Post ISTH 2023

Haemophilia - emicizumab

Haemophilia A
Portfolio

M-CZ-00003345

Agenda of ISTH 2023 - emicizumab

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- **Special population**
  - ✓ ***PUPs PedNet (Oral presentation OC 43.1)*** *– Koenigs Ch, et al. – A survey on clinical praxis in initiating emicizumab prophylaxis in previously untreated patients in the PedNet centers*
  - ✓ ***ITI (Oral presentation OC 43.5) –*** *Levy-Mendelovich S, et al. – Should immune tolerance be pursued in the era of emicizumab? Longitudinal follow-up of a FVIII inhibitor cohort – Real World Data*
  - ✓ ***Physical activity (Poster PB0641)*** *– Fujii T, et al. – Association between physical activity and bleeding events in people with hemophilia A receiving emicizumab prophylaxis: interim analysis of the TSUBASA study*
  - ✓ ***PwHA aged ≥50 years with comorbidities (Poster PB0625)*** *– Buckner TW, et al. – Emicizumab prophylaxis in people with hemophilia A aged ≥50 years with comorbidities: experience from the ATHN 7 hemophilia natural history study*
- **Real World Data (RWD) – long term efficacy and safety**
  - ✓ ***Germany (Oral presentation OC 43.4)*** *– Oldenburg J, et al. – Effectiveness of emicizumab under Real-world conditions in patients of all ages with hemophilia A with and without inhibitors: Interim analysis of the non-interventional study EMIIL*
  - ✓ ***Germany (Poster PB0643)*** *– Mondorf W, et al. – Efficacy of emicizumab prophylaxis in patients with severe hemophilia A in Germany: Follow-up evaluation of real-life-data documented by smart medication eDiary*
- **Real World Data (RWD) – management of invasive procedures**
  - ✓ ***France (Oral presentation OC 43.3)*** *– Brakta Ch, et al. – Surgery in people with hemophilia A receiving emicizumab prophylaxis: Real – world experience from a single French Treatment Center of Hemophilia*
  - ✓ ***Israel (Poster PB0627)*** *– Cohen O, et al. – Management of invasive procedures in patients with Hemophilia A receiving Emicizumab prophylaxis: Real-world data from a national Hemophilia treatment center*

A survey on clinical praxis in initiating emicizumab prophylaxis in previously untreated patients in the PedNet centers

Upraveno podle ústní prezentace OC 43.1 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

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Learning objectives

- Reflect on the use of emicizumab or FVIII in young children with haemophilia
- Recognize the current practise of the use of emicizumab in PedNet centres in Israel, Canada and Europe
- Describe open question on safety, efficacy and immunology on the use of emicizumab or FVIII in young children with haemophilia A

F, factor; PedNet, The European Paediatric Network for Haemophilia Management;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Use of emicizumab in young children

- Emicizumab offers an attractive alternative for prophylaxis in young children
- Data on treatment of young children with emicizumab is scarce
- PUP trial (HAVEN 7) is ongoing
- Many open questions
  - ✓ Strategy when and how to start
  - ✓ Efficacy in early life
  - ✓ Role of tolerance to FVIII
  - ✓ Inhibitor risk under emicizumab prophylaxis and FVIII for bleed treatment
  - ✓ Strategies after inhibitor development and after potential ITI
  - ✓ ???

F, factor; ITI, Immune Tolerance Induction;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Aim

- Assess the current clinical practice on the use of emicizumab prophylaxis in children in the PedNet centres

PedNet, The European Paediatric Network for Haemophilia Management;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

PedNet Hemophilia Registry

- 32 centres in 19 countries
- 2759 children in PedNet in January 2023
  - ✓ 2302 with HA, 1491 with severe HA including 445 children with inhibitor development

PedNet, The European Paediatric Network for Haemophilia Management; HA, haemophilia A

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Questionnaire

- Assess the current clinical practice on the use of emicizumab prophylaxis in children in the PedNet centres
  - ✓ Availability including indication
  - ✓ Strategies in PUPs, MTPs, PTPs
    - Start of prophylaxis, concomitant therapies,...
    - Practical issues
  - ✓ Monitoring
  - ✓ Strategies at inhibitor development in PUPs
  - ✓ Strategies in patients with persistent inhibitors

- Captured in a Redcap survey until February 2023

PedNet, The European Paediatric Network for Haemophilia Management; PUPs, previously untreated patient; MTPs, minimally treated patient; PTPs, previously treated patient;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

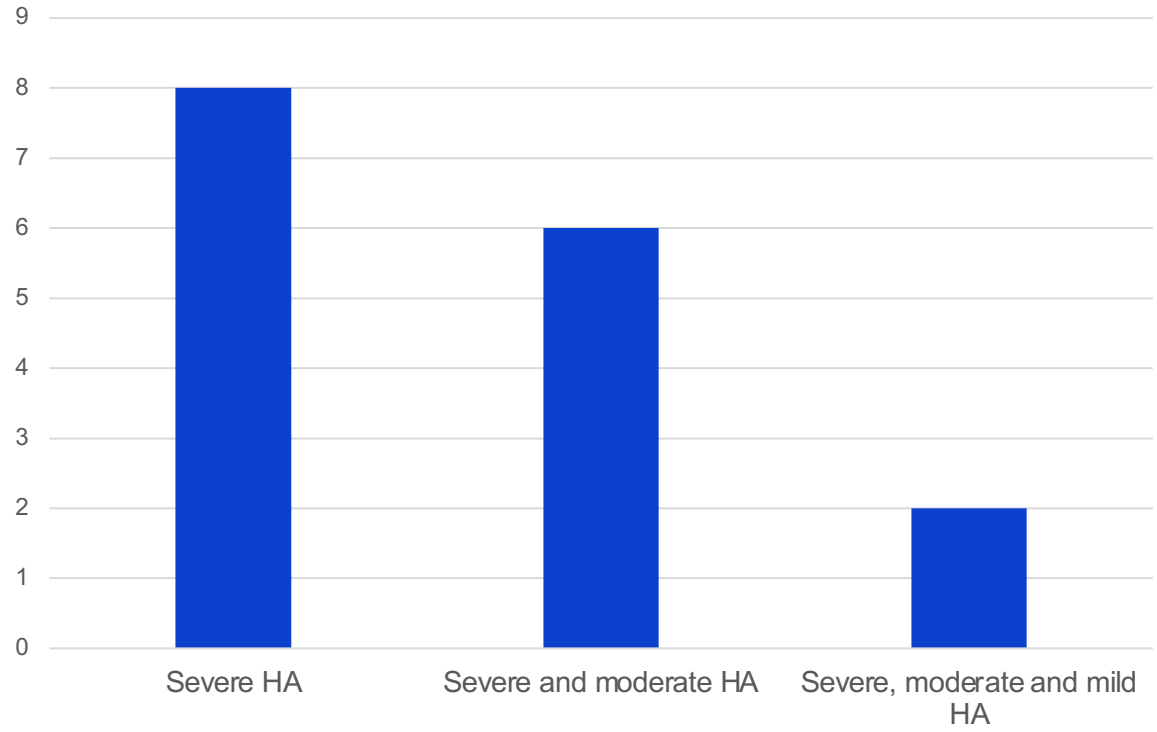
Results

- 28/32 PedNet centres responded (88%)
  - ✓ Emicizumab was available in 26/28 centres in clinical routine
    - For patients with or without inhibitors
    - For PUPs/MTPs
    - In one centre only for patients with inhibitors or special clinical situations
  - ✓ Emicizumab was available in 2/28 centres in clinical routine only for inhibitor patients

PedNet, The European Paediatric Network for Haemophilia Management; PUPs, previously untreated patient; MTPs, minimally treated patient;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

In which patients do you use emicizumab?



HA, haemophilia A;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Strategies for emicizumab prophylaxis in PUPs

- 18/28 centres use emicizumab alone
- 3/28 centres use emicizumab and concomitant regular FVIII in PUPs

✓ Remaining 7 centres concomitant FVIII is used...

- In PUPs with family history of inhibitors
- In patients with inhibitors in order to eredicate inhibitor
- In patients after inhibitor eradication
- In patients with inhibitors in order to eradicate and after eradication
- In som PUPs/MTPs
- In patients with good venous access
- In two teenagers playing sports at a competitive level

F, factor; PUPs, previously untreated patient; MTPs, minimally treated patient;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Prophylaxis in PUPs with emicizumab as first agent

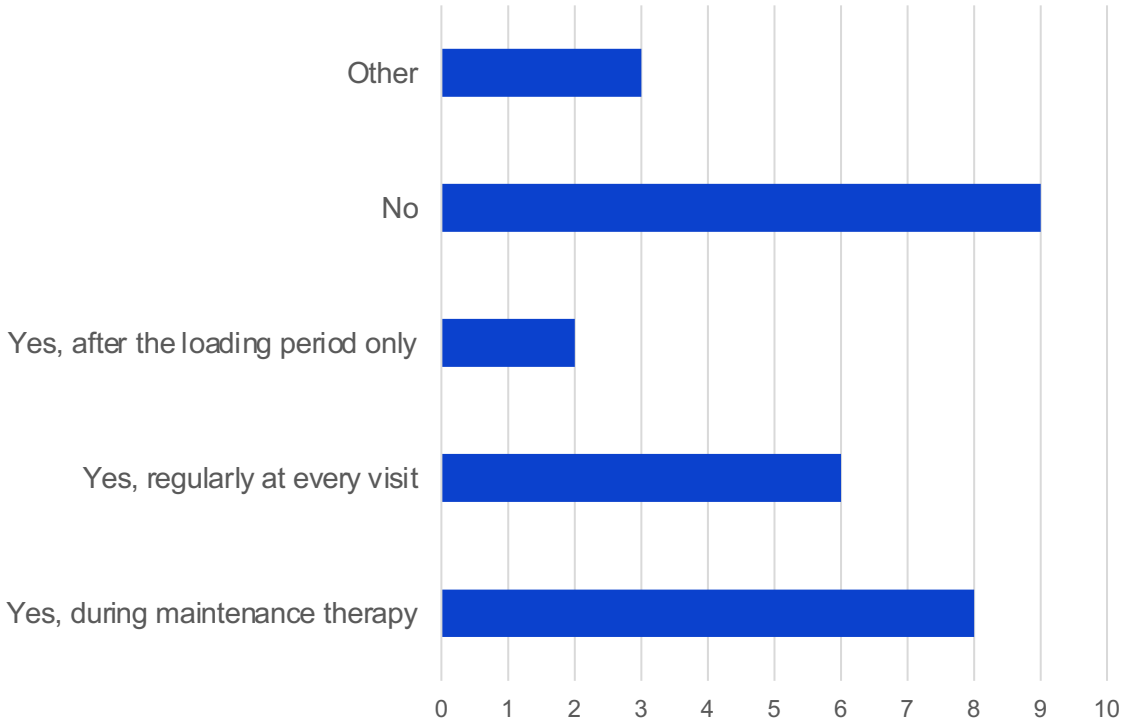
- 20 out of 26 centres (2 missing) use emicizumab as first line prophylaxis
- Anticipated start of prophylaxis:

< 3 months of age	2
3 - < 6 months of age	4
6 - < 12 months of age	11
12 - < 18 months of age	3

PUPs, previously untreated patient;

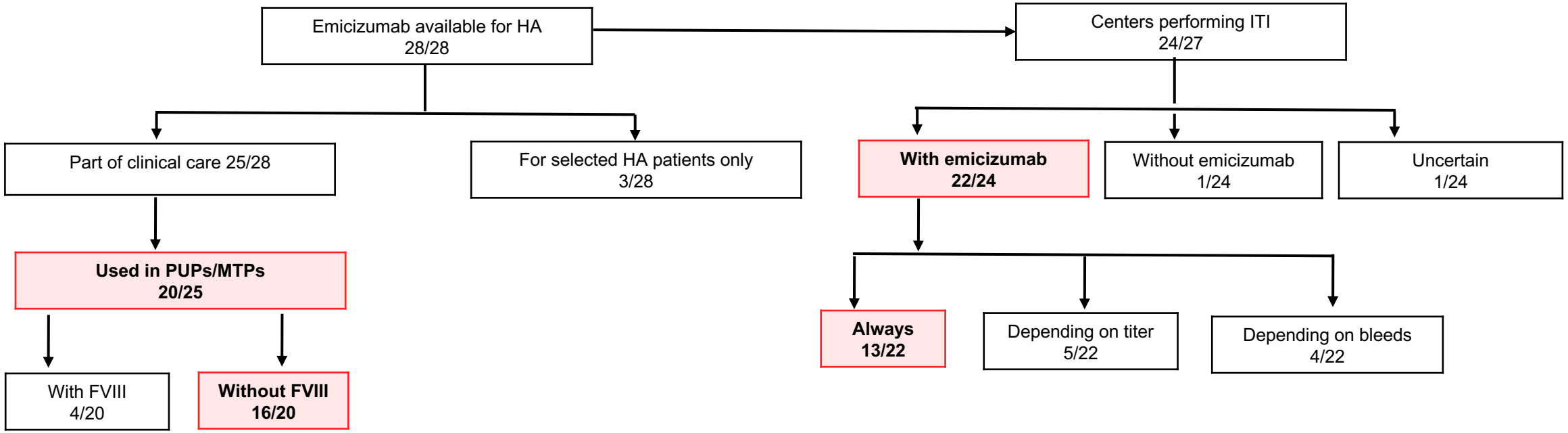
Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Monitoring of emicizumab levels



Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

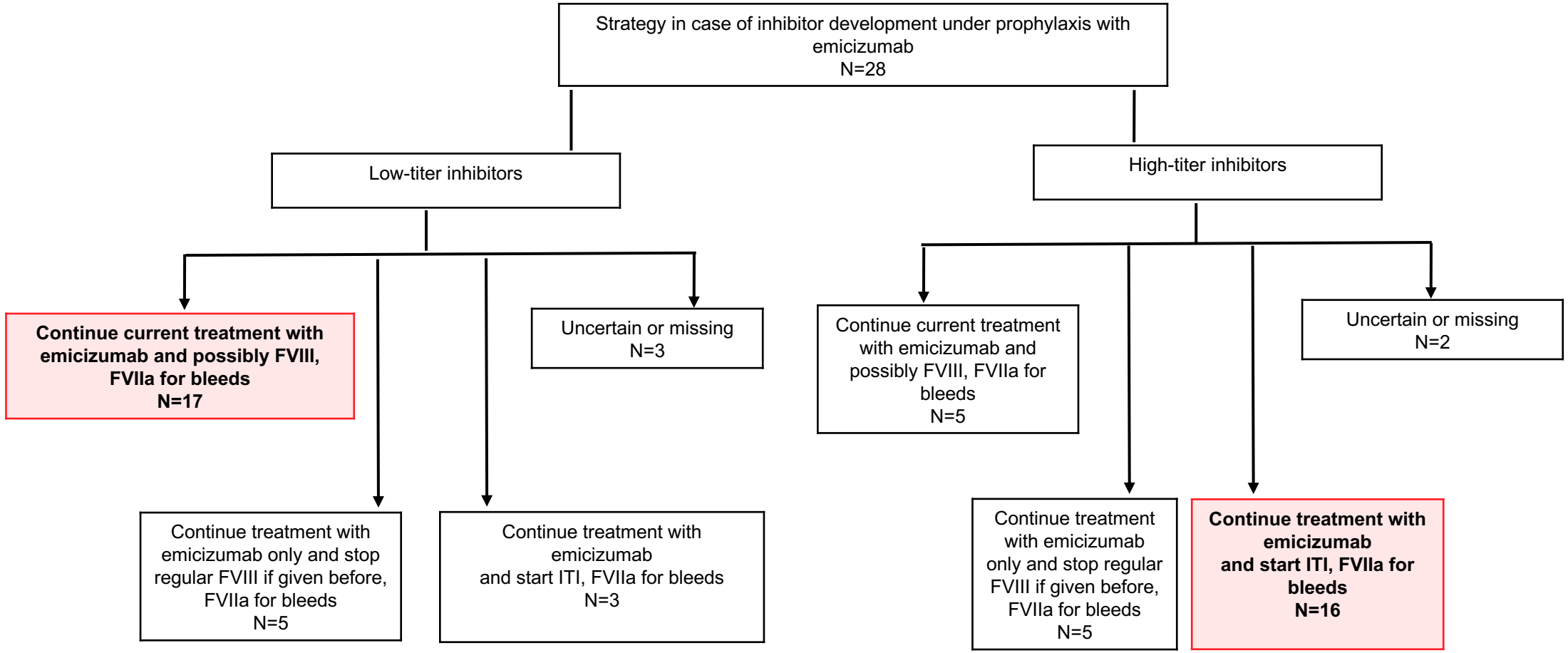
Strategy for use of emicizumab in PUPs and during ITI



F, factor; PUPs, previously untreated patient; MTPs, minimally treated patient; ITI, Immune Tolerance Induction; HA, haemophilia A;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Strategy for use of emicizumab in patients with inhibitors



F, factor; ITI, Immune Tolerance Induction; HA, haemophilia A; FVIIa; recombinant activated FVII

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Conclusions

- Emicizumab is widely used in young children in PedNet centres
  - ✓ Strategies on timing and concomitant FVIII prophylaxis vary
- Monitoring of emicizumab levels and FVIII inhibitors is performed in most centres with varying approaches
  - ✓ Uncertainties on FVIII inhibitor risks
- ITI is performed in most centres and includes emicizumab
  - ✓ Highly varying strategies

F, factor; ITI, Immune Tolerance Induction;

Koenigs Ch, et al. ISTH 2023; ústní prezentace OC 43.1.

