately 60 patients in Cohort A}. Upon completion of recruitment to Cohort A, and following review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifying no

safety concerns, recruitment with alternating allocation of patients to Cohorts B and C via IxRS could begin up to a maximum of approximately 10 patients in each cohort. See Section 3.3.1.1 for details.

SECTION 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.*

SECTION 9.6: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

... The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>.

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM AND ASSENTS

The sample Informed Consent Form and Assents have been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A MULTICENTER, OPEN-LABEL, PHASE III
CLINICAL TRIAL TO EVALUATE THE EFFICACY,
SAFETY, AND PHARMACOKINETICS OF
SUBCUTANEOUS ADMINISTRATION OF
EMICIZUMAB IN HEMOPHILIA A PEDIATRIC
PATIENTS WITH INHIBITORS

PROTOCOL NUMBER: BH29992

VERSION NUMBER: 4

EUDRACT NUMBER: 2016-000073-21

IND NUMBER: 122954

TEST PRODUCT: Emicizumab (RO5534262)

MEDICAL MONITOR: [REDACTED] M.D., M.A.S.

SPONSOR: F. Hoffmann-La Roche Ltd and
Chugai Pharmaceutical Co. 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 this form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE: A MULTICENTER, OPEN-LABEL, PHASE III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF SUBCUTANEOUS ADMINISTRATION OF EMICIZUMAB IN HEMOPHILIA A PEDIATRIC PATIENTS WITH INHIBITORS

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PHASE: Phase III

INDICATION: Hemophilia A

SPONSOR: F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co. Ltd.

Objectives and Endpoints

The objectives of the study are to investigate (with no formal hypothesis testing) the efficacy, safety, and pharmacokinetics of SC emicizumab *administered at 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W* in pediatric patients with hemophilia A and factor VIII (FVIII) inhibitors who are currently receiving treatment with bypassing agents. *A total of approximately 80 patients are planned: approximately 60 patients in Cohort A (1.5 mg/kg QW) and approximately 10 patients each in Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W). Patients younger than 12 years of age are planned for enrollment, with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent to further evaluate dosing of emicizumab in patients <40 kg. Of note, enrollment in Cohort A may be left open exclusively for patients <2 years of age until approximately 5 such patients have been enrolled.*

Efficacy Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The efficacy objectives for this study are as follows:

- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate) *
- To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate (intra-patient comparison, *Cohort A only, as patients enrolled in Cohorts B and C will not have previously participated in the non-interventional study*) *
- To characterize the efficacy of up-titration on an intra-patient level, *based on the basis of the number of bleeds over time* *
- To evaluate the health-related quality of life (HRQoL) of children 8–17 years of age according to Haemo-QoL-Short Form (SF) (completed by patients)
- To evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)

- To assess the number of days missed from daycare/school and days hospitalized

* Analyses will be performed for: treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

Safety Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The safety objective for this study is to evaluate the overall safety of emicizumab in pediatric patients with hemophilia A and inhibitors on the basis of the following endpoints:

- Incidence and severity of adverse events
- Incidence and severity of thromboembolic events
- 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
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- Incidence and severity of thrombotic microangiopathy
- Incidence and clinical significance of anti-emicizumab antibodies

Pharmacokinetic Objective

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W).

The pharmacokinetic (PK) objective for this study is to characterize the exposure (C_{trough}) of emicizumab in patients receiving 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W prior to drug administration on Day 1 and at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during Weeks 5–9 on emicizumab
- Every 4 weeks during Weeks 13–37 on emicizumab
- Every 8 weeks during Weeks 41–49 on emicizumab
- Every 12 weeks from Week 57 thereafter while continuing on emicizumab, until the end of the study
- Additional PK samples will be taken in patients who require up-titration (see schedule of assessments in the protocol)

Pharmacodynamic Biomarker Objective

The pharmacodynamic (PD) biomarker objective for this study is as follows:

- To assess potential PD biomarkers of emicizumab, including but not limited to aPTT and FVIII activity, at designated timepoints throughout the study.

Study Design

Description of Study

This *non-randomized*, multicenter, open-label, Phase III clinical study will enroll children with hemophilia A who have inhibitors against FVIII. Children with hemophilia A and documented historical FVIII inhibitor titer (≥ 5 BU) must currently be receiving treatment with bypassing agents. At least 40 patients younger than 12 years age and up to *approximately* 80 patients are planned for enrollment, with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent. Patients will receive SC doses of emicizumab at 1.5 mg/kg QW (Cohort A) for a minimum of 52 weeks or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first. After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may

continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study.

Because of the uncertainty of the dosing regimen needed in patients < 12 years of age or < 40 kg to achieve similar exposure as in adults and adolescents, this study will *first* evaluate the appropriate dosing regimen in children by starting with the same *weekly* dosing regimen (1.5 mg/kg QW) being evaluated in the Phase III study (BH29884) in adult/adolescent patients with hemophilia A with inhibitors (see protocol for details). Emicizumab will be administered with a weekly dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 1.5 mg/kg QW (*Cohort A*) for the remainder of the treatment period. During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see protocol).

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg QW) after the first 3–5 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks. A Joint Monitoring Committee (JMC; see protocol) will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) to provide recommendations on increasing the starting maintenance dose (if necessary) to target a similar plasma emicizumab trough concentration as the one being targeted in adolescents and adults (i.e., 45 µg/mL). All patients enrolled following the first interim data review will receive the starting maintenance dose selected by the JMC. Those patients enrolled prior to the first interim data review who had not had their dose up-titrated will remain on their current maintenance dose, unless they meet eligibility for up-titration based on protocol-defined criteria (see protocol).

In order to include and safely treat the youngest patients (birth to < 2 years of age), this study will include a staggered approach to enrollment by age. Patients ≥ 2 to < 12 years of age and patients 12–17 years of age who weigh < 40 kg will enroll first. A second interim data review will occur once at least 10 patients between ≥ 2 and < 12 years of age have been dosed for a minimum of 12 weeks, at which time all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated to provide recommendations for enrollment of children < 2 years of age, as well as on any additional adaptations of the maintenance dose if necessary.

Furthermore, should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose (*Cohort A*). After the JMC recommendations are released following both interim data reviews, the study will continue to enroll in *Cohort A* up to approximately 60 patients.

Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) *Cohort A* is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients.

Recruitment to *Cohort B* (3 mg/kg Q2W) and *Cohort C* (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via 1xRS, for a total of approximately 10 patients per cohort. Of note, enrollment to *Cohorts B* and *C* will be limited to patients 2–11 years of age.

Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 3 mg/kg Q2W (*Cohort B*) and 6 mg/kg Q4W (*Cohort C*) for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see protocol). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab.

The entire study will enroll up to approximately 80 patients with allowance for additional patients < 2 years of age in *Cohort A*.

A patient who fulfills the inclusion and exclusion criteria should be enrolled at the Week 1 visit. Prophylactic use of bypassing agents should be discontinued *the day before* the first dose of emicizumab is given.

The primary analysis for all cohorts will be performed 52 weeks after all patients in the primary population of *Cohort A* have been enrolled or withdrawn prematurely, whichever occurs first.

The primary population of *Cohort A* consists of all patients enrolled prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define

the timing of the primary analysis of Cohorts A, B, and C. If no patients <2 years of age are included in the primary population of Cohort A, the primary analysis will still occur at the specified time; however, enrollment to Cohort A may be left open exclusively for patients <2 years of age in order to enroll approximately 5 such patients. Note that these patients will be included in the primary analysis of Cohort A regardless of their follow-up time. *Additionally, all available data from patients enrolled in Cohorts B and C (efficacy period approximately 6 months) will be included in the primary analysis of Cohort A.*

During the study, caregivers will be asked to enter any individual bleeds, hemophilia-related medications, and emicizumab treatments that occur on an electronic, handheld device. Entries should be made at least weekly, *and also* at any time a bleed occurs or a hemophilia medication, *including emicizumab*, is administered. Detailed information about bleeds (type, location, date/time) will be captured. Detailed information about hemophilia medications (agent, dose, reason for administration, date/time) and emicizumab dosing (total volume, date/time) will also be captured. In addition, HRQoL using the Haemo-QoL-SF (completed by children 8 years of age and older), proxy-reported HRQoL and aspects of caregiver burden using Adapted InhibQoL (completed by caregivers of all children) and missed daycare/school will be collected on a separate electronic, handheld device during a patient's visit prior to emicizumab injection at Week 1 and every 12 weeks thereafter, as outlined in the schedule of assessments (see protocol). The number of days the child was hospitalized, if applicable, will be derived from data collected on eCRF.

Emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred). Therefore, in this study all patients will continue to receive episodic treatment for breakthrough bleeds as needed. Breakthrough bleeds should preferably be treated with rFVIIa at the lowest expected dose to achieve hemostasis and captured as they occur on the electronic, handheld device. There is 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, and 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/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 3 *serious* thromboembolic events were observed in patients who concomitantly used > 100 U/kg/day of aPCC on average for ≥ 24 hours for the treatment of breakthrough bleeds (see protocol). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that the use of aPCC or other bypassing agents should be avoided or limited (see protocol). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see protocol). Investigators will be asked to 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 the patient's benefit-risk of continued treatment.

Physical examinations, vital sign assessments, ECG, and safety laboratory assessments will be collected as per the schedule of assessments (see protocol). Adverse events will be captured on an ongoing basis as they occur during the study. All patients in this study will undergo PK assessments. Blood samples will also be collected to assess the PD properties of emicizumab (i.e., aPTT, FVIII activity), as well as to assess immunogenicity (i.e., anti-emicizumab antibodies and anti-FVIII antibodies). A detailed list is provided in the schedule of assessments (see protocol).

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. Pediatric patients who are enrolled in the non-interventional Study BH29768 are eligible to enroll in this study, as long as they meet the inclusion and exclusion criteria and are able to enroll at a participating site while the study is open for enrollment. *All patients who participated in the non-interventional study will be enrolled in Cohort A.*

Number of Patients

At least 40 children younger than 12 years of age and up to 80 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: *approximately 60 patients in Cohort A with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent and approximately 10 patients each in Cohort B and Cohort C.*

Target Population

Approximately 80 children <12 years of age with hemophilia A and with FVIII inhibitors previously treated with bypassing agents will be enrolled in the study (approximately 60 patients in Cohort A, 10 patients in Cohort B, and 10 patients in Cohort C). In addition to this primary population of children <12 years of age, patients 12–17 years of age who weigh <40 kg at the time of informed consent will also be eligible to enroll. These patients, as well as those <2 years of age at the time of informed consent, will only be eligible to enroll in Cohort A. Of note, enrollment in Cohort A may be left open exclusively for patients <2 years of age until approximately 5–10 such patients have been enrolled prior to the closure of Cohorts B and C, whichever occurs first.

Inclusion Criteria

Children 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 with allowance for the following:
 - Patients 12–17 years of age and who weigh <40 kg at the time of informed consent (*Cohort A only*)
 - Patients <2 years of age will be allowed to participate only after the protocol-defined interim data review criteria are met (*Cohort A only*)
- 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 patient-reported outcome (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)
- Requires treatment with bypassing agents
- For patients ≥ 2 years of age:
 - If on an episodic bypassing agent regimen: ABR of ≥ 6 (3 bleeds in the last 24 weeks)
 - OR
 - If on a prophylactic bypassing agent regimen: inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or central venous access device (CVAD) placement medically not feasible or deemed unsafe by investigator
- For patients <2 years of age (*Cohort A only*): determined by investigator to be in high unmet medical need
- 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 upper limit of normal (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 $\leq 1.5 \times \text{ULN}$ for age. When the serum creatinine is $\geq 1.5 \times \text{ULN}$, creatinine clearance by Bedside Schwartz formula must be $> 70 \text{ mL/min/1.73m}^2$
- At screening, in the rare cases of hemophilia in female patients who are of childbearing potential, patients will be required to have a negative serum pregnancy test result (with urine pregnancy tests performed at subsequent specified visits) and will have to agree to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of $< 1\%$ per year and are approved by local health authorities and ethics committees during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug.

Exclusion Criteria

Children 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) immune tolerance induction (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 disease [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 TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Use of systemic immunomodulators (e.g., interferon or corticosteroids) at enrollment or planned use during the study period
- 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

End of Study

The primary analysis will take place at the same time for Cohorts A, B, and C. It will occur after all patients in the primary population of Cohort A have completed 52 weeks of treatment, or have withdrawn prematurely, whichever occurs first. All data from patients enrolled in Cohorts B and C will be included regardless of follow-up time.

After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study. Patients who discontinue emicizumab will have a safety follow-up visit at 24 weeks after the last emicizumab dose.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Completed 52 weeks of emicizumab and either transferred to a separate extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

OR

- Completed the end of study safety follow-up visit 24 weeks after discontinuing emicizumab

OR

- Consent has been withdrawn

OR

- Lost to follow-up

Length of Study

The length of the entire study from screening of the first patient to the last patient completing 52 weeks in the study and/or the end-of-study follow-up visit (24 weeks after discontinuing emicizumab) will be approximately 152 weeks.

Investigational Medicinal Product

Test Product (Investigational Drug)

Emicizumab *treatment will begin with a loading dose of 3 mg/kg QW for the first 4 weeks (Day 1 of each week) followed on Week 5 by a maintenance dose of either 1.5 mg/kg QW (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg/kg Q4W (Cohort C). Note that the cumulative dose studied in all three cohorts is identical, but the dose administration schedule differs between cohorts.* Patients will receive *prophylactic* emicizumab for a minimum of 52 weeks or until unacceptable toxicity or discontinuation from the study due to any cause. *See protocol for treatment details.*

Emicizumab will be administered as a SC injection in the home setting 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. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions should be considered (see protocol). The fourth and fifth scheduled study drug administrations must also be performed in the monitored setting, and the patient/caregiver will be trained and have the opportunity to ask any questions to 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 the 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, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections.

Non-Investigational Medicinal Products

None.

Statistical Methods

Efficacy Analyses

The efficacy analyses are to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate), and to characterize the efficacy of up-titration on an intra-patient level. These analyses will be conducted using different bleed definitions such as treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

The primary analysis will be performed 52 weeks after the last patient in the primary *population* of Cohort A has been enrolled or withdrawn prematurely, whichever occurs first. The primary *population* consists of all patients enrolled in Cohort A prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis. *The primary analysis will also include all available data from patients enrolled in Cohorts B and C, regardless of their follow-up time.* Enrollment in Cohort A may be left open exclusively for patients < 2 years of age in order to enroll approximately 5–10 such patients. Note that these patients will be included in the primary *population analysis* regardless of their follow-up time. Further analyses *may* be conducted while the study is ongoing (see protocol).

Safety Analyses

Safety analyses will be performed for each cohort separately and overall as appropriate.

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, and anti-emicizumab antibodies.

To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade.

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

Data on the impact of immunogenicity (anti-emicizumab antibodies and anti-FVIII antibodies) on safety, efficacy, and/or pharmacodynamics and pharmacokinetics will be summarized using standard language/terminology.

Pharmacokinetic Analyses

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by dose groups (1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W, 3 mg/kg QW *in case of up-titration*), including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will 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 area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and Phase III Studies. These analyses will be reported in a dedicated report.

Patient-Reported Outcome Analyses

Scale scores for the Haemo-QoL-SF and the Adapted InhibQoL Including Aspects of Caregiver Burden will be calculated for each assessment, with change scores being examined for the assessments over the course of the study. These will be summarized descriptively *by cohort*. A descriptive summary of the number of daycare/school days missed and days hospitalized will also be presented *by cohort*.

Pharmacodynamic Biomarker Analyses

PD parameters (e.g., aPTT, FVIII activity) will be presented using summary statistics by dose groups, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. *These analyses will be presented by cohort.*

Interim Data Review

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg/week). This dosing regimen may be adapted following analysis of all available data (e.g., safety, efficacy, pharmacokinetics) by the JMC (see protocol) if a majority of the first 3–5 patients (aged ≥ 2 to < 12 years of age) fail to achieve optimal control of bleeds after the first 12 weeks of treatment; or if their plasma emicizumab concentration trough level is lower than the one being targeted in adolescents and adults (i.e., 45 $\mu\text{g/mL}$).

Should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this first interim data review, available data from these patients will also be included.

A second interim data review will occur once at least 10 patients between 2 and 12 years of age have been dosed for a minimum of 12 weeks. All available cumulative data (e.g., safety, efficacy, pharmacokinetics) will be evaluated by the JMC to provide recommendations for the enrollment of children < 2 years of age, as well as on any further adaptations of the maintenance dose if necessary. Again, should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this second interim data review, available data from these patients will also be included.

Should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose.

JMC Recommendations and Enrollment of Q2W/Q4W in Pediatric Patients

On 7 December 2016, based on a combined interim analysis of the first 20 patients enrolled, the JMC recommended to continue enrolling patients to Cohort A at the maintenance dose of 1.5 mg/kg QW, and to begin enrollment of patients < 2 years of age. See protocol for details.

After the JMC recommendations were released following this interim analysis, the study continued to enroll up to approximately 60 patients in Cohort A. Upon completion of recruitment to Cohort A, and following review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifying no safety concerns, recruitment with alternating allocation of patients to Cohorts B and C via IxRS could begin up to a maximum of approximately 10 patients in each cohort. See protocol for details.

Additional interim data reviews will be prespecified in the Statistical Analysis Plan; other analyses may be conducted at various timepoints to support regulatory submissions.

Determination of Sample Size

The sample size for this study 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 with inhibitors available for participation in this study. Hence, at least 40 children younger than 12 years of age and up to 80 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: *approximately 60 patients in Cohort A with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent and approximately 10 patients each in Cohort B and Cohort C.*

During the study, a re-assessment of the initially specified sample size based on enrollment consideration may be performed. This may result in an increase in sample size, if necessary, to expand the safety database.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	annualized bleeding rate
ADA	anti-drug antibody
aHUS	atypical hemolytic uremic syndrome
aPCC	activated prothrombin complex concentrate
AUC	area under the curve
BA	bioavailability
BU	Bethesda unit
C _{max}	maximum plasma concentration
CVAD	central venous access device
cyFcγR	cynomolgus monkey Fcγ receptor
cyFcRn	cynomolgus monkey neonatal Fc receptor
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
FDA	U.S. Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIX	factor IX
FIX:Ag	factor IX antigen
FIXa	activated factor IX
FVIII	factor VIII
FVIIIa	activated factor VIII
FX	factor X
FX:Ag	factor X antigen
HBV	hepatitis B virus
HCP	healthcare provider
HCV	hepatitis C virus
hFcγR	human Fcγ receptor
hFcRn	human neonatal Fc receptor
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-Related Quality of Life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	Instructions For Use

Abbreviation	Definition
IgG4	immunoglobulin G4
ISTH	International Society on Thrombosis and Haemostasis
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITI	immune tolerance induction
IV	intravenous
IxRS	interactive voice or Web Response System
JMC	Joint Monitoring Committee
LPLV	last patient, last visit
MAA	Marketing Authorization Application
MAD	multiple ascending dose
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	<i>every 2 weeks</i>
Q4W	<i>every 4 weeks</i>
QTcF	QT interval corrected using Fridericia's formula
QW	<i>once weekly</i>
rFVIII	recombinant FVIII
rFVIIa	recombinant activated factor VII
SAD	single ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
$t_{1/2}$	half-life
t_{\max}	time to maximum plasma concentration
TMA	thrombotic microangiopathy
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON PEDIATRIC HEMOPHILIA A WITH INHIBITORS

Hemophilia A is a bleeding disorder characterized by congenital underproduction of or dysfunction of factor VIII (FVIII), an essential protein in promoting clot formation. The gene that encodes FVIII is located on the long arm of the X chromosome. Genetic aberrations causing this disease are transmitted via X-linked recessive inheritance, from mothers with one affected FVIII gene (“carriers”), to half of their newborn sons. An estimated 400,000 people worldwide are living with hemophilia ([WFH 2012a](#)), with an incidence of approximately 1 in 5,000 live male births. Hemophilia A affects approximately 320 newborns each year in the United States ([CDC 2014](#); [NIH 2014](#); [Franchini and Mannucci 2013](#); [WFH 2013a](#)). In the European Union, this would equate to around 415 newborns with hemophilia A in 2014. No racial differences have been reported in the distribution of patients with hemophilia and the number of patients with hemophilia A registered in 2013, in various regions across the world, including 4,761 individuals in Japan; 15,963 in North America; and 19,397 in the five major European nations (United Kingdom, France, Germany, Italy, and Spain [Spain estimate from 2012]) ([WFH 2013a](#)).

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, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, or even death ([WFH 2013a](#)). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients ([Brown et al. 2009](#)).

Treatments for hemophilia A can be broadly categorized into two types: episodic (or “on-demand”), in which treatments are administered in response to the occurrence of bleeding symptoms; and prophylactic, in which treatments are administered on a scheduled basis to prevent the onset of bleeding.

The standard treatment, for patients with hemophilia A without inhibitors, is intravenous (IV) FVIII replacement therapy with recombinant FVIII (rFVIII) or plasma-derived FVIII concentrates. Prophylaxis has been shown to markedly reduce the bleeding rate in adults with severe hemophilia A ([Valentino et al. 2012](#); [Manco-Johnson et al. 2013](#)). 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).

Unfortunately, up to 30% of patients with hemophilia A develop neutralizing alloantibodies (inhibitors) against FVIII (Franchini et al. 2012). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with high titer inhibitor (≥ 5 Bethesda units [BU]/mL), FVIII replacement therapy is rendered ineffective, precluding the use of a safe and effective standard-of-care and markedly increasing the risk of morbidity and mortality due to bleeding complications (Franchini et al. 2012). The overall incidence of inhibitors among patients with hemophilia A is 20%–30% (Franchini et al. 2012); but 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).

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 central venous access devices (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 recent 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 [IQR (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 ([Vepsäläinen 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 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), and NovoSeven[®], a recombinant activated human FVII (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/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 addition, as opposed to the 8–12-hour half-life and 15–20-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.

Recent 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. Following scientific consultations that the Sponsor conducted with pediatric hematology experts in the European Union, United States, and Japan, no consensus was apparent regarding whether NovoSeven® or FEIBA® should be the standard-of-care therapy for children with inhibitors to FVIII. Furthermore, both prophylactic and episodic regimens with bypassing agents are proposed as appropriate for children with inhibitors to FVIII.

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 recent 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](#)).

Because current available therapies are suboptimal, there is a need to develop alternative therapeutic options for pediatric patients with hemophilia A and FVIII inhibitors ([Gringeri et al. 2013](#)). Limitations of bypassing agents include an increased risk of thrombosis, suboptimal efficacy, and lack of administration convenience that collectively increase the likelihood of severe bleeds and the associated complications that impair HRQoL ([Hedner 2011](#)). Given the significant management challenges in children with hemophilia, there is a need for development of effective prophylactic treatment options that demonstrate more reliable efficacy, decreased immunogenicity, and less treatment burden to prevent bleeding and minimize long-term morbidity of children with hemophilia.

1.2 BACKGROUND ON EMICIZUMAB

Description of the Molecule

Emicizumab (also referred to as RO5534262 or ACE910) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIX) and factor X (FX), mimicking the co-factor function of FVIII.

Mechanism of Action

FVIII is a glycoprotein found in plasma that, in its activated form, serves as a cofactor for FIXa and FX, facilitating the reaction, whereby FX is catalyzed to FXa ([Mann et al. 1990](#)). After coagulation is initiated by the complex of exposed tissue factor and activated factor VII (FVIIa) in plasma and a small amount of thrombin is produced, FVIII undergoes enzymatic cleavage by thrombin and is converted into activated FVIII (FVIIIa). Because it enhances the FIXa-induced FX activation reaction by 200,000-fold, FVIIIa

plays a critical role in accelerating the explosive burst of thrombin production in the propagation phase of the coagulation reaction process ([van Dieijen et al. 1981](#)).

Emicizumab binds with moderate affinity (in the low μM range) to FIXa and FX, and has cofactor activity that substitutes for FVIII. Emicizumab mimics FVIII and, therefore, is capable of promoting the activation of FX by FIXa and downstream hemostasis at the site of bleeding in patients with hemophilia A who have decreased or no circulating levels of FVIII, irrespective of the presence of FVIII inhibitors ([Sampei et al. 2013](#)). Furthermore, as emicizumab has no structural relationship to FVIII or other coagulation factors, emicizumab is not expected to induce or enhance the development of direct inhibitors to FVIII or other coagulation factors. Due to the favorable pharmacokinetic (PK) properties of this antibody with the possibility of less frequent SC administration of emicizumab compared with IV FVIII therapies, this novel compound may have the potential to significantly change the treatment of patients with hemophilia A with and without FVIII inhibitors.

Nonclinical Studies

Binding studies of emicizumab to cynomolgus monkey FIX and FX showed a similar affinity as to the human factors. Mechanistic in vitro studies were conducted in human and cynomolgus FVIII-neutralized plasma and in various coagulation factor-specific assay testing systems, which revealed that emicizumab shortened aPTT and promoted thrombin generation. Emicizumab bound to human Fc γ receptor (hFc γ R), cynomolgus monkey Fc γ receptor (cyFc γ R), human neonatal Fc receptor (hFcRn), and cynomolgus monkey neonatal Fc receptor (cyFcRn) with similar affinities as a human IgG4 antibody, natalizumab.

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

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

The pharmacokinetics/toxicokinetics of emicizumab were assessed in cynomolgus monkeys after single and multiple doses were administered IV and via the intended clinical SC route. After a single IV dose of 6 mg/kg emicizumab in male cynomolgus monkeys, the plasma clearance was 3.62 mL/day/kg and the terminal plasma half-life

($t_{1/2}$) of emicizumab was 19.4 days. The single SC administration study (dose levels: 0.06, 0.6, and 6 mg/kg) indicated slow (time to maximum plasma concentration [t_{max}]: 3.00–5.33 days) and complete absorption (bioavailability [BA]: 102% at 6 mg/kg). The IV and SC multiple dosing studies (toxicokinetic monitoring) revealed a $t_{1/2}$ in the range of 14.9–30.8 days. Overall, exposures in terms of maximum plasma concentration (C_{max}) and area under the curve (AUC) increased in an approximately dose proportional manner.

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

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

The conducted in vitro and in vivo studies demonstrated the mode of action of emicizumab and provided supportive data on efficacious dose levels in a relevant hemophilia A disease model which were used for dose extrapolation to humans.

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

Clinical Studies

The experience with emicizumab in humans includes data from one completed Phase I study (Study ACE001JP, last patient, last visit [LPLV] on 17 April 2015) and its ongoing extension, a Phase I/II study (Study ACE002JP). See the Emicizumab Investigator's Brochure for additional details on clinical studies with emicizumab.

Study ACE001JP was a single study conducted in 3 parts, including both healthy subjects (Part A and Part B) and patients with hemophilia A (Part C). The objective of Parts A and B in healthy subjects was to investigate the tolerability, safety, PK, and pharmacodynamic (PD) response of SC administered emicizumab in adult Japanese and Caucasian males and to evaluate for racial differences, if any, in their PK and PD response. Healthy male volunteers aged 20–44 were eligible for enrollment. A total of 64 healthy volunteers were enrolled in Parts A and B from August 2012 to April 2013. In Part C, the objective was to investigate the tolerability, safety, PK, and PD response of SC administered emicizumab in patients with hemophilia A. Patients were eligible for enrollment if they were 12–59 years of age, ≥ 40 kg in weight, had a diagnosis of severe congenital hemophilia A, and had documentation of bleeds and/or treatment with coagulation factor in the last 6 months. For those with inhibitors, patients must have had

≥ 6 bleeds in the 6 months prior to enrollment, and for those without inhibitors, patients were required to have received ≥ 150 lifetime doses of FVIII replacement, including in the last 6 months. A total of 18 patients with hemophilia A were enrolled from May 2013 to June 2014.

In the SAD portion of Study ACE001JP, healthy volunteers (Japanese [Part A] and Caucasian [Part B]) received a single SC injection of emicizumab (48 patients) or placebo (16 patients), at dose levels ranging from 0.001–1 mg/kg. Six subjects received emicizumab and 2 subjects received placebo at each dose level. In Part C (the MAD portion) of Study ACE001JP, a total of 18 patients with hemophilia A were enrolled in three cohorts of 6 patients each for each dose level (Cohort C-1: 1 mg/kg loading dose followed by weekly SC injections of 0.3 mg/kg [0.3 mg/kg/week group]; Cohort C-2: 3 mg/kg loading dose followed by weekly SC injections of 1 mg/kg [1 mg/kg/week group]; Cohort C-3: 3 mg/kg weekly SC injections [3 mg/kg/week group]).

Study ACE002JP is an extension study that allows for continued treatment with emicizumab of patients enrolled in Part C of Study ACE001JP. In order to be eligible for the extension study, patients must have completed 12 weeks of assigned treatment in Study ACE001JP and had bleeds prior to study entry. Study ACE002JP allows for dose escalation in patients who have an inadequate response to emicizumab—if the current dose is safe and well-tolerated, in such cases, his or her dose should be increased. Study ACE002JP will enable patients from Study ACE001JP to continue receiving emicizumab until the drug has received marketing approval or emicizumab development is discontinued, whichever is sooner.

Study ACE001JP has been completed (LPLV on 17 April 2015) and Study ACE002JP is currently ongoing. Seventeen of 18 patients in Part C of Study ACE001JP completed the 12-week treatment period. One patient moved to the follow-up period. A total of 16 of the 17 patients who completed the 12-week treatment period subsequently enrolled into extension Study ACE002JP and 1 of the 17 patients moved to the post-treatment follow-up period of Study ACE001JP. In Cohort C, there were 5 adolescent patients (12-18 years old): 1 patient (■ years old) in Cohort C-1; 2 patients (■ years old, ■ years old) in Cohort C-2; and 2 patients (■ years old, ■ years old) in Cohort C-3. There were 11 patients with inhibitors: 4 patients in Cohort C-1; 4 patients in Cohort C-2; and 3 patients in Cohort C-3.

The Phase I and I/II studies, have shown promising results for emicizumab prophylaxis in reducing the ABR in Japanese patients with hemophilia A with and without inhibitors against FVIII. During the 6 months before study enrollment, patients without FVIII inhibitors had received FVIII prophylactic replacement therapy, while the patients with inhibitors had received episodic therapy and/or prophylactic therapy with bypassing agents. During the course of emicizumab administration, ABRs decreased in all patients compared with the pretreatment period, regardless of whether or not they had inhibitors, with the exception of one non-inhibitor patient previously on FVIII prophylaxis in the

3 mg/kg/week group who had a baseline ABR of 0 (in this patient, the ABR was maintained at 0 while receiving emicizumab). Among all patients, (excluding those who had dose escalations), ABR reduction ranged from 22.8%–100% in the 0.3 mg/kg/week group, from 78.9%–100% in the 1 mg/kg/week group, and from 86.4%–100% in the 3 mg/kg/week group. Three patients had dose escalations after starting Study ACE002JP. The dose of emicizumab was escalated from 0.3 mg/kg/week to 1 mg/kg/week and then to 3 mg/kg/week in 2 of 6 patients in Cohort C-1 who transitioned to Study ACE002JP. In one of these patients, with inhibitors against FVIII, treatment with 0.3, 1, and 3 mg/kg/week resulted in 49.3%, 57.5%, and 84.7% reductions in ABR, respectively, compared with that of pre-dose. In the other patient without inhibitors against FVIII, treatment with 0.3, 1, and 3 mg/kg/week resulted in 22.8%, 62.3%, and 97.5% reductions in ABR, respectively, compared with that of pre-dose. One additional patient without inhibitors against FVIII in the 0.3 mg/kg/week group started an escalated dose of 1 mg/kg/week just before the data cutoff.

Emicizumab was safe and well-tolerated in these patients. Most adverse events were of mild intensity, except for five moderate adverse events (upper respiratory tract infection, bipolar I disorder, hemophilia [i.e., left hip joint bleeding due to hemophilia], headache, and asthma) and two severe adverse events (appendicitis and mesenteric hematoma). None of the moderate or severe adverse events were considered by investigators to be related to emicizumab. Local injection-site reactions were observed in 7 patients (38.9% of patients). These local injection-site reactions included injection-site erythema (3 patients), injection-site hematoma (2 patients), injection-site pruritus (2 patients), injection-site rash (1 patient), injection-site pain (1 patient), and injection-site discomfort (1 patient). All local injection-site reactions were of mild intensity and all resolved except for two cases: 1 patient, who started at the 0.3 mg/kg/week dose level and received an increased dose, reported a case of injection-site pruritus, which remained ongoing at the last data cutoff; and in another patient, a case of injection-site hematoma in the 3 mg/kg/week group (considered to be not related to study therapy) remains unresolved. Other adverse events reported in more than 20% of patients included nasopharyngitis (7 patients, 38.9%), dental caries (6 patients, 33.3%), pharyngitis (5 patients, 27.8%), excoriation (4 patients, 22.2%), and headache (4 patients, 22.2%). Two severe adverse events were observed: appendicitis and mesenteric hematoma. Both events were considered to be serious adverse events and not related to emicizumab administration. In the Phase I/II Studies ACE001JP and ACE002JP, no *thrombotic microangiopathy (TMA)*, thromboembolic adverse events, or systemic hypersensitivity reactions have been reported in any dosing cohort thus far, including those patients who required concomitant FVIII concentrates or bypassing agent therapy to treat bleeds.

In the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), as of April 2017, TMA was observed in 3 patients receiving emicizumab and bypassing agents; and 3 cases of serious thromboembolic

events were observed in 2 patients receiving emicizumab and bypassing agents. For more details refer to Sections [5.1.1.3](#) and [5.1.1.4](#).

In terms of PK, emicizumab exhibited linear PK after single SC administration. Following single SC injection, its mean elimination $t_{1/2}$ (4–5 weeks) was similar to that of other human IgG antibodies. Furthermore, comparison of PK profiles between Japanese and Caucasian patients did not reveal racial differences.

In patients with hemophilia A, emicizumab trough plasma concentrations increased in a dose-dependent manner with weekly dosing to achieve a plateau (steady state) after approximately 12 weeks in the first two dosing groups, while they continued to increase in the highest dose group where no loading dose was administered and steady state was expected later.

In the Phase I/II Studies ACE001JP and ACE002JP, emicizumab has been administered to 48 healthy subjects and 18 patients with hemophilia A. A total of 6 subjects/patients tested positive for anti-drug antibodies (ADAs) on at least one occasion. Four subjects/patients presented with treatment emergent ADAs. Out of these 4 subjects/patients, 1 healthy subject had a neutralizing ADA (based on its PK and PD profiles). Safety profiles in subjects/patients who tested positive for ADAs did not generally differ from those of subjects/patients who tested negative for ADAs. Likewise, the presence or absence of ADAs had no impact on efficacy profiles in patients with hemophilia A.

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

For patients with hemophilia A who are diagnosed with inhibitors, permanent eradication of inhibitors is the ultimate goal. This can be achieved by means of intensive FVIII administration over many months with ITI, which is successful in approximately 60%–80% of treated inhibitor patients ([Mariani et al. 2003](#); [Santagostino et al. 2009](#); [Hay and DiMichele 2012](#)). However, hemostatic management may be challenging during the time interval required to achieve ITI success. Furthermore, ITI is not viewed as a viable option for inhibitor patients in many countries, owing to its high cost, the scarce local supply of FVIII concentrates, practical issues and potential complications associated with CVADs, and psychological stress on patients and their families for this highly demanding therapeutic endeavor.

Therefore, for those patients with inhibitors who are unable to eradicate their inhibitors or are not candidates for ITI, bypassing agents are required to treat or prevent bleeds. Unfortunately, the hemostatic effect of bypassing agents is unstable in comparison with

that of FVIII concentrates. As opposed to the 8–12-hour half-life and 15–20-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 or extended IV infusions, respectively. In practice, some inhibitor patients will have bleeds that respond better to NovoSeven while others will respond better to FEIBA. Several recent publications evaluating the efficacy of prophylactic therapy in adults and children with the bypassing agents NovoSeven (Konkle et al. 2007) and FEIBA (Leissinger et al. 2007; Ettingshausen et al. 2010; Leissinger et al. 2011; Antunes et al. 2014) showed decreased bleeding rates compared with episodic treatment.

In the FEIBA prophylaxis pivotal study (PROOF study), patients with inhibitors on episodic bypassing agents were eligible for participation if they had a minimum historical ABR of ≥ 12 . Thirty-six patients (age range 7–56) were enrolled, including 5 children of 7–11 years of age and 4 children of 12–15 years of age. On prophylactic aPCC, their median ABR (interquartile range) decreased from 28.7 (32.3) to 7.9 (8.1) (Antunes et al. 2014), suggesting that while this treatment was partially efficacious for some, there still exists suboptimal control of bleeds and unmet medical need in this population.

Given the hemostatic management challenges in hemophilia A patients with inhibitors, there is an urgent need for therapeutics that have more reliable efficacy, an extended half-life, and reduced treatment burden to prevent bleeding for patients with hemophilia A with inhibitors.

The nonclinical and clinical data related to emicizumab to-date support a positive benefit-risk assessment. As described in Section 1.2, evaluation of in vivo pharmacodynamics and efficacy in a cynomolgus monkey model of hemophilia A demonstrated the ability of emicizumab to significantly reduce bleeding tendency under both spontaneous and local trauma-induced bleeding conditions. No toxicologically relevant changes attributable to SC (at doses up to 30 mg/kg weekly) or IV (at doses up to 100 mg/kg weekly) administration of emicizumab were observed, and the NOAEL was the highest tested dose in each toxicity study. Due to the PK properties of emicizumab, with the possibility of less frequent SC administration compared with FVIII therapies, emicizumab may have the potential to significantly improve the treatment of hemophilia A adult, adolescent, and pediatric patients, both with and without FVIII inhibitors, who are in need of treatment to prevent bleeding episodes. Furthermore, emicizumab has no structural relationship to FVIII and, therefore, is not expected to induce or enhance the development of direct inhibitors to FVIII or other coagulation factors.

The positive benefit-risk assessment of emicizumab was corroborated in the Phase I/II studies, which included 5 adolescents (two ■-year-old patients, one ■ year-old patient, and two ■-year-old patients), where clinically meaningful reductions in ABR at all dose

levels tested have been seen to-date along with a favorable risk-benefit profile. Emicizumab was well tolerated in the Phase I/II studies. The majority of adverse events were of mild intensity. The majority of adverse events were not considered related to emicizumab. In these studies, no thromboembolic or systemic hypersensitivity adverse events were observed; however, in the ongoing Phase III Study BH29884, 3 cases of TMA and 3 serious thromboembolic events were observed in patients on emicizumab who received bypassing agents for the treatment of breakthrough bleeds. Four out of these 5 patients have fully recovered and 1 patient died due to severe rectal bleeding (see Sections 5.1.1.3 and 5.1.1.4).

