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Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b, open-label trial

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Abstract:
Subcutaneous emicizumab enables prophylaxis for people with hemophilia A (HA) from birth, potentially reducing risk of bleeding and intracranial hemorrhage (ICH). HAVEN 7 (NCT04431726) is the first clinical trial of emicizumab dedicated to infants, designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in those ≤12 months of age with severe HA without factor (F)VIII inhibitors. Participants in this phase 3b trial received emicizumab 3 mg/kg maintenance dose every 2 weeks for 52 weeks, and are continuing emicizumab during the 7-year long-term follow-up. Efficacy endpoints included annualized bleed rate (ABR): treated, all, treated spontaneous, and treated joint bleeds. Safety endpoints included adverse events (AEs), thromboembolic events (TEs), thrombotic microangiopathies (TMAs), and immunogenicity (anti-emicizumab antibodies [ADAs] and FVIII inhibitors). At primary analysis, 55 male participants had received emicizumab (median [range] treatment duration: 100.3 [52–118] weeks). Median (range) age at informed consent was 4.0 months (9 days–11 months 30 days). Model-based ABR (95% confidence interval [CI]) for treated bleeds was 0.4 (0.30–0.63), with 54.5% of participants (n = 30) having zero treated bleeds. No ICH occurred. All 42 treated bleeds in 25 (45.5%) participants were traumatic. Nine (16.4%) participants had ≥1 emicizumab-related AE (all Grade 1 injection-site reactions). No AE led to treatment changes. No deaths, TEs, or TMAs occurred. No participant tested positive for ADAs. Two participants were confirmed positive for FVIII inhibitors. This primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors.

Conflict of interest: COI declared - see note

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Emicizumab prophylaxis in infants with hemophilia A (HAVEN 7): primary analysis of a phase 3b, open-label trial

Short title (49/50 characters, including spaces): Emicizumab prophylaxis in infants with hemophilia

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- Subcutaneous emicizumab given from birth has potential to reduce the risk of intracranial hemorrhage and joint bleeds before damage occurs [140/140 characters]
- Primary analysis of the HAVEN 7 trial indicates emicizumab is efficacious and well tolerated in infants with severe hemophilia A [130/140 characters]

Explanation of novelty (497/500 characters):

Many infants with severe hemophilia A do not receive prophylaxis until at least 1 year of age due to the challenges of factor VIII administration in this population. Subcutaneous emicizumab allows prophylaxis from birth, with the potential to reduce the risk of bleeds and life-threatening intracranial hemorrhage. HAVEN 7 is the first clinical trial of emicizumab dedicated to infants; the primary analysis reported here demonstrates the tolerability and efficacy of emicizumab in this population.

Abstract (249/250 words)

Subcutaneous emicizumab enables prophylaxis for people with hemophilia A (HA) from birth, potentially reducing risk of bleeding and intracranial hemorrhage (ICH). HAVEN 7 (NCT04431726) is the first clinical trial of emicizumab dedicated to infants, designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in those ≤12 months of age with severe HA without factor (F)VIII inhibitors. Participants in this phase 3b trial received emicizumab 3 mg/kg maintenance dose every 2 weeks for 52 weeks, and are continuing emicizumab during the 7-year long-term follow-up. Efficacy endpoints included annualized bleed rate (ABR): treated, all, treated spontaneous, and treated joint bleeds. Safety endpoints included adverse events (AEs), thromboembolic events (TEs), thrombotic microangiopathies (TMAs), and immunogenicity (anti-emicizumab antibodies [ADAs] and FVIII inhibitors). At primary analysis, 55 male participants had received emicizumab (median [range] treatment duration: 100.3 [52–118] weeks). Median (range) age at informed consent was 4.0 months (9 days–11 months 30 days). Model-based ABR (95% confidence interval [CI]) for treated bleeds was 0.4 (0.30–0.63), with 54.5% of participants (n = 30) having zero treated bleeds. No ICH occurred. All 42 treated bleeds in 25 (45.5%) participants were traumatic. Nine (16.4%) participants had ≥1 emicizumab-related AE (all Grade 1 injection-site reactions). No AE led to treatment changes. No deaths, TEs, or TMAs occurred. No participant tested positive for ADAs. Two participants were confirmed positive for FVIII inhibitors. This primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors.

Introduction

Congenital hemophilia A (HA) is an X-linked hereditary disorder characterized by a deficiency of factor VIII (FVIII), which increases risk for frequent bleeding into joints, muscles and soft tissues, often without evident trauma or injury.[1] Severity of HA can be classified by endogenous FVIII levels, although this categorization does not uniformly correlate with bleeding phenotype.[2] Severe HA (intrinsic FVIII levels <1%) is usually associated with high bleeding frequency from early childhood.[3]

In children, and especially infants, every bleed matters, as the damage incurred accrues early in life and may lead to joint arthropathy and disability in adulthood.[4] Furthermore, infants with HA not receiving prophylaxis have a 33-times higher risk of life-threatening intracranial hemorrhages (ICH) compared with infants without hemophilia, with the potential for severe long-term sequelae.[5],[6] For this reason, starting prophylaxis very early in life should be the standard of care.[1] Until recently, prophylaxis has required intravenous FVIII replacement.[7] However, the frequent (2–4 times weekly) infusions mean many young children have a central venous access device (CVAD) inserted to facilitate frequent, regular and long-term venous access and reduce the treatment burden.[8,9] Since the use of CVADs is associated with complications such as infections or thrombosis,[9] prophylaxis is often delayed until after 1 year of age, in order to access peripheral veins without the need for the insertion of a device.[10] However, there is substantial risk of ICH in the first year of life (2.1% [95% confidence interval: 1.5–2.8] incidence per 100 live births of infants with hemophilia in the neonatal period alone),[5],[11] and joint damage can also occur during this untreated period.[4] Moreover, around 30% of people with severe HA receiving FVIII develop inhibitors, at a median age of 15.5 months following a median of 9–36 exposure days (EDs) to FVIII treatment.[12,13] This reduces the benefits of FVIII therapy and worsens their clinical outcomes.[14,15]