Should immune tolerance be pursued in the era of emicizumab? Longitudinal follow-up of a FVIII inhibitor cohort – Real World Data

Upraveno podle ústní prezentace OC 43.5 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

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Introduction

- Approximately 30% of the SHA patients develop anti-FVIII antibodies (inhibitors) that may render CFC treatment futile. ITI is a treatment strategy that aims to eliminate inhibitors to FVIII in these patients. However, ITI yields eradication of FVIII inhibitors in only about two thirds of patients

- Inhibitor eradication remains the recommmended approach among hemophilia treaters, with clinical and economic justification for using emicizumab to prevent bleeding during ITI

F, factor; ITI, Immune Tolerance Induction; SHA, severe haemophilia A; CFC, clotting factor concentrate

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Introduction

- Following emicizumab prophylaxis initiation, the majority of patients and their caregivers, may choose to refrain from continued FVIII therapy
- Decision regarding ITI initiation, regimen and preservation of tolerance remain to be elucidated

F, factor; ITI, Immune Tolerance Induction;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Rational and Aim of study

- Data regarding ITI and post ITI tolerance maintenance in patients with hemophilia A treated by emicizumab are scarce
- Our aim was to study the course of FVIII inhibitor in HA patients with FVIII inhibitor or a history of FVIII inhibitors, receiving emicizumab prophylaxis

F, factor; ITI, Immune Tolerance Induction; HA, haemophilia A

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Methods

- All HA patients, with either FVIII inhibitors or a history of a FVIII inhibitor, aged 1 month to 80 years, followed at the Israeli National HTC and treated with emicizumab were eligible for the current study whether or not they underwent ITI
- Three study groups were compared: Failed ITI, successful ITI, deferred ITI
- Inhibitor levels were examined every 3 – 6 month of following exposure to FVIII (chromogenic inhibitor assays)
- Patients documented ABR and any FVIII ED

F, factor; ITI, Immune Tolerance Induction; HA, haemophilia A; HTC, Hemophilia Treatment Centre; ED, exposure days; ABR, annual bleeding rate;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

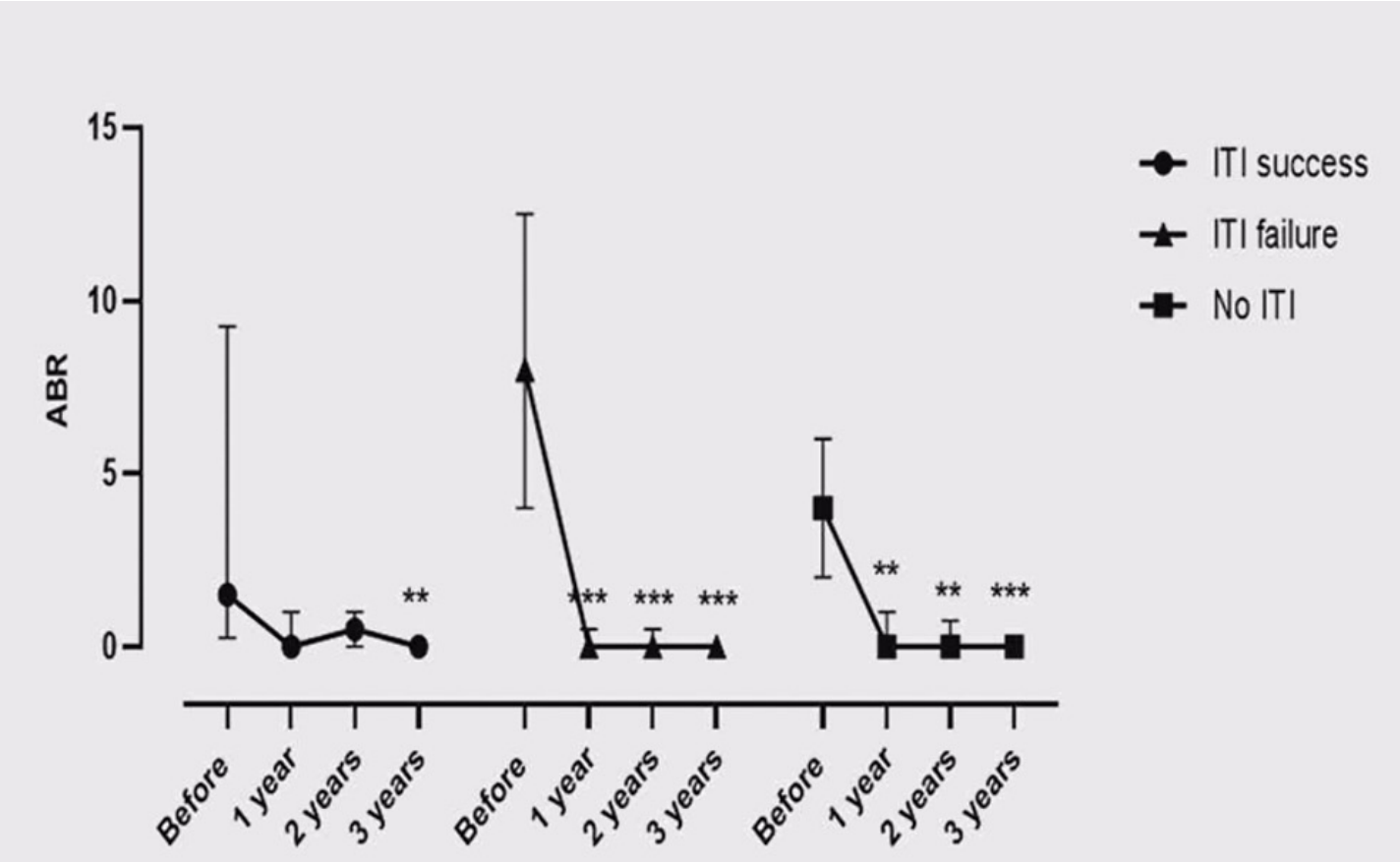
Results

	Failed ITI N=15	Successful ITI N=15	No ITI N=21	P value
Mutations	• Inversion22- 9 pt. • c.3439C>T p.Gln1147(Q1147> stop)- 1 pt. • Deletion of exon 8+9- 1 pt. • Deletion of exon 14-21- 1 pt. • Unknown- 2 pt.	• Inversion22- 10 pt. • Unknown- 6 pt.	• Inversion22- 10 pt. • c.75C>G p.Tyr25- 1 pt. • c.6976C>T p.Arg2326- 1pt. • Deletion of exon 1-14- 1 pt. • Unknown- 9 pt.	-
Age of initiation of emicizumab, years, median (IQR)	5.5 (1.1; 31.4)	14.5 (9.5; 29.4)	2 (0.8; 19.8)	0.045
Inhibitor Peak level, BU, median (range)	21.5 (0.5 – 900)	25 (0.5 – 284)	16 (0.5 – 192)	>0.999
Inhibitor level before emicizumab, BU, median (IQR)	4.0 (1.1 – 12.0)	0.0 (0.0 – 0.5)	1.3 (0.5 – 5.1)	<0.001
ABR prior to emicizumab, median (IQR)	7 (3 – 10)	1 (0 – 7.75)	3 (1 – 6)	0.036

pt, patients; ITI, Immune Tolerance Induction; ABR, annual bleeding rate; IQR, interquartile range; BU, Bethesda units;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

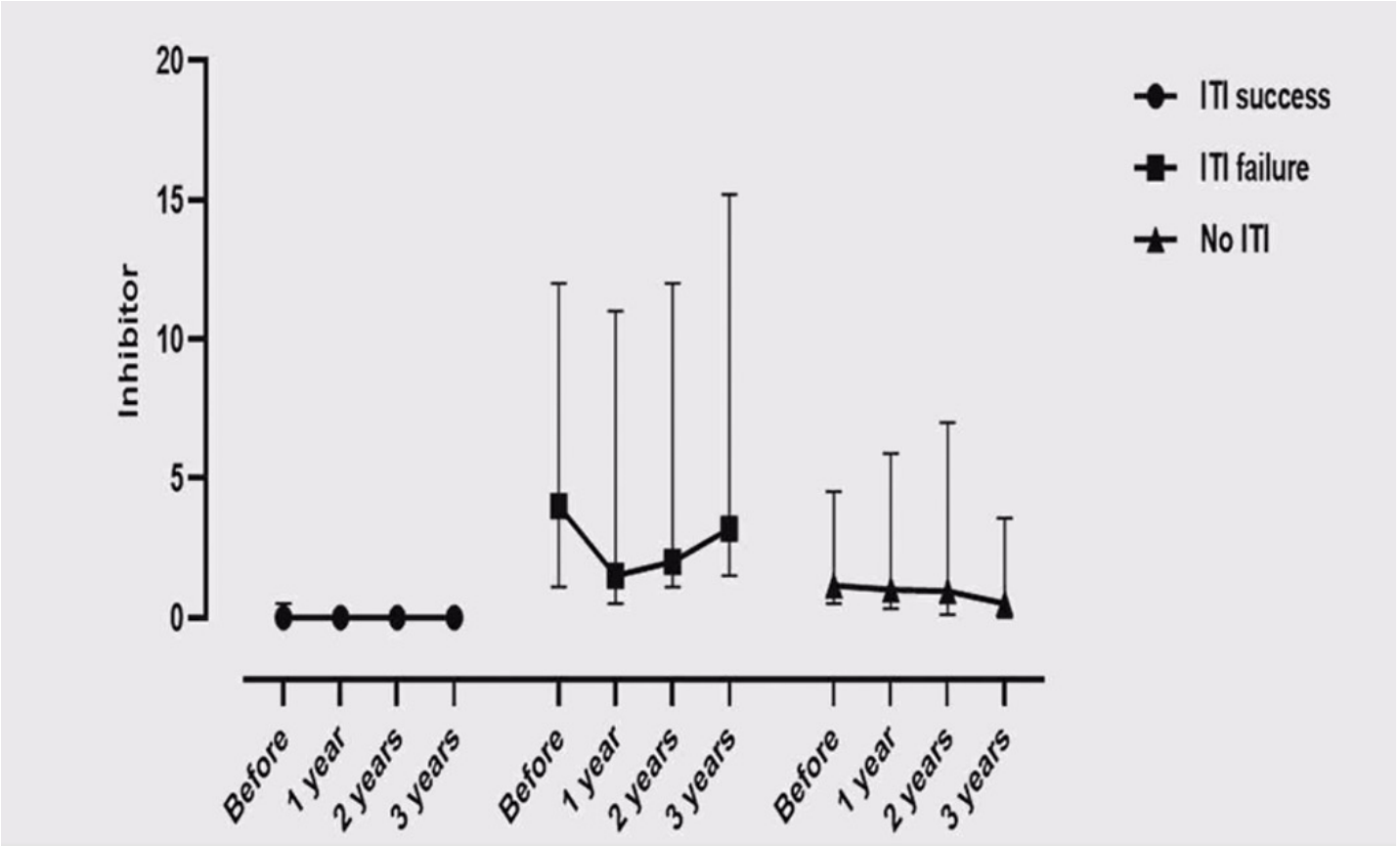
ABR in the patient groups at different time points in the study



ABR, annual bleeding rate; ITI, Immune Tolerance Induction;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

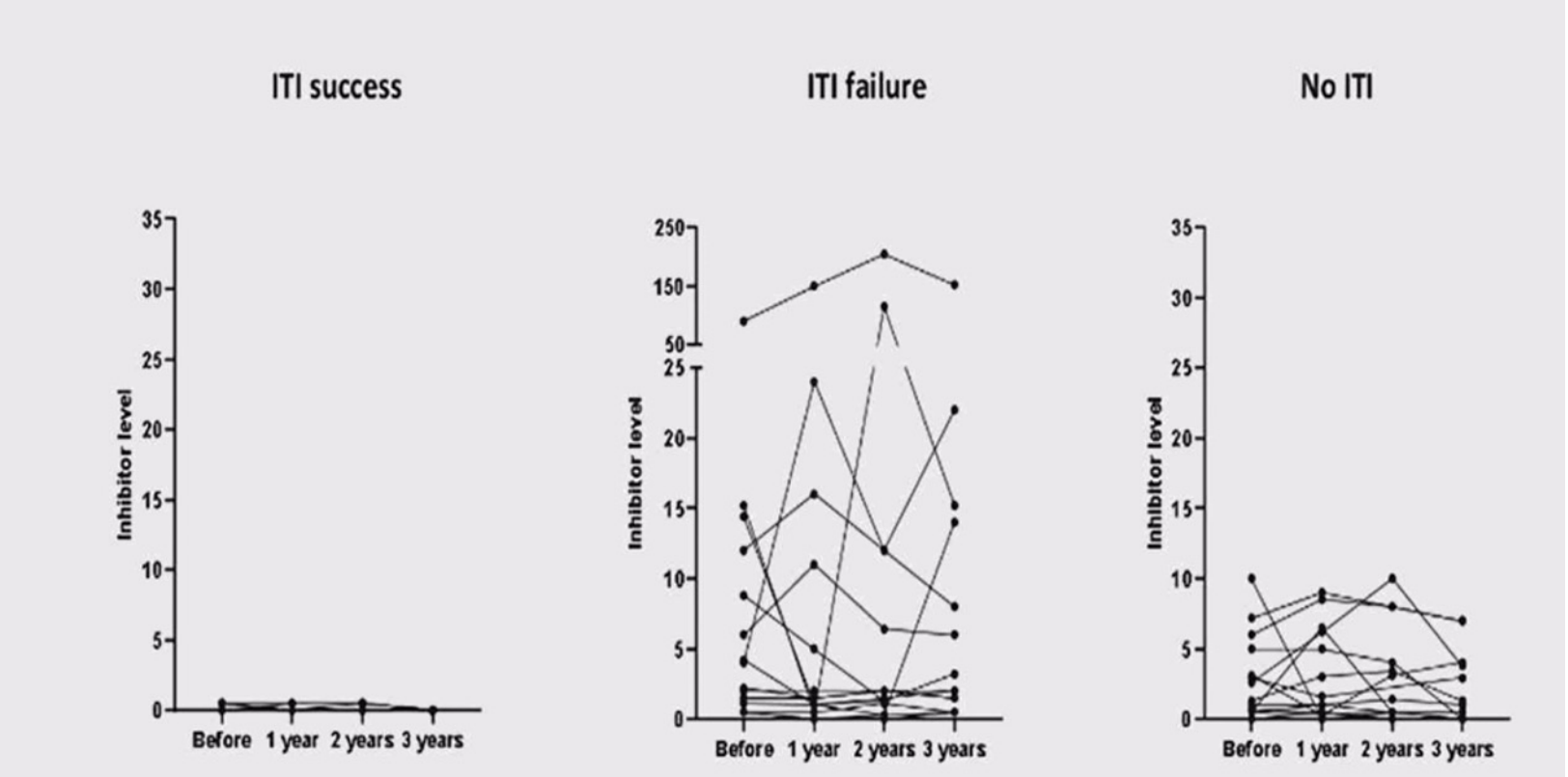
Median inhibitor levels in the different cohort´s subgroups before and during emicizumab prophylaxis