Given the significant unmet medical need among pediatric patients with hemophilia A with FVIII inhibitors and positive benefit-risk assessment for emicizumab, initiation of a pediatric Phase III study is appropriate. See Section 3.3 for the details of the design and rationale for Study BH29992.

This current study is designed to evaluate the efficacy, safety, and pharmacokinetics of emicizumab administered subcutaneously initially once weekly (QW) in pediatric patients with hemophilia A with FVIII inhibitors. Following review of data in adult and adolescent patients with hemophilia A from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg every 2 weeks (Q2W; BH30071) and 6 mg/kg every 4 weeks (Q4W; BO39182), this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients (see Section 3.3.1).

2. OBJECTIVES AND ENDPOINTS

The objectives of the study are to investigate (with no formal hypothesis testing) the efficacy, safety, and pharmacokinetics of SC emicizumab administered at 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W in pediatric patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents. A total of approximately 80 patients are planned: approximately 60 patients in Cohort A (1.5 mg/kg QW) and approximately 10 patients each in Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W). Patients younger than 12 years of age are planned for enrollment, with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent to further evaluate dosing of emicizumab in patients <40 kg. Of note, enrollment in Cohort A may be left open exclusively for patients <2 years of age until approximately 5 such patients have been enrolled.

2.1 EFFICACY OBJECTIVES

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The efficacy objectives for this study are as follows:

- To evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate) *
- To evaluate the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate (intra-patient comparison, *Cohort A only, as patients enrolled in Cohorts B and C will not have previously participated in the non-interventional study*) *
- To characterize the efficacy of up-titration on *an* intra-patient level, *based* on the basis of the number of bleeds over time *
- To evaluate the HRQoL of children 8–17 years of age according to Haemo-QoL-Short Form (SF) (completed by patients)
- To evaluate proxy-reported HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children (completed by caregivers)
- To assess the number of days missed from daycare/school and days hospitalized

* Analyses will be performed for: treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

2.2 SAFETY OBJECTIVE

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W), and overall as appropriate.

The safety objective for this study is to evaluate the overall safety of emicizumab in pediatric patients with hemophilia A and inhibitors on the basis of the following endpoints:

- Incidence and severity of adverse events
- Incidence and severity of thromboembolic events
- 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
- Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
- Incidence and severity of TMA
- Incidence and clinical significance of anti-emicizumab antibodies

2.3 PHARMACOKINETIC OBJECTIVE

The endpoints will be analyzed separately for the three cohorts: Cohort A (1.5 mg/kg QW), Cohort B (3 mg/kg Q2W), and Cohort C (6 mg/kg Q4W).

The PK objective for this study is to characterize the exposure (C_{trough}) of emicizumab in patients receiving 1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W prior to drug administration on Day 1 and at the following timepoints:

- Every week during Weeks 1–4 on emicizumab
- Every 2 weeks during Weeks 5–9 on emicizumab
- Every 4 weeks during Weeks 13–37 on emicizumab
- Every 8 weeks during Weeks 41–49 on emicizumab
- Every 12 weeks from Week 57 thereafter while continuing on emicizumab, until the end of the study
- Additional PK samples will be taken in patients who require up-titration (see schedule of assessments in [Appendix 1](#))

2.4 PHARMACODYNAMIC BIOMARKER OBJECTIVE

The PD biomarker objective for this study is as follows:

- To assess potential PD biomarkers of emicizumab, including but not limited to aPTT and FVIII activity, at designated timepoints throughout the study.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This *non-randomized*, multicenter, open-label, Phase III clinical study will enroll children with hemophilia A who have inhibitors against FVIII. Children with hemophilia A and documented historical FVIII inhibitor titer (≥ 5 BU) must currently be receiving treatment with bypassing agents. At least 40 patients younger than 12 years of age and up to *approximately 80* patients are planned for enrollment, with allowance of patients 12–17 years of age who weigh < 40 kg at the time of informed consent. Patients will receive SC doses of emicizumab at 1.5 mg/kg QW (Cohort A) for a minimum of 52 weeks, or until unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see [Figure 1](#)). After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future separate emicizumab extension study.

Because of the uncertainty of the dosing regimen needed in patients < 12 years of age or < 40 kg to achieve similar exposure as in adults and adolescents, this study will *first* evaluate the appropriate dosing regimen in children by starting with the same *weekly* dosing regimen (1.5 mg/kg QW) being evaluated in the Phase III study (BH29884) in adult/adolescent patients with hemophilia A with inhibitors (see Section [3.3.1](#) for details). Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first

4 weeks followed by a maintenance dose of 1.5 mg/kg QW (*Cohort A*) for the remainder of the treatment period. During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see Section 4.5.2).

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg QW) after the first 3–5 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks. A Joint Monitoring Committee (JMC; see Section 9.5) will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) to provide recommendations on increasing the starting maintenance dose (if necessary) to target a similar plasma emicizumab trough concentration as the one being targeted in adolescents and adults (i.e., 45 µg/mL). All patients enrolled following the first interim data review will receive the starting maintenance dose selected by the JMC. Those patients enrolled prior to the first interim data review who had not had their dose up-titrated will remain on their current maintenance dose, unless they meet eligibility for up-titration based on protocol-defined criteria (see Section 4.5.2).

In order to include and safely treat the youngest patients (birth to < 2 years of age), this study will include a staggered approach to enrollment by age. Patients ≥ 2 to < 12 years of age and patients 12–17 years of age who weigh < 40 kg will enroll first. A second interim data review will occur once at least 10 patients between ≥ 2 and < 12 years of age have been dosed for a minimum of 12 weeks, at which time all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated to provide recommendations for enrollment of children < 2 years of age, as well as on any additional adaptations of the maintenance dose if necessary.

Furthermore, should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose (*Cohort A*). After the JMC recommendations are released following both interim data reviews, the study will continue to enroll in *Cohort A* up to approximately 60 patients.

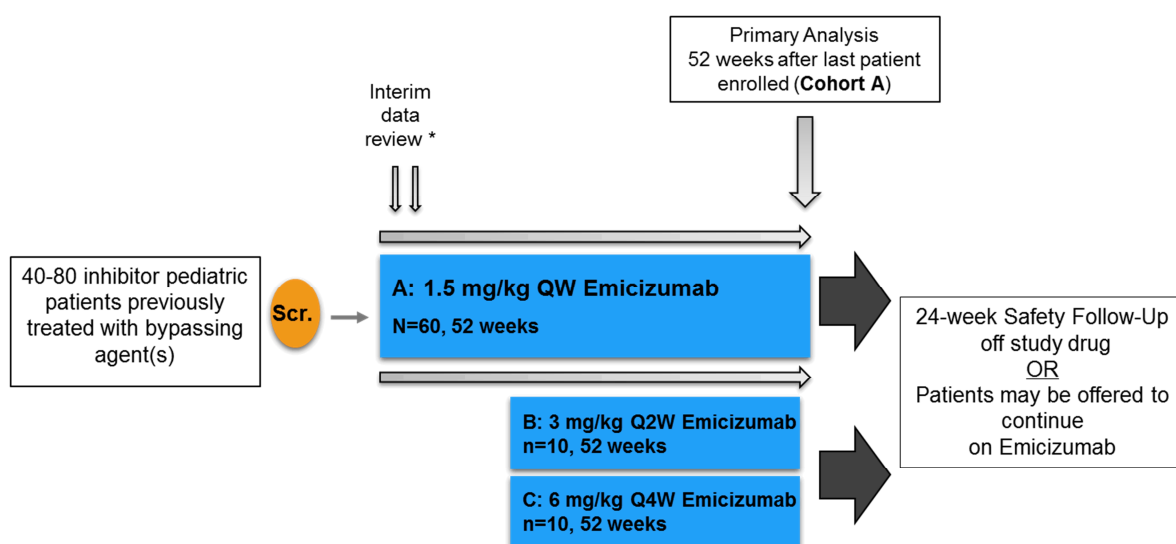
Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3) review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Recruitment to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via 1xRS, for a total of approximately 10 patients per cohort. Of note, enrollment to Cohorts B and C will be limited to patients 2–11 years of age. Emicizumab will be administered with a loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of 3 mg/kg Q2W (Cohort B) and 6 mg/kg Q4W (Cohort C) for a minimum of 52 weeks, or until

unacceptable toxicity, discontinuation from the study due to any cause, or other criteria set forth in the protocol, whichever occurs first (see [Figure 1](#)). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab.

The entire study will enroll up to approximately 80 patients with allowance for additional patients < 2 years of age in Cohort A.

A patient who fulfills the inclusion and exclusion criteria should be enrolled at the Week 1 visit. Prophylactic use of bypassing agents should be discontinued *the day before* the first dose of emicizumab is given.

Figure 1 Study Schema



JMC=Joint Monitoring Committee; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; Scr=screening.

* In a first interim data review, the starting maintenance dose will be evaluated after the first 3–5 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks. A JMC will review all cumulative data (e.g., safety, efficacy, and pharmacokinetics) to provide recommendations on increasing the starting maintenance dose. A second interim data review will occur by the JMC once at least 10 patients (≥ 2 to < 12 years of age) have been dosed for a minimum of 12 weeks, at which time all available cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated to provide recommendations for the enrollment of children < 2 years of age, as well as on the maintenance dose. Should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold after the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose. After the JMC recommendations are released following both interim data reviews, the study will continue to enroll up to a maximum of approximately 60 patients in Cohort A. Subsequently, should no safety concerns arise from review of adult/adolescent data at Q2W (BH20071) and Q4W (BO39182) dosing, parallel enrollment with alternate cohort allocation to Cohorts B and C (up to approximately 10 patients per cohort, respectively) will commence.

The primary analysis *for all cohorts* will be performed 52 weeks after *all* patients in the primary *population of Cohort A* have been enrolled or withdrawn prematurely, whichever occurs first. The primary *population of Cohort A* consists of all patients enrolled prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients) and is used to define the timing of the primary analysis *of Cohorts A, B, and C*. If no patients < 2 years of age are included in the primary *population of Cohort A*, the primary analysis will still occur at the specified time; however, enrollment *to Cohort A* may be left open exclusively for patients < 2 years of age in order to enroll *approximately 5* such patients. Note that these patients will be included in the primary *analysis of Cohort A* regardless of their follow-up time. *Additionally, all available data from patients enrolled in Cohorts B and C (efficacy period approximately 6 months) will be included in the primary analysis of Cohort A.*

During the study, caregivers will be asked to enter any individual bleeds, hemophilia-related medications, and emicizumab treatments that occur on an electronic, handheld device. Entries should be made at least weekly, *and also* at any time a bleed occurs or a hemophilia medication, *including emicizumab*, is administered. Detailed information about bleeds (type, location, date/time) will be captured. Detailed information about hemophilia medications (agent, dose, reason for administration, date/time) and emicizumab dosing (total volume, date/time) will also be captured. In addition, HRQoL using the Haemo-QoL-SF (completed by children 8 years of age and older), proxy-reported HRQoL and aspects of caregiver burden using Adapted InhibQoL (completed by caregivers of all children) and missed daycare/school will be collected on a separate electronic, handheld device during a patient's visit prior to emicizumab injection at Week 1 and every 12 weeks thereafter, as outlined in the schedule of assessments (see [Appendix 1](#)). The number of days the child was hospitalized, if applicable, will be derived from data collected on eCRF.

Emicizumab is intended in this study for prophylactic use only (i.e., not to treat bleeds that have already occurred). Therefore, in this study all patients *may* continue to receive episodic treatment for breakthrough bleeds as needed. Breakthrough bleeds should preferably be treated with rFVIIa at the lowest expected dose to achieve hemostasis and captured as they occur on the electronic, handheld device. There is 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, and 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/II studies. However, in the ongoing Phase III Study BH29884 (adolescent and adult patients with hemophilia A with FVIII inhibitors), 3 events of TMA and 3 *serious* thromboembolic events were observed in patients who concomitantly used > 100 U/kg/day of aPCC *on average for ≥ 24 hours* for the treatment of breakthrough bleeds (see Sections [1.2](#), [1.3](#), [5.1.1.3](#), and [5.1.1.4](#)). Therefore, it is recommended that breakthrough bleeds are treated with rFVIIa only, if possible, and that

the use of aPCC or other bypassing agents should be avoided or limited (see Sections 4.6.1 and 4.6.2). Also, local and central laboratory assessments are required to monitor the risk for thromboembolic events or TMA as per the schedule of assessments (see Appendix 1 and Appendix 2). Investigators will be asked to 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 the patient's benefit-risk of continued treatment.

Physical examinations, vital sign assessments, ECG, and safety laboratory assessments will be collected as per the schedule of assessments (see Appendix 1). Adverse events will be captured on an ongoing basis as they occur during the study. All patients in this study will undergo PK assessments. Blood samples will also be collected to assess the PD properties of emicizumab (i.e., aPTT, FVIII activity), as well as to assess immunogenicity (i.e., anti-emicizumab antibodies and anti-FVIII antibodies). A detailed list is provided in the schedule of assessments (see Appendix 1).

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. Pediatric patients who are enrolled in the non-interventional Study BH29768 are eligible to enroll in this study, as long as they meet the inclusion and exclusion criteria and are able to enroll at a participating site while the study is open for enrollment. *All patients who participated in the non-interventional study will be enrolled in Cohort A.*

3.2 END OF STUDY AND LENGTH OF STUDY

LENGTH OF STUDY

The length of the entire study from screening of the first patient to the last patient completing 52 weeks in the study and/or the end of study follow-up visit (24 weeks after discontinuing emicizumab) will be approximately 152 weeks.

END OF STUDY

The primary analysis will take place at the same time for Cohorts A, B, and C. It will occur after all patients in the primary population of Cohort A have completed 52 weeks of treatment, or have withdrawn prematurely, whichever occurs first. All data from patients enrolled in Cohorts B and C will be included regardless of follow-up time.

After 52 weeks of treatment, an individual patient who continues to derive clinical benefit may continue receiving prophylactic emicizumab as part of this study or a future

separate emicizumab extension study. Patients who discontinue emicizumab will have a safety follow-up visit at 24 weeks after the last emicizumab dose.

The end of this study is defined as the date when the last remaining patient has completed the last visit (i.e., LPLV), as defined below:

- Completed 52 weeks of emicizumab and either transferred to a separate extension study to receive further emicizumab as per Roche Global Policy on Continued Access to Investigational Medicinal Products or to commercial product

OR

- Completed the end of study safety follow-up visit 24 weeks after discontinuing emicizumab

OR

- Consent has been withdrawn

OR

- Lost to follow-up

3.3 RATIONALE FOR STUDY DESIGN

Regulatory Agencies introduced the concept of extrapolation of efficacy from adult to pediatric patients in the European Union with the Guidelines, "Concept paper on extrapolation of efficacy and safety in medicine development" (EMA 2013) and in the United States with 1994 Final Regulation on Pediatric Labeling. Indeed, recent registration studies of clotting factor concentrates (Eloctate SBA, Novoeight SBA, Advate SBA), for children with hemophilia A, have defined pharmacokinetics and safety in pediatric patients with extrapolation of efficacy data from adults and adolescents. The Sponsor has chosen a similar approach utilizing a *non-randomized*, descriptive study to investigate the pharmacokinetics, safety, and efficacy of emicizumab in pediatric hemophilia A patients with FVIII inhibitors. Extrapolation of efficacy from the adult population to the pediatric population has helped to maximize the use of existing information to increase the efficiency of pediatric drug development programs while maintaining the goal of increasing the number of safe effective medicines approved for pediatric use on the basis of scientifically robust data (Dunne et al. 2011). As such, no formal hypothesis is planned. There are no anticipated differences in the effect of emicizumab in pediatric patients compared with adults, and similar exposure in adult/adolescent and pediatric patients < 12 years of age is assumed to produce similar efficacy. This strategy is consistent with recent recommendations published by the International Society on Thrombosis and Haemostasis (ISTH). The Project Group on Clinical Trials for New Products in Hemophilia recommends, in the framework of the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) pediatric regulation mandating the generation of pediatric data to support Marketing Authorization Application (MAA), to adopt an appropriate clinical development approach to limit the risks in delaying access to products for all patients with hemophilia for an extended time, given the relative rarity of this condition and logistics of conducting clinical studies

(DiMichele et al 2015). The proposed study, BH29992, will *therefore* evaluate the use of prophylactic emicizumab, in children with inhibitors to FVIII previously treated with bypassing agents in a *non-randomized*, multicenter, open-label study.

3.3.1 **Rationale for Emicizumab Dose and Schedule**

Loading doses of 3 mg/kg *QW* emicizumab for 4 weeks *will be* followed by a maintenance dose of 1.5 mg/kg *QW* for patients *enrolled in Cohort A*. Subsequent dose adaptation will be made as required based on efficacy and exposure, as detailed below.

Emicizumab prophylaxis has been administered subcutaneously in 18 Japanese patients with hemophilia A (with and without FVIII inhibitors) in Study ACE001JP and in its ongoing extension Phase I/II Study ACE002JP. One patient receiving weekly doses of 1 mg/kg discontinued emicizumab during Study ACE001JP. Three dose cohorts (of 6 patients each) received the following treatment (administration period of 12 weeks):

- Cohort C-1: a loading dose of 1 mg/kg followed by weekly doses of 0.3 mg/kg
- Cohort C-2: a loading dose of 3 mg/kg followed by weekly doses of 1 mg/kg
- Cohort C-3: weekly doses of 3 mg/kg

Three dose cohorts included 5 adolescent patients: 1 patient (■-year-old inhibitor) in Cohort C-1; 2 patients (■-year-old inhibitor, ■-year-old non-inhibitor) in Cohort C-2; and 2 patients (■-year-old inhibitor, ■-years-old inhibitor) in Cohort C-3.

Emicizumab was safe and well-tolerated in these patients (see Section 1.2 and the Emicizumab Investigator's Brochure). The maximum clinical dose of 3 mg/kg weekly is associated with a 10.3-fold and 11.2-fold safety margin relative to the preclinical NOAEL based on C_{max} and AUC_{τ} , respectively. No clear difference in the plasma concentrations of emicizumab was observed between adolescent 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 weekly (see Table 1). ABR decreased in all patients, regardless of age or the presence of FVIII inhibitors. See the Emicizumab Investigator's Brochure for additional details on clinical studies with emicizumab.

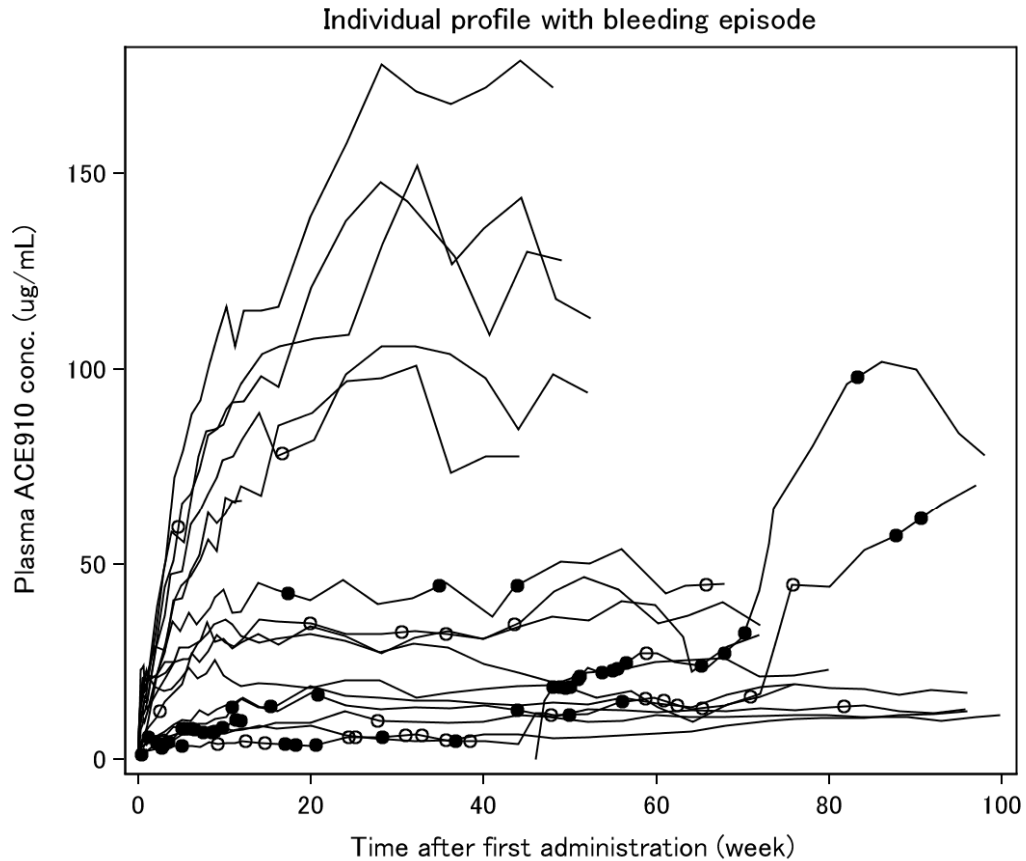
Table 1 Mean Reduction (%) of Annualized Bleeding Rates in Inhibitor and Non-Inhibitor Patients Enrolled in ACE001JP/ACE002JP

Emicizumab Dose	0.3 mg/kg weekly	1 mg/kg weekly	3 mg/kg weekly
Mean ABR reduction	74.7%	85.8%	93.0%

ABR=annualized bleeding rate.

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



0.05 ug/mL was assigned if below the lower limit of quantification.
 Filled and open circles represent the predicted values of analyte at the beginning time of each bleeding episode required coagulation factor treatment including and not including joint bleeding, respectively.
 Predicted value was obtained based on linear interpolation between previous and next observed values around the beginning time of each bleeding episode, or last observation carried forward if bleeding episode occurred after the last observed time of analyte included in the analysis.
 Datetime: June 8, 2015 14:59:00

ACE910=emicizumab.

- Joint bleed
- 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 concentration $\geq 45 \mu\text{g/mL}$. On the basis of population PK modeling, a median trough plasma concentration of $45 \mu\text{g/mL}$ is predicted to be achieved after treatment with 4 weekly doses of 3 mg/kg and maintained, thereafter, with weekly doses of 1.5 mg/kg.

The loading doses of 3 mg/kg weekly 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 weekly investigated in the Phase I/II studies. Thereafter, a dose and schedule of 1.5 mg/kg weekly was chosen in order to reduce the peak-trough fluctuations and to maintain emicizumab plasma concentrations above 45 µg/mL over the entire dosing interval. This dosing regimen (i.e., 3 mg/kg weekly for 4 weeks followed by 1.5 mg/kg weekly) was, therefore, chosen to be investigated in the adult and adolescent study, BH29884.

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](#)). Furthermore, 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. 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). Preliminary investigations of the effect of body weight on emicizumab pharmacokinetics suggest that exposure decreases slightly with decreased body weight. A maintenance dose of 1.5 mg/kg/week is predicted to maintain a median trough concentration above the cutoff of 45 µg/mL in patients weighing ≥ 40 kg. In order to predict which weekly maintenance dose would be needed in pediatric patients to achieve the desired trough plasma concentration of emicizumab, simulations of steady-state trough plasma concentrations were performed using age as a predictor of body weight. Simulations based on this body weight effect indicated that a weekly maintenance dose of 2.25 mg/kg/week would be needed in patients aged 1–12 years, and 3 mg/kg/week in patients aged < 1 year. However, body weight changes, alone, do not explain changes in drug disposition due to maturation of organ, tissue, enzyme, and transporter systems in neonates and infants ([Anderson 2008](#); [2013](#)). Age was, therefore, also used as a predictor of maturation of clearance, in addition to body weight, and simulations indicated that a weekly maintenance dose of 1.5 mg/kg would be needed in patients aged 1–12 years, and 2.25 mg/kg in patients aged < 1 year. In light of the opposing effect of body weight and clearance maturation on the emicizumab exposure, and the uncertainty associated with the effect of clearance maturation, there is a possibility that the same dosing regimen in adolescent/adult and pediatric patients (i.e., loading doses of 3 mg/kg *QW* for 4 weeks, followed by a maintenance dose of 1.5 mg/kg *QW*) provides the same efficacy trough of 45 µg/mL. Thus, Study BH29992 will evaluate the appropriate dosing regimen in children by starting with the same dosing regimen as the adult and adolescent study, BH29884.

Individual pediatric patients may have their dose up-titrated if they experience suboptimal control of bleeding on emicizumab (see Section 4.5.2). Prophylactic treatment with FEIBA currently provides the most efficacious treatment for hemophilia A patients with inhibitors, with a median ABR of 8 (Antunes et al. 2014); thus, suboptimal control of bleeding in this study has been defined as an ABR \geq 8. In Study BH29992, up-titration may be required if the patient experiences more than two bleeding events during a 12-week treatment period at a given dose (which corresponds to an ABR of 8). Dose up-titration will, therefore, be guided by bleeding control on the current dose and by discussion with and approval of the Medical Monitor. Using a safety and efficacy guided up-titration scheme allows for more accurate assessment of bleeding events in light of safety considerations and each patient's duration of exposure at a particular dose.

If a majority of the initially enrolled patients require up-titration, or their emicizumab trough plasma concentration is on average lower than 45 $\mu\text{g/mL}$, the choice of the initial maintenance dose may not be appropriate. Thus, the Sponsor plans to re-evaluate the starting maintenance dose after the first 3–5 patients (2–11 years of age) have been treated for a minimum of 12 weeks. All cumulative data (safety, efficacy, and pharmacokinetics) will be evaluated by a JMC to provide recommendations of changing the starting maintenance dose for the subsequent patients enrolled (see Section 4.5.2).

3.3.1.1 Interim Analysis, JMC Recommendations, and Rationale for Enrollment of Q2W/Q4W in Pediatric Patients

The initial maintenance dose of 1.5 mg/kg QW was evaluated by the Study BH29992 JMC during an interim data review (clinical cutoff date: 28 October 2016). As enrollment occurred faster than anticipated, the two planned data review meetings were combined into one. All available data (including safety, efficacy, and pharmacokinetics) from the first 20 patients enrolled in Cohort A was assessed by the JMC to determine the appropriateness of the starting maintenance dose, as well as to decide whether the study could begin enrolling patients <2 years of age. On 7 December 2016, the JMC recommended continuing enrollment of patients in Cohort A at the maintenance dose of 1.5 mg/kg QW, as well as to open enrollment to patients < 2 years of age at that same maintenance dose. Since exposure at 1.5 mg/kg QW was similar between patients 3–12 years of age and adolescent/adult patients, the up-titration scheme for children has been modified to be the same as the one used in adolescent/adult patients, that is, individual up-titration to 3 mg/kg QW should they experience suboptimal control of bleeding on emicizumab (see Section 4.5.2).

Furthermore, two Phase III studies investigating 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) have been initiated in adolescent/adult patients with hemophilia A without inhibitors (BH30071) and with and without inhibitors (BO39182). All three dosing regimens are predicted to achieve similar exposure (in terms of steady-state average concentration, $C_{\text{avg,ss}}$; see Table 2), and despite higher peak concentrations and lower trough concentrations with less frequent dosing regimens, all are expected to result in similar treatment response (all three dosing regimens provide

similar predicted ABR distribution) and safety profiles. Of note, the exposures achieved with these three dosing regimens remain well below the safe and well-tolerated one achieved with the highest dose of 3 mg/kg QW (observed trough concentration of $120 \pm 26.8 \mu\text{g/mL}$). Ultimately, these three dosing regimens will provide the option for patients to receive emicizumab at different scheduled intervals, while still delivering the same cumulative dose.

Table 2 Simulated Median Pharmacokinetic Parameters

Parameters	Maintenance Dose		
	1.5 mg/kg QW	3 mg/kg Q2W	6 mg/kg Q4W
$C_{\text{max,ss}}$ ($\mu\text{g/mL}$)	54.6	56.8	63.4
$C_{\text{trough,ss}}$ ($\mu\text{g/mL}$)	51.5	48.0	40.7
$C_{\text{avg,ss}}$ ($\mu\text{g/mL}$)	53.0	53.1	53.0

$C_{\text{avg,ss}}$ = average concentration (AUC/τ) at steady state; $C_{\text{max,ss}}$ = maximum plasma concentration at steady state; $C_{\text{trough,ss}}$ = trough concentration at steady state; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = once weekly.

An independent Data Monitoring Committee (iDMC) conducted a scheduled review of the safety data in Study BH30071, which detected no unforeseen safety signals in adult/adolescent patients treated with emicizumab at 3 mg/kg Q2W. Meanwhile, an interim analysis of 6 mg/kg Q4W in a run-in cohort of 7 adolescent/adult patients in Study BO39182 indicated that observed PK parameters at 6 mg/kg Q4W were as expected, in line with earlier simulations. This study is ongoing with no safety concerns raised by the iDMC to date. Therefore in this current study, following completion of accrual to Cohort A (1.5mg/kg QW), enrollment to Cohorts B (3 mg/kg Q2W) and C (6 mg/kg Q4W) can commence.

The emicizumab regimens to be evaluated in this study consist of a loading dose of 3 mg/kg weekly for 4 weeks, followed by a maintenance dose administered either 1.5 mg/kg QW, 3 mg/kg every Q2W, or 6 mg/kg Q4W. Of note, a maintenance dose of 3 mg/kg QW may also be evaluated in the setting of patients who have their dose up-titrated.

3.3.2 Rationale for Patient Population

As described in Section 1.1, pediatric patients from birth to 11 years of age with hemophilia A and inhibitors against FVIII who are treated with bypassing agents prior to study entry will comprise the primary population for this Phase III study evaluating the pharmacokinetics, safety, and efficacy of prophylactic emicizumab. However, due to the current uncertainty of dosing in patients < 40 kg (with some patients > 12 years of age falling into this category), patients 12–17 years of age who weigh < 40 kg will also be allowed to enroll (in Cohort A).

Although the initial severity of a patient's hemophilia A is directly related to the endogenous FVIII activity, the treatment of patients of any severity (mild, moderate, or severe) with high-titer inhibitors is similar (i.e., with bypassing agents). Because the initial severity of hemophilia A, which is defined at diagnosis on the basis of FVIII activity, is no longer prognostic of clinical phenotype and risk of bleeding in patients who have developed high titer inhibitors, this will not be used to determine study eligibility.

Instead, eligibility criteria aim to select a cohort of hemophilia A patients with inhibitors who have a high, unmet medical need. Thus, pediatric patients ≥ 2 years of age with inhibitors treated with bypassing agents on an episodic basis will be required to have an ABR of ≥ 6 (e.g., ≥ 3 bleeds in the last 24 weeks). Patients treated with bypassing agents on a prophylactic basis will be required to be inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or with CVAD placement medically not feasible or deemed unsafe by investigator. In such cases, deficiencies associated with bypassing agents, including decreased efficacy, increased thrombotic risk, and increased burden of care, render these patients on prophylaxis in high unmet medical need. Finally, pediatric patients < 2 years of age with inhibitors treated with bypassing agents, and determined by investigator to be at high risk of bleed, will also be allowed to enroll (*in Cohort A*).

Based on its mechanism of action (mimetic of FVIII co-factor activity) and clinical study results to-date, prophylactic emicizumab is expected to provide significant and clinically meaningful benefit for pediatric patients with inhibitors who are in need of a reliably efficacious therapy to prevent bleeds.

Based on current treatment algorithms for patients with hemophilia A with inhibitors ([Kempton and White 2009](#); [Srivastava et al. 2013](#)), it is anticipated that the majority of adults and adolescents treated with emicizumab will have previously undergone ITI without success or are not candidates for ITI, although prior ITI will not be required for study entry.

Because clinical safety data related to the concomitant use of prophylactic emicizumab in the presence of high doses of FVIII, such as are administered during ITI, are not available at this time, patients currently receiving ITI will not be eligible for enrollment in this study. Because the presence or amount of FVIII inhibitors in their plasma does not impact the efficacy of emicizumab, and inhibitor titers may drop when patients are not exposed to FVIII for a prolonged period of time, patients' inhibitor titers at the time of study entry will not influence their study eligibility. However, patients will be required to have a history of a high-titer inhibitor documented in the medical record in order to be eligible for the study.

3.3.3 Rationale for the Efficacy Analyses

The objective of the efficacy analysis is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate). Another efficacy

analysis will also characterize the efficacy of up-titration on an intra-patient level. As mentioned in Section 3.1, the *primary* efficacy analysis will be performed 52 weeks after the last patient from the primary *population of Cohort A* has been enrolled or withdrawn prematurely, whichever occurs first. *Primary efficacy analyses for Cohorts B and C will occur at the time of the primary analysis for Cohort A. Additional efficacy analyses will be performed at the end of the study and as needed to support regulatory interactions.*

In the multiple-ascending dose Phase I study involving Japanese patients with hemophilia A (Study ACE001JP), a clinically meaningful reduction in median ABR to 0 after 12 weeks of treatment in the 1 and 3 mg/kg/week emicizumab dose cohorts was demonstrated. In the Japanese Phase I/II extension study (ACE002JP), the median ABR of the 1 and 3 mg/kg/week dose cohorts remained 0 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 in inhibitor patients is associated with maintenance of ABR reduction ([Antunes et al. 2014](#)). At the cutoff date of 17 April 2015, the duration of safety follow-up for all patients in the 1 and 3 mg/kg/week cohorts in Study ACE001JP/Study ACE002JP ranges from 69.3–80.3 weeks and 45.1–54.6 weeks, respectively (see the Emicizumab Investigator's Brochure for additional details on clinical studies with emicizumab).

3.3.4 Rationale for Patient-Reported Outcome Assessments

HRQoL is an important outcome in the care of children with hemophilia ([Brown et al. 2009](#)). HRQoL in hemophilic patients is multifaceted and impacted by disease symptoms (pain, bleeding), treatment (prophylactic and on-demand), anxiety (around injections), and limitations in daily activities.

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 different 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](#)). Because children often require assistance in the administration of their hemophilia medication, it is equally important to assess the potential burden and impact on HRQoL that this may have on caregivers. In a recent 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 in the current study 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. These HRQoL measures will be assessed at

baseline and every 12 weeks using a tablet device during a patient's visit in clinic. HRQoL questionnaires include the Haemo-QoL-SF (to be completed by patients 8–17 years of age) and the Adapted InhibQoL with Aspects of Caregiver Burden (to be completed by caregivers of all patients enrolled in this study).

3.3.5 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. Refer to Section 5.1.3 for more information about effects of emicizumab on existing laboratory assays. Plasma samples will be collected for central PD biomarker assessment in parallel with PK samples to demonstrate evidence of biologic activity of emicizumab in patients and to monitor the patients' coagulation status. These biomarkers include but are not limited to coagulation-related assays such as aPTT, PT/INR, D-dimer, and FVIII activity assays. The aPTT and thrombin generation 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). The central aPTT assay will be run both in standard form and with a modification to ensure that the assay range covers all levels of emicizumab exposure.

Exploratory plasma biomarkers will include factor IX antigen (FIX:Ag) and factor X antigen (FX:Ag) 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 or assays. Finally, residual blood from collected samples may be used for additional emicizumab-related research. These banked plasma samples will not be used for general, disease-related research purposes but instead for research directly related to emicizumab.

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 EC Guideline on Ethical considerations for clinical studies on medicinal products conducted with the pediatric 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. Refer to the laboratory manual for detailed weight-based blood sampling guidelines.

3.3.6 Rationale for Pharmacokinetic Sample Schedule

One of the aims of this study is to provide dosing recommendations for pediatric patients aged less than 12 years. A median ABR of 0 has been predicted to be achieved for an emicizumab trough plasma concentration of ≥ 45 $\mu\text{g/mL}$ based on data in adolescent and adult patients with hemophilia A (Study ACE001JP/ACE002JP). As no differences in the action of emicizumab are anticipated between pediatric and adult patients (see Section 3.3.1), it is the Sponsor's intention to identify a dose in children < 12 years that may provide such a trough plasma concentration.

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

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 80 children < 12 years of age with hemophilia A and with FVIII inhibitors previously treated with bypassing agents will be enrolled in the study (approximately 60 patients in Cohort A, 10 patients in Cohort B, and 10 patients in Cohort C). In addition to this primary population of children < 12 years of age, patients 12–17 years of age who weigh < 40 kg at the time of informed consent will also be eligible to enroll. These patients, as well as those < 2 years of age at the time of informed consent, will only be eligible to enroll in Cohort A. Of note, enrollment in Cohort A may be left open exclusively for patients < 2 years of age until approximately 5–10 such patients have been enrolled prior to the closure of Cohorts B and C, whichever occurs first.

4.2 INCLUSION CRITERIA

Children must meet all 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 with allowance for the following:
 - Patients 12–17 years of age and who weigh < 40 kg at the time of informed consent (*Cohort A only*)
 - Patients < 2 years of age will be allowed to participate only after the protocol-defined interim data review criteria are met (*Cohort A only*)
- 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 patient-reported outcome (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)
- Requires treatment with bypassing agents
- For patients ≥ 2 years of age:
 - If on an episodic bypassing agent regimen: ABR of ≥ 6 (e.g., 3 bleeds in the last 24 weeks)
 - OR
 - If on a prophylactic bypassing agent regimen: inadequately controlled (e.g., 2 bleeds since starting prophylaxis or 1 life-threatening bleed) or CVAD placement medically not feasible or deemed unsafe by investigator
- For patients < 2 years of age (*Cohort A only*): determined by investigator to be in high unmet medical need
- 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 upper limit of normal (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. When the serum creatinine is $\geq 1.5 \times$ ULN, creatinine clearance by Bedside Schwartz formula must be > 70 mL/min/1.73m²
- At screening, in the rare cases of hemophilia in female patients who are of childbearing potential, patients will be required to have a negative serum pregnancy test result (with urine pregnancy tests performed at subsequent specified visits) and will have to agree to remain abstinent or use single or combined highly effective contraceptive methods that result in a failure rate of $< 1\%$ per year and are approved by local health authorities and ethics committees during the treatment period and for at least 5 elimination half-lives (24 weeks) after the last dose of study drug.

4.3 EXCLUSION CRITERIA

Children 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 TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
- Use of systemic immunomodulators (e.g., interferon or corticosteroids) at enrollment or planned use during the study period
- 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

4.4 METHOD OF TREATMENT ASSIGNMENT

The study is a *non-randomized*, open-label, Phase III, multicenter study of emicizumab in pediatric patients <12 years of age and 12–17 years of age who weigh <40 kg with hemophilia A with inhibitors.

The study consists of three cohorts. Patients will receive an initial loading dose of 3 mg/kg QW for the first 4 weeks followed by a maintenance dose of either 1.5 mg/kg QW (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg Q4W (Cohort C). The study will begin by recruiting patients in Cohort A. Once 1) the exposure at 1.5 mg/kg QW has been characterized in this pediatric population; 2) Cohort A is fully enrolled; and 3)

review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifies no safety concerns, this study will open two additional non-randomized cohorts to investigate Q2W and Q4W regimens in pediatric patients. Recruitment to Cohort B (3 mg/kg Q2W) and Cohort C (6 mg/kg Q4W) will occur in parallel with alternate cohort allocation via IxRS.

The time between screening and enrollment of eligible patients should be ≤ 28 days; otherwise, patients must be re-screened to determine if they continue to meet the inclusion and exclusion criteria.

4.5 STUDY TREATMENT

4.5.1 Formulation, Packaging, and Handling

4.5.1.1 Emicizumab

Emicizumab IMP will be supplied by the Sponsor as a sterile liquid for SC injection, contains no preservatives, and requires storage at 2–8° Celsius (do not freeze and protect from light). Single-use vials contain 30, 60, or 150 mg (nominal) of emicizumab at pH 6.0. The emicizumab IMP 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, three configurations of the IMP are intended to be used in this study, differing from each other only in emicizumab concentration or filling volume: nominal vial strength 150 mg (150 mg/mL, 1.0 mL); nominal vial strength 60 mg (150 mg/mL, 0.4 mL); nominal vial strength 30 mg (30 mg/mL, 1.0 mL). This will enable safe subcutaneous weight-based volume dosing of small children with sufficient precision. The excipient composition and primary packaging is identical for all configurations. For information on the handling of emicizumab, see the “Instructions for Use” (IFU) document.

4.5.2 Dosage, Administration, and Compliance

Emicizumab *treatment will begin with a loading dose of 3 mg/kg QW for the first 4 weeks (Day 1 of each week) followed on Week 5 by a maintenance dose of either 1.5 mg/kg QW (Cohort A), 3 mg/kg Q2W (Cohort B), or 6 mg/kg Q4W (Cohort C). Note that the cumulative dose studied in all three cohorts is identical, but the dose administration schedule differs between cohorts. Patients will receive prophylactic emicizumab for a minimum of 52 weeks, or until unacceptable toxicity or discontinuation from the study due to any cause.*

On 7 December 2016, the JMC recommended continued enrollment to Cohort A at the original starting maintenance dose of 1.5 mg/kg QW, and to open enrollment to patients < 2 years of age at that same maintenance dose. Moreover, review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) has identified no safety concerns to date. See Section 3.3.1.1 for details.

During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab. *Patients in Cohorts A, B, or C with ≥ 2 qualifying bleeds within a 12-week interval may have the opportunity to have their maintenance emicizumab dose increased to 3 mg/kg QW starting on Week 17, if they receive approval from the Medical Monitor. Of note, for patients from Cohorts B or C who have a dose up-titration, their dosing regimen will change from Q2W or Q4W to QW. Qualifying bleeds are defined as spontaneous and clinically significant, physician verified (e.g., with diagnostic imaging, clinical examination, photograph), and occurring while on prophylactic emicizumab at steady-state on the maintenance dose (after Week 5). Should patients meet protocol-defined criteria for up-titration, the investigator will contact the Medical Monitor to initiate a discussion about possible up-titration. Upon up-titration to the new maintenance dose of 3 mg/kg QW, the patient's schedule of assessments will reset to Week 1, and the next five visits must take place at the site.*

Based on ongoing evaluation of efficacy, safety, and PK data, including interim analyses, the Sponsor and/or the JMC may recommend a dose higher than 3 mg/kg QW for a patient or a patient population. Dosing above 3 mg/kg QW (not higher than 6 mg/kg QW) may, therefore, occur while ensuring that the exposure will not exceed the exposure achieved with the safe and well tolerated highest dosing regimen tested in clinic.

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 and approval to resume dosing is given. Should unanticipated events occur during the study that require treatment with multiple daily administrations of bypassing agents or FVIII concentrates for multiple days, 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. Any other emicizumab dose adjustment request will require discussion of the clinical case with and approval from 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 IFU document. Patients/caregivers will in turn be trained by an HCP on study medication preparation and self-administration/administration at the recommended sites of injection as detailed in the IFU. The HCP is to 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., $\pm 10\%$), the new volumetric dose to be administered must be communicated to the patient/caregiver.*

In order to minimize the number of injections for pediatric patients in certain high weight categories, the administration per single injection of up to 2 mL of 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 of a given concentration (i.e., vial pooling) into a single syringe using a new transfer needle for each vial. The detailed procedure for vial pooling is described in the IFU. *Vials of different emicizumab concentrations must not be combined.*

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

Emicizumab will be administered as a SC injection in the home setting 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. For patients with a previous history of a clinically significant hypersensitivity reaction, additional precautions as described in Section 5.1.1.2 should be considered. The fourth and fifth scheduled study drug administrations must also be performed in the monitored setting, and the patient/caregiver will be trained and have the opportunity to ask any questions to 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 the 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, then arrangements may be made to identify a trained caregiver or HCP to administer the SC injections.

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 recorded and competence of the patient or caregiver to administer at home will be documented in the electronic Case Report Form (eCRF). If necessary, patients/caregivers or their HCP may choose to continue administration of study drug in the clinic. Compliance in the home setting is to be monitored by recording emicizumab administration on an electronic, handheld device and recording collected used and unused vials during each patient's clinic visit.

Study medication should be administered on the scheduled dosing day. On days when trough plasma PK samples are to be collected, patients will be dosed after those samples are drawn.

- For patients in Cohort A (QW dosing), if the patient/caregiver forgets or cannot administer study medication on the scheduled dosing day, the 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/caregiver should administer his or her next dose at the next

scheduled time (with the study medication dosing resumed in accordance with the original dosing schedule).

- *For patients in Cohort B (Q2W dosing), if the patient/caregiver forgets or cannot administer study medication on the scheduled dosing day, study medication should be administered as soon as possible within a window of 7 days from the scheduled dosing date. If more than 7 days have passed, the patient/caregiver 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.*
- *For patients in Cohort C (Q4W dosing), if the patient/caregiver 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 have passed, the patient/caregiver 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.*

All emicizumab dosing should be clearly documented on the handheld, electronic patient-reported outcome (ePRO) device, both during patient's visits in clinic and when the patient is out of the clinic.

Any overdose or incorrect administration of study drug will be determined from emicizumab data entered into the handheld ePRO device. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Patients and/or caregivers will be provided with alert 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, alert cards are designed to notify non-study healthcare providers that emicizumab will interfere with certain coagulation laboratory tests (see the Emicizumab Investigator's Brochure for more information) and the investigator should be contacted for assistance in interpreting the test results.

Guidelines for treatment interruption or discontinuation are provided in Section 4.8.2.

If in the investigator's judgment, the individual patient would be eligible for or benefit from ITI therapy, the discontinuation of emicizumab and initiation of this ITI therapy should be discussed with the Medical Monitor.

4.5.3 Investigational Medicinal Product Accountability

Emicizumab, the only investigational medicinal product (IMP) in Study BH29992, 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 response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

Used and unused IMP vials will be returned by patient's caregiver to the study 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. If the investigator prefers to destroy the IMP at his or her site, 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.

4.5.4 Post-Study Access to Emicizumab

The Sponsor will offer post-study 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 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 with FVIII inhibitors
- 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

4.6 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 initiation of study treatment to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF page.

Medications given to treat a bleed (e.g., rFVIIa or aPCC) will be reported only via the electronic, handheld device and not in the eCRF.

4.6.1 Permitted Therapy

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

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

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

Use of aPCC 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 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 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 caregivers at the beginning and throughout the study. Repeated dosing of rFVIIa, aPCC, or other bypassing agents should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing. For rFVIIa, aPCC, and other bypassing agents, laboratory monitoring by additional local and central laboratory assessments should be performed as per the schedule of assessments (see [Appendix 1](#)).

- 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
- Local anesthetic cream for emicizumab SC administration
- Vaccinations should be administered following national immunization schedules. As per the WFH recommendations for vaccinations ([WFH 2012b](#)), patients with hemophilia should be vaccinated. Thus, vaccinations should be administered according to the WFH 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.

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

4.6.2 Prohibited Therapy

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

- Use of aPCC or Byclot® as concomitant prophylactic treatment, including for short-term prophylaxis (*note: this criterion does not apply to the 4 weeks prior to initiation of study treatment*)
- Use of anti-fibrinolytics in conjunction with aPCC or 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 doses or short-term prophylaxis (e.g., around the time of surgery), however, are permitted

- Use of drugs that would affect hemostasis (e.g., aspirin, non-steroidal anti-inflammatory drugs that are not selective or preferential COX-2 inhibitors, or anticoagulants [other than to flush, dwell, or de-clot a CVAD]) 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
- Use of systemic immunomodulators (e.g., rituximab, corticosteroids) other than anti-retroviral therapy
- Elective surgery (excluding minor procedures such as tooth extraction, CVAD removal, incision and drainage, as well as emergency surgeries)
- Use of other investigational drugs

If prohibited therapy is administered for any reason, it should be recorded on the eCRF (except any hemophilia-related medication, which will be recorded on the bleed/medication questionnaire). 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.

4.7 STUDY ASSESSMENTS

4.7.1 Informed Consent Forms and Screening Log

For participation in the study, written informed Consent must be obtained from parent/legally acceptable representative and an Assent from the child when applicable (latest approved version by the IEC/IRB) before performing any study-specific screening

tests or evaluations. Informed Consent/Assent Forms for enrolled patients and for patients who are not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before *enrollment*. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.7.2 Medical History and Demographic Data

Medical history includes hemophilia-related history, clinically significant diseases, procedures within the past year, and medication allergies. In particular, sites should record whether the patient has any history of prior ITI, anaphylaxis, or known thrombophilia. It should also include all medication taken in the 4 weeks prior to screening (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies), see Section 4.6 for details. Bleed information (i.e., number, type) should be documented during the last 24 weeks prior to study entry. Number of daycare/school days missed and number of days hospitalized should be documented prior to study entry.

Demographic data will include age, sex, and self-reported race and ethnicity (as per specific country regulations).

4.7.3 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. Additional targeted physical examination of joints (for bleeds, evidence of arthropathy) and skin (for bruises, hematomas, injection-site reactions, and lipodystrophies) should be conducted as noted in the schedule of assessments (see [Appendix 1](#)) or as clinically indicated. Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened abnormalities from screening should be recorded as adverse events.

4.7.4 Vital Signs

Vital signs will include measurement of pulse and respiratory rate, temperature (oral, rectal, axillary, or tympanic), systolic and diastolic blood pressure using age-adapted measurements, height/length and weight and should be recorded before study drug administration. Frequency of vital sign assessments should follow the schedule of assessments (see [Appendix 1](#)) but may also be taken any time as unscheduled assessments as judged by the investigator.

4.7.5 Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will be performed as indicated on the schedule of assessments (see [Appendix 1](#)). On days of study drug administration, 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, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and RBC distribution width)
- Serum chemistries (sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, creatine phosphokinase, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT, and AST)
- Pregnancy test: All female patients who are of childbearing potential will be required to have a serum pregnancy test at screening.

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.

- 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 TMA:

Platelet count

Serum creatinine

LDH

Peripheral blood smear analysis to evaluate for schistocytes

A plasma sample should also be provided for local (first aliquot) and central (second aliquot) laboratory monitoring of:

Prothrombin fragment 1+2

Fibrinogen

D-dimer

If the test for prothrombin fragment 1+2 is not available at the site, the sample should be sent to the local reference laboratory, if available and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision-making.

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 *“Local Lab Following Treatment with Bypassing Agents” eCRF page*.

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 (anti-FVIII antibodies and anti-emicizumab antibodies)

- Plasma for exploratory PD biomarker assessments (aPTT, FVIII activity, and others as listed in [Appendix 2](#))

4.7.6 Electrocardiograms

ICH guidelines note large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for pro-arrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies ([ICH 2015](#)). Current data from the Phase I/II studies did not reveal clinically significant or dose-dependent changes in ECG parameters. Though dedicated QT assessments have not been required from any regulatory authority, the Sponsor committed to ensure some collection of baseline and periodic on treatment ECGs. Collection times will be targeted around expected steady state concentrations of emicizumab. Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see [Appendix 1](#)) 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 (and reported by the instrument): QT, RR, HR, QTcB, QT interval corrected using Fridericia's formula [QTcF], 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 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 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.

4.7.7 Electronic Patient-Reported Outcomes

To capture bleed data, emicizumab use, and other hemophilia medication use during study treatment, caregivers will complete the Bleed/Medication Questionnaire on an electronic, handheld device that will be provided to them during the Week 1 visit at the site. This device will remain with the caregiver for the duration of the study to enter bleed and medication data on a weekly basis at minimum. Patients and/or caregivers will complete HRQoL, proxy HRQoL, 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 various questionnaires will be provided by the investigator staff. 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. Of note, if the electronic data collection system becomes unavailable, the Sponsor may instruct sites to collect PRO data (bleed data, emicizumab use, hemophilia medication use, and HRQoL on paper). 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 (DCR) Form process or via a Web-based portal, once implemented.

HRQoL:

Only patients 8 years of age and above will be assessed for HRQoL using the Haemo-QoL-SF questionnaire (Short Form), which will be completed by the patients during clinic visits (see [Appendix 3](#)). The Haemo-QoL-SF is derived from the Haemo-QoL questionnaire, which has been developed in 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](#)). The Haemo-QoL-SF version contains 35 items, which cover 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.

Adapted InhibQoL Including Aspects of Caregiver Burden:

Proxy assessment of HRQoL and aspects of caregiver burden for all children, regardless of age, will be collected using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire (see [Appendix 4](#)). This will be completed by caregivers as per the schedule of assessments during clinic visits (see [Appendix 1](#)).

Daycare/School Absences and Hospitalizations: Caregivers will also 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.

4.7.8 Bleed Definitions

Definition of a Bleed

For the purposes of the efficacy analyses, a standardized definition of bleed, adapted from standard criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX

subcommittee of the ISTH and similar to that used in a recent clinical study, will be utilized in this study ([Blanchette et al. 2014](#); [Mahlangu et al. 2014](#)).

- An event is considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding (pain, swelling, etc.). An additional definition of all bleeds (i.e., both treated and not treated with coagulation factors) will be applied as well.
- 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 ≤ 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.

Definitions of Bleed Sites

- Target joints are defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry)
- Joint bleeds (sites as per the Bleed/Medication Questionnaire)
- Muscle bleeds (sites as per the Bleed/Medication Questionnaire)
- Other bleeds (sites as per the Bleed/Medication Questionnaire)

Definitions of 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 caregiver records a bleed when there is no known contributing factor such as definite trauma, antecedent “strenuous” activity or “overuse” or “procedure/surgery.” The determination of what constitutes “strenuous” or “overuse” will be at the discretion of the caregiver. 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 caregiver 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 with preceding 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 but will be collected on the bleed/medication questionnaire. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Caregivers will complete the bleed/medication questionnaire any time a patient experiences a bleed. At this time, the caregivers will also answer questions detailing the location, type and time of the bleed. Caregivers will also complete this medication questionnaire weekly as well as any time a hemophilia medication is administered, whether for prophylaxis (i.e., weekly emicizumab) or for treatment of bleed (i.e., bypassing agent).

4.8 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.8.1 Patient Discontinuation

Patients and parents/legally acceptable representatives 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 despite appropriate education measures taken by the clinical site.

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 page. However, patients will not be followed for any reason after consent has been withdrawn.

4.8.2 Study Treatment Discontinuation

Patients must stop study treatment if they experience the following:

- Pregnancy

If the patient discontinues study treatment, bleed and bleed medication data should be provided by the caregiver via the electronic, handheld device until the safety follow-up visit (24 weeks after last study drug administration).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF page. 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.

4.8.3 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:

- 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 Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

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

5.1.1 Risks Associated with Emicizumab

5.1.1.1 Injection-Site Reactions

In the completed and ongoing Japanese studies, injection-site reactions have been observed in some patients with hemophilia A. These local injection-site reactions included injection-site erythema, injection-site hematoma, injection-site rash, injection-site discomfort, injection-site pain, and injection-site pruritus. All local

injection-site reactions were of mild intensity. Further details of the observed injection-site reactions are available in the Investigator's Brochure.

Instructions for emicizumab administration should be followed as outlined in Section 3.3.1 and Section 4.5.2 and in the IFU. This includes alternating the site of injection, from one injection to the next, in the recommended injection-site locations listed in the IFU.

5.1.1.2 Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction

Since emicizumab is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions, may occur. In completed and ongoing clinical studies of emicizumab, no severe hypersensitivity reactions have been reported. These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3.

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 6](#)). 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 and/or 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, for 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.

5.1.1.3 Hypercoagulation and Thromboembolic Events

As of April 2017, there have been 3 *serious* thromboembolic events reported in 2 patients *who were treated with bypassing agents* while receiving emicizumab prophylaxis in Study BH29884. [REDACTED]

[REDACTED]

For more details please refer to the


These events should be reported as Serious Adverse Events or Adverse Events of Special Interest as described in Section 5.2.3. HCPs should educate patients/caregivers to recognize signs and symptoms of potential thromboembolism *or thrombosis* (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; *or if in the skin, blackening and associated pain*) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or caregivers will also receive two alert cards to remind them of this information and these instructions should thromboembolism be suspected.

5.1.1.4 Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is used to describe a group of disorders with clinical features of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage that can include the kidneys, gastrointestinal system, or central nervous system, and so. As of April 2017, 3 cases of TMA were observed in Study BH29884 involving patients with hemophilia A with inhibitors *who were treated with bypassing agents* while receiving emicizumab. [REDACTED]

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[REDACTED]

 For more details please refer to the Emicizumab Investigator's Brochure.

Any TMA 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 Sections 5.2.2 and 5.2.3). HCPs should educate patients/caregivers to recognize signs and symptoms of potential TMA (i.e., confusion, weakness, swelling of arms and legs, yellowing of skin and eyes, vague abdominal or back pain, nausea, vomiting, or decreased urination, etc.) and ensure that they understand the importance of seeking appropriate medical attention. Patients and/or caregivers will also receive two alert cards to remind them of this information and these instructions should TMA be suspected.

5.1.1.5 *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 by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis (see Section 5.1.3 and the Emicizumab Investigator's Brochure). Due to the long $t_{1/2}$ 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 a practitioner other than the emicizumab-prescribing practitioner in settings such as an emergency room or in an acute-care setting.

Emicizumab's 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 April 2017, no instances of under-treatment of bleeding events due to unreliable standard coagulation tests and inhibitor assays in the setting of emicizumab were observed.

5.1.2 Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in [Table 3](#). Additional guidelines are provided in the subsections below.

Table 3 Guidelines for Management of Specific Adverse Events

Event	Actions to Be Taken
Injection-Site Reaction	<ul style="list-style-type: none">• 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 and caregivers will be given guidance on reporting injection-site reactions when administering drug at home or after they leave the clinic.
Hypersensitivity Reaction, Anaphylaxis, Anaphylactoid Reaction	<ul style="list-style-type: none">• 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.• 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 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 caregiver 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.
Hypercoagulation and Thromboembolic Events	<ul style="list-style-type: none">• Please see Section 4.7.5 for guidance on required laboratory monitoring <i>in the event of use of bypassing agents</i>.• 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, further administration of study drug should be interrupted. Decision to resume emicizumab after a thromboembolic event must be discussed with and approved by the Medical Monitor.

Table 3 Guidelines for Management of Specific Adverse Events (cont.)

Event	Actions to Be Taken
Thrombotic microangiopathy	<ul style="list-style-type: none">• Please see Section 4.7.5 for guidance on required laboratory monitoring <i>in the event of use of bypassing agents</i>.• HCPs should be vigilant for patients who exhibit signs/symptoms consistent with TMA and immediately begin work-up and treatment, as per local guidelines.• If a patient has a TMA event, further administration of study drug should be interrupted. Decision to resume emicizumab after an event of TMA must be discussed with and approved by the Medical Monitor.

HCP = healthcare provider; TMA = thrombotic microangiopathy.

5.1.3 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 4](#) summarizes the coagulation tests affected and unaffected by emicizumab. See the Emicizumab Investigator's Brochure for additional details on which tests can be used and how the test results can be interpreted.

Table 4 Coagulation Test Results Affected and Unaffected by Emicizumab

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

ACT = activated clotting time; APC-R = Activated Protein C Resistance; aPTT = activated partial thromboplastin time; ELISA = enzyme linked immunosorbent assay; FVIII = factor VIII; PT = prothrombin time; TT = thrombin time.

^a *For important considerations regarding FVIII chromogenic activity assays, please see information provided above in Section 5.1.3.*

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. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), 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 on the appropriate adverse event eCRF page regardless of whether the bleeds are consistent with patients' pre-study disease state (the bleed will remain recorded as well on the bleed/medication questionnaire). New, non-serious bleeds consistent with patients' pre-study disease state will not be considered adverse events and will not be recorded on the eCRF but will 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 Grade 1–4, according to the World Health Organization [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 6)
- Thromboembolic events
- Microangiopathic hemolytic anemia or TMA (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 Section 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/caregiver 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 initiation of study drug**, 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 initiation of study drug, all adverse events will be reported until the patient completes his or her last study visit, which includes the post-treatment visit 24 weeks following discontinuation of the drug. 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 World Health Organization (WHO) toxicity grading scale (see Appendix 5) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 5 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 or not 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, considering especially 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 are judged to be related to study drug injection should be captured as an "injection-site reaction" on the Adverse Event eCRF. Associated signs and symptoms (e.g., injection-site erythema or injection-site rash) should be recorded on the dedicated Injection-Site Reaction eCRF. If a 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 patient, 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 $5 \times$ 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 if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

For concerns about laboratory findings on coagulation-related tests in patients receiving emicizumab, refer to Section 5.1.3 or contact the Medical Monitor.

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 ($> 2 \times$ 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 cause 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.

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

Medical occurrences or symptoms of deterioration that are anticipated as part of hemophilia should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in terms of severity (e.g., increased number of doses of bypassing agents to stop bleeds with emicizumab, in the absence of neutralizing anti-emicizumab antibodies, compared with before study entry), frequency of bleeds, or nature of hemophilia at any time during the study. Should any of these occur (according to the investigator's clinical assessment), they 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").

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:

- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

The 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, 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 4.7.7. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Although sites are not expected to review the PRO data pertaining to the HRQoL, they are expected to review the Bleed/Medication Questionnaire. Given that, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF. The patient-reported 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/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [REDACTED], M.D., M.A.S. (primary)
Telephone No.: [REDACTED]

Medical Monitor: [REDACTED], M.D. (secondary)
Telephone No.: [REDACTED]

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

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting 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 emailing the form with use of the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 emailing the form with use of the fax number or email 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

Caregivers of female patients of childbearing potential will be instructed to immediately inform the investigator if the patient becomes 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 emailing the form with use of the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the caregivers and 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, as the margin between the minimal anticipated biological effect level (MABEL) 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 to be consistent with this, no proactive collection of pregnancy information for female partners of male patients treated with emicizumab will be required.

5.4.3.3 Abortions

Any 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](#)).

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](#) 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, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as

24 weeks after the last dose of study drug or rollover to a future separate extension study), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email 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, Ethics Committees (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

No formal hypothesis testing is planned in the study. All the analyses will be descriptive *and be performed for each cohort separately.*

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for this study 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 with inhibitors available for participation in this study. Hence, at least 40 children younger than 12 years of age and up to 80 patients with hemophilia A and FVIII inhibitors who are currently receiving treatment with bypassing agents will be enrolled in this study: *approximately 60 patients in Cohort A with allowance of patients 12–17 years of age who weigh <40 kg at the time of informed consent and approximately 10 patients each in Cohort B and Cohort C.*

During the study, a re-assessment of the initially specified sample size based on enrollment consideration may be performed. This may result in an increase in sample size, if necessary, to expand the safety database.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study *in each cohort* will be summarized. Moreover, reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

Variables from the eCRF used to establish how many subjects 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 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, weight etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by *cohort (i.e., Cohort A: 1.5 mg/kg QW; Cohort B: 3 mg/kg Q2W; Cohort C: 6 mg/kg Q4W) and overall as appropriate.*

6.4 EFFICACY ANALYSES

The efficacy analyses are to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time (i.e., bleed rate), and to characterize the efficacy of up-titration on an intra-patient level. These analyses will be conducted using different bleed definitions such as treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds.

The primary analysis will be performed 52 weeks after the last patient in the primary *population of Cohort A* has been enrolled or withdrawn prematurely, whichever occurs first. The primary *population* consists of all patients enrolled *in Cohort A* prior to the close of enrollment for patients ≥ 2 years of age (up to approximately 60 patients), and is used to define the timing of the primary analysis. *The primary analysis will also include all available data from patients enrolled in Cohorts B and C, regardless of their follow-up time.* Enrollment in *Cohort A* may be left open exclusively for patients < 2 years of age in order to enroll *approximately 5–10* such patients. Note that these patients will be included in the primary *population analysis* regardless of their follow-up time. Further analyses *may* be conducted while the study is ongoing (see Section 6.9).

6.4.1 Efficacy Endpoints

One efficacy objective is to evaluate the clinical effect of prophylactic emicizumab on the number of bleeds over time. *This analysis will be performed for each cohort separately*

as well as overall as appropriate. Another objective is to characterize the efficacy up-titration on an intra-patient level. The comparison between historical and on-study treatment period for bleeds over time will also be evaluated for patients who were previously enrolled in Study BH29768. *These patients will enroll exclusively in Cohort A, therefore this intra-patient analysis will be conducted only in patients receiving the 1.5 mg/kg QW maintenance dose.* The definition of a bleed is described in Section 4.7.8. All definitions (i.e., treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds, treated target joint bleeds) will be evaluated for each of the efficacy objectives.

Characterizing the effect of emicizumab on-study treatment period for bleed over time as well as analyses of up-titration and the comparison between historical and on study treatment period for bleed over time will be performed *for Cohort A and for the overall analysis* using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of bleeds as a function of the time that each patient stays in the study included as an offset in the model.

The number of bleeds will be also annualized (Annualized Bleeding Rate—ABR) *for Cohorts B and C as well as* for each patient using the following formula:

$$\text{ABR} = \left(\frac{\text{Number of bleeds during the efficacy period}}{\text{Total number of days during the efficacy period}} \right) \times 365.25$$

Of note, if the convergence of the negative binomial model is not achieved or is questionable, the efficacy analysis will be based on the ABR (formula just above).

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.

Efficacy endpoints will be analyzed separately by cohort (i.e., Cohort A: 1.5 mg/kg QW; Cohort B: 3 mg/kg Q2W; Cohort C: 6 mg/kg Q4W) and overall as appropriate. Patients who require up-titration will be reported in their original maintenance dose group, and a listing based on their up-titration period will be provided. A detailed description of the statistical methods that will be used for the efficacy analyses will be provided in the SAP.

6.4.2 Exploratory Efficacy Endpoints

Summary statistics of the number of daycare/school and days hospitalized will be presented *for each cohort separately.*

6.5 SAFETY ANALYSES

Safety analyses will be performed for each cohort separately and overall as appropriate.

The safety analyses population will be based on all patients who received at least one administration of emicizumab. Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry and hematology including complete blood count with differential and platelet counts), ECGs, vital signs, and anti-emicizumab antibodies.

To evaluate the overall safety of emicizumab, the incidence of adverse events will be summarized and presented by System Organ Class mapped term, appropriate thesaurus level, and toxicity grade.

For clinical laboratory data, summary statistics will be presented. In addition, shift tables describing changes from baseline will be presented using the WHO toxicity grading scale (WHO 2003).

Data on the impact of immunogenicity (anti-emicizumab antibodies and anti-FVIII antibodies) on safety, efficacy, and/or pharmacodynamics and pharmacokinetics will be summarized using standard language/terminology ([Shankar et al. 2014](#)).

6.6 PHARMACOKINETIC ANALYSES

For all patients, pre-dose (trough) plasma concentrations of emicizumab will be presented descriptively by dose groups (*1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W, 3 mg/kg QW in case of up-titration*), including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

Nonlinear mixed effects modeling will 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 area under the curve, will be derived from individual post-hoc predictions. Data may be pooled with data from previous Phase I/II studies and Phase III Studies. These analyses will be reported in a dedicated report.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

Scale scores for the Haemo-QoL-SF and the Adapted InhibQoL Including Aspects of Caregiver Burden will be calculated for each assessment, with change scores being examined for the assessments over the course of the study. These will be summarized descriptively *by cohort*. A descriptive summary of the number of daycare/school days missed and days hospitalized will also be presented *by cohort*.

6.8 PHARMACODYNAMIC BIOMARKER ANALYSES

PD parameters (e.g., aPTT, FVIII activity) will be presented using summary statistics by dose groups, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. *These analyses will be presented by cohort.*

6.9 INTERIM DATA REVIEW

6.9.1 Planned Interim Data Review

In a first interim data review, the appropriateness of the initial dosing regimen will be evaluated (maintenance dose of 1.5 mg/kg/week). This dosing regimen may be adapted following analysis of all available data (e.g., safety, efficacy, pharmacokinetics) by the JMC (see Section 9.5) if a majority of the first 3–5 patients (aged ≥ 2 to < 12 years of age) fail to achieve optimal control of bleeds after the first 12 weeks of treatment; or if their plasma emicizumab concentration trough level is lower than the one being targeted in adolescents and adults (i.e., 45 $\mu\text{g/mL}$). Should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this first interim data review, available data from these patients will also be included.

A second interim data review will occur once at least 10 patients between 2 and 12 years of age have been dosed for a minimum of 12 weeks. All available cumulative data (e.g., safety, efficacy, pharmacokinetics) will be evaluated by the JMC to provide recommendations for the enrollment of children < 2 years of age, as well as on any further adaptations of the maintenance dose if necessary. Again, should patients ≥ 12 years of age and < 40 kg be enrolled at the time of this second interim data review, available data from these patients will also be included.

The evaluation of the interim data review will be performed on the efficacy endpoint—number of bleeds over time—as well as on the safety and PK results.

Should patient recruitment be faster than anticipated, enrollment will be placed on a temporary hold following the first 20 patients until the JMC releases its recommendations on the appropriateness of the maintenance dose.

6.9.1.1 *JMC Recommendations and Enrollment of Q2W/Q4W in Pediatric Patients*

On 7 December 2016, based on a combined interim analysis of the first 20 patients enrolled, the JMC recommended to continue enrolling patients to Cohort A at the maintenance dose of 1.5 mg/kg QW, and to begin enrollment of patients < 2 years of age. See Section 3.3.1.1 for details.

After the JMC recommendations were released following this interim analysis, the study continued to enroll up to approximately 60 patients in Cohort A. Upon completion of recruitment to Cohort A, and following review of data in adults and adolescents from two ongoing Phase III studies evaluating emicizumab at 3 mg/kg Q2W (BH30071) and 6 mg/kg Q4W (BO39182) identifying no safety concerns, recruitment with alternating

allocation of patients to Cohorts B and C via IxRS could begin up to a maximum of approximately 10 patients in each cohort. See Section 3.3.1.1 for details.

Additional interim data reviews will be pre-specified in the Statistical Analysis Plan; other analyses may be conducted at various timepoints to support regulatory submissions.

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.

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 PATIENT-REPORTED OUTCOME DATA

Patient-reported outcome data will be collected with use of electronic, handheld 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 FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted electronically in real-time to a centralized, secure database. The data from the bleed/medication, HRQoL, proxy HRQoL, and Aspects of Caregiver Burden questionnaires are available for view only via secure access to a Web portal provided by

the vendor. 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 devices and all relevant study documentation.

Once the study is complete, the PRO data, audit trail, and study and system documentation will be archived. The investigator will receive 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical 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, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and additional local regulatory requirements. Assessments that require blood draws will be monitored closely to ensure that institutional mandates or EU guidelines ([European Union 2008](#)) regarding total sample blood volumes are followed.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form for parent/legally acceptable representative and Assent Form for the child (when applicable, in age-adapted format) 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 and Assent 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 and parent/legally acceptable representative the objectives, methods, and potential risks associated with each optional procedure. Patient and parent/legally acceptable representative 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 from the parent/legally acceptable representative and the child (when applicable) 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's legally authorized representative and the patient (when applicable) 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's legally authorized representative and the patient. 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.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Pediatric patients who could potentially participate in this study are declared legally incompetent. When a child meets the qualifications for participation in the study and because emicizumab prophylaxis may directly benefit this population with high unmet

medical need, investigator or authorized designee will obtain informed consent from parent/legally acceptable representative 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 his or her behalf. Any indication on the part of the patient that he or she is not willing to participate in the study will be honored.

In cases where there is reason to question the competence of a parent/legally acceptable representative 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 and Assent Forms, any information to be given to the parent/legally acceptable representative and 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 [9.7](#)).

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

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each 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 parent/legally acceptable representative, 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.

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

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

Patient-reported outcomes will be captured on electronic, handheld devices provided by a third-party vendor for all patients globally.

Central laboratories will be used for a subset of laboratory assessments specified in Section 4.7.5.

9.5 JOINT MONITORING COMMITTEE

A JMC composed of selected internal Sponsor members (Pediatric Medical Specialist, Safety Scientist, Clinical Pharmacologist, and Statistician) constituting the Internal Monitoring Committee and external pediatric hemostasis/thrombosis Experts (including an external Clinical Pharmacology Expert) will be in place throughout the duration of the study. Internal Monitoring Committee members will be selected on the basis that they have no contact with the sites as part of their responsibilities. The external pediatric hemostasis/thrombosis experts will have as a role to enhance safety monitoring and leverage external experts' scientific expertise by providing advice on data interpretation and will function as a consultative body to the Sponsor.

If a majority of the initial 3–5 patients 2–11 years of age treated for a minimum of 12 weeks require up-titration, or if their plasma emicizumab concentration trough does not meet a target of 45 µg/mL, the Sponsor may suggest adaptation of the starting maintenance dose. Thus, in a first interim data review, all cumulative data (e.g., safety, efficacy, and pharmacokinetics) will be evaluated by the JMC to provide recommendations of changing the starting maintenance dose for the subsequent patients to be enrolled (see Section 4.5.2).

Once at least 10 patients, aged 2–11 years have been dosed for a minimum of 12 weeks, a second interim data review of all available data (e.g., safety, efficacy, and pharmacokinetics) will be conducted to draw study and/or dosing recommendations produced by the JMC to allow children from <2 years of age to participate. As a result of this interim data review, further adjustments to the maintenance dose can also be made if necessary. The JMC will also monitor patient safety at pre-specified intervals and ad hoc as needed throughout the study. Specific operational details, such as committee composition, member roles and responsibilities, frequency, and timing of meetings and interim data review will be detailed in a separate JMC Agreement.

9.6 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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 study 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 studies 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.

9.7 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 (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments

Schedule of Assessments – Cohorts A, B, C																				
	Screening	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	Study Drug Discontinuation Visit ^a	Safety F/U Visit ^a	
Informed consent/assent ^b	x																			
Inclusion/exclusion criteria	x																			
Medical history and demographics ^c	x																			
Physical examination ^d	x					x			x			x ^d			x		x	x ^d	x	
Vital signs ^e	x	x ^e	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications ^f		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG ^{g, h}	x	x				x												x		
Safety laboratory assessments ^{h, i, j}	x ⁱ		x		x			x	x	x	x	x	x	x	x	x	x	x	x	
Anti-FVIII antibodies ^{j, k}	x ^k		x						x			x			x		x		x	
Anti-emicizumab antibodies ^{h, j, l}		x				x				x				x			x	x	x	
Bleed/medication questionnaire ^{m, n}		<-----weekly ^o ----->															x	x	x	
Bleed/medication data review ^o		x				x		x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1
Schedule of Assessments (cont.)

<i>Schedule of Assessments – Cohorts A, B, C</i>																			
	Screening	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	<i>Study Drug Discontinuation Visit^a</i>	Safety F/U Visit^a
Following treatment with bypassing agents		Monitoring for thromboembolic events and thrombotic microangiopathy ^p																	
Adverse events ^q		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
IMP management ^r		x	x	x	x	x	x ^r	x	x	x	x	x	x	x	x	x	x	x	
Haemo-QoL-Short Form ^s		x							x			x			x		x	x	
Adapted InhibQoL ^t		x							x			x			x		x	x	
PK assessment ^{h, j, u}		x	x	x	x	x	x ^r	x	x	x	x	x	x	x	x	x	x	x	x
PD biomarkers assessment ^{h, j, v}		x		x		x		x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

<i>Schedule of Assessments – Cohorts A, B, and C</i>				
	Every 12 Weeks from Wk 57	Every 24 Weeks from Wk 57	Study Completion/ET ^a	Safety F/U Visit ^a
Physical examination ^d	x		x	x
Vital signs ^e	x		x	x
Concomitant medications ^f	x		x	x
ECG ^{g, h}			x	
Safety laboratory assessments ^{h, i, j}	x		x	x
Anti-FVIII antibodies ^{j, k}	x			x
Anti-emicizumab antibodies ^{h, j, l}	x		x	x
Bleed/medication questionnaire ^{m, n}	x		x	x
Bleed/medication data review ^o	x		x	x
Adverse events ^q	x		x	x
IMP management ^r	x		x	
Haemo-QoL-Short Form ^s		x	x	
Adapted InhibQoL ^t		x	x	
PK assessment ^{h, j, u}	x		x	x
PD biomarkers assessment ^{h, j, v}	x		x	x

Appendix 1

Schedule of Assessments (cont.)

eCRF = electronic Case Report Form; ePRO = electronic patient-reported outcome; ET = early termination; F/U = follow-up; FVIII = factor VIII; HRQoL = Health-Related Quality of Life; IMP = investigational medicinal product, PD = pharmacodynamic; PK = pharmacokinetic; Wk = Week.

Notes: The maximum allowable time between screening and enrollment is 28 days; if the elapsed time between screening and enrollment is more than 28 days, screening must be repeated. All assessments should be performed within ± 2 days of the scheduled visit for the first 12 weeks (including the Week 13 visit), then ± 7 days thereafter. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Except for the bleed/medication questionnaire, all other patient data will be collected during office visits. On treatment days, pre-injection blood collection should be made 0–120 minutes before the injection. Emicizumab will be administered subcutaneously at a loading dose of 3 mg/kg QW for the first 4 weeks (Day 1 of each week) followed by a starting maintenance dose of 1.5 mg/kg QW (Cohort A), 3 mg/kg Q2W (Cohort B), and 6 mg/kg Q4W (Cohort C). During the 52-week treatment period, individual patients may have their dose up-titrated if they experience suboptimal bleeding control on emicizumab (see Section 4.5.2). In case of up-titration to a new maintenance dose, the next five weekly visits must occur at the site.

- ^a The study treatment discontinuation visit refers to the visit that occurs when a patient discontinues study drug. A safety follow-up visit will occur 24 weeks after discontinuing emicizumab for any reason.
- ^b Written informed consent must be obtained from parents/legally acceptable representative and an assent from the child (when applicable) before distribution of the electronic, handheld device and collection of any data. Enrollment form will be completed after informed consent form and assent form (when applicable) are obtained. If patient fulfills the inclusion/exclusion criteria, the patient should be enrolled in the study on the same day when the first dose of emicizumab is administered (Day 1).
- ^c Collected from patient medical records and documented in the eCRF.
- ^d A complete physical examination will be performed at screening and 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), in addition to other organ systems as clinically indicated and/or report of new or worsening adverse event.
- ^e Body temperature (oral, rectal, axillary, or tympanic), blood pressure, pulse rate, respiratory rate, height/length, and weight to be entered into eCRF. If Screening and Week 1 occur on the same date, the vital signs should be measured only once. If Screening and Week 1 occur on different dates, vital signs should be repeated for both assessments.
- ^f Concomitant medications (e.g., extra pain medication with bleed) will be asked about at each clinic visit and documented in the eCRF, excluding treatments for bleeds (i.e., bypassing agents and other medications to treat bleeds), which will be collected on the bleed/medication questionnaire. Hemostatic medications to treat or prevent bleeds in the 4 weeks prior to starting emicizumab will be collected on eCRF.
- ^g If screening ECG abnormal, repeat at Week 1 (or Week 2 if Screening and Week 1 occur on the same date). ECGs will also be performed 4 weeks after starting emicizumab or after each dose up-titration, as well as at study completion/early termination.
- ^h 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.

Appendix 1

Schedule of Assessments (cont.)

- ⁱ Laboratory data (performed locally) includes complete blood count with differential and serum chemistries (i.e., sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, creatine phosphokinase, total protein, albumin, creatinine, total and direct bilirubin, alkaline phosphatase, ALT, and AST). Female patients of childbearing potential will be required to have a negative serum pregnancy test result at screening and urine pregnancy tests performed at Weeks 13, 25, 37, and 49; every 12 weeks starting from Week 57; and study completion/early termination.
- ^j 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.
- ^k 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.
- ^l Samples to detect anti-emicizumab antibodies will be collected prior to emicizumab injection at Weeks 1, 5, 17, 33, 49, every 12 weeks starting from week 57, study completion/early termination and at the 24-week safety follow-up visit. If patients continue on emicizumab past 52 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.
- ^m At the Week 1 visit, caregivers will be trained on how to use their handheld device to record the bleeds and the hemophilia medication use. The bleeding/medication questionnaire will be completed by the caregiver and includes start date and time, reason, type, location of each bleed, as well as start date and time, reason, type, and dose of each injection.
- ⁿ Caregivers will be instructed to complete on weekly basis to complete the bleed/medication questionnaire when the patient has a bleed or hemophilia medication use.
- ^o At subsequent visits as marked, investigator review of patient-reported bleed/medication questionnaire information will be conducted for completeness and accuracy.
- ^p 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 schistocytes within 24–48 hours of initial bypassing agent use. A plasma sample should also be provided for local (one aliquot) and central (a second aliquot) laboratory monitoring of fibrinogen, prothrombin fragment 1+2, and D-dimer. If prothrombin fragment 1+2 test cannot be done at the site, the sample should be send to the local reference laboratory, if available, and if the results from the local reference laboratory can be obtained within a reasonable timeframe to allow for decision making. 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 eCRF page titled *“Local Lab Following Treatment with Bypassing Agents.”*

Appendix 1

Schedule of Assessments (cont.)

- ^q Patients are advised to inform the investigator about adverse events at every visit. Adverse events will be reported on the eCRF by the investigator. 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 bypassing agents 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").
- ^r Drug accountability will not be performed at the first visit of emicizumab receipt. Drug dispensation will not occur at the study completion/early termination visit. *Note: for Cohort C, there are visits where emicizumab is not administered per schedule.*
- ^s Haemo-QoL-Short Form (children 8 years of age and older) assessed on an electronic, handheld device by patients during patient's visit in clinic prior to emicizumab injection at Weeks 1, 13, 25, 37, 49, every 24 weeks from Week 57, and study completion/early termination.
- ^t Proxy assessment of HRQoL and aspects of caregiver burden using the Adapted InhibQoL Including Aspects of Caregiver Burden questionnaire for all children assessed on electronic, handheld device by caregivers during patient's visit in clinic prior to emicizumab injection at Weeks 1, 13, 25, 37, 49, every 24 weeks from Week 57 and study completion/early termination.
- ^u Emicizumab concentration. Plasma samples for this assessment should be taken prior to emicizumab injection.
- ^v PD biomarkers will be measured at a central laboratory. See [Appendix 2](#), for detailed explanation of PD biomarker assessments. 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.

Appendix 2

Schedule of PD Assessments

Sample	Visit ^a	Biomarker assays ^b
PD Set 1	Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, every 8 weeks from Week 41, every 12 weeks from Week 57 Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator) while on emicizumab ^c	PT/INR D-dimer aPTT
PD Set 2 ^d	Weeks 1, 3, 5, 9, 13, 17, 21, 25, 29, 33, 37, every 8 weeks from Week 41, every 12 weeks from Week 57 Study Completion/Early Termination Safety Follow-up Visit Unscheduled visit (at the discretion of the investigator) while on emicizumab ^c	FVIII activity FIX antigen FX antigen

FIX = factor IX; FVIII = factor VIII; FX = factor X; PD = pharmacodynamic.

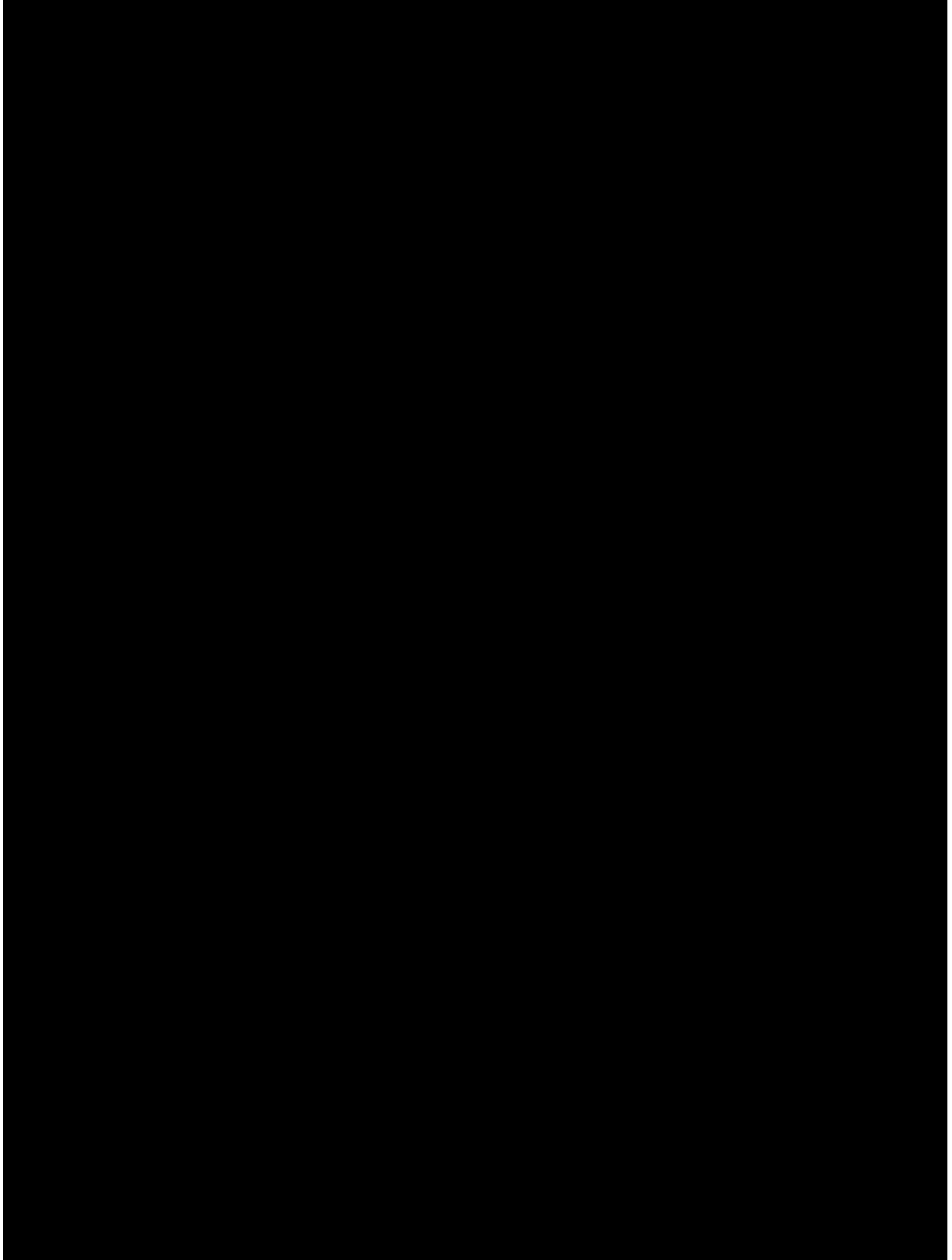
^a All samples are to be collected on Day 1 of the indicated week, prior to emicizumab injection (if applicable). All PD samples will be citrate plasma.

^b Biomarker assays will include but are not limited to those listed. Where blood volumes allow, additional plasma may be frozen and banked for future exploratory research related to emicizumab. Blood volumes and processing procedures will be specified in the Laboratory Manual.

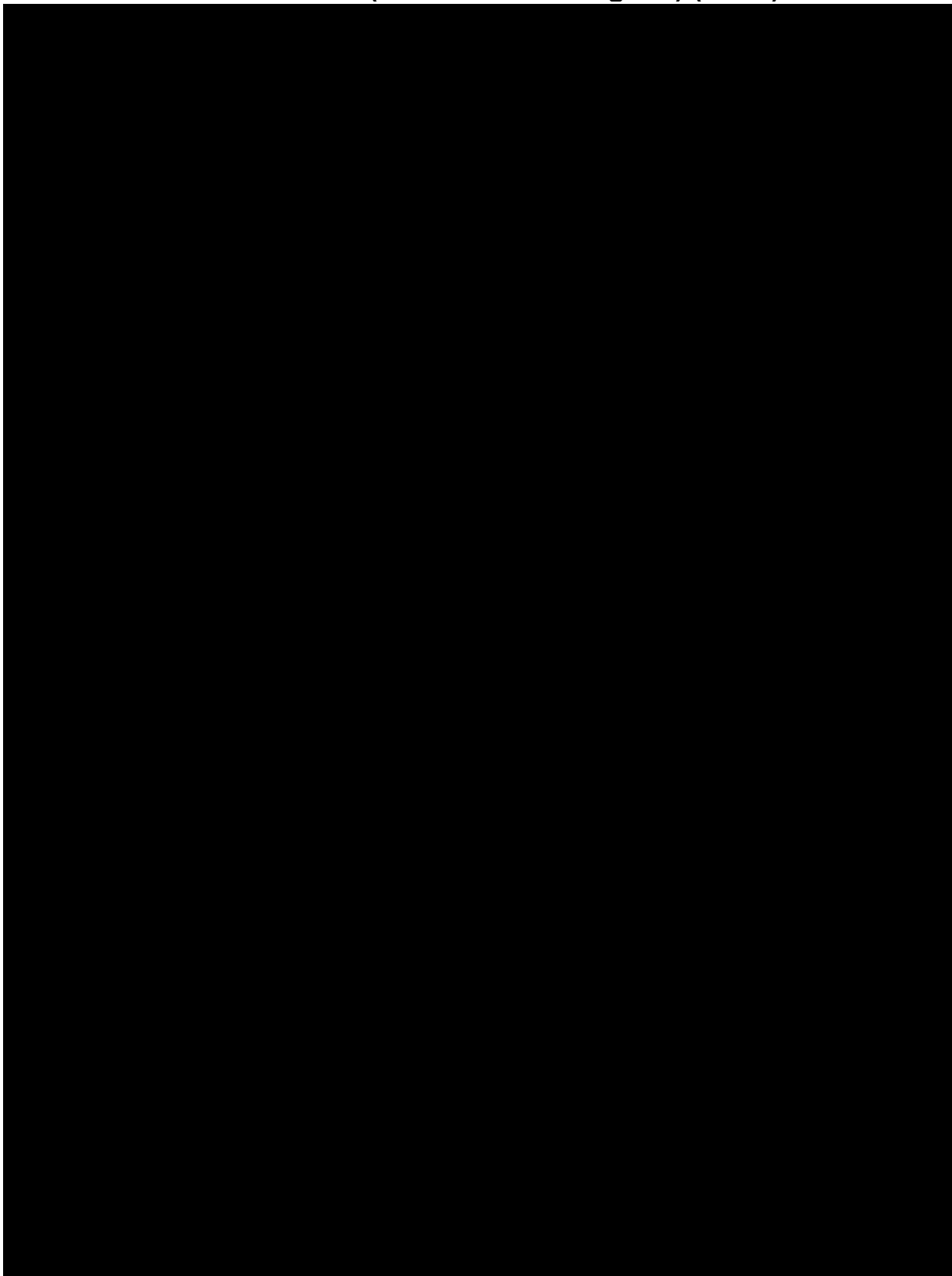
^c Reasons for unscheduled visits may include evaluation or treatment for bleeds or hypersensitivity reactions.

^d These plasma samples will only be collected if the permitted blood volumes allow (based on patient body weight as described in Section 3.3.5). Please refer to the Laboratory Manual for details.

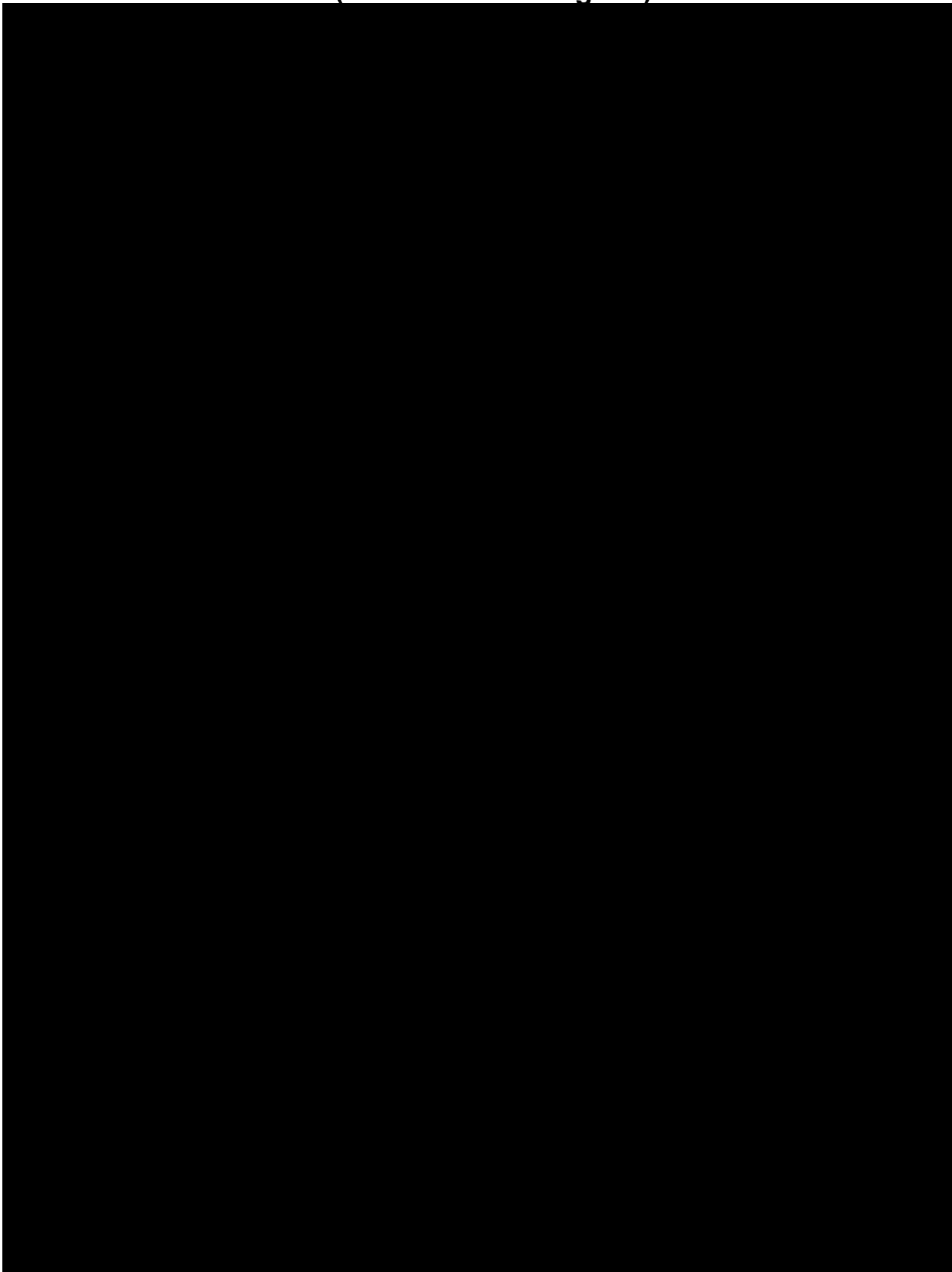
Appendix 3
Haemo-QoL-SF (United States/English)



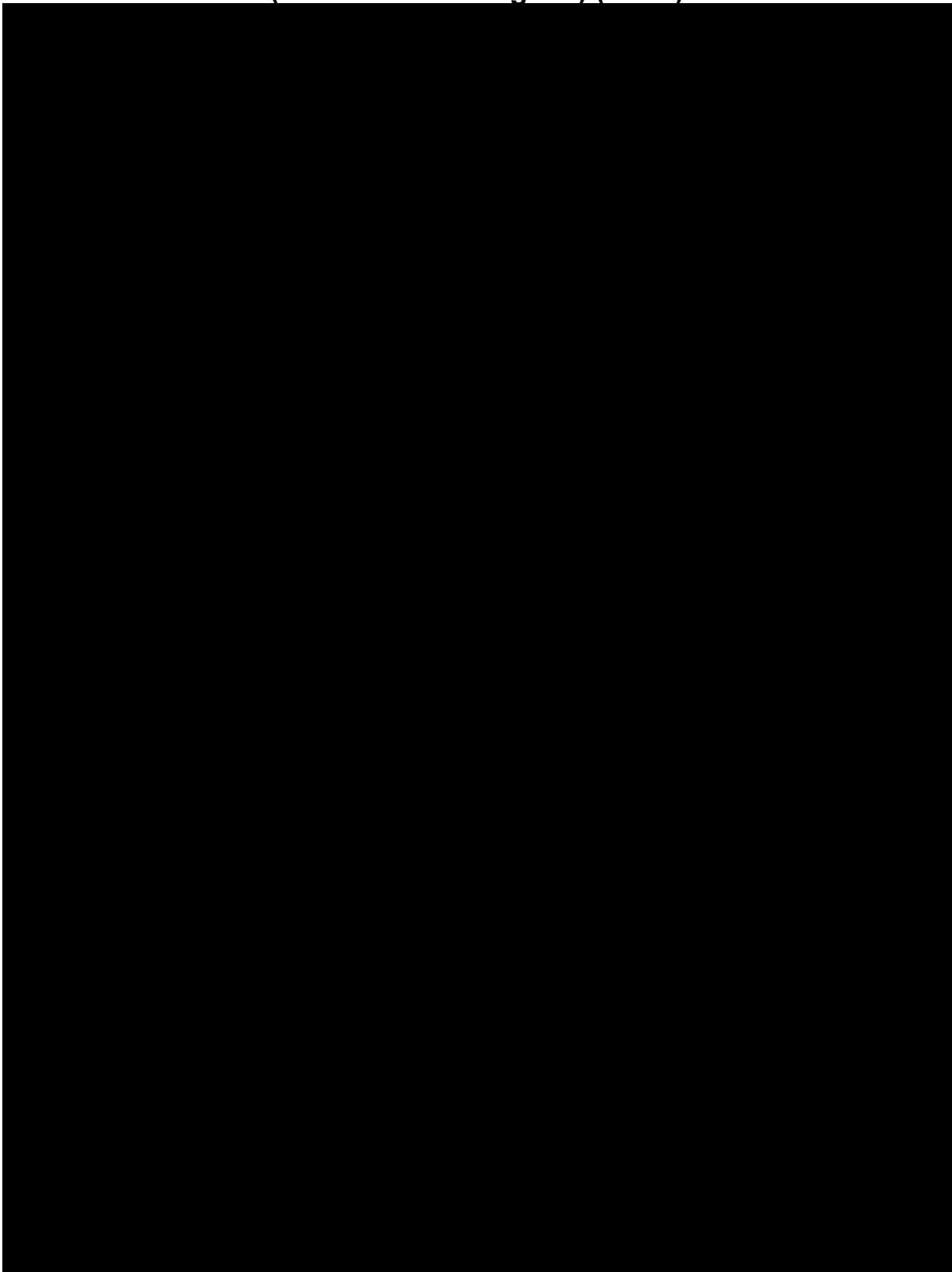
Appendix 3
Haemo-QoL-SF (United States/English) (cont.)



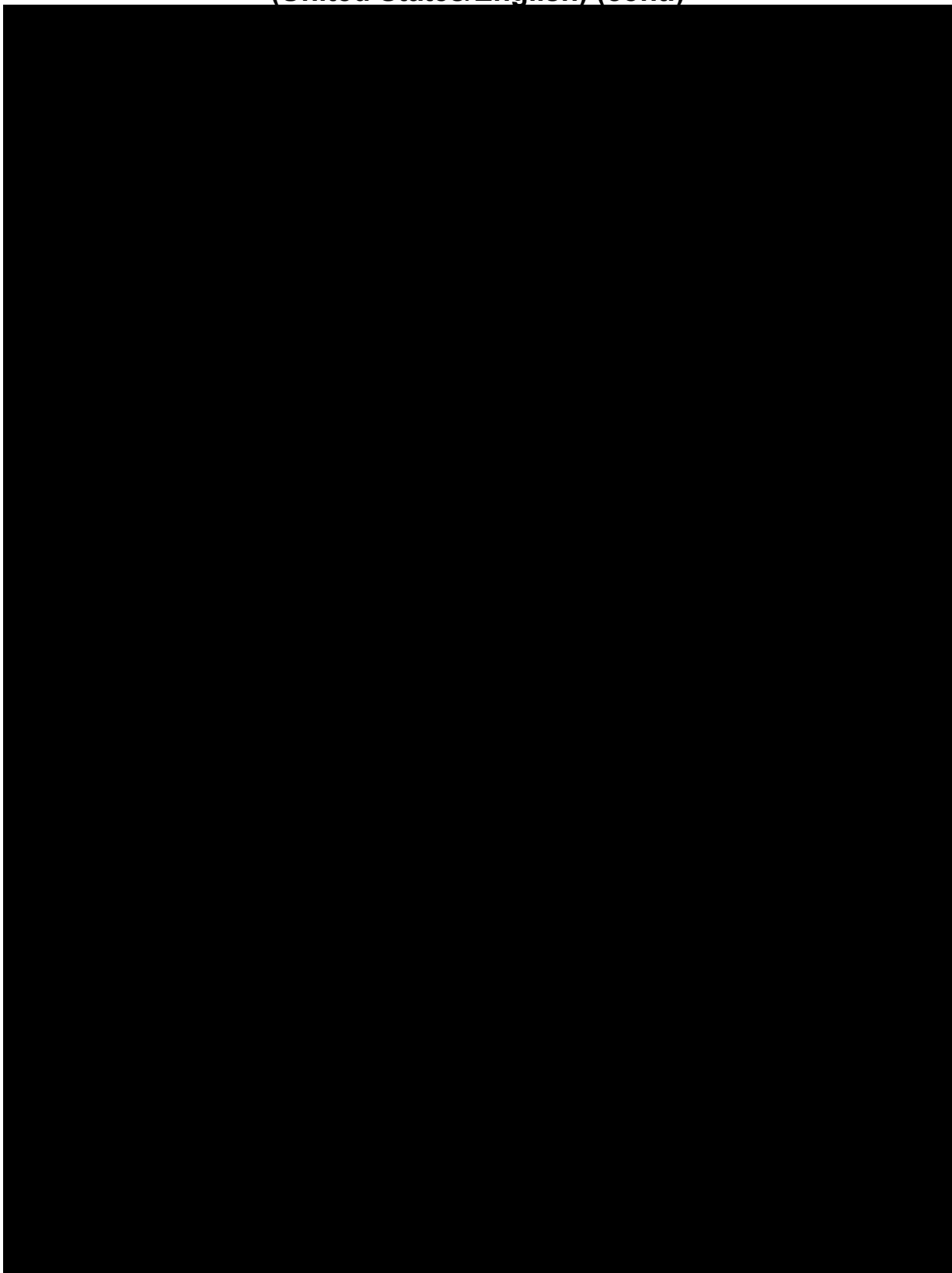
Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English)



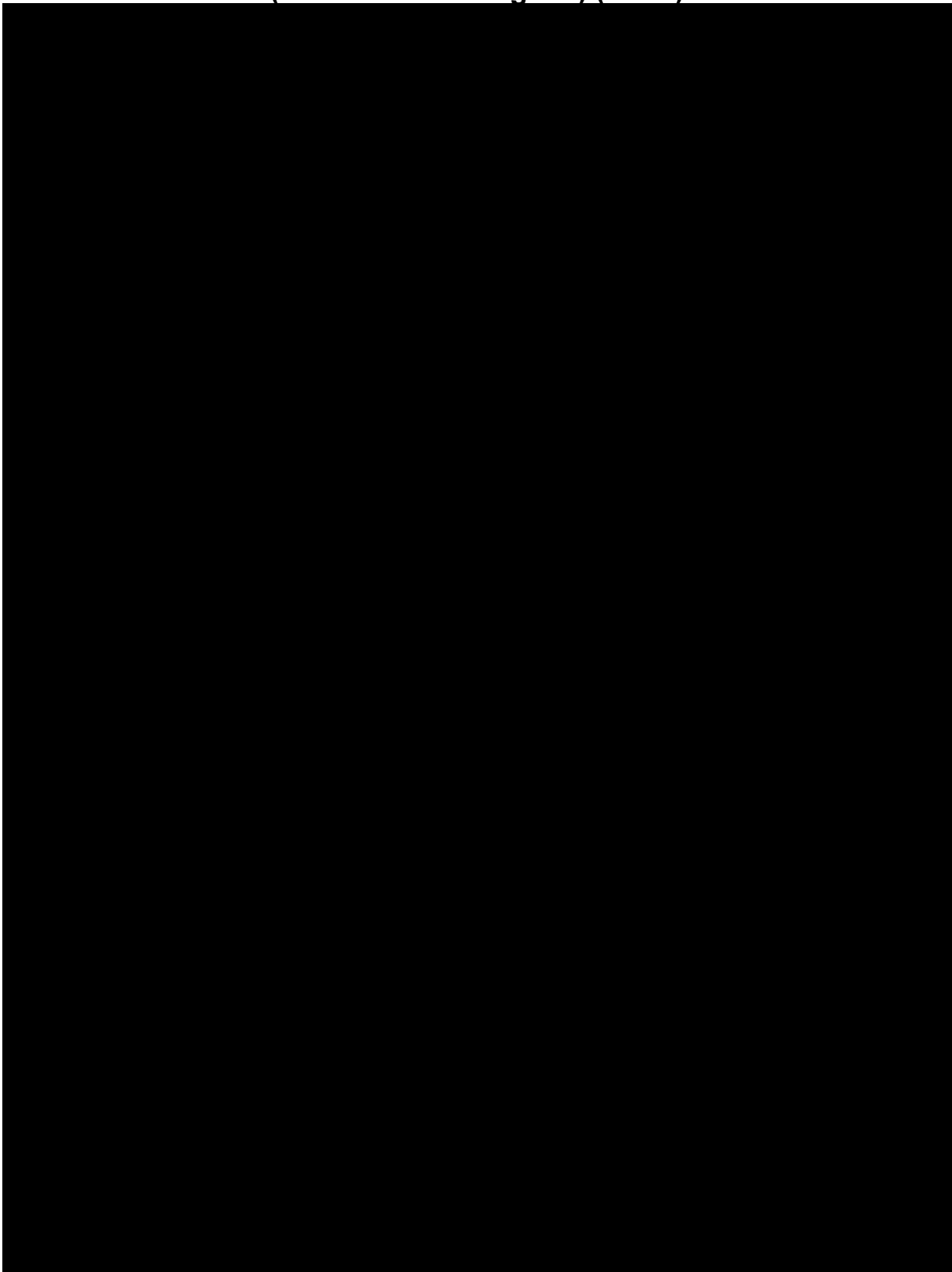
Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English) (cont.)



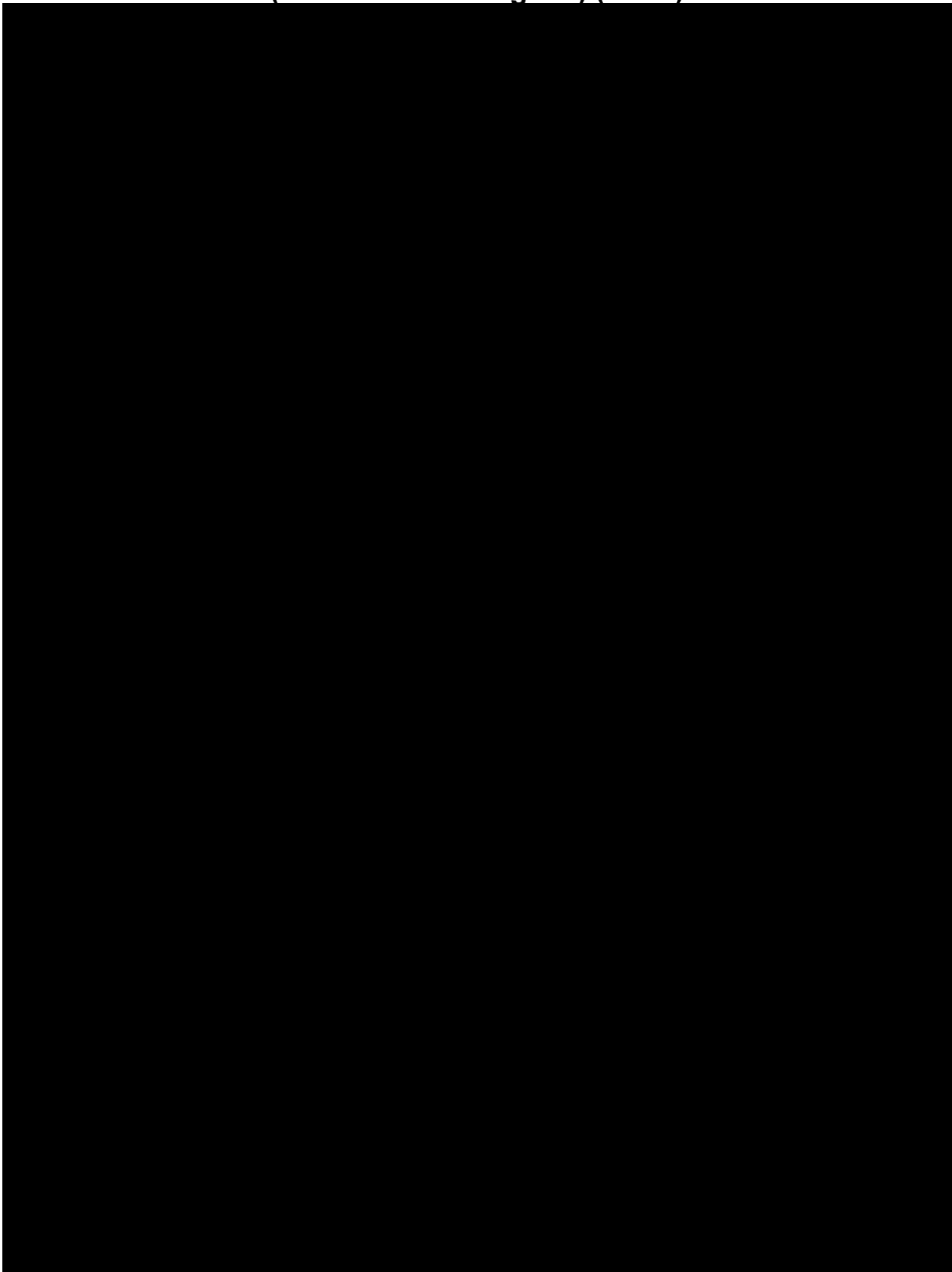
Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English) (cont.)



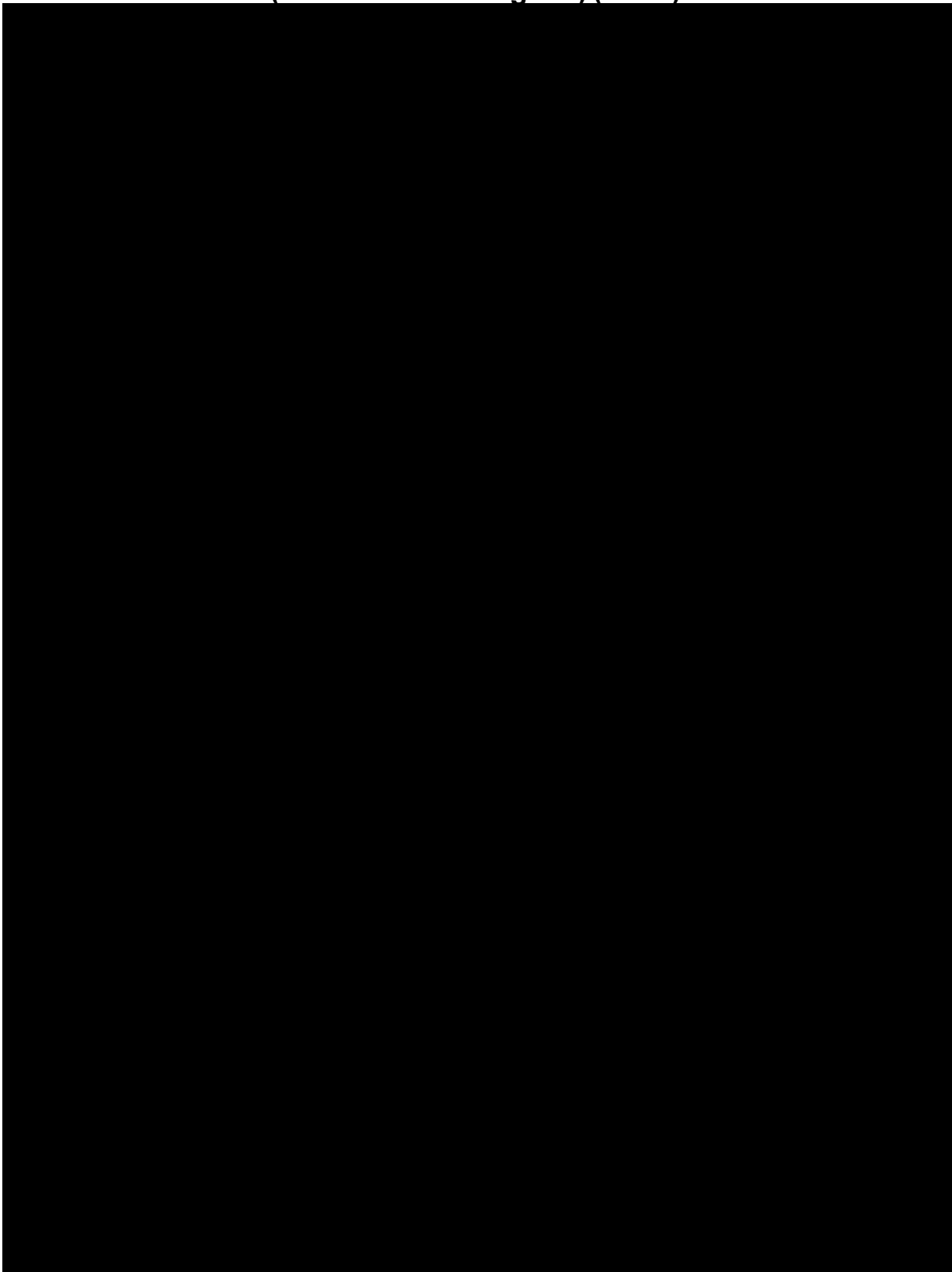
Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English) (cont.)



Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English) (cont.)



Appendix 4
Adapted InhibQoL Including Aspects of Caregiver Burden
(United States/English) (cont.)



Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1000–1500/mm ³	750–999/mm ³	500–749/mm ³	<500/mm ³
Platelets	75000–99999/mm ³	50000–74999/mm ³	20000–49999/mm ³	<20000/mm ³
Prothrombin time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	> 3 × ULN
Activated partial thromboplastin (APTT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25 - 0.49 × 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 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Alkaline phosphatase	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	>5.0 × ULN

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
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

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES continued				
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
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 or 1–2 g loss/day	4+ or >1.0% or >10 g/L or 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

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION continued				
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
RESPIRATORY				
Cough	transient; no Rx	treatment-associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 70%–79% FEV ₁ (or peak flow)	requires Rx normalizes with bronchodilator; FEV ₁ 50%–69% (or peak Flow)	no normalization with bronchodilator; FEV ₁ 25%–49% (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

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
GASTROINTESTINAL continued				
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
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

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
NEURO AND NEUROMUSCULAR continued				
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 99.9–101.3 F	38.6–39.5 C or 101.4–103.1 F	39.6–40.5 C or 103.2–104.9 F	> 40.5 C or > 104.9 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
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	Induration ≥ 10 cm or ulceration	necrosis

Appendix 5

WHO Toxicity Grading Scale for Determining the Severity of Laboratory Abnormalities and Adverse Events (cont.)

Item	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
OTHER PARAMETERS continued				
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

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

Appendix 6

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 pressure²
 - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

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.

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