Subcutaneous administration of emicizumab allows prophylaxis initiation at a very young age, with potential to reduce bleeds and life-threatening ICH while avoiding complications associated with CVADs. Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated FIX and FX to substitute for the function of deficient activated FVIII.[16,17] Based on the results of the phase 3 HAVEN clinical trial program, in which over 500 participants have been enrolled and treated to date,[18-23] emicizumab is indicated for routine prophylaxis in people of all ages with HA in many regions, including the United States of America and Japan.[16] In the European Union, emicizumab is indicated for routine prophylaxis in people of all ages with FVIII inhibitors, and those without FVIII inhibitors if they

have severe HA, or moderate HA with severe bleeding phenotype.[17] At all approved dose regimens, emicizumab offers stable and sustained therapeutic plasma concentrations.[24]

Limited experience with early emicizumab prophylaxis has been reported in clinical trials and real-world data. Two reported trials of emicizumab have included children: HAVEN 2 (85 children aged 14 months to 11 years) and HOHOEMI (13 children aged 4 months to 10 years).[25,26] These trials included 11 children <2 years of age, including one child aged <1 year.[25,26] Real-world data on emicizumab use in infants are mostly case series and reports,[27-29] yet they are consistent with the efficacy and safety profile observed in older children with HA in HAVEN 2 and HOHOEMI.[25,26] A population pharmacokinetic (PK) model, performed to characterize the PK of emicizumab in people with HA enrolled in phase 1–3 trials, predicted lower exposure that remains at the plateau of the exposure–response relationship in newborns.[24,30,31] Based on this modelling, the approved dosing of emicizumab applies for PwHA of all ages, including infants.

Building on these early experiences, the aim of the HAVEN 7 trial is to investigate the efficacy, safety, PK and pharmacodynamics (PD) of emicizumab in infants from birth to ≤12 months of age. Here, we report the primary analysis results.

Methods

Study design and participants

HAVEN 7 (NCT04431726) is a phase 3b, multi-center, open-label, single-arm trial of emicizumab in infants with severe congenital HA (intrinsic FVIII level <1%) without FVIII inhibitors (<0.6 Bethesda Unit [BU]/mL and no documented history). Eligible participants were newborns to ≤12 months of age weighing ≥3 kg at the time of informed consent. Participants were previously untreated (PUPs) or minimally treated (MTPs). MTPs were defined as having 1–5 EDs (defined as a calendar day when ≥1 dose was received by an individual) with hemophilia-related treatment containing FVIII, such as plasma-derived FVIII, recombinant FVIII, fresh-frozen plasma, cryoprecipitate, or whole blood products. Those who had only received antifibrinolytics were still considered to be PUPs. Participants had no evidence of active ICH and had normal hematologic, hepatic, and renal function (definitions in the appendix). Full inclusion/exclusion criteria are provided in the appendix.

The objective of HAVEN 7 was to evaluate the efficacy, safety, PK, and PD of emicizumab prophylaxis in this population, administered subcutaneously at 3 mg/kg once weekly (QW) for 4 weeks as a loading dose, followed by maintenance dosing of 3 mg/kg once every 2 weeks (Q2W) for a total of 52 weeks. The protocol was approved by the institutional review board/ethics committee at each site and the trial was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and all applicable regulations.

After 52 weeks of treatment, participants continued to receive emicizumab 3 mg/kg Q2W, or could switch to 1.5 mg/kg QW or 6 mg/kg once every 4 weeks (Q4W), for the 7-year follow-up period. Participants with >2 qualifying bleeds within a 12-week interval could have their dose up-titrated to 3 mg/kg QW from week 17. Qualifying bleeds were defined as spontaneous, clinically significant, clinician verified (e.g. with diagnostic imaging, clinical examination or a photograph), and occurring while receiving emicizumab maintenance.

Objectives

The efficacy objective of HAVEN 7 was to evaluate emicizumab based on bleed endpoints, including treated bleed rate, all bleed rate, treated spontaneous bleed rate, and treated joint bleed rate (definitions in the appendix). For participants whose dose was up-titrated, only efficacy data prior to up-titration are included. Joint health will be assessed during the long-term follow-up period in participants aged ≥4 years; the Hemophilia Joint Health Score 2.1 (HJHS) and additive magnetic resonance imaging (MRI) scale score of the International Prophylaxis Study Group of specific joints will aid in evaluating preservation of joint health in

the setting of earliest initiation of prophylaxis.[32,33] Participants' HJHS will be measured annually from year 4 to year 8 and a bilateral MRI of the knees, ankles, and elbows will be performed at year 5 and year 8.

Safety assessments included incidence of adverse events (AEs) (and severity according to the World Health Organization Toxicity Grading Scale), thromboembolic events (TEs) or thrombotic microangiopathies (TMAs), AEs leading to emicizumab discontinuation, injection-site reactions, severe hypersensitivity, anaphylaxis, and anaphylactoid events.

Emicizumab PK profile was characterized based on plasma trough concentrations of emicizumab. The biomarker endpoints included PD parameters (activated partial thromboplastin time [aPTT], thrombin generation [TG] peak height, FVIII-like activity), and concentrations of emicizumab targets (antigen levels of FIX and FX).

Immunogenicity endpoints comprised the incidence and significance of anti-emicizumab antibodies (ADAs) and *de novo* development of FVIII inhibitors.

Assessments and data collection

Medical history, including clinically significant diseases, procedures, allergies, history of anaphylaxis, or known thrombophilia since birth, were recorded on the electronic Case Report Form (eCRF). All bleeds experienced since birth and before enrolling in the trial on day 1 were documented on the eCRF.

Medication administered to the participant from 4 weeks prior to enrollment through study completion or safety follow-up was reported on the Concomitant Medications eCRF. Hemophilia-related treatments administered to participants since birth and before enrolling in the trial were documented on the eCRF.

On-study bleed and medication-related observer-reported outcome data were collected at home or in the clinic throughout the trial. Emicizumab administration, bleeds experienced, and hemophilia-related treatments received by a participant were reported by parents/caregivers through a Bleed and Medication Questionnaire (eBMQ) on an electronic handheld device provided at enrollment. Parents/caregivers were asked to record and confirm these data at least weekly, and data entered since a participant's previous clinic visit were reviewed for completeness and accuracy by the parents/caregivers and the investigator at subsequent visits.

PK and biomarkers were assessed Q2W during weeks 1–9 and Q4W during weeks 13–53, prior to emicizumab administration. Trough plasma concentrations of emicizumab were measured by validated enzyme-linked immunosorbent assay (ELISA).[24] aPTT, TG, FVIII

activity (using a chromogenic assay containing human FIX and FX, considered FVIII-like activity), and FIX and FX antigen concentrations, were assessed as previously described.[34] FVIII-like activity does not represent a true FVIII equivalence due to different biochemical properties of the proteins, but can be used to measure the relative PD effect of emicizumab.

ADAs were measured by bridging ELISA in all participants at baseline;[35] on study at weeks 1, 5, 17, 29, 41, and 53; and during long-term follow-up in the case of clinical suspicion. FVIII inhibitors were measured by chromogenic Bethesda assay in MTPs at baseline.[36] FVIII inhibitor development was tested for after any three FVIII EDs, or a block of EDs (defined as a minimum of two consecutive FVIII doses).

Parents/caregivers could withdraw the participant voluntarily from the trial at any time for any reason and investigators could withdraw a participant for reasons listed in the appendix.

Statistical analysis

No formal hypothesis testing was planned; all analyses were descriptive. No adjustment for multiplicity of endpoints was considered.

The sample size was based on recruitment feasibility and clinical, rather than on statistical, considerations, in view of the limited number of infants from birth to ≤12 months of age available for participation in clinical trials, and to collect sufficient data to assess the efficacy, safety, PK, and PD of emicizumab in this population.

Bleed data are presented as calculated median (interquartile range) annualized bleed rates (ABRs) using individual ABRs,[23] and model-based ABRs, using a negative binomial regression model, which takes into account variations in participant follow-up time.[37]

The primary analysis was planned to be performed when the last participant had completed 52 weeks on study, was lost to follow-up, or had withdrawn from trial treatment, whichever came first.

Results

Participant characteristics

In total, 55 male participants were recruited between February 2021 and May 2022 (**Figure 1**). All participants completed 52 weeks in the study receiving emicizumab prophylaxis 3 mg/kg Q2W and have entered the long-term follow-up period. Upon entering follow-up, 49 (89.1%) participants continued to receive emicizumab 3 mg/kg Q2W, five (9.1%) switched to 6 mg/kg Q4W, and one was up-titrated to 3 mg/kg QW.

At the clinical cut-off date (CCOD) for this analysis (22 May 2023), median (min, max) treatment duration (date of the last dose of study medication minus the date of the first dose, plus one day) before up-titration was 100.3 (52, 118) weeks. Overall, participant compliance with the expected emicizumab dosing was high, with only one participant missing doses (no safety events or bleeding were reported during this period) and two participants receiving less than the full dose at one timepoint each. The median (min, max) age at informed consent was 4.0 months (9 days, 11 months 30 days; **Table 1**); median (min, max) age at CCOD was 29 (12, 39) months. Approximately half (45.5%; n = 25) of the participants were aged 0–<3 months at time of informed consent; 30 (54.5%) were aged 3–12 months. Most participants (74.5%; n = 41) had a family history of HA, with confirmed maternal inheritance of the affected *F8* gene. Family history of FVIII inhibitors was reported for seven (12.7%) participants.

Thirty (54.5%) of the 55 participants were MTPs and 25 (45.5%) were PUPs. MTPs had a median (min, max) of 2 (1, 6) FVIII EDs. Pre study, one participant received six doses of FVIII, two of which were given on consecutive calendar days, considered two EDs despite being given within 24 hours. Before study entry, 34 (61.8%) of the 55 total participants had received a total of 85 administrations of factor-based therapies or antifibrinolytics, mostly for bleed treatment; four of these participants had received only antifibrinolytics, and were therefore still classed as PUPs.

Almost two-thirds (65.5%; n = 36/55) of participants had already experienced ≥1 bleed (treated or untreated) prior to receiving emicizumab (**Table 1**; individual historical and on-study bleeding episodes can be found in **Figure S1**). The reporting period was variable across the 36 participants who had ≥1 bleed prior to receiving emicizumab, with the median (min, max) age at time of first historical treated or untreated bleed being 1 (0, 49) week(s). Around a third (32.5%) of the 77 pre-study bleeds were spontaneous, 24.7% were traumatic, and 42.9% procedural/surgical (including, but not limited to, procedures such as birth delivery method, vaccination, vitamin K administration, and heel-prick metabolic tests).

Seven (12.7%) participants had experienced ≥1 joint bleed, and age at time of first joint bleed ranged from 14–34 weeks.

Efficacy

Model-based ABRs were consistently low across bleeding endpoints (**Table 2**). The model-based ABR (95% CI) was 2.0 (1.49–2.66) for all bleeds, 0.4 (0.30–0.63) for treated bleeds, 0.0 (0.01–0.09) for treated joint bleeds, and 0.1 (0.02–0.12) for treated muscle bleeds. There were no treated spontaneous bleeds, as all treated bleeds were traumatic.

After a median (min, max) duration of 101.9 (52.6–119.7) weeks in the efficacy period, 54.5% of participants had zero treated bleeds, 16.4% had zero all bleeds, and 94.5% had zero treated joint bleeds.

Overall, 207 bleeds were reported in 46 (83.6%) participants, 87.9% of which were traumatic. Two participants experienced >10 bleeds, but none were treated or occurred in the joint or muscle: 27 bleeds in one participant (19 traumatic, 8 spontaneous), and 21 bleeds in the other (all traumatic). In total, 42 treated bleeds, all traumatic, were reported in 25 (45.5%) participants. No participant experienced >3 treated bleeds.

One participant had his emicizumab dose up-titrated to 3 mg/kg QW per investigator request based on locally assessed decreasing emicizumab levels (confirmed retrospectively via central assessment to be 6.6 µg/mL at the lowest). This participant experienced three treated bleeds before up-titration start (day 374), and two untreated bleeds after up-titration until CCOD (328 days later); all were traumatic.