ITI, Immune Tolerance Induction;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Individual changes of FVIII inhibitor in each of our patients

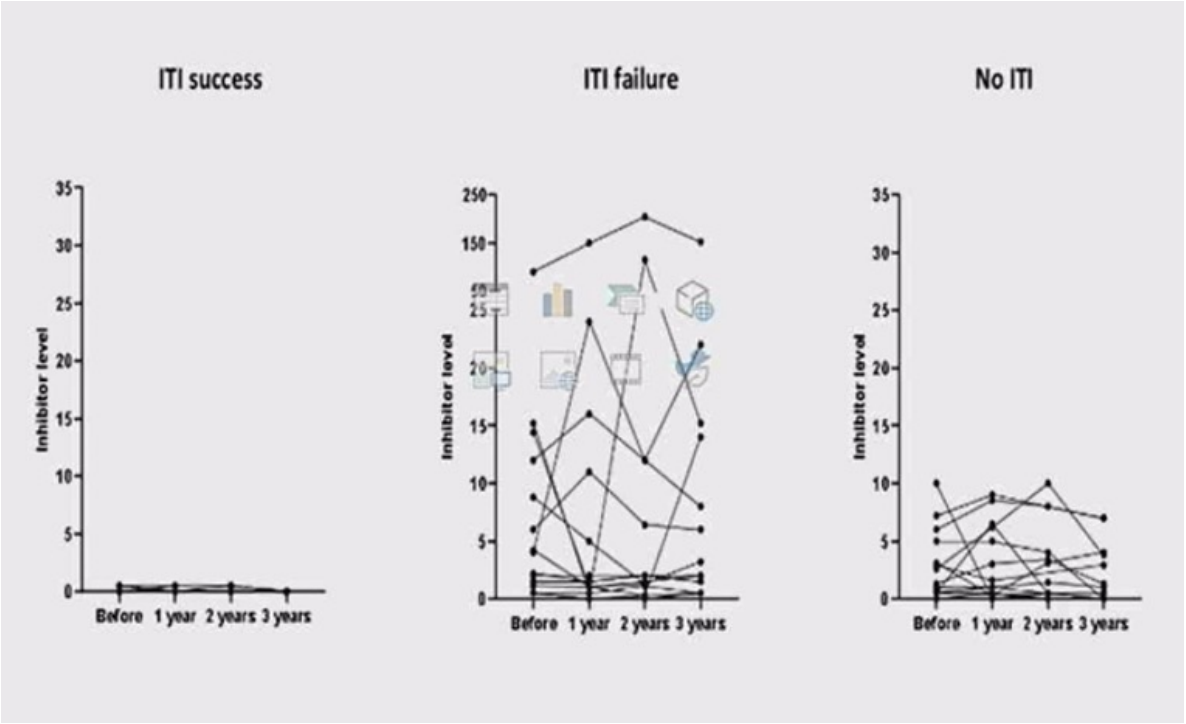


F, factor; ITI, Immune Tolerance Induction; F, factor

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Individual changes

- Failed ITI (n= 15)
  - ✓ 5 patients inhibitor increased
  - ✓ 1 MVA (8 ED)
  - ✓ 3 (1-2 ED)
  - ✓ 1 No exposure (low responding 0.5 – 2 BU)
- Successful ITI (n= 15)
  - ✓ 8/15 exposed to FVIII (1 – 2 ED)
  - ✓ No inhibitor increase
- Deferred ITI (n= 21)
  - ✓ 8/21 patients exposed to FVIII (1 – 2 ED)
  - ✓ 1 increased 2 - 7 BU (following head trauma)
  - ✓ 1 increased despite lack of exposure (4 – 12 BU)
  - ✓ All decreased within 6 months



F, factor; ITI, Immune Tolerance Induction; HA, haemophilia A; MVA, ; ED, exposure days; BU, Bethesda units; MVA, Motor vehicle accident

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Clinical outcomes of our patients

	Failed ITI	Successful ITI	No ITI	P value
Time on emicizumab, years, median (IQR)	3.8 (3.3 – 4.1)	3.0 (2.3 – 3.2)	3.1 (1.3 – 3.5)	<0.001
ABR following one year after emicizumab initiation – median (IQR)	0 (0; 0.25)	0 (0; 1)	0 (0; 1)	0.99
Inhibitor after 3 years, median (IQR)	2.0 (1.1 – 12.0)	0.0 (0.0 – 0.5)	0.6 (0.0 –5.0)	<0.001

ITI, Immune Tolerance Induction; ABR, annual bleeding rate; IQR, interquartile range;

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Conclusion

- Our study shows that in a longitudinally followed cohort of emicizumab treated HA patients with FVIII inhibitor, occasional exposure to FVIII may induce a transient anamnestic response

- Non the less, in patients who underwent successful ITI years ago, no FVIII inhibitor recurrence was noted following short FVIII exposures

F, factor; ITI, Immune Tolerance Induction; HA, haemophilia A

Levy-Mendelovich S, et al. ISTH 2023; ústní prezentace OC 43.5.

Association between physical activity and bleeding events in people with hemophilia A receiving emicizumab prophylaxis: interim analysis of the TSUBASA study

Upraveno podle posteru PB0641 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Background

- Historically, many PwHA restricted their physical activity to reduce the risk of bleeding events and resultant arthropathy
- Since prophylactic FVIII replacement therapy became the standard of care, however, participation in sports and exercise has been encouraged by clinicians, due to the associated health benefits
- Limited data are currently available on the relationship between bleeding outcomes and physical activity in PwHA who are receiving emicizumab
- The TSUBASA study (UMIN-CTR-ID: UMIN000037448) was initiated to evaluate the association between physical activity and bleeding events, safety, and QoL in PwHA initiating emicizumab
- This poster presents the association between physical activity and bleeding events, and safety data, from an interim analysis of the TSUBASA study

M-CZ-00003345

PwHA, patients with haemophiliia A; F, factor; QoL, quality of life

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Methods

- **TSUBASA, a prospective, multicenter, observational study, recruited PwHA without FVIII inhibitors scheduled to begin emicizumab across 50 participating institutions in Japan**
  - ✓ Following a loading dose period (3mg/kg QW for 4 weeks), participants received emicizumab prophylaxis at one of the three approved maintenance dosages (1.5mg/kg QW, 3mg/kg Q2W or 6mg/kg Q4W)
  - ✓ Participants will be followed up until Week 97 after treatment initiation, or until discontinuation of emicizumab treatment
  - ✓ Physical activity, bleeding events, and QoL were captured using the ePRO application; a wearable activity tracker was also employed.
  - ✓ To measure physical activity, all participants ≥6 years of age continually wore an activity tracker while awake on the wrist of their non-dominant hand for five specified 8-day monitoring periods at Weeks 5, 25, 49, 73, and 97
  - ✓ AEs were documented
  - ✓ Informed consent and ethics approval were obtained

F, factor; PwHA, patients with haemophilia A; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; QoL, quality of life; AE, adverse events;

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Demographics

- **In total, 129 participants with severe or moderate HA are included in the interim analysis safety population**
  - ✓ By data cut-off (May 31, 2022), 129 PwHA were enrolled and had received emicizumab, constituting the safety population
  - ✓ Median (range) follow-up was 561 (47–917) days
  - ✓ The median (range) age was 32 (0–73) years; 108 (83.7%) participants had severe HA and 21 (16.3%) had moderate HA

	Participants (N=129)
Male, n (%)	129 (100.0)
Median age (range), years	32.0 (0–73)
Age group, n (%)	
<2 years	17 (13.2)
2–5 years	8 (6.2)
6–17 years	21 (16.3)
18–65 years	76 (58.9)
>65 years	7 (5.4)
HA severity, n (%)	
Moderate	21 (16.3)
Severe	108 (83.7)
Bleeding present in 12 weeks prior to study, n (%)	
<2 years of age	13/17 (76.5)
≥2 years of age	70/112 (62.5)
Use of factor products prior to study, n (%)	
None	7 (5.4)
Prophylaxis	92 (71.3)
On demand	30 (23.3)
History of ITI therapy, n (%)	5 (3.9)
Presence of target joints,* n (%)	23 (17.8)

*Defined as joints with ≥3 bleeds during the 24 weeks prior to study entry. Target joints were not defined for participants <2 years with no records of bleeding events in the 24 weeks prior to study entry.
ITI, immune tolerance induction.PwSHA, patients with severe haemophiliia A; HA, haemophilia A;

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Physical activity reported in participants ≥6 years of age (n=100)

- **Of 100 participants who were ≥6 years old with physical activity data available, 71% recorded ≥1 activity event**
  - ✓ Of the 129 participants, 100 had data on physical activities, with 71 (71.0%) participants recording ≥1 activity event
    - The most common physical activities were walking (n=37; 37.0%), cycling (n=15; 15.0%), and swimming (n=8; 8.0%)
  - ✓ A total of 866 activity events were documented, with a median IQR duration of 30 (15–60) minutes

Exercise type*	Participants with activity event, n (%)	No. of activity events	Median (IQR) duration of exercise, minutes	Median (IQR) METs†
Overall	71 (71.0)	866	30.0 (15–60)	2.28 (1.57–3.16)
Walking	37 (37.0)	339	30.0 (15–45)	2.24 (1.66–3.21)
Cycling	15 (15.0)	106	30.0 (15–60)	2.43 (1.79–2.92)
Swimming	8 (8.0)	19	60.0 (50–90)	1.13 (0.99–1.47)
Jogging / running	5 (5.0)	15	60.0 (15–60)	2.67 (1.68–5.52)
Soccer	5 (5.0)	11	45.0 (35–90)	3.05 (1.78–3.93)
Track and field / marathon	5 (5.0)	7	35.0 (30–40)	3.94 (3.56–4.16)
Radio calisthenics	4 (4.0)	52	5.0 (5–10)	2.75 (2.45–3.14)
Golf	4 (4.0)	26	270.0 (135–360)	1.67 (1.40–2.41)
Weight training	4 (4.0)	22	12.5 (10–15)	3.51 (1.51–4.19)
Dodgeball	3 (3.0)	15	15.0 (15–25)	3.86 (2.01–5.71)
Badminton	3 (3.0)	4	20.0 (15–35)	3.71 (1.82–4.67)
Trekking / climbing	3 (3.0)	3	100.0 (30–180)	3.76 (2.57–4.17)
Fishing	2 (2.0)	23	195.0 (170–240)	1.42 (1.33–1.54)
Basketball	2 (2.0)	8	54.5 (35–120)	5.47 (5.22–6.88)
Skipping rope	2 (2.0)	4	40.0 (23–45)	3.76 (0.86–5.66)
Baseball / softball	2 (2.0)	4	81.0 (29–169)	5.89 (5.49–6.06)
Motorcycling	2 (2.0)	3	220.0 (150–300)	2.28 (1.34–2.36)
Bowling	2 (2.0)	2	90.0 (60–120)	2.60 (2.42–2.78)
Exercise not on list	33 (33.0)	141	35.0 (25–75)	1.78 (1.38–2.48)

*Named activities are those reported by more than one participant, as chosen from a pre-specified list on the ePRO, created with reference to the SasakawaSports Foundation. 'Overall' includes all events; †in participants who wore the activity tracker. MET is the ratio of working metabolic rate relative to resting metabolic rate. One MET is equal to the energy expended when at rest.
IQR, interquartile range; MET, metabolic equivalent.

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Physical activity relative to bleeding activity by HA severity

- **Out of 866 documented activity events during the reporting period, only four events were associated with bleeding**
  - ✓ Three different types of activity events were associated with bleeding: weight training (two separate bleeding events) and jogging/running, all in one participant, and fishing in another participant. All four bleeding events were treated with FVIII replacement therapy
  - ✓ The median duration of activity for participants by disease severity and association with bleeding is shown in table. Given the small sample size of participants who experienced bleeding events associated with physical activity, it is not possible to draw any conclusions regarding bleeding risk relative to type of activity or duration
  - ✓ Both participants who experienced activity-associated bleeds had severe HA

	Participants with activity event, n (%)	No. of activity events	Median (IQR) duration of exercise, minutes	Median (IQR) METs*
Moderate HA (n=12)	**12**	108	30.0 (21.5–50)	2.14 (1.49–3.67)
No hemorrhage	12	108	30.0 (21.5–50)	2.14 (1.49–3.67)
Hemorrhage	0	0	N/A	N/A
Severe HA (n=59)	59	758	31.0 (15–60)	2.31 (1.57–3.13)
No hemorrhage	59	754	30.0 (15–60)	2.32 (1.57–3.14)
Hemorrhage	2	4	60.5 (60–113)†	1.35 (1.03–1.51)

*In participants who wore the activity tracker; †one participant engaged in fishing for 165 minutes.
HA, haemophilia A; IQR, interquartile range; MET, metabolic equivalent; N/A, not applicable.

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Summary of safety data in the interim analysis population

- **Emicizumab prophylaxis was well tolerated to date in this population**
  - ✓ Overall, 42 (32.6%) of the 129 PwHA in the safety population experienced a total of 88 AEs
  - ✓ A total of 10 (7.8%) participants experienced a SAE, none of which were deemed to be related to emicizumab
  - ✓ Four (3.1%) participants experienced a total of five adverse reactions to emicizumab (two injection-site erythema; three injection-site reactions)

	Severity of HA		
	Overall N=129	Moderate HA n=21	Severe HA n=108
Participants who experienced ≥1 AE, n (%)	42 (32.6)	5 (23.8)	37 (34.3)
Total number of AEs	88	7	81
Participants who experienced ≥1 SAE, n (%)	10 (7.8)	2 (9.5)	8 (7.4)
Total number of SAEs	12*	2	10
Participants who interrupted emicizumab due to SAE, n (%)	1 (0.8)	0 (0.0)	1 (0.9)
Participants who experienced ≥1 treatment-related AE, n (%)	4 (3.1)	0 (0.0)	4 (3.7)
Number of treatment-related AEs†	5	0	5
Participants who discontinued emicizumab due to treatment-related AE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

*Reported SAEs were periodontitis, bladder cancer, postoperative wound infection, anemia, humerus fracture, Mallory–Weiss syndrome, Kawasaki's disease, sepsis, osteomyelitis, necrotising fasciitis, intervertebral disc protrusion, and cervical spine stenosis; occurred in one participant each.
†All treatment-related AEs were injection-site reactions (n=3) or injection-site erythema (n=2).
AE, adverse event; HA, haemophilia A; SAE, serious adverse event.

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Conclusion

- For PwHA receiving emicizumab in the TSUBASA study, there were few bleeding events associated with physical activity
- Emicizumab was well tolerated in this population, with no new safety signals
- This interim analysis suggests that people receiving routine emicizumab prophylaxis are able to engage in various forms of physical activity with a low risk of experiencing associated bleeding events
- Further analysis is ongoing and future publications will provide additional evidence

PwHA, patients with haemophiliia A;

Fujii T, et al. ISTH 2023; prezentace posteru PB0641.

Emicizumab prophylaxis in people with hemophilia A aged ≥50 years with comorbidities: experience from the ATHN 7 hemophilia natural history study

Upraveno podle posteru PB0625 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Background

- ATHN 7(NCT03619863), collects real-world data describing long-term safety and effectiveness of therapies, including emicizumab, for the prevention and treatment of bleeding in PwHA and PwHB in the US.
- Emicizumab is a bispecific monoclonal antibody that bridges activated FIX and FX to substitute for the function of absent or deficient activated FVIII in PwHA
- In the HAVEN and STASEY clinical trials, the efficacy and safety of emicizumab in PwHA aged ≥50 years with comorbidities was found to be consistent with PwHA in the overall population
- This analysis aims to examine the characteristics and real-world safety of emicizumab prophylaxis in PwHA aged ≥50 years with comorbidities from the ATHN 7 study

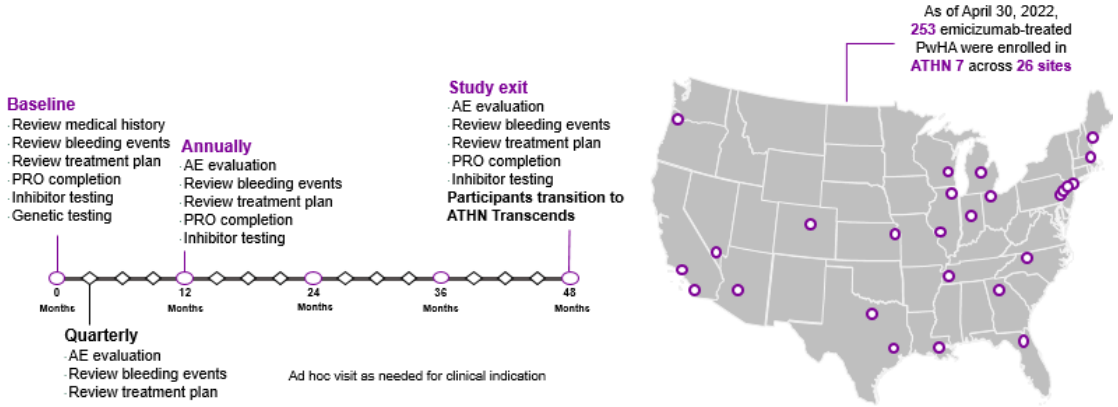
PwHA, patients with haemophiliia A; PwHB, patients with haemophiliia B; ATHN 7, A Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Hemophilia; F, factor; US, United States

Recht M, et al. ISTH 2023; prezentace posteru PB0625.

Methods and study design

- **ATHN 7 is a longitudinal, observational cohort study. As of April 30, 2022, 253 emicizumab-treated PwHA were enrolled at 26 American Thrombosis and Hemostasis Network (ATHN)-affiliated sites**

  - ✓ PwHA aged ≥50 years and receiving emicizumab at participating sites were eligible for this analysis
  - ✓ Clinical information was collected at baseline and at least quarterly through participant interview and medical record review
  - ✓ Participants were considered to have a comorbidity if they had CV risk factors (history of CV disease or current hypertension, diabetes, hyperlipidemia, or obesity), or HCV and/or HIV infection
  - ✓ AEs were documented according to the EUHASS categorization
  - ✓ AEs of special interest (thrombotic events, thrombotic microangiopathies, injection site reactions and allergic reactions) were also documented
  - ✓ Descriptive statistics of medical history and demographic data, as well as longitudinal data, were used to characterize the study population



PwHA, patients with haemophiliia A; ATHN 7, A Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Hemophilia; F, factor; CV, cardiovascular; HCV, hepatitis C virus; HIV, human immunodeficiency virus; AE, adverse events; EUHASS, European Haemophilia Safety Surveillance group; PRO, patient-reported outcome;

Recht M, et al. ISTH 2023; prezentace posteru PB0625.

Demographics

- **As of the data cut-off (April 30, 2022), 15 PwHA aged ≥50 years and treated with emicizumab were enrolled in ATHN 7, representing 22.4 patient-years of exposure to emicizumab**

  - ✓ Of these, 11 (73.3%) participants had severe hemophilia and 4 (26.7%) participants had moderate haemophilia
  - ✓ Five (33.3%) participants had FVIII inhibitors and 10 (66.7%) participants did not have inhibitors
  - ✓ Of the participants with CV risk factors, 10 (66.7%) participants had ≥1 CV risk factor(s) and 6 (40.0%) had ≥2 CV risk factors
  - ✓ Five (33.3%) participants had HCV infection alone and 9 (60.0%) participants had HIV/HCV co-infection

	Participants (N=15)
Age at baseline (years)	
n	15
Mean (SD)	61.1 (8.6)
Median (Min, Max)	60.0 (50.0, 79.0)
Baseline FVIII inhibitor status, n (%)	
Inhibitor	5 (33.3)
Non-inhibitor	10 (66.7)
Severity of hemophilia, n (%)	
Mild	0 (0)
Moderate	4 (26.7)
Severe	11 (73.3)
Exposure (weeks)	
n	14
Mean (SD)	83.5 (50.7)
Median (Min, Max)	84.4 (11.9, 148.0)
CV risk factors, n (%)	
≥1	10 (66.7)
≥2	6 (40.0)
HIV and/or HCV infection, n (%)	
HIV infection only	0 (0)
HCV infection only	5 (33.3)
HIV + HCV coinfection	9 (60.0)
Missing	1 (6.7)

PwHA, patients with haemophiliia A; ATHN 7, A Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Hemophilia; F, factor; CV, cardiovascular; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation

Recht M, et al. ISTH 2023; prezentace posteru PB0625.

Results

- **Of the 15 eligible participants, three reported a total of four AEs**
  - ✓ Four AEs, in three participants, were reported; all were deemed unrelated to emicizumab by the investigator
  - ✓ The four AEs were: a malignancy (metastasis of malignant prostate tumor) in one participant, a subdural hematoma in one participant, and one case of hemorrhagic shock secondary to a presumed gastrointestinal bleed, which resulted in death (previously reported) in the other participant
  - ✓ No AEs of special interest were reported

	People with hemophilia A aged ≥50 years with reported adverse events, n (%)				
	Total (N=15)	≥1 CV risk factor (n=10)	≥2 CV risk factor (n=6)	HCV positive only (n=5)	HIV+HCV positive (n=9)
Any adverse event	3 (20.0)	3 (30.0)	3 (50.0)	2 (40.0)	1 (11.1)
Malignancy	1 (6.7)	1 (10.0)	1 (16.7)	1 (20.0)	0
Death	1 (6.7)	1 (10.0)	1 (16.7)	0	1 (11.1)
Other*	2 (13.3)	2 (20.0)	2 (33.3)	1 (20.0)	1 (11.1)

*Other adverse events were hemorrhagic shock and subdural hematoma. CV, cardiovascular; HCV, hepatitis C virus; HIV, human immunodeficiency virus

Recht M, et al. ISTH 2023; prezentace posteru PB0625.

Conclusion

- No thromboses or AEs related to emicizumab were reported in PwHA aged ≥50 years and treated with emicizumab in the ATHN 7 study
- This analysis is limited by the small study population and limited overall data in aging PwHA, regardless of prophylaxis type
- The data contribute to the pool of evidence for emicizumab in PwHA aged ≥50 years with comorbidities, a population that is expected to grow due to increasing availability of improved prophylaxis
- Safety was consistent with previous studies of emicizumab prophylaxis in PwHA, including analyses of emicizumab in a similar population of PwHA aged ≥50 years in the HAVEN and STASEY clinical trials
- Continuous data collection is ongoing in the ATHN Transcends study (NCT04398628) to further evaluate the safety and effectiveness of emicizumab prophylaxis in PwHA

PwHA, patients with haemophiliia A; AEs, adverse events; ATHN 7, A Natural History Cohort Study of the Safety, Effectiveness, and Practice of Treatment for People with Hemophilia; F, factor

Recht M, et al. ISTH 2023; prezentace posteru PB0625.

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

Upraveno podle ústní prezentace OC 43.4 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Learning Objectives

At the conclusion of this presentation, participants will be able to:

- Describe the indication and use of subcutaneous treatment with emicizumab
- Interpret the beneficial effect of emicizumab on bleeding endpoints in a real-world setting
- Recognize the consistent effectiveness and the favorable safety profile of emicizumab treatment in patients with severe hemophilia A

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Background

- The x-chromosomal recessive bleeding disorder hemophilia A is caused by absence or functional deficiency of the coagulation factor VIII
- Emicizumab is a monoclonal, humanized bispecific antibody binding to coagulation factors IXa and X and thereby taking over the coagulation function of activated FVIII, even in the presence of FVIII inhibitors
- Emicizumab is approved for routine prophylaxis in adult and pediatric PwHA with and without FVIII inhibitors[a]
- Subcutaneous administration of emicizumab has demonstrated a positive benefit-risk profile in clinical trial settings and several published real-world reports

[a]In the EU, emicizumab is approved for routine prophylaxis in adult and pediatric PwHA with FVIII inhibitors and in PwHA without FVIII inhibitors who have severe disease (FVIII <1%) or moderate disease (FVIII ≥1% and ≤5%) with severe bleeding phenotype. In Switzerland, emicizumab is also approved for treatment of congenital haemophilia A with mild (FVIII >5% and <40%) severity.
FVIII, factor VIII; PwHA, patients with hemophilia A

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

M-CZ-00003345

Objective and Methods

EMIIL
Emicizumab in real Life

Objective

- The prospective non-interventional study EMIIL (ISRCTN58752772) aims to evaluate the long-term effectiveness of emicizumab prophylaxis under real-world conditions in patients of all ages with congenital hemophilia A measured by the annualized bleeding rates of treated bleeds

Methods

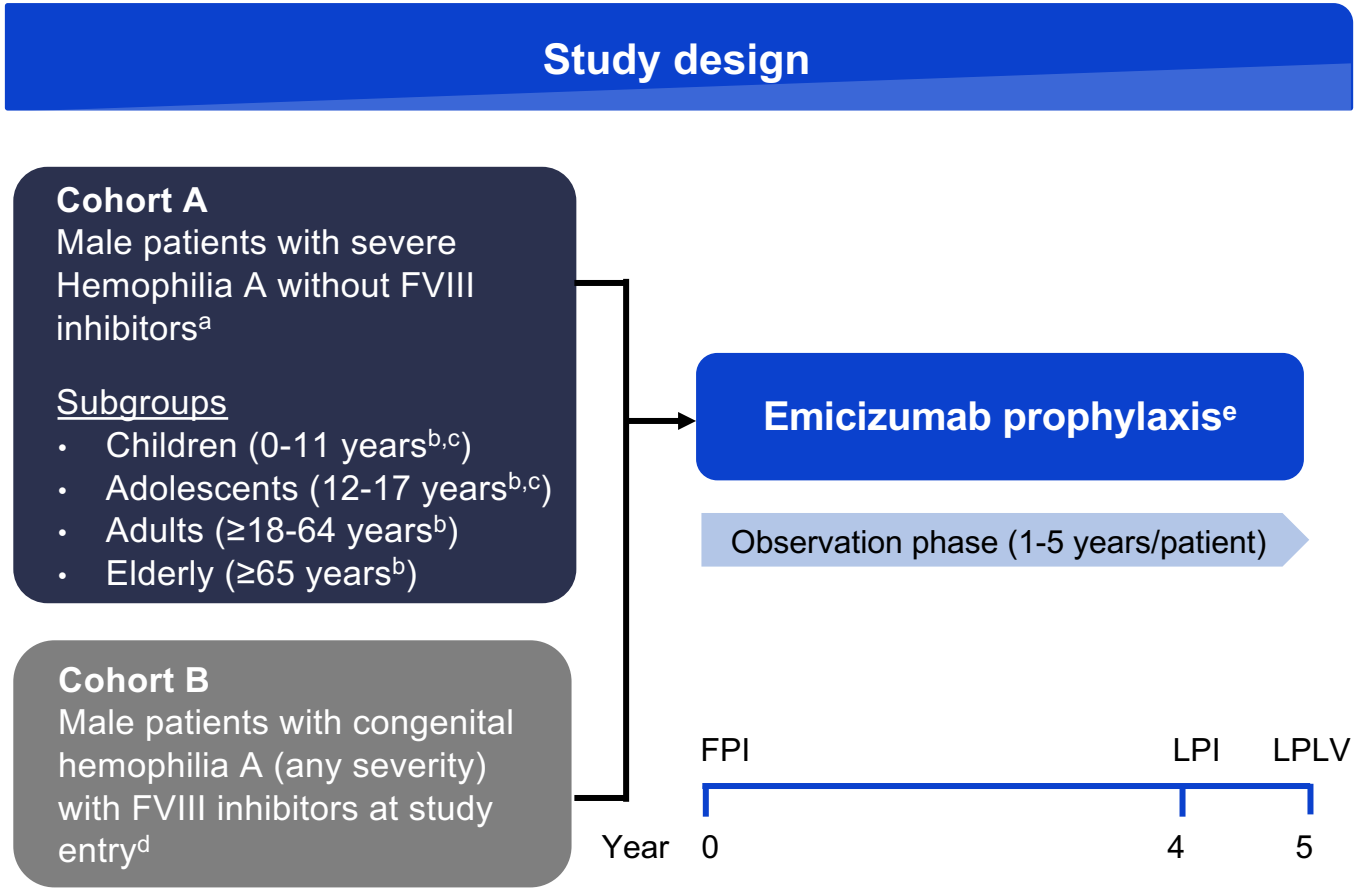
- Data were evaluated descriptively.
- The primary effectiveness variable in Cohort A, the ABR of treated bleeds was estimated using a generalized linear model (GLM) assuming a negative binomial-distribution for bleeding events and using observation time as off-scale parameter

EMIIL: Phase IV non-interventional study to investigate the effectiveness of emicizumab under real world conditions in pediatric, adolescent and adult patients with hemophilia a with and without FVIII inhibitors
FVIII, factor VIII

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

EMIIL study design and methods

- Ongoing single-arm, prospective, multicenter, non-interventional study in Germany and Switzerland of emicizumab prophylaxis in people with **Hemophilia A with or without inhibitors**
- Primary endpoint: **Annualized bleeding rates (ABR) of treated bleeds**
- Safety endpoints include AEs, SAEs, TEs and TMAs
- Secondary endpoints include:
  - ABRs and percentage of patients with zero bleeds for treated joint / target joint / spontaneous bleeds
  - Dosing regimen and plasma levels of emicizumab
  - Health-related quality of life
  - Joint health
  - Development of FVIII inhibitors and neutralizing antibodies



[a]Congenital severe HA (<1% FVIII activity); <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.
The sample size calculation is based on patients without FVIII inhibitors (cohort A).
AE, adverse event; FPI, first patient in; FVIII, Factor VIII; LPI, last patient in; LPLV, last patient last visit; SAE, serious adverse event; TE, thromboembolic event; TMA, thrombotic microangiopathy

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Baseline characteristics

Demographic parameters	N=85
Age at screening [years]	
Mean (SD)	26.66 (21.30)
Median (range)	25.00 (0.0-75.0)
Age group, n (%)	
Children (0-11 years)	30 (35.3)
Adolescents (12-17 years)	4 (4.7)
Adults (18-64 years)	48 (56.5)
Elderly (≥65 years)	3 (3.5)
Ethnicity, n (%)	
White	73 (85.9)
Black or African American	2 (4.2)
Asian	2 (2.4)
Not reported	8 (9.4)

Demographic parameters	N=85
Time since hemophilia A diagnosis [years]	
Mean (SD)	23.76 (20.67)
Median (range)	18.64 (0.0-73.8)
Severity at baseline	
Severe (<1% FVIII activity)	85 (100.0)
FVIII inhibitors history[a], n (%)	
Yes	4 (4.7)
Missing	81 (95.3)
Current treatment regimen[b], n (%)	
Prophylactic	67 (78.8)
Episodic	19 (22.4)

Until data cut-off, only one patient had enrolled into cohort B, thus all results refer to cohort A.

Data cut-off date: 9 May 2022
Median (range) treatment duration was 419 days (range 15-873; mean (SD) 425.5 (251.0))

[a]Highest measurement before start of treatment; Note: No present FVIII inhibitor defined as <0.6 BU;
[b]Patients may have received both, prophylactic as well as on demand treatment prior to therapy with emicizumab.
FVIII, factor VIII; SD, standard deviation

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

No new safety signals identified

	Participants (N=85)	
	n patients (%)	n events
Total number of AEs	38 (44.7)	113
AE with fatal outcome	0 (0)	0
Treatment-related AE*	12 (14.1)	30
Grade ≥3 AE (severe AE)	9 (10.6)	17
Treatment-related severe AE**	1 (1.2)	4
Total number of SAEs	12 (14.1)	20
Treatment-related SAE†	2 (2.4)	4
AEs of special interest		
Systemic hypersensitivity/anaphylactic /anaphylactoid reaction	0 (0)	0
Thromboembolic event	0 (0)	0
Thrombotic microangiopathy	0 (0)	0

- COVID-19, headache and pyrexia were the most common AEs, with all of them reported in 5.9% of participants (n=5)
- For 55.3% of patients no AEs were reported
- The majority of participants (85.9%) did not experience an AE considered as emicizumab-related by the investigator

At data cut-off, **no deaths, no thromboembolic events** or **thrombotic microangiopathies** were observed.

