HEMLIBRA® ▼ (emicizumab) clinical trial programme in patients with haemophilia A

Dr G Dolan
Guy's and St Thomas' Hospital
London
UK

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Introduction: indication for HEMLIBRA (emicizumab)

- HEMLIBRA is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) who have
  - Severe haemophilia A (FVIII <1%) without factor VIII inhibitors
  - Haemophilia A with factor VIII inhibitors
- HEMLIBRA is intended for long-term prophylactic treatment
- HEMLIBRA can be used in all age groups

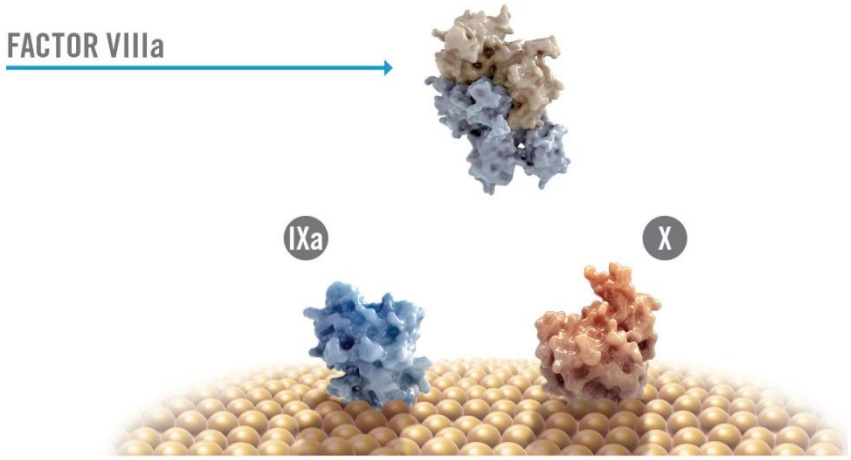
HEMLIBRA Summary of Product Characteristics.

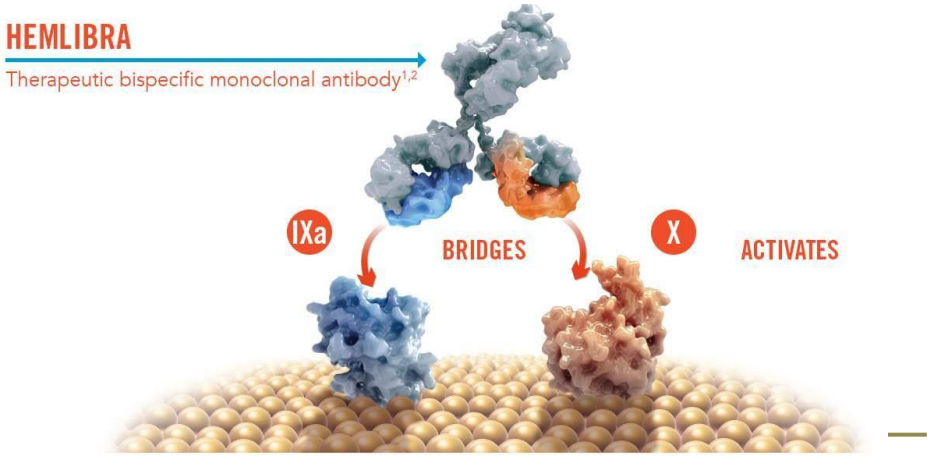
FVIII=factor VIII

HEMLIBRA: a bispecific antibody that bridges FIXa and FX to allow the clotting cascade to continue

- Emicizumab has no structural relationship or sequence homology to factor VIII, therefore it is not affected by factor VIII inhibitors and does not induce or enhance the development of factor VIII inhibitors

- The half-life of emicizumab is 4–5 weeks. Therapeutic blood levels are sustained with every week, every 2 week, or every 4 week dosing





1. HEMLIBRA Summary of Product Characteristics.
2. Kitazawa T, et al. Nat Med. 2012;18:1570-4.

Overview

HAVEN clinical trial programme:

HAVEN 1
Prophylaxis with HEMLIBRA® (emicizumab) in adult and adolescent patients (aged ≥12 years-old) who have haemophilia A with factor VIII inhibitors[1]

HAVEN 2
Prophylaxis with HEMLIBRA® (emicizumab) in children (aged <12 years-old) who have haemophilