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Effectiveness of emicizumab under real-world conditions in patients of all ages with hemophilia A with and without FVIII inhibitors: Fourth interim analysis of the non-interventional study EMIIL

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Conclusions

- The results from the fourth interim analysis support the effectiveness and safety of emicizumab in a real-world setting.
- Particularly, data on ABR and the proportion of patients with zero bleeds are consistent with results from previous clinical trials.
- No new safety signals were identified with emicizumab.

Background and Objective

- Emicizumab, approved for routine prophylaxis in adult and pediatric patients with hemophilia A (PwHA) with or without factor VIII (FVIII) inhibitors, is a monoclonal, humanized bispecific antibody bridging coagulation factors IXa and X and thereby replacing the coagulation function of activated FVIII even in the presence of FVIII inhibitors.[1]
- Subcutaneous administration of emicizumab has demonstrated a positive benefit/risk profile in clinical trial settings[2-5] and several published real-world reports.[6,7]
- The aim of the ongoing non-interventional study EMIIL (ISRCTN58752772) is to better understand the long-term effectiveness of emicizumab prophylaxis in PwHA with and without FVIII inhibitors under real-world conditions.

Methods

Study Design

- EMIIL is an ongoing single-arm, two-cohort, prospective, multicenter, non-interventional study in Germany and Switzerland collecting primary observational data in patients with congenital hemophilia A newly treated with emicizumab.
- Here we report results from the fourth interim analysis of cohort A and cohort B (data cut-off: May 13, 2024).

Primary Endpoint

- Annualized bleeding rate (ABR) of treated bleeds

Statistics

- Data were evaluated descriptively. The primary effectiveness variable in Cohort A, the ABR of treated bleeds was estimated using a generalized linear model (GLM) assuming a negative binomial-distribution for bleeding events and using observation time as off-scale parameter.

Cohort A
Male patients with severe congenital hemophilia A without FVIII inhibitors[a]

Subgroups
- Children (0-11 years[b,c])
- Adolescents (12-17 years[b,c])
- Adults (≥18-64 years[b])
- Elderly (≥65 years[b])

Cohort B
Male patients with congenital hemophilia A (any severity) with FVIII inhibitors at study entry[d]

Observation phase (1-5 years/patient)

Emicizumab prophylaxis[e]

[a]<0.6 BU, FVIII half-life ≥6 hours or FVIII recovery ≥66%, patients who completed successful immune tolerance induction (ITI) before start of emicizumab treatment are eligible; [b]At study entry; [c]At least 30 patients into subgroups children and adolescents; [d]≥0.6 BU, FVIII half-life <6 hours or FVIII recovery <66% or ongoing ITI at start of emicizumab treatment; [e]According to summary of product characteristics.

Results

- For this fourth interim analysis, a total of 125 male patients in cohort A and 7 male patients in cohort B were available for evaluation.
- Median treatment duration for Cohort A was 918 days (range 190-1608; mean (SD) 941.10 (374.39)) and 378 days for Cohort B (range 77-1260; mean (SD) 452.43 (403.06)) .
- The predominant dosing regimen used at least once throughout the study was 3 mg/kg Q2W in slightly more than half of patients in both cohorts.

Patient demographics

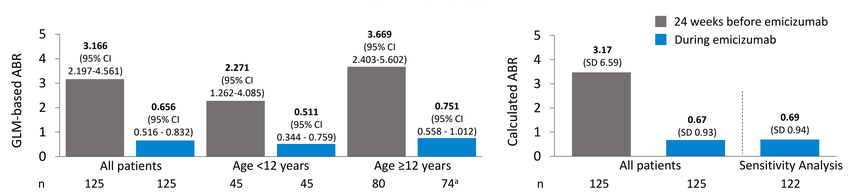
Demographic parameters	Cohort A N=125	Cohort B N=7
Age at screening [years]		
Mean (SD)	26.34 (21.07)	23.57 (22.62)
Median (range)	25.0 (0.0-75.0)	14.0 (1.0-67.0)
Age group, n (%)		
Children (0-11 years)	45 (36.0%)	2 (28.6%)
Adolescents (12-17 years)	7 (5.6%)	2 (28.6%)
Adults (18-64 years)	69 (55.2%)	2 (28.6%)
Elderly (≥65 years)	4 (3.2%)	1 (14.3%)
Ethnicity, n (%)		
White	113 (90.4%)	6 (85.7%)
Black or African American	2 (1.6%)	0
Asian	2 (1.6%)	0
Not reported	8 (6.4%)	1 (14.3%)
Time since hemophilia A diagnosis [years]		
Mean (SD)	22.68 (19.49)	19.84 (19.92)
Median (range)	18.64 (0.0-73.8)	13.89 (1.1-57.1)
Severity at baseline, n (%)		
Mild (>5-40% FVIII activity)	0	1 (14.3%)
Moderate (1-≤5% FVIII activity)	0	1 (14.3%)
Severe (<1% FVIII activity)	125 (100.0%)	5 (71.4%)
FVIII inhibitors history[a], n (%)		
Yes	5 (4.0%)	6 (85.7%)
Missing	120 (92.3%)	1 (14.3%)[b]
Treatment regimen prior to emicizumab, n (%)		
Prophylactic	98 (78.4%)	3 (42.9%)
On-demand	24 (19.2%)	3 (42.9%)
No Hemophilia A treatment (PUPs)	8 (6.4%)	1 (14.3%)[c]

[a]Highest measurement before start of treatment; no present FVIII inhibitor defined as <0.6 BU; [b]For this patient, it was documented that Factor VIII inhibitors occurred before and at start of treatment but no value for Bethesda units was listed; [c]No previous HA treatment listed for this patient; but patient shows FVIII inhibitors and was treated with ITI indicating previous HA treatment

Annualized bleeding rate for Cohort A

- None of the patients in Cohort B had treated bleeds; therefore, the following bleed results only focus on cohort A.
- After a median treatment duration of 918 days (range 190-1608), the GLM-based ABR for Cohort A (primary endpoint) was 0.656 (95% CI 0.516 – 0.832), based on 257.91 patient years and 159 treated bleeds.
- The calculated mean (SD) ABR for treated bleeds was 3.17 (SD 6.59) before emicizumab initiation and 0.67 (0.93) during the study.

ABR treated bleeds

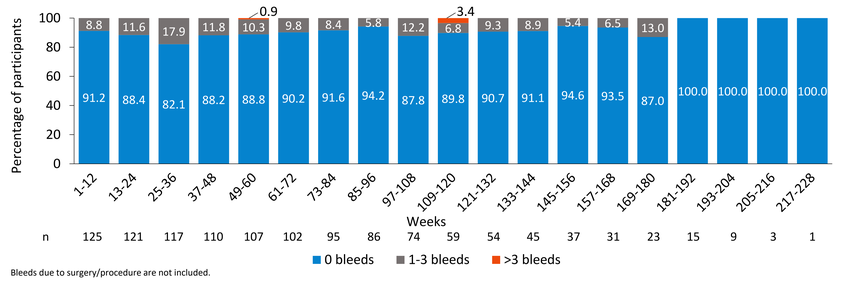


Bleeds due to surgery/procedure are not included. For GLM-based ABR, before emicizumab initiation, the following confounder variables are included in the model: Age (<12 years, ≥12 years). Additionally, during emicizumab treatment, number of treated bleeds in the past 24 weeks prior to start of emicizumab treatment (<9, ≥9) are included as confounders. For calculated ABR, ABR = Number of treated bleeds for the whole study duration / study duration in years; with study duration defined as Duration = (max. visit date with treated bleed assessment – Date of first emicizumab administration)/365.25. Descriptive summary for ABR of treated bleeds in the 24 weeks prior emicizumab treatment. Missing values for bleeds were set to zero, ABR was set to zero if no bleeds were recorded. In the sensitivity analysis, patients with zero bleeds before their first visit and/or short study duration were counted as "missing" (in total 3 patients). [a]<9 treated bleeds before emicizumab.

Efficacious bleed protection over time

- Recorded in 12-week time windows, most patients in Cohort A experienced zero treated bleeds across the study period (range 87.8%-94.2%; mean (SD) study duration 941.10 (374.39) days).

Proportion of participants in Cohort A with 0, 1-3 or >3 treated bleeds over time



Bleeds due to surgery/procedure are not included.

Patients with zero treated bleeds

- The mean (SD) number of treated bleeds in the overall population (Cohort A) was 1.27 (1.78). The proportion of patients with zero treated bleeds was 44.8%. Zero treated spontaneous bleeds were recorded in 76.0%, zero treated joint bleeds in 66.4%, and zero treated target joint bleeds in 95.2% of patients.
- All patients of Cohort B had zero treated bleeds.

Safety

- Out of 132 safety-evaluable patients, 87 (65.9%) patients experienced 313 adverse events (AEs). Of these, 308 AEs were reported in 82 patients within Cohort A, while 5 AEs were reported in 5 patients within Cohort B.
- The most frequently reported AEs in Cohort A were fall (9.6%), pyrexia (7.2%), headache (6.4%), arthralgia (5.6%) and COVID-19 (5.6%). In Cohort B, all 5 AEs occurred as single events in one patient each.
- In total, 30 patients (22.7%) reported 60 serious AEs (SAEs), all occurring in Cohort A. SAEs occurring more than once were fall (in 3 patients), COVID-19, pilonidal disease, concussion, ascites, hemarthrosis and muscle hemorrhage (each in 2 patients).
- There were 3 patients with newly occurring FVIII inhibitors in Cohort A (1 transient, 1 persisting and 1 to be confirmed whether transient or persisting).

Adverse events

N patients (%) – n events	Cohort A N=112	Cohort B N=7
Total number of adverse events	82 (65.6%) - 308	5 (71.4%) - 5
Adverse events ≥ Grade 3[a]	21 (16.8%) - 48	0 (0.0%) - 0
Serious adverse events	30 (24.0%) - 60	0 (0.0%) - 0
Adverse drug reactions	26 (20.8%) - 55	0 (0.0%) - 0
Adverse drug reactions ≥ Grade 3[a]	4 (3.2%) - 9	0 (0.0%) - 0
Serious adverse drug reactions	5 (4.0%) - 9	0 (0.0%) - 0
Adverse events of special interest[b]	1 (0.8%) - 1	0 (0.0%) - 0
Adverse events leading to treatment discontinuation	1 (0.8%) - 1	0 (0.0%) - 0
Adverse events with fatal outcome[c]	2 (1.6%) - 3	0 (0.0%) - 0

AE data was coded using MedDRA version 26.0. [a]According to WHO toxicity grading Grade 3 and 4. [b]The AESI was classified as thromboembolic event, which was reported after a CT scan for staging a pre-existing lung adenocarcinoma in the patient. [c]Two patients experienced 3 AEs leading to death. One patient was reported with cardiotoxicity and lung adenocarcinoma. One patient with a history of comorbidities was reported with unexplained death.

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Abbreviations

ABR, annualized bleeding rate; AE, adverse event; AESI, adverse event of special interest; BU, Bethesda Units; CI, confidence interval; CT, computer tomography; FVIII, factor VIII; GLM, generalized linear model; HA, hemophilia A; ITI, immune tolerance induction; PT, preferred term; PUPs, previously untreated patients; PwHA, patients with hemophilia A; Q2W, every two weeks; SAE, serious adverse event; SD, standard deviation; WHO: World Health Organization

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