No ADAs or newly developed FVIII inhibitors were observed up to cut-off date.

AEs were classified as treatment-related when the causality was yes, unknown or not provided. *Treatment-related AEs classified as causality yes all belonged to the SOC general disorders and administration site conditions.**Treatment-related severe AEs were all classified as causality unknown or not provided. †One treatment-related SAE was classified as causality yes (drug ineffective), all other SAEs were classified as causality unknown and included one case each of lymphadenopathy, seizure and lung adenocarcinoma. ADA, anti-drug antibody; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SOC, system organ class

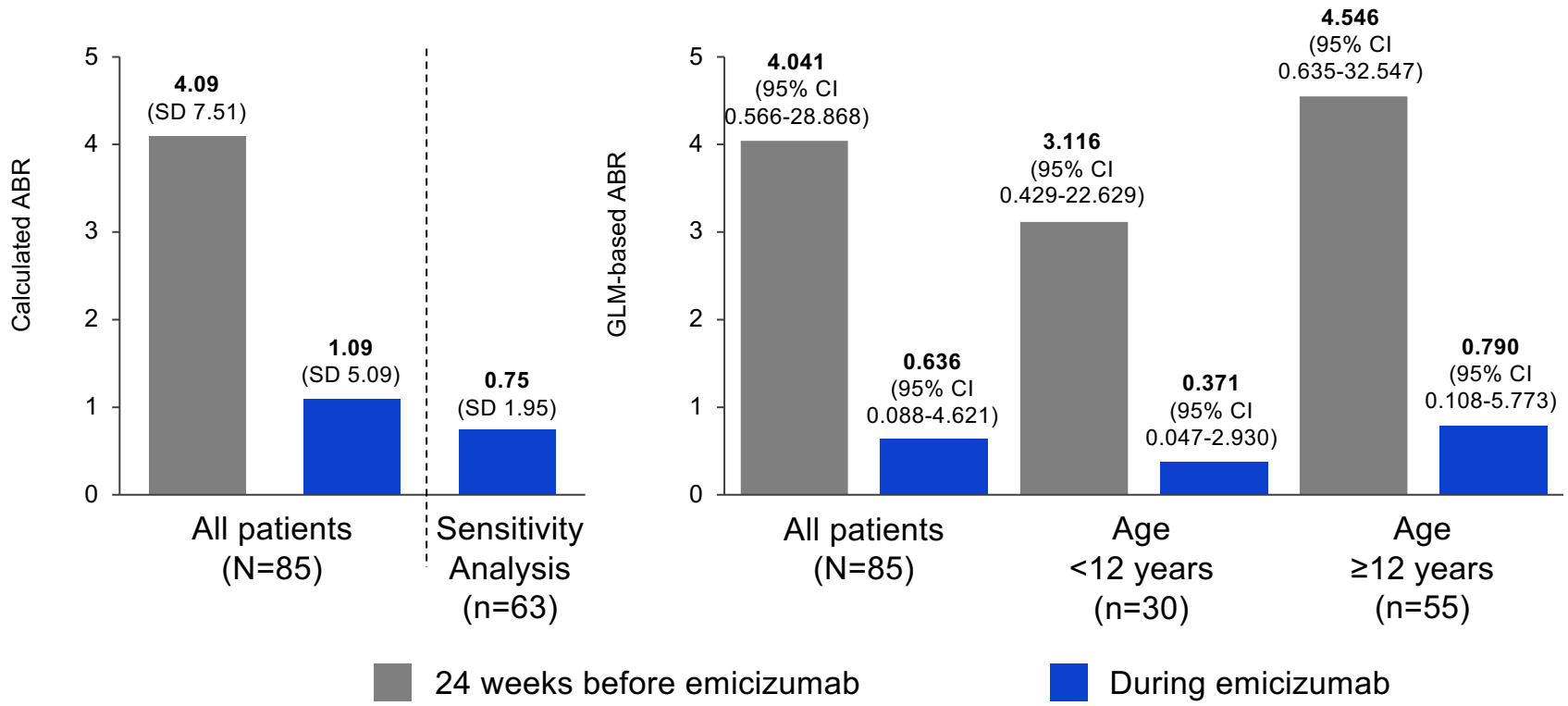
Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

ABR was low with emicizumab

The primary efficacy endpoint was ABR for treated bleeds.

The calculated mean (SD) ABR for treated bleeds prior to study was 4.09 (7.51).

The calculated mean (SD) ABR for treated bleeds on study was 1.09.



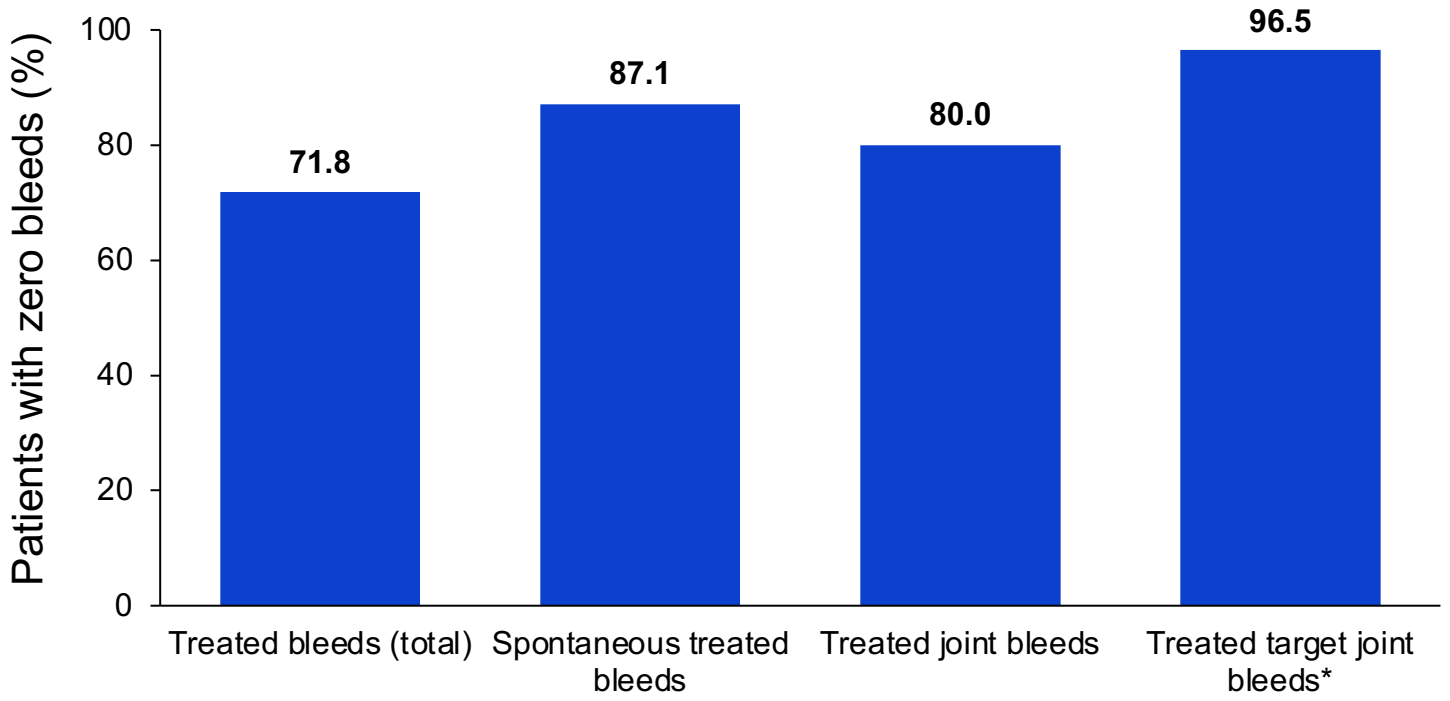
Bleeds due to surgery/procedure are not included. For GLM-based ABR, before emicizumab initiation, the following confounder variables are included in the model: Age (<12 years, ≥12 years). Additionally, during emicizumab treatment, number of treated bleeds in the past 24 weeks prior to start of emicizumab 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 were only included if they had their first visit, otherwise they were missing. One patient was set to missing due to short study duration.
ABR, annualized bleeding rate; CI, confidence interval; GLM, generalized linear model; SD, standard deviation

M-CZ-00003345

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Emicizumab was efficacious for preventing various types of bleeding events

71.8% of patients had zero treated bleeds during the entire study duration.



N=85
Median study duration:
419 days (Range 15-873)

All median bleed rates were zero.

*Definition of target joint bleeds: three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period, the joint is no longer considered a target joint (Blanchette VS, et al. J Thromb Haemost. 2014;12(11):1935-9).

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Emicizumab showed efficacious bleed protection

Model-based ABR*

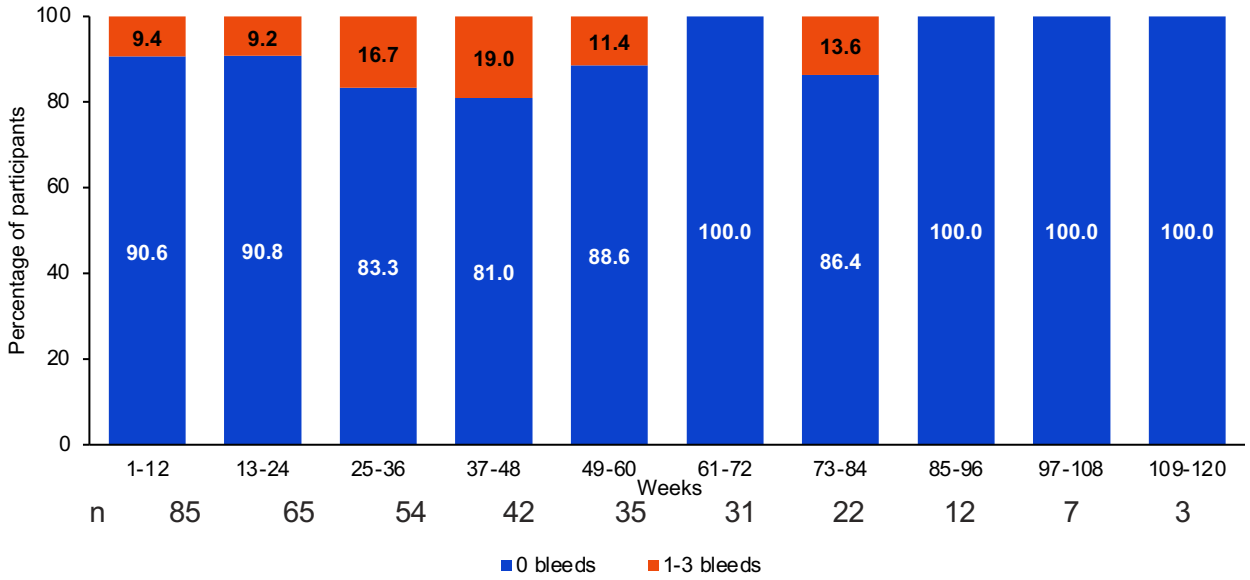
Treated bleeds:
0.636 (95% CI 0.088-4.621)

Emicizumab is similarly effective across the entire study period, presented as 12-week intervals.

No patient experienced >3 treated bleeds in analyzed 12 week intervals

Treated bleeds over time

Proportion of participants with 0 or 1-3 treated bleeds over time



Bleeds due to surgery/procedure are not included. 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. ABR was based on 66.0 patient years and 42 treated bleeds. Of note: At data cut-off for this interim analysis, not all patients had completed the total study time yet. Therefore, the declining patients numbers do not indicate drop-outs.
ABR, annualized bleeding rate; CI, confidence interval

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

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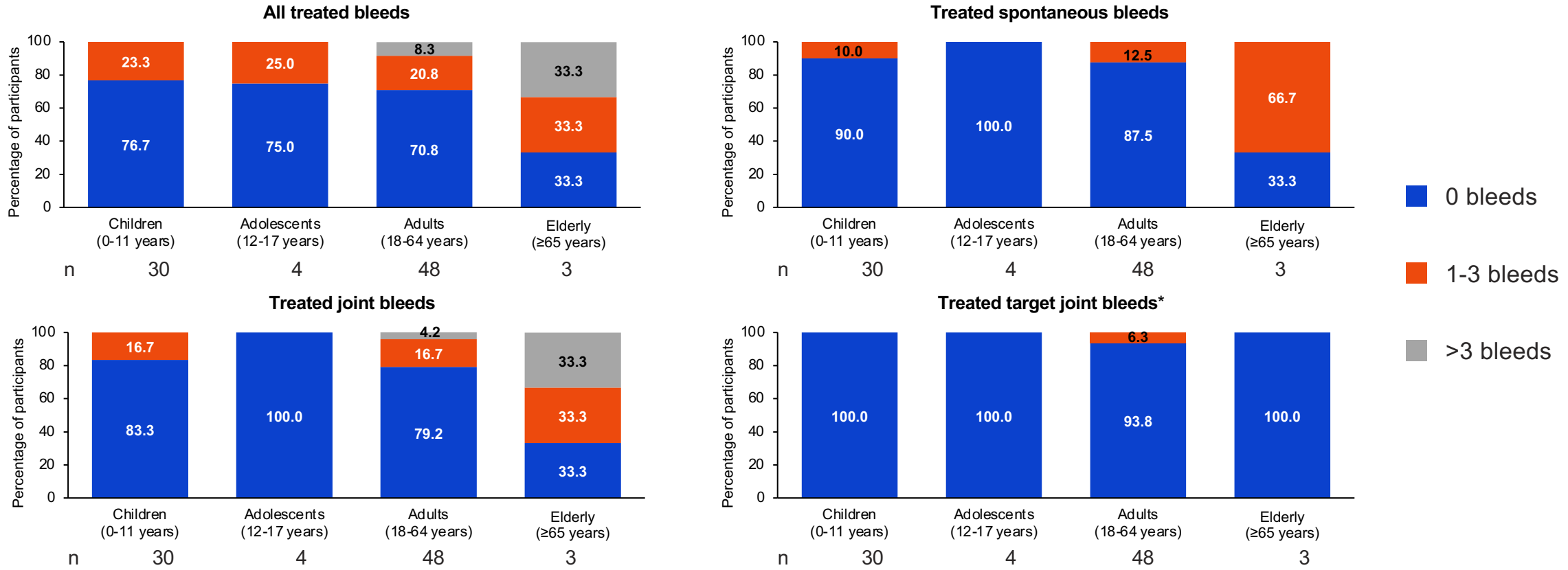
Bleeding rates by age category

Emicizumab was effective in all bleeding endpoints.



Median study duration: 419 days (Range 15-873). *Definition of target joint bleeds: three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period, the joint is no longer considered a target joint (Blanchette VS, et al. J Thromb Haemost. 2014;12(11):1935-9).

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Conclusions

- Consistent effectiveness across all bleeding endpoints demonstrates clinically meaningful bleed control in line with prior HAVEN and real-world-studies.
- No new safety signals were identified with emicizumab.
- Emicizumab offers an efficacious treatment option with a favorable safety profile for patients with congenital hemophilia A.
- EMIIL contributes to real-world data on emicizumab prophylaxis of hemophilia A patients with or without FVIII inhibitors in Germany and Switzerland.

Oldenburg J, et al. ISTH 2023; ústní prezentace OC 43.4.

Efficacy of emicizumab prophylaxis in patients with severe hemophilia A in Germany: Follow-up evaluation of real-life-data documented by smart medication eDiary

Upraveno podle posteru PB0643 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Background

- Systematically documented data on real-world use of emicizumab prophylaxis in PwSHA in Germany are still lacking

- We present real-life data on efficacy of emicizumab in PwSHA across German HTCs as of Dec 31, 2022, documented with the electronic diary smart medication for monitoring home treatment of hemophilia patients – developed and provided by VFTH, a non-profit association focused on the advancement of telemedicine

PwSHA, patients with severe haemophiliia A; HTCs, Haemophilia Treatment Centres;

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Aims

- Evaluation of self-reported bleed rate (total treated bleeds per year/ABR, total joint bleeds per year/AJBR and life – threatening bleed) in PwSHA undergoing emicizumab prophylaxis and compared with previous FVIII prophylaxis captured in the real-world datea set of smart medication eDiary

PwSHA, patients with severe haemophiliia A; F, factor;

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Patients and methods

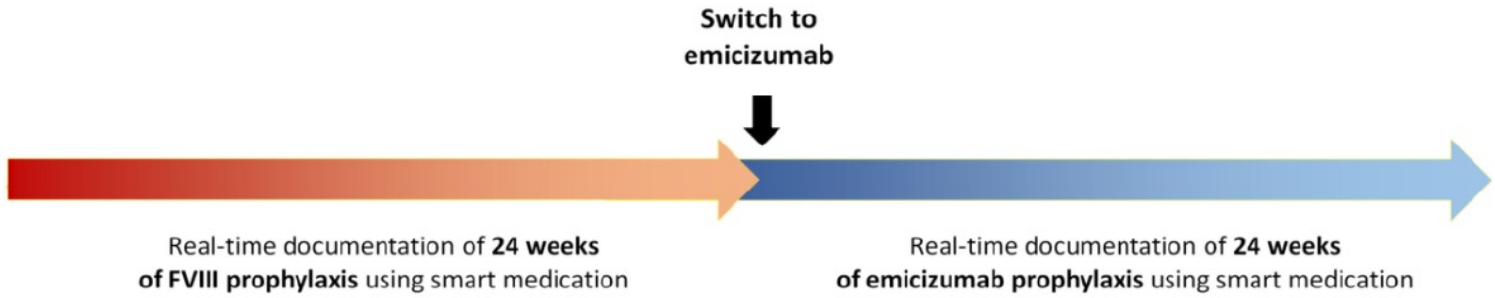
- Included were patients from an unselected cohort when switching to emicizumab prophylaxis fulfilling the following inclusion criteria:
  - ✓ Severe hemophilia A (FVIII<1%)
  - ✓ Negative FVIII inhibitor (<0.6 BU/ml)
  - ✓ 24 weeks of documented prophylaxis with emicizumab using smart medication eDiary application
  - ✓ Subgroup evaluation – 24 weeks of documented FVIII prophylaxis before switch to emicizumab using smart medication eDiary application

F, factor; BU, Bethesda units;

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Patients and methods

- Smart medication is a mobile website platform in interconnect patients, physicians, pharmacies and public registry (e.g. DHR) and a EU registered medical device. Data on treatment modalities - medication, dose, batch number, date, reason of treatment as well as bleeding events (location, bleeding type, bleeding cause, pain, photo upload, etc.) are captured in real - time by the patient and transmitted to the HTC. Outcome of emicizumab treatment and self - reported bleeds (ABR, AJBR and life-threatening bleeds) over a period of 24 weeks were evaluated. Whenever available, 24-weeks FVIII prophylaxis before switching to emicizumab and outcome was compared to outcome of consecutive emicizumab prophylaxis

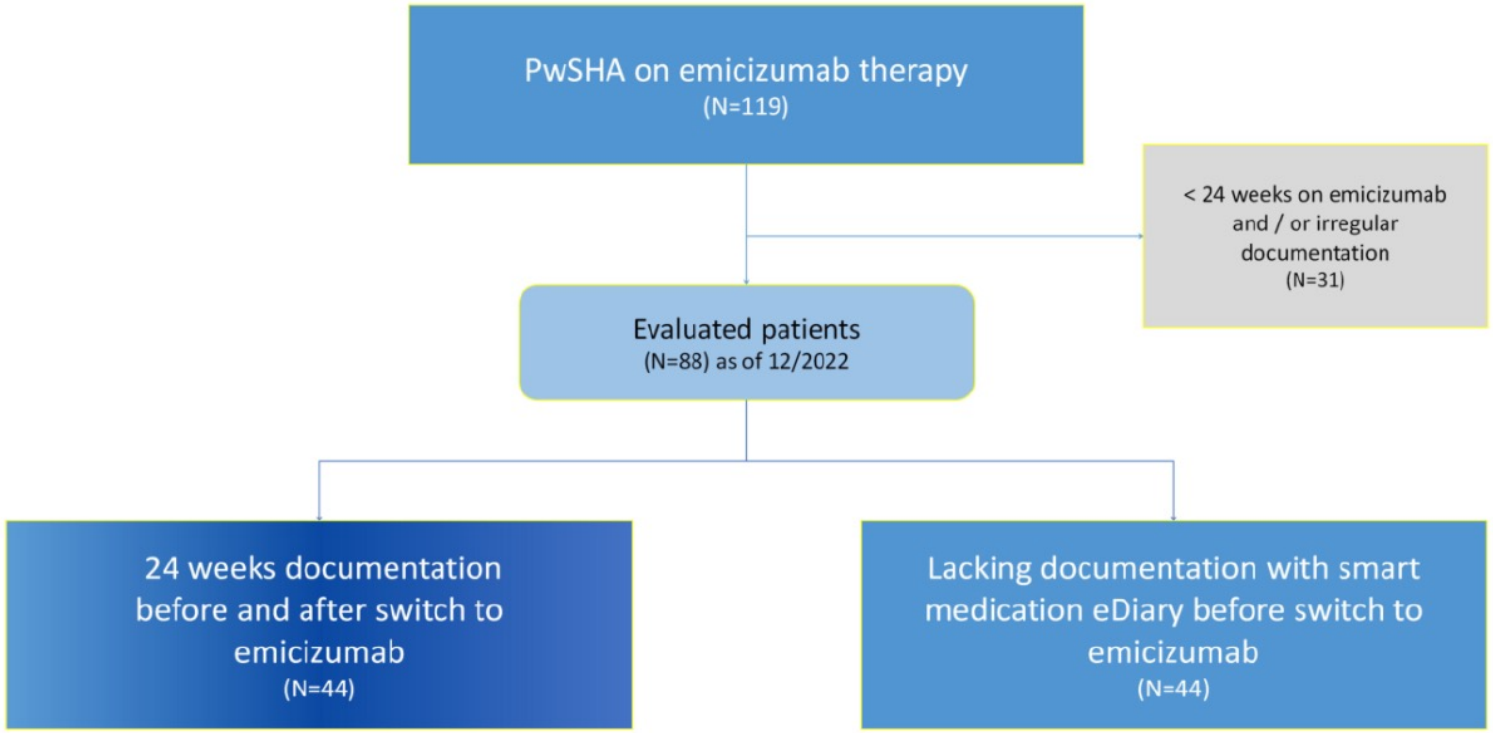


DHR, German hemophilia registry; HTCs, Haemophilia Treatment Centres; ABR, total treated bleeds per year; AJBR, total joint bleeds per year; F, factor

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Results

- As of December 2022, 88 pediatric and adult PwSHA from HTCs in Germany meeting all inclusion criteria were included



PwSHA, patients with severe haemophiliia A; HTCs, Haemophilia Treatment Centres;

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Results

- The median age was 35 years (IQR 35) – 71% were 18 years and older
- 44 PwSHA started with electronic documentation when switched to emizicumab
- In 44 patients with electronic documentation before and after switch could be evaluated and 24 weeks of FVIII prophylaxis coulde be compared with 24 weeks of emicizumab prophylaxis
- FVIII prophylaxis included prophylaxis with SHL and EHL – FVIII at 1 – 5 daily intervals with weekly doses from 21.2 – 179.8 IU/kg

IQR, interquartile range; HTCs, Haemophilia Treatment Centres; PwSHA, patients with severe haemophiliia A; F, factor, SHL, standard half-life; EHL, extended half-life; IU, international units;

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Results

- After switching to emicizumab prophylaxis, patients showed a mean AJBR of 0.30 and the mean ABR of 0.78 in all patients (n=88)
- In the subgroup of 44 PwSHA with documentation before and after switch, the mean AJBR dropped significantly from 2.08 under prophylaxis FVIII to 0.40 under emicizumab prophylaxis ($p < 0.01$)
- The mean ABR of all bleeds decreased from 3.19 to 1.20

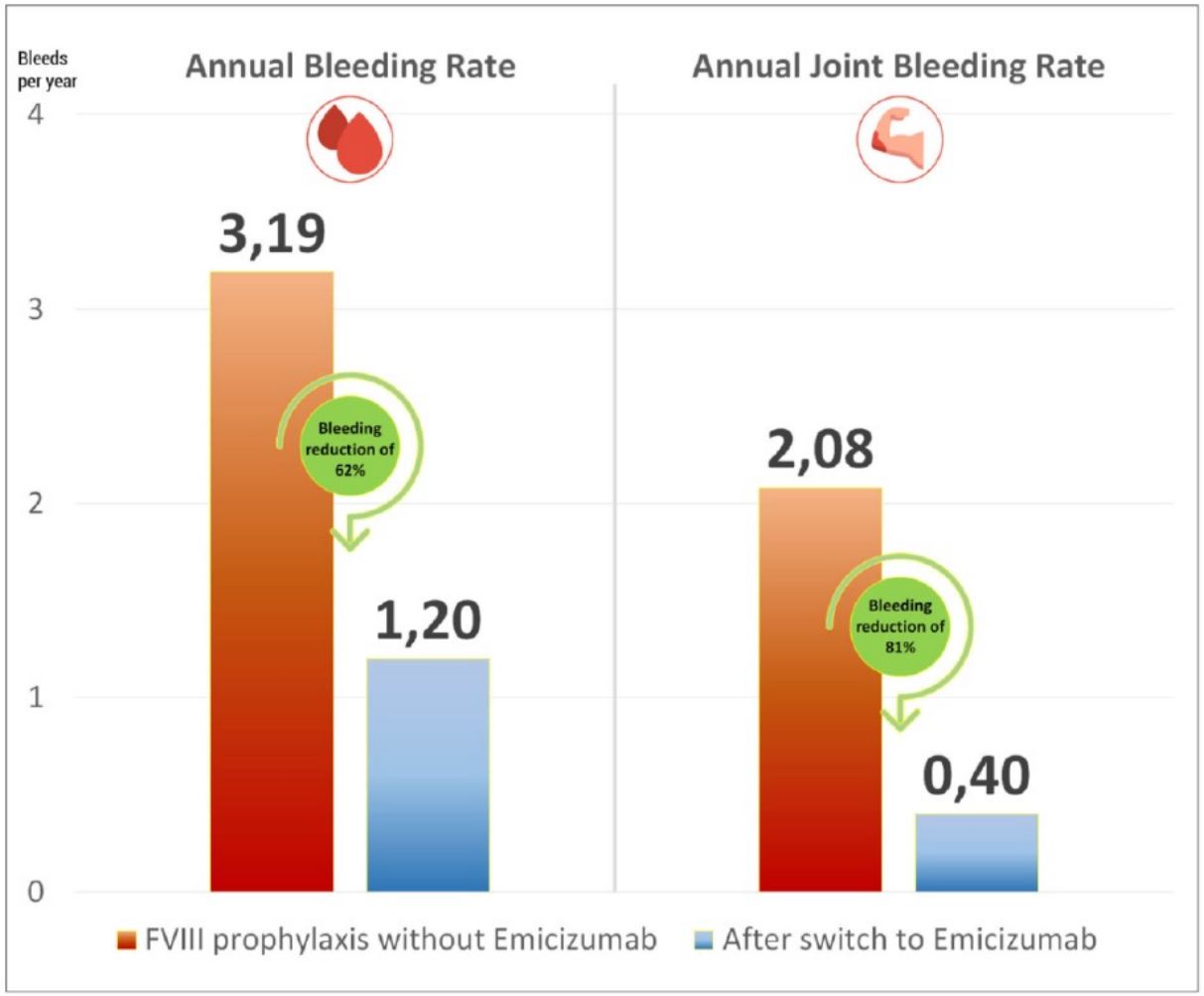
- The proportion of joint- patients with zero AJBR increased from 64% with FVIII prophylaxis to 91% with emicizumab prophylaxis. Despite of additional FVIII treatment in 39% of patients after the switch to emicizumab (e.g. during loading phase), only 6 (7%) needed additional FVIII due to joint bleeds.

PwSHA, patients with severe haemophiliia A; HTCs, Haemophilia Treatment Centres; ABR, total treated bleeds per year; AJBR, total joint bleeds per year; F, factor

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Results

- After switching to emicizumab prophylaxis, patients showed a mean AJBR of 0.30 and the mean ABR of 0.78 in all patients (n=88)
- In the subgroup of 44 PwSHA with documentation before and after switch, the mean AJBR dropped significantly from 2.08 under prophylaxis FVIII to 0.40 under emicizumab prophylaxis ($p < 0.01$) corresponding to a bleed reduction of 81%
- The mean ABR of all bleeds decreased from 3.19 to 1.20, corresponding to a bleed reduction of 62%

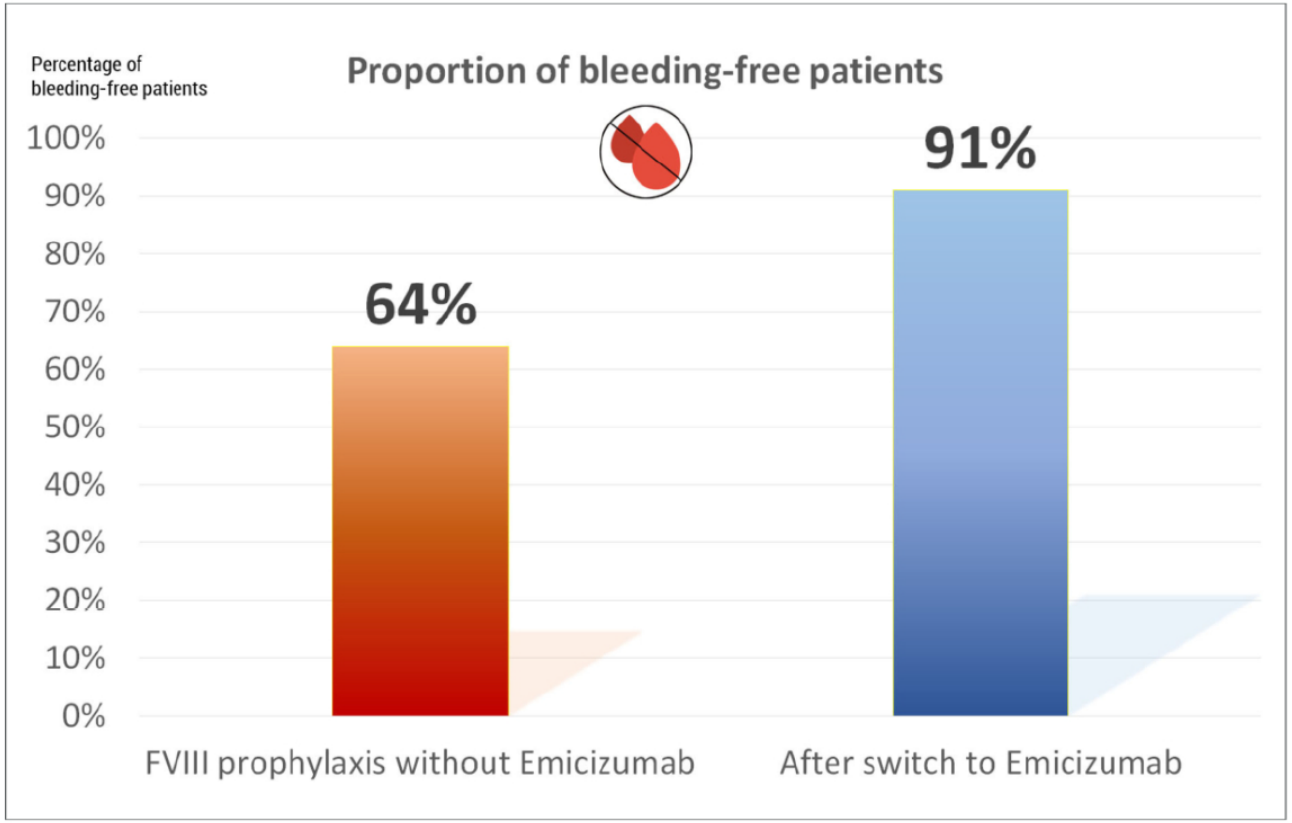


PwSHA, patients with severe haemophiliia A; ABR, total treated bleeds per year; AJBR, total joint bleeds per year; F, factor

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Results

- The proportion of patients with zero AJBR increased from 64% with FVIII prophylaxis to 91% with emicizumab prophylaxis
- Despite of additional FVIII treatment in 39% of patients after the switch to emicizumab (e.g. during loading phase), only 6 (7%) needed additional FVIII due to joint bleeds
- No life – threatening bleeds have been reported



AJBR, total joint bleeds per year; F, factor

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Conclusion

- The real life-data show a significant decrease of bleeding episodes after switching PwSHA from regular FVIII prophylaxis to emicizumab prophylaxis and confirm the favorable data from previous clinical trials
- E-diaries like smart medication support real – life documentation and evaluation of current and new treatment strategies

PwSHA, patients with severe haemophiliia A; F, factor

Mondorf W, et al. ISTH 2023; prezentace posteru PB0643.

Surgery in people with hemophilia A receiving emicizumab prophylaxis: Real – world experience from a single French Treatment Center of Hemophilia

Upraveno podle ústní prezentace OC 43.3 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Background

- Emicizumab prophylaxis is increasing in PwSHA
- No guidelines are currently available for managing surgery in PwSHA without inhibitors whilst in emicizumab
- Practical experience from a French Treatment Center for Hemophilia:
  - ✓ 61 PwSHA currently receive prophylaxis with emicizumab

PwSHA, patients with severe hemophilia A;

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Patients and Methods

- 40 surgical procedures
- 18 adult PwSHA without inhibitors
- January 2020 – December 2022
- Registry FranceCoag
- Type of procedures: minor or major
  - ✓ Santagostino et al.: Haemophilia 2015
- Perioperative use of FVIII concentrates
- Bleeding events or adverse events

PwSHA, patients with severe hemophilia A; F, factor

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Patients and Procedure

- Patients: N=18
- Median age: 47.5 +/- 9.4 years
  (min – max: 28-71)
- Median time on emicizumab prophylaxis:
  12.2 +/- 8.8 months
  (min – max: 1-33)

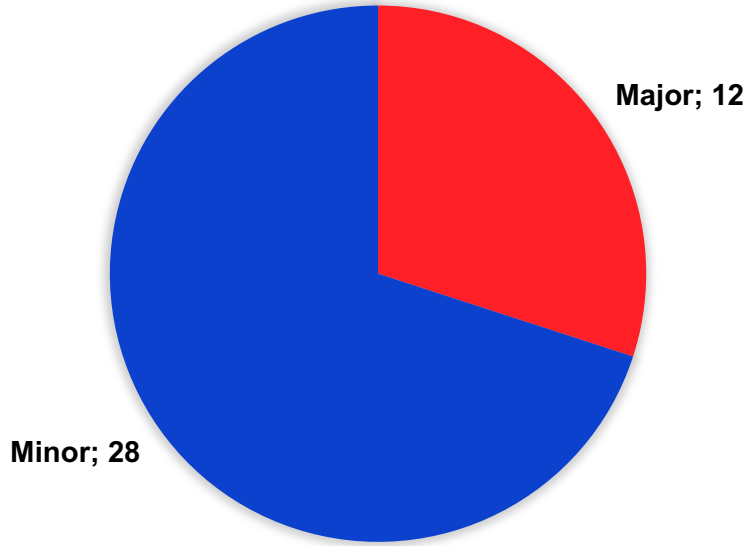
- Procedures: N=40
- Type of procedures:
  - ✓ 28 minor in 16 patients
  - ✓ 12 major in 7 patients
- Number of procedures/patients:
  - ✓ N=1: 44% (8/18)
  - ✓ N=2: 22% (4/18)
  - ✓ N>2: 33% (6/18)

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Procedure characteristics

- 3 prosthesis (2 knee, 1 hip)
- 3 arthrodesis
- 2 deep abscess
- 1 nerve release
- 1 osteotomy material removal
- 1 knee wash
- 1 radial head resection

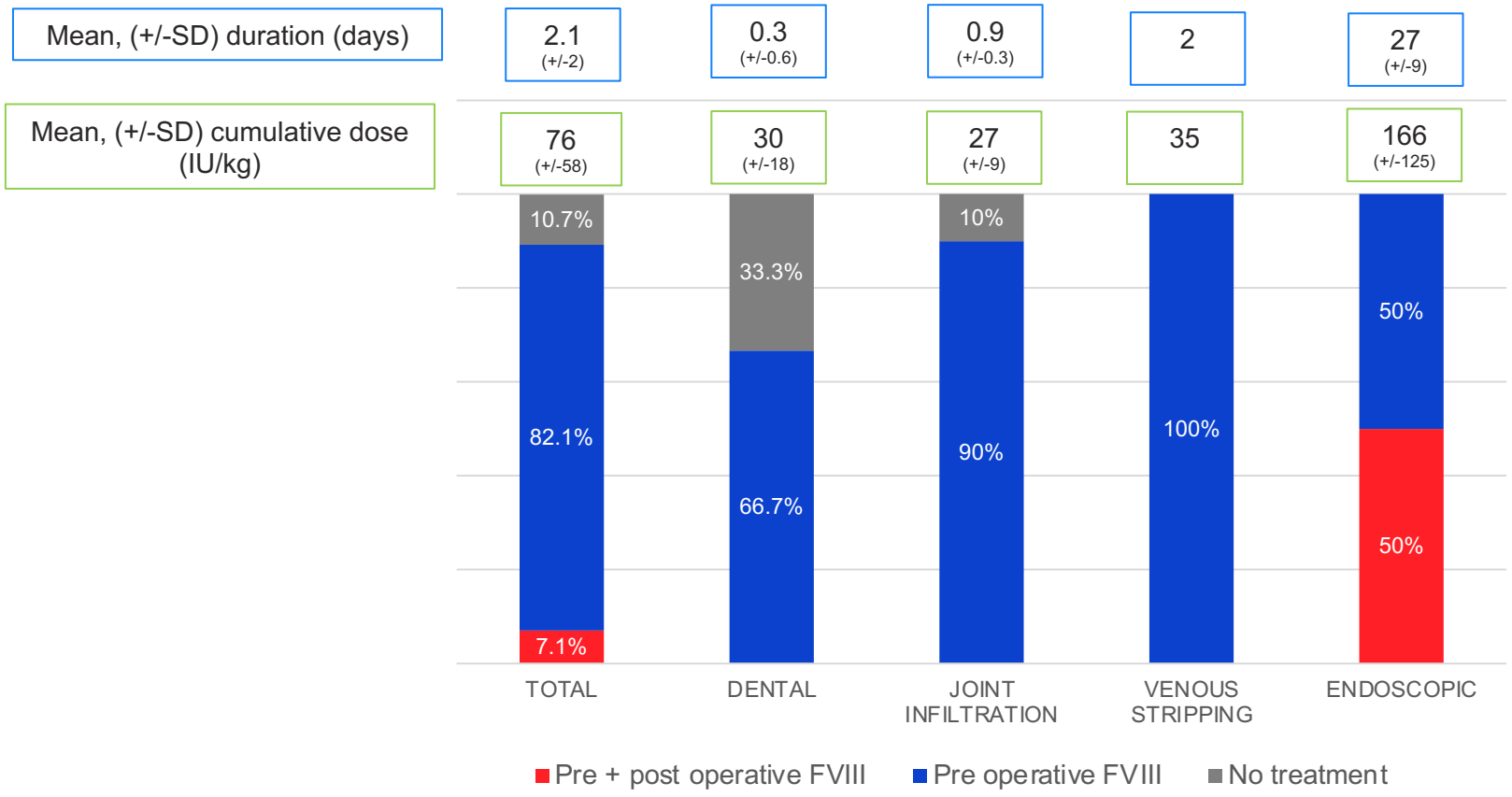
- 1 venous stripping
- 3 dental
- 4 endoscopic
- 20 joint infiltrations



Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Management and outcome of minor procedures

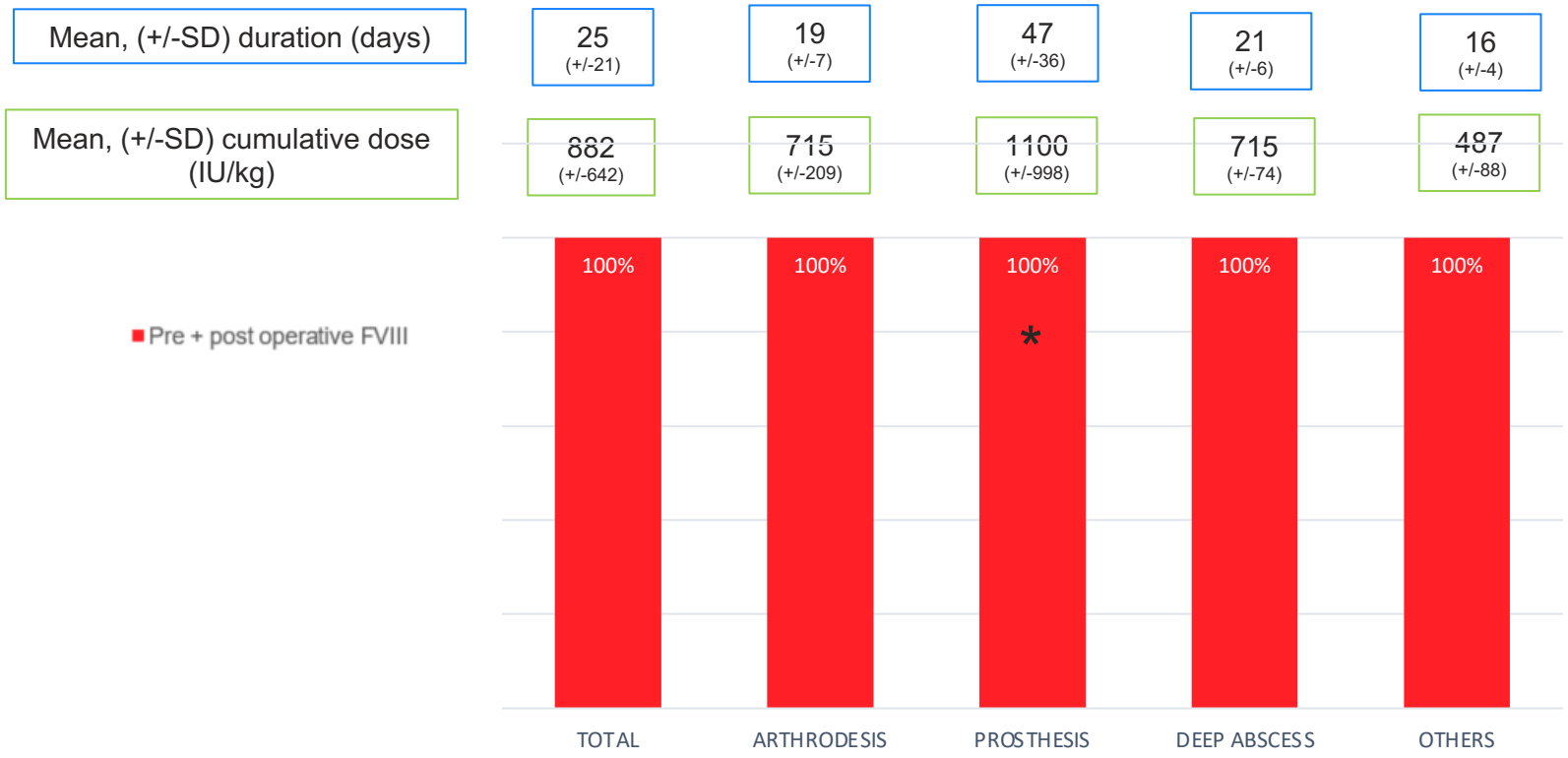
✓ **No bleed, no thrombosis**



F, factor; SD, standard deviation; IU, International units

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Management and outcome of major procedures



- ✓ **1/12 bleed - * knee prosthesis rehabilitation: hematoma, hemarthrosis, RBC transfusion**
- ✓ **No thrombosis**

F, factor, RBC, red blood cell; SD, standard deviation; IU, International units

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Biological monitoring of the 12 major surgeries

Procedures	Peak (FVIII:C, %)	Trough (FVIII:C, %)
Total knee prothesis	82	77
Hip prosthesis	111	52
Knee prothesis	89	81
Elbow arthrodesis	161	99
Pseudoarthrodesis of the elbow	111	102
Disarthrodesis	112	42
Deep abcess	84	59
Deep abcess	87	64
Knee wash	116	77
Ulnar nerve release	104	62
Removal of osteotomy material	82	52
Radial head resection	116	95

Methods:

- FVIII:C Siemens®
- Peak: 1 h post infusion, day of surgery
- Trough level: day 3 – day 7

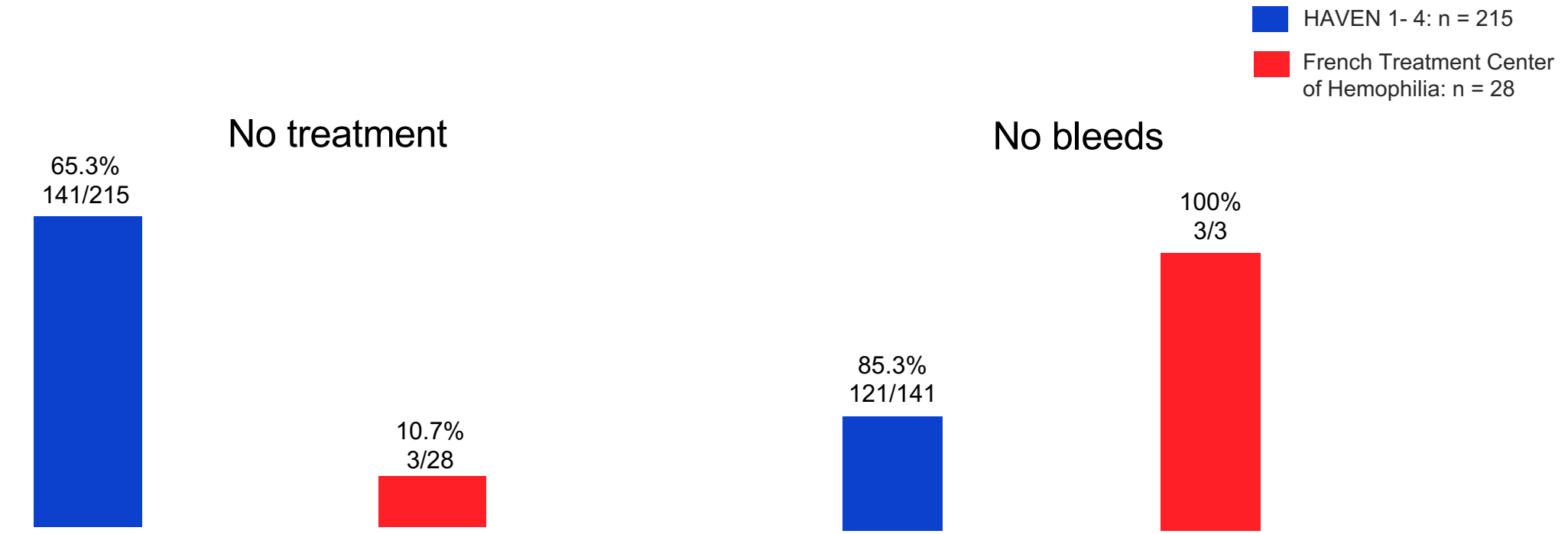
Results:

- Peak: FVIII:C >80%
- Trough: FVIII:C >50%

FVIII:C, factor VIII clotting assay;

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Minor procedures: comparison with the HAVEN 1- 4 clinical trials



Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Conclusion/Perspective

- French Treatment Center of Haemophilia 3-year experience:

✓ Surgical procedures in PwSHA without inhibitors on emicizumab prophylaxis are safe

✓ Major procedures:
  - FVIII coverage seems to be similar with or without emicizumab prophylaxis
  - Appropriate biological surveillance

✓ Minor procedures:
  - FVIII concentrates use might be reduced

PwSHA, patients with severe hemophilia A; F, factor

Brakta Ch, et al. ISTH 2023; ústní prezentace OC 43.3.