The median (min, max) age at the time of the first on-study bleed was 53.0 (12, 127) weeks (n = 46). At CCOD, only four (7.3%) participants had reported an on-study joint bleed (all traumatic), which occurred at an age of 29 to 124 weeks.

Safety

At primary analysis, no ICH had occurred, and no new safety signals were identified, with no AEs leading to study discontinuation or treatment changes or withdrawal (**Table 3**). All participants experienced an AE, with 631 reported in total. Sixteen (29.1%) participants experienced a total of 30 serious adverse events (SAEs), most of which were infant specific, and including respiratory-related and head-injury events (detailed in **Table 3** footnotes). In all cases, these were considered serious due to required or prolonged hospitalization. No SAEs were considered related to emicizumab.

Thirty emicizumab-related AEs occurred in nine (16.4%) participants, all Grade 1 injection-site reactions. One Grade 2 anaphylactic reaction was reported in one (1.8%) participant.

This event resolved, was confirmed to be due to egg allergy and deemed unrelated to emicizumab. No TEs or TMA were reported.

Pharmacokinetics

Mean (95% CI) trough concentrations of emicizumab increased during loading, reaching 62.0 (58.3–65.6) µg/mL at week 5 (**Figure 2A**). Thereafter, steady-state concentrations were sustained at 57–66 µg/mL. Mean steady-state trough concentrations increased slightly with age until participants reached approximately 6 months of age, whereupon trough concentrations were maintained at ≥60 µg/mL (**Figure 2B**).

Biomarkers

Mean FIX and FX antigen concentrations were not impacted by emicizumab treatment (**Figure S2A** and **Figure S3A**), but did increase with age (**Figure S2B** and **Figure S3B**).

aPTT was shortened to within reference range by day 15 in most participants, the first time point at which blood samples were obtained, due to limitations on sampling in infants (**Figure S4A**; results by age in **Figure S4B**).

Mean TG peak height increased during loading and was maintained between 67 and 88 nmol/L thereafter (**Figure S5A**; results by age in **Figure S5B**).

Mean (standard deviation [SD]) FVIII-like activity increased from 1.0 (0.9) U/dL at baseline (n = 48) to 22.5 (6.1) U/dL at week 5 (n = 50), and was sustained between 21 and 26 U/dL thereafter (**Figure S6A**; results by age in **Figure S6B**).

Immunogenicity

All 55 participants were evaluable for immunogenicity; none tested positive for ADAs to emicizumab.

On study, 28 (50.9%) participants received a total of 139 administrations of factor-based therapy, including FVIII in all 28 participants and recombinant activated FVII in one participant following development of FVIII inhibitors. Median (min, max) on-study FVIII ED(s) was 1.0 (0, 10), with a mean (SD) of 1.8 (3.3) doses. On-study FVIII EDs were similar between PUPs (median [min, max]: 1.0 [0, 10] in 14/25 participants) and MTPs (median [min, max]: 0.0 [0, 10] in 14/30 participants). At CCOD, 11/25 (44.0%) PUPs and 16/30 (53.3%) MTPs had not reported an on-study FVIII ED. The median (min, max) cumulative dose of FVIII received per participant was 1250 IU (250, 15,600 IU). In 25 (45.5%) participants, factor-based therapy was received for the treatment of a bleed; in four (7.3%) participants, as additional prophylaxis before activity (no information about the activity was available); and

in five (9.1%), as additional prophylaxis for a procedure/surgery; some participants received factor-based therapy for more than one of these reasons.

During the study, 24 (43.6%) participants were tested for FVIII inhibitors following FVIII exposure, with two (3.6%) testing positive. These two participants were both PUPs aged 0–<3 months at informed consent, with confirmed maternal inheritance of the affected *F8* gene, and one of the two participants had a reported family history of inhibitors. One PUP was confirmed for inhibitors on day 603 (6.9 chromogenic BU [CBU]/mL) and on day 681 (1.5 CBU/mL), following three non-consecutive standard half-life FVIII EDs for bleed treatment. The other tested positive for inhibitors (28.4 CBU/mL) on day 428, following 10 non-consecutive extended half-life FVIII EDs related to bleed treatment and surgical procedures; inhibitors were confirmed on day 532 (9.0 CBU/mL). Narratives can be found in the appendix.

Discussion

Early prophylaxis in infants with HA is important to protect long-term joint function and reduce potentially life-threatening bleeds such as ICH, which remains a significant concern in this population.[5] The subcutaneous nature of emicizumab administration makes prophylaxis initiation practicable at a very young age. Primary analysis of the HAVEN 7 trial indicates the efficacy and favorable safety profile of emicizumab prophylaxis for infants ≤12 months of age with severe HA without FVIII inhibitors. Results support the guidance of the World Federation of Hemophilia and the National Bleeding Disorders Foundation's Medical and Scientific Advisory Council, which both indicate that infants should be considered for prophylaxis with emicizumab any time after birth, given the increased risk of ICH in this population.[1,38] In addition, at study entry, 65.5% of participants had already experienced ≥1 bleed and 12.7% ≥1 joint bleed, with the age at first bleed and first joint bleed ranging from 0 to 49 weeks and 14 to 34 weeks, respectively. These data support the need for very early prophylaxis, before 3 months of age.

After a median efficacy period of 101.9 weeks, no cases of ICH were recorded, despite four SAEs of head injury. These data suggest that emicizumab prophylaxis may reduce the risk of ICH, given the known incidence of ICH and risk continuum;[5] however, it should be noted that the study was not powered to demonstrate this. Model-based ABR (95% CI) was 0.4 (0.30–0.63) for treated bleeds (all traumatic), consistent with results from HAVEN 2; children in HAVEN 2 receiving emicizumab 1.5 mg/kg QW (n = 65, including eight infants <2 years of age) had a model-based treated bleed ABR (95% CI) of 0.3 (0.17–0.50).[25] The proportion of participants with zero treated bleeds in HAVEN 7 was also consistent with findings from other emicizumab clinical trials when accounting for variable follow-up periods. The HAVEN 7 interim analysis had a median (min, max) exposure duration of 42.1 (1, 60) weeks. As expected, a higher proportion of participants (77.8% [42/54]) had zero treated bleeds after the shorter follow-up time at interim analysis than primary analysis (54.5%),[39] consistent with the 77% of participants reported in the 1.5 mg/kg QW group of HAVEN 2 (median [min, max] efficacy period: 57.6 [17.9–92.6] weeks), 100% of participants <2 years of age in HOHOEMI (n = 3; efficacy period: 24.1–38.4 weeks), and adults and adolescents in other HAVEN trials with similar follow-up periods.[18,20,22,23,25,26,40] In the real-world setting, Barg *et al.* reported no joint or spontaneous bleeds over a median of 36 weeks in 11 infants with HA receiving emicizumab with a median age of 26 months at study entry,[27] Garcia and Zia reported no joint or spontaneous bleeds in three infants aged <3 years after receiving emicizumab for 9–15 months,[28] and Mason and Young reported no bleeds in four infants receiving emicizumab aged <2 years after median follow-up of 12 months.[29]

At CCOD, only four participants had experienced an on-study joint bleed, with age range at the time being 29 to 124 weeks. Joint bleeds typically occur at an older age than other bleed types,[39] and results of the 7-year follow-up will provide data on long-term joint health in the setting of earliest initiation of emicizumab prophylaxis.

In line with the safety profile of emicizumab in clinical trials,[18,20,22,23,25,40] no new safety signals were found at primary analysis of HAVEN 7, and all emicizumab-related AEs were Grade 1 injection-site reactions. Most SAEs in HAVEN 7 were infant specific, including respiratory-related AEs such as bronchiolitis leading to hospitalization, and head injuries following which the infant was brought to hospital for observation, with imaging in some cases to confirm absence of ICH.

Mean steady-state emicizumab concentrations were 57–66 µg/mL at CCOD, above those reported previously in older people with HA in the phase 3 HAVEN 1–4 trials (46.7 [SD: 14.9] µg/mL, for participants receiving emicizumab 3 mg/kg Q2W).[24] No confirmed explanation has been identified for these higher concentrations in comparison with other HAVEN trials. Age is not believed to be a factor, since the emicizumab concentrations reported here are numerically higher compared with data from HAVEN 2 and HOHOEMI, which included children with HA of similar ages,[25,26] while a population PK model suggested lower exposure at <1 year of age.[31] Emicizumab injection site may have played a role, as during the first five weekly administrations in HAVEN 7 when emicizumab injection sites were recorded, 80% of administrations were in the thigh, and a numerical trend for higher exposure following thigh injection compared with the abdomen or upper arm has been observed in a study of the relative bioavailability of emicizumab across injection sites.[41] In contrast to the higher exposure, analysis of coagulation biomarkers in HAVEN 7 indicates that, at the same emicizumab concentration, TG and FVIII-like activity are somewhat lower in infants compared with older populations[42] and therefore the hemostatic effect of emicizumab is expected to be correspondingly lower.

Similar to our observation of increasing FIX and FX protein levels up to 9 months of age in participants, FIX and FX activities in healthy infants have been shown to increase during development from low levels in infancy to reach near adult levels at 6 months.[43] Lower FIX and FX plasma levels in the youngest participants may have had an impact on the PD results. However, increases in FVIII-like activity and TG were seen at “steady-state” emicizumab in all age groups. Irrespective of considerations regarding the developing coagulation system at such young ages, treatment of infants in HAVEN 7 with the approved dose of emicizumab was well tolerated and efficacious.

No participant in HAVEN 7 had tested positive for ADAs at CCOD. This reflects the low immunogenicity rate for emicizumab reported in a pooled analysis of the phase 3 clinical trials HAVEN 1–5, HOHOEMI, and STASEY, across which 5.1% of participants developed ADAs, including 0.6% for whom ADAs were associated with a decrease in emicizumab exposure.[35] In HAVEN 7, 24 participants were tested for FVIII inhibitors following at least three EDs or two consecutive doses of FVIII; two participants (3.6% of the trial population; 8.3% of those tested), both PUPs, tested positive for confirmed *de novo* FVIII inhibitors. As approximately half of the trial population (28/55) received FVIII treatment on study (with a median of one ED), and only 24/55 were tested for FVIII inhibitors, many participants are still in the ED risk period for inhibitor development. The long-term follow-up will provide further data on the impact of emicizumab on rate and timing of FVIII inhibitor development.

The HAVEN 7 trial has limitations to note. It is open-label and single-arm, and all analyses are descriptive as no formal hypothesis testing was planned. In addition, almost half of the participants were <3 months of age at the time of informed consent, and so comparison with bleed history since birth is limited, although two-thirds had already experienced ≥1 treated or untreated bleed at baseline. Moreover, the relatively short follow-up time limits accurate assessment of the effect of emicizumab on joint health and time to first bleed, although the long-term follow-up period will offer further insight. Finally, despite efforts to recruit female infants, none were enrolled due to the low frequency of severe HA in females and later diagnosis in comparison with males.[44]

This primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe HA without FVIII inhibitors at a currently approved dose. No participant developed ADAs. Future analyses of HAVEN 7 will describe the natural history of children with HA who initiate emicizumab prophylaxis soon after birth, including, but not limited to, safety and joint health outcomes, over the 7-year follow-up period.

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Authorship

Contribution:

S.W.P, P.C, C.D, G.K, C.S, M.B, V.J-Y, F.P, G.Y, J.O, M.E.M, A.K, M.N, T.C, K.F conceptualized and designed the study. S.W.P, P.C, C.D, G.K, V.J-Y, F.P, G.Y, J.O, M.E.M, K.K, K.F contributed to the study conduct. S.W.P, P.C, C.D, G.K, C.S, M.B, V.J-Y, F.P, G.Y, J.O, K.K, A.K, S.D, M.N, T.C, M.L, K.F acquired, analyzed, or interpreted the data. All authors revised the manuscript critically and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Conflict of interest disclosures:

S.W.P is a member of the scientific advisory board for GeneVentiv and Equilibra Bioscience and has received grants or contracts from Siemens; consulting fees from Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, Freeline, LFB, Novo Nordisk, Pfizer, Regeneron/Intellia, Genentech, Inc./F. Hoffmann-La Roche Ltd, Sanofi, Takeda, Spark Therapeutics and uniQure. P.C is a member on an entity's Board of Directors for the HAVEN 7 trial steering committee and a member of the UK Haemophilia Centre Doctors' Organisation, which has received a research grant from F. Hoffmann-La Roche Ltd. C.D is an employee of F. Hoffmann-La Roche Ltd. G.K has received grants/research support funding from BSF, Pfizer, F. Hoffmann-La Roche Ltd, Tel Aviv University, Sheba research authorities; consulting fees from ASC Therapeutics, Bayer, BioMarin, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sobi, Sanofi-Genzyme, Takeda, uniQure; honoraria from Bayer, BioMarin, BPL, CSL Behring, Pfizer, Novo Nordisk, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme and Spark Therapeutics; participated on a Data Safety Monitoring Board or Advisory Board for ASC Therapeutics, BioMarin, Pfizer, Novo Nordisk, uniQure, F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Sobi, Spark Therapeutics and has a leadership role for PedNet Research foundation. C.S and M.B are employees and stockholders of F.

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Tables

Table 1. Participant demographics, baseline clinical characteristics, and medical history

	Participants (N = 55)
Age at informed consent, months	
Mean (SD)	5.0 (3.9)
Median (min, max)	4.0 (9 days, 11 months 30 days)
Age group, n (%)	
0–<3 months	25 (45.5)
3–12 months	30 (54.5)
Sex, n (%)	
Male	55 (100)
Ethnicity, n (%)	
Hispanic or Latino	5 (9.1)
Not Hispanic or Latino	49 (89.1)
Unknown	1 (1.8)
Race, n (%)	
Asian	3 (5.5)
Black or African American	1 (1.8)
Native Hawaiian or other Pacific Islander	1 (1.8)
White	48 (87.3)
Unknown	2 (3.6)
Weight at baseline, kg	
Median (min, max)	7.1 (3.2, 12.0)
Mode of delivery, n (%)	
Vaginal delivery (not assisted)	18 (32.7)
Vaginal delivery (assisted)	6 (10.9)
Planned cesarean section	30 (54.4)
Emergency cesarean section	1 (1.8)
Family history of HA, n (%)	41 (74.5)
Family history of FVIII inhibitors	7 (12.7)
Prior treatment status, n (%)	
MTP*	30 (54.5)

PUP	25 (45.5)
Hemophilia treatments received prior to first emicizumab dose	
Participants with ≥1 treatment, n (%)	34 (61.8)
Total number of treatments, n	85
Purpose of treatment, n (%)	
Treatment for a bleed	30 (54.5)
Preventative dose before activity	4 (7.3)
Preventative dose for procedure/surgery	3 (5.5)
Historical bleeding episodes prior to first emicizumab dose	
Participants with ≥1 bleed, n (%)	36 (65.5)
Total number of bleeds, n	77
Cause/type of bleed, n (%)	
Spontaneous	**25 (32.5)**
Joint	8 (32.0)[†]
Muscle	6 (24.0)[‡]
Other	11 (44.0)[§]
Traumatic	**19 (24.7)**
Joint	0 (0.0)
Muscle	1 (5.3)[‡]
Other	18 (94.7)[§]
Procedural/surgical	**33 (42.9)**
Joint	0 (0.0)
Muscle	8 (24.2)[‡]
Other	25 (75.8)[§]

Age is calculated relative to the date when the informed consent form was signed. *Defined as a participant with ≤5 exposure days to hemophilia-related treatments containing FVIII, such as plasma-derived FVIII, recombinant FVIII, fresh frozen plasma, cryoprecipitate, or whole blood products. [†]Of the eight total pre-study joint bleeds, two each occurred in the elbow and hip and one each occurred in the ankle, fingers/thumb, knee, and shoulder. [‡]Of the 15 total pre-study muscle bleeds, the majority (eight bleeds [n = 7participants]) occurred in the thigh. HA diagnosis was known in four of these participants at the time of these bleeds in the thigh. Six of the eight bleeds in the thigh were procedural bleeds: three for vaccination (n =3 participants); three for vitamin K administration (n = 2 participants; [in one participant, one bleed in the left thigh; in another participant, one bleed in the left thigh and one bleed in the right thigh]). The remaining two bleeds in the thigh were two spontaneous bleeds in the left thigh (n = 2 participants). [§]Of the 54 total pre-study other bleeds, nine occurred in the sole/heel (all due to heel prick for metabolic tests [n = 6 participants], with 2/6 having received HA diagnosis at the time of these bleeds), six in the back of the hand or the mouth

(HA diagnosis known in 5/6 cases [n = 4 participants] at the time of these bleeds), and the remainder were distributed across the rest of the body.

FVIII, factor VIII; HA, hemophilia A; MTP; minimally treated patient; PUP, previously untreated patient; SD, standard deviation

Table 2. Bleeding outcomes: overall population

	Participants (N = 55)
Median (min, max) follow-up,* weeks	101.9 (52.6, 119.7)
Model-based ABR (95% CI)	
All bleeds	2.0 (1.49–2.66)
Treated bleeds	0.4 (0.30–0.63)
Treated spontaneous bleeds	0.0†
Treated joint bleeds	0.0 (0.01–0.09)
Calculated median ABR (IQR)	
All bleeds	1.0 (0.53–2.93)
Treated bleeds	0.0 (0.00–0.81)
Treated spontaneous bleeds	0.0 (0.00–0.00)
Treated joint bleeds	0.0 (0.00–0.00)
Participants with zero bleeds, n (%)	
Zero all bleeds	9 (16.4)
Zero treated bleeds	30 (54.5)
Zero treated spontaneous bleeds	55 (100.0)
Zero treated joint bleeds	52 (94.5)
Participants with ≥1 bleed, n (%)	46 (83.6)
Total number of bleeds,‡ n	207
Cause/type of bleed, n (%)	
Spontaneous	**18 (8.7)**
Joint	0 (0.0)
Muscle	0 (0.0)
Other	18 (100.0)
Traumatic	**182 (87.9)**
Joint	4 (2.2)
Muscle	5 (2.7)
Other	173 (95.1)
Procedural/surgical§	**7 (3.4)**
Joint	0 (0.0)
Muscle	1 (14.3)
Other	6 (85.7)
Participants with ≥1 treated bleed, n (%)	25 (45.5)

Total number of treated bleeds, n	42
Cause/type of treated bleed, n (%)	
Traumatic	**42 (100.0)**
Joint	3 (7.1)
Muscle	5 (11.9)
Other	34 (81.0)

At time of the primary analysis, the median (min, max) age of the participants was 29 (12, 39) months. *The start of the efficacy period for each individual participant is defined as the day of the first emicizumab dose. The end of the efficacy period is defined as the date of the clinical cut-off or the date of withdrawal from the study period (i.e., 'Open Label Treatment' and 'Long-term Follow-up' according to electronic Case Report Form), whichever is earlier. †ABR could not be estimated via the negative binomial regression model as no treated spontaneous bleeds were observed in the study; as a result, a value of 0.0 is reported in the table instead. ‡Two participants experienced >10 bleeds, none treated and none in joint or muscle. One participant experienced 27 bleeds (19 traumatic, 8 spontaneous; 20/27 being nosebleeds), with the first bleed recorded at approximately 11.6 months of age. The other participant experienced 21 bleeds (all traumatic), with the first bleed reported at approximately 13.8 months of age. §Of the seven procedural/surgical bleeds, four bleeds were reported in one participant and one bleed each was reported in three participants.

ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range

Table 3. Safety summary

Adverse event	Participants (N = 55)
Total number of AEs, n	631
Participants with ≥1 AE, n (%)	55 (100)
AE with fatal outcome	0 (0)
AE leading to withdrawal from treatment	0 (0)
AE leading to dose modification/interruption	0 (0)
Participants with ≥1 Grade ≥3 AE, n (%)	17 (30.9)
Participants with ≥1 treatment-related AE,* n (%)	9 (16.4)
Injection-site reaction, number of events	30
Total number of SAEs,† n	30
Participants with ≥1 SAE, n (%)	16 (29.1)
AEs of special interest, n (%)	1 (1.8)
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	1 (1.8)‡
Thromboembolic event	0 (0)
Thrombotic microangiopathy	0 (0)

*All treatment-related AEs were Grade 1 local injection-site reactions. †None of the SAEs were considered emicizumab related, and all were considered serious due to hospitalization. SAEs included: fall (n = 4); head injury (n = 4); bronchiolitis, bronchitis, pneumonia, tonsillitis, mouth hemorrhage, tongue hemorrhage (n = 2 for each); ear infection, laryngitis, upper respiratory tract infection, urinary tract infection, viral infection, eyelid contusion, post-procedural fever (liver biopsy due to fluctuating liver enzymes assessed locally; a serology test for EBV, CMV, HHV 6 and hepatitis A, B and C was negative, and no liver pathology was found), post-procedural hemorrhage (tonsillectomy), skin laceration, tongue injury (n = 1 for each). ‡One anaphylactic reaction due to an egg allergy was reported in one participant, considered not related to emicizumab.

AE, adverse event; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV 6, human herpes virus 6; SAE, serious adverse event

Figures

Figure 1. Participant disposition

*Emicizumab dose was up-titrated in one participant on day 374 while starting the long-term follow-up period. Up-titration was per investigator request based on locally assessed decreasing emicizumab levels (confirmed retrospectively to be 6.6 µg/mL in a central assessment). This participant experienced three treated and two untreated bleeds (all traumatic) before and after up-titration, respectively. †Bleed endpoints consider data before up-titration only.

Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly

Figure 2. Mean (95% CI) emicizumab trough concentration at visit (A) over time and (B) by age at visit during the maintenance period

For the participant whose dose was up-titrated, only data before up-titration are included. For the analysis by age, only samples from week 5 onwards (maintenance period) were considered.

CI, confidence interval

Figure 1

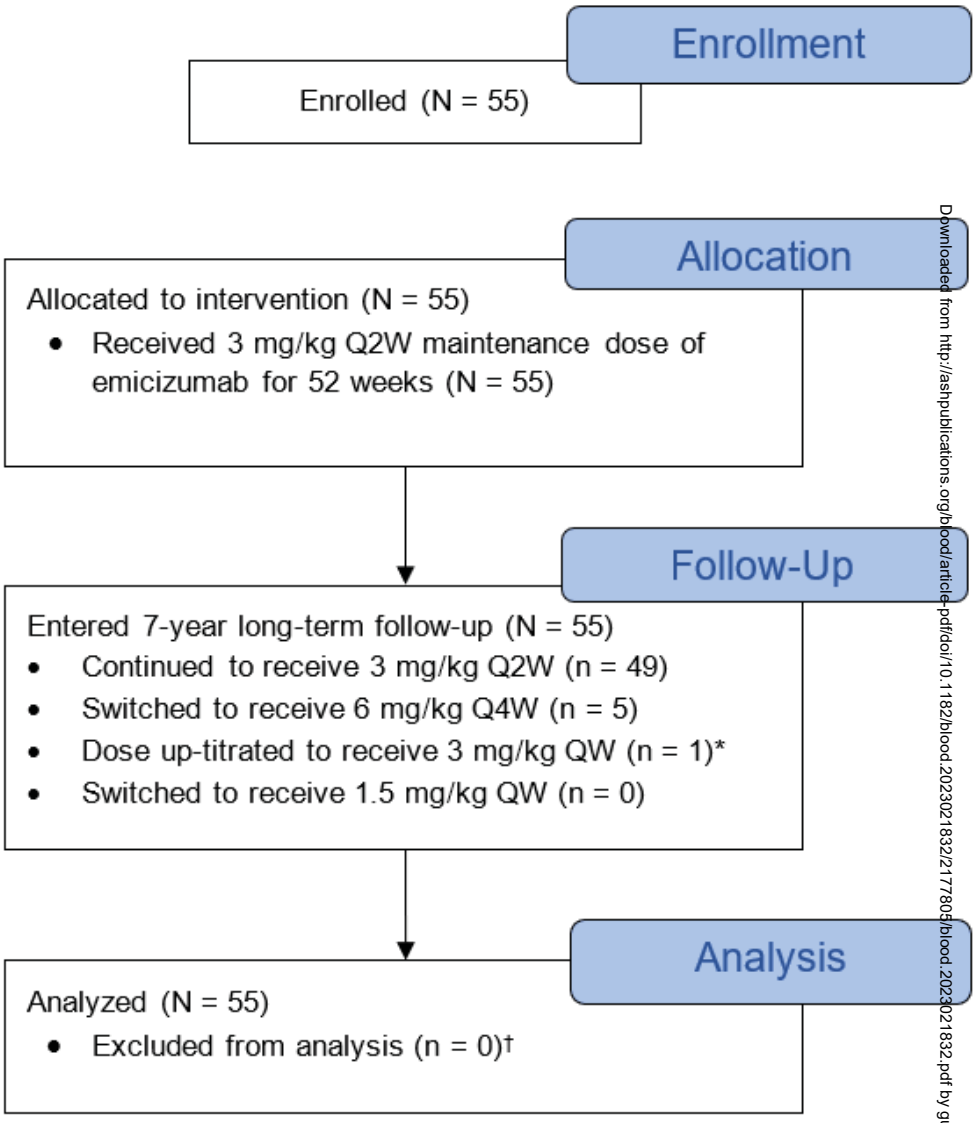
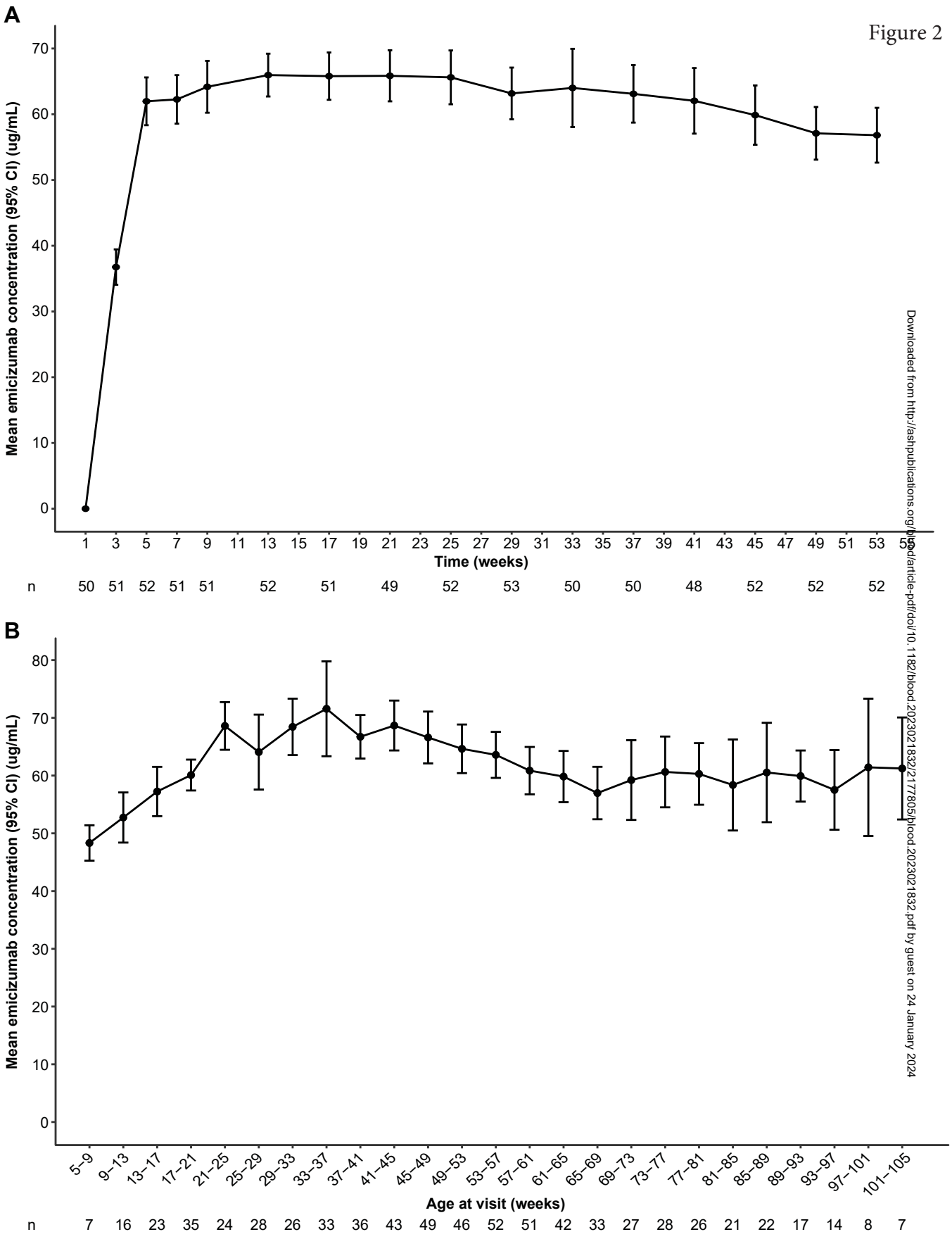
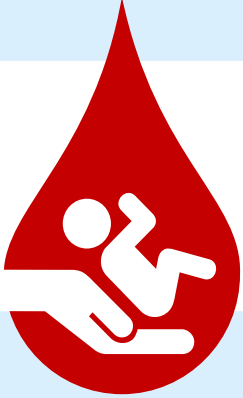


Figure 2



Emicizumab prophylaxis in infants with hemophilia A: HAVEN 7 primary analysis

Emicizumab was investigated for ≥52 weeks in participants ≤12 months of age with severe hemophilia A without factor VIII inhibitors



55 males

Median emicizumab treatment duration: **100.3 weeks**

Median age at informed consent: **4.0 months**

The **annualized treated bleed rate** was **0.4**; all were traumatic

54.5% **of participants** (n=30) had **zero treated bleeds**

49.1% of participants (n=27) did **not require factor VIII infusions**

No intracranial hemorrhages occurred

No new safety signals were identified, and no anti-emicizumab antibodies developed

The primary analysis of HAVEN 7 indicates that emicizumab is efficacious and well tolerated in infants with severe hemophilia A without factor VIII inhibitors