Management of invasive procedures in patients with Hemophilia A receiving Emicizumab prophylaxis: Real-world data from a national Hemophilia treatment center

Upraveno podle posteru PB0627 přednesené na kongresu *Mezinárodní společnosti pro trombózu a hemostázu (ISTH)*,
24. – 28. června 2023
Abstrakt je dostupný na: https://isth2023.eventscribe.net/searchGlobal.asp

M-CZ-00003345

Introduction

- Emicizumab prophylaxis supports hemostasis in PwHA with and without inhibitors to FVIII
- Data from the HAVEN studies previously demonstrated that PwHA receiving emicizumab prophylaxis can safely undergo minor and major surgeries, although major surgeries often require additional FVIII or rFVIIa prophylaxis
- Real world data on invasive procedures in PwHA receiving emicizumab prophylaxis are limited

PwHA, patients with haemophiliia A; rFVIIa, recombinant factor VIIa; F, factor

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

Aim and Methods

Aim

- To evaluate the safety of invasive procedures in PwHA receiving emicizumab prophylaxis and their outcomes in a longitudinally followed real world cohort

Methods

- Prospectively collected data from medical records of PwHA with and without FVIII inhibitors receiving emicizumab prophylaxis, who underwent all types of invasive procedures were retrieved
- Outcomes of interest were bleeding of any severity and thrombotic complications
- The study was approved by an institutional review board, and all patients provided informed consent

PwHA, patients with haemophiliia A; rFVIIa, recombinant factor VIIa; F, factor

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

Results

- Overall, 35 patients underwent 56 invasive procedures, of them 18 (32.1%) were major
- The median IQR age was 37 (10-56) years, 12 patients (34.3%) were younger than 18 years at the time of procedure, 26 (74.3%) were patients with FVIII inhibitors

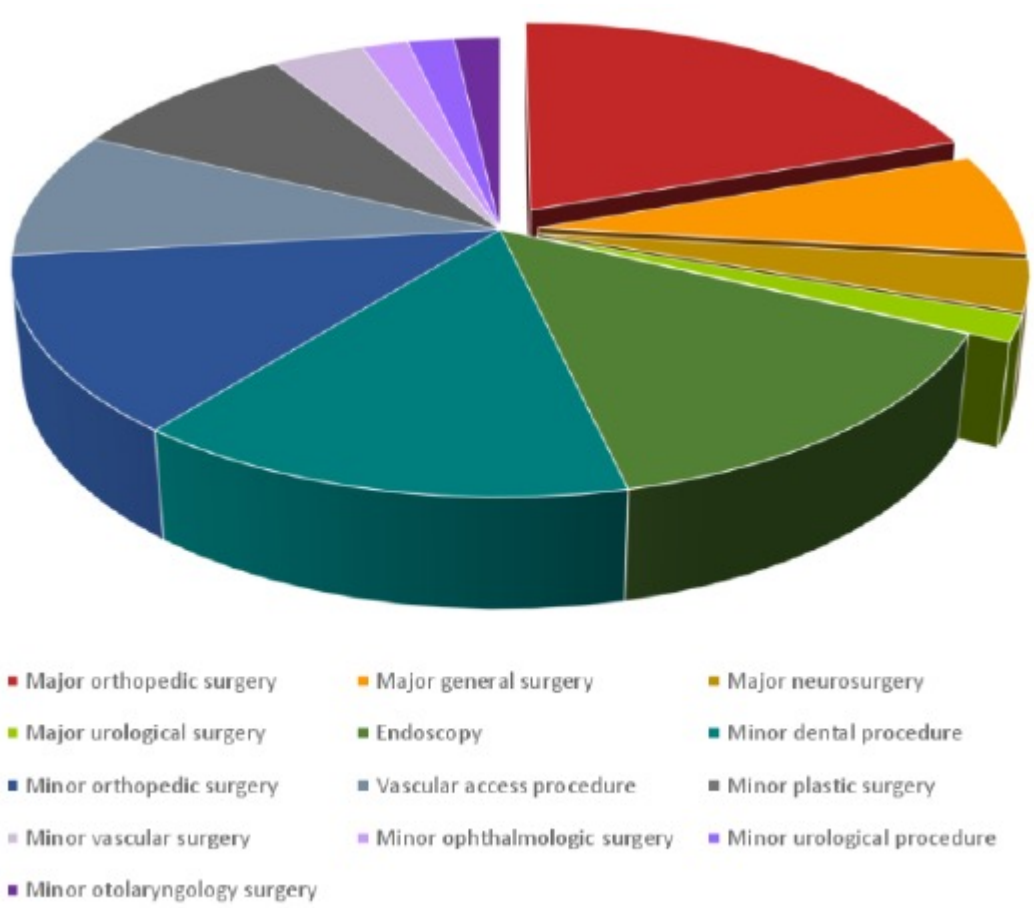
	Number of procedures	Number of patients	Age (Years), Median (IQR)*	Number of patients with FVIII inhibitors	Time on Emicizumab prophylaxis (months), Median (IQR)*
Major procedures					
Orthopedic surgery	11	9	36 (25.5-54.5)	4	9 (3.5-39)
General surgery	4	4	32 (16-50.5)	0	10 (5-20.5)
Neurosurgery	2	1	3	1	7
Urological surgery	1	1	37	0	2
Minor procedures					
Endoscopy	8	7	52 (38-62)	2	24.5 (9-35)
Dental procedure	8	6	44 (4.5-59.5)	3	18 (10.5-28.5)
Orthopedic surgery	7	6	41.5 (17-49)	3	19 (9-28)
Vascular access	5	5	6 (3-12.5)	4	5 (1.5-8)
Plastic surgery	5	5	63 (27.5-72)	2	28 (10-34)
Vascular surgery	2	2	44, 62	0	27, 28
Urological procedure	1	1	0.25	1	0.5
Ophthalmologic surgery	1	1	6	0	43
Otolaryngology surgery	1	1	62	0	27

PwHA, patients with haemophiliia A; IQR, interquartile range; rFVIIa, recombinant factor VIIa; F, factor

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

Results

- Among major procedures, orthopedic surgeries prevailed. All patients who underwent major procedures received factor replacement either with rFVIIa 90 µg/kg (patients with inhibitors, n=15) or FVIII 35-50 IU/kg (patients without inhibitors, n=3)
- Factor concentrates were administered prior to 32 (84%.2) of minor procedures
- Repeated doses were given according to international expert opinion recommendations and patients' condition



PwHA, patients with haemophiliia A; IQR, interquartile range; rFVIIa, recombinant factor VIIa; F, factor; IU, international units

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

Results

- Six patients experienced bleeding, 4 were major bleeds, including one patient who underwent a minor procedure without factor replacement
- None of the patients experienced a thrombotic complication

Patient #	Age at time of the procedure (years)	Comorbidities	Time on emicizumab (months)	FVIII inhibitor	Inhibitor level at procedure (BU)	Emicizumab level (μ/ml)	Type of procedure	Procedure	Factor replacement therapy prophylaxis	Bleeding severity	Length of hospital stay (days)	ICU admission
1	79	Diabetes, Adenoca. of pancreas, s/p Whipple	51	Yes	7.2	29	Major orthopedic surgery	Epidural abscess drainage, spinal fusion and internal fixation	Recombinant FVIIa	Major bleeding	45	No
2	79	Diabetes, Adenoca. of pancreas, s/p Whipple	51.5	Yes	7.2	29	Major orthopedic surgery	Incision and drainage of spinal hematoma	Recombinant FVIIa	Major bleeding	30	No
3	27	NASH	7	No	–	45	Major general surgery	Laparoscopic single anastomosis gastric bypass	Recombinant FVIII	Major bleeding	9	No
4	37	None	24	No	–	45	Major urological surgery	Retrograde intrarenal surgery with stent insertion	Recombinant FVIII	CRNMB	2	No
5	0.25	None	1	Yes	4	54	Minor urological procedure	Circumcision	None	Major bleeding	4	Yes
6	62	IHD, s/p PCI, Diabetes, HCV, HIV, Lymphoma	27	No	–	28	Minor otolaryngology surgery	Tympanoplasty	Recombinant FVIII	CRNMB	2	No

PwHA, patients with haemophiliia A; IQR, interquartile range; rFVIIa, recombinant factor VIIa; F, factor; Adenoca, adenocarcinoma; BU, Bethesda units; CRNMB, clinically relevant non-major bleeding; HCV, hepatitis C virus carrier; IHD, ischemic heart disease; NASH, nonalcoholic steatohepatitis; ICU, intensive care; PCI, percutaneous coronary intervention; s/p, status post

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

Conclusion

- Invasive procedures can be performed safely in patients receiving emicizumab prophylaxis
- Factor concentrates may be advised in selected patients undergoing minor procedures

Cohen O, et al. ISTH 2023; prezentace posteru PB0627.

HEMLIBRA 30 mg/ml injekční roztok, HEMLIBRA 150 mg/ml injekční roztok
– Zkrácená informace o přípravku

Účinná látka: emicizumab. **Držitel rozhodnutí o registraci:** Roche Registration GmbH, Grenzach - Wyhlen, Německo. **Registrační číslo:** EU/1/18/1271/001-004. **Indikace:** Přípravek Hemlibra je indikován k rutinní profylaxi krvácivých epizod u pacientů s hemofilií A s inhibitorem faktoru VIII, u pacientů s těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII < 1 %) bez inhibitoru faktoru VIII a u pacientů se středně těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII ≥ 1 % a ≤ 5 %) se závažným krvácivým fenotypem bez inhibitoru faktoru VIII. Přípravek Hemlibra mohou používat všechny věkové kategorie. **Dávkování a způsob podání:** Léčba musí být zahájena pod dohledem lékaře se zkušeností s léčbou hemofilie a/nebo krvácivých poruch. Den před zahájením léčby přípravkem Hemlibra musí být ukončena léčba (včetně rutinní profylaxe) bypassovými přípravky. Profylaxe faktorem VIII (FVIII) může pokračovat během prvních 7 dnů léčby přípravkem Hemlibra. Doporučená dávka je 3 mg/kg jednou týdně během prvních 4 týdnů (nasycovací dávka), po kterých následuje od týdne 5 udržovací dávka buď 1,5 mg/kg jednou týdně, nebo 3 mg/kg každé dva týdny nebo 6 mg/kg každé čtyři týdny, všechny dávky podávané formou subkutánní injekce. Režim nasycovací dávky je vždy stejný bez ohledu na režim udržovací dávky. Při sestavování celkového objemu dávky pro podání nesměšujte různé koncentrace roztoku Hemlibra (30 mg/ml a 150 mg/ml) v jedné injekční stříkačce. Nepodávejte objem větší než 2 ml na injekci. Přípravek Hemlibra je určen k dlouhodobé profylaktické léčbě. Nejsou doporučeny žádné úpravy dávkování přípravku Hemlibra. Přípravek Hemlibra je určen pouze k subkutánnímu použití a musí být aplikován pomocí vhodné aseptické techniky. Během léčby přípravkem Hemlibra mají být jiné léčivé přípravky k subkutánní aplikaci aplikovány přednostně v jiných místech. Přípravek Hemlibra je určen k používání pod vedením zdravotnického pracovníka. Po důkladném zaškolení v aplikaci subkutánní injekce jej může aplikovat pacient nebo pečovatel, uzná-li to lékař za vhodné. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. **Imunogenita:** U pacientů s klinickými projevy ztráty účinnosti (např. nárůst počtu průlomových krvácivých příhod) je třeba okamžitě zhodnotit etiologii a při podezření, že příčinou jsou neutralizující protilátky proti emicizumabu, je třeba zvážit jiné možnosti léčby. **Významné interakce:** S emicizumabem nebyly provedeny žádné adekvátní ani dostatečně kontrolované studie interakcí. Klinické zkušenosti naznačují, že emicizumab interaguje s aPCC. Emicizumab zvyšuje koagulační potenciál; dávka FVIIa nebo FVIII potřebná k zajištění hemostázy může být proto nižší než bez profylaxe přípravkem Hemlibra. Zkušenosti se souběžným podáváním antifibrinolytik s aPCC nebo rFVIIa u pacientů léčených emicizumabem jsou omezené. Při podávání systémových antifibrinolytik v kombinaci s aPCC nebo rFVIIa u pacientů léčených emicizumabem je však třeba vzít v úvahu možnost trombotických příhod. **Hlavní klinicky významné nežádoucí účinky:** Nejzávažnějšími nežádoucími účinky hlášenými v klinických studiích s přípravkem Hemlibra byly trombotická mikroangiopatie (TMA) a trombotické příhody včetně trombózy kavernózního splavu (CST) a trombóza povrchových žil s kožní nekrózou. Nejčastějšími nežádoucími účinky u pacientů léčených přípravkem Hemlibra byly reakce v místě vpichu, bolest kloubů a bolest hlavy. Celkem tři pacienti na profylaxi přípravkem Hemlibra v klinických studiích ukončili léčbu kvůli nežádoucím účinkům, ke kterým patřila TMA, kožní nekróza současně s povrchovou tromboflebitidou a bolest hlavy. **Druh obalu a dostupná balení:** Injekční lahvička 3ml, Hemlibra s koncentrací 30 mg/ml obsahuje 30 mg emicizumabu v 1ml injekčního roztoku. Injekční lahvička 3ml, Hemlibra s koncentrací 150 mg/ml obsahuje 60 mg emicizumabu v 0,4 ml injekčního roztoku, nebo obsahuje 105 mg emicizumabu v 0,7 ml injekčního roztoku, nebo obsahuje 150 mg emicizumabu v 1 ml injekčního roztoku, nebo obsahuje 300 mg emicizumabu ve 2 ml injekčního roztoku. Balení obsahuje vždy jednu injekční lahvičku. **Podmínky uchovávání:** Uchovávejte v chladničce (2–8 ºC). Neotevřené injekční lahvičky lze po vyjmutí z chladničky uchovávat při pokojové teplotě (do 30 °C) až po dobu 7 dnů kumulativně. Chraňte před mrazem a před světlem.

Datum registrace: 23.2.2018 **Datum poslední úpravy textu Zkrácené informace o přípravku:** 2.3.2023. **Aktuální verze Souhrnu údajů o přípravku je dostupná na** https://www.sukl.cz, **resp.** https://www.roche.cz/cs/produkty-vpois/produkty-lekari.html

Výdej léčivého přípravku je vázán na lékařský předpis. Léčivý přípravek Hemlibra je v indikaci rutinní profylaxe krvácivých epizod u pacientů s hemofilií A s inhibitorem faktoru VIII a v indikaci rutinní profylaxe krvácivých epizod u pacientů s těžkou hemofilií A (vrozená deficience koagulačního faktoru VIII, FVIII < 1 %) bez inhibitoru faktoru VIII hrazen z prostředků veřejného zdravotního pojištění. Léčivý přípravek zatím není hrazen u pacientů se středně těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII ≥ 1 % a ≤ 5 %) se závažným krvácivým fenotypem bez inhibitoru faktoru VIII. Podmínky úhrady viz www.sukl.cz. Další informace o přípravku získáte z platného Souhrnu údajů o přípravku Hemlibra, nebo na adrese Roche s.r.o., Sokolovská 685/136f, 18600 Praha 8, Tel: +420 220382111. Podrobné informace o tomto přípravku jsou uveřejněny na webových stránkách Evropské lékové agentury (EMA) http://www.ema.europa.eu/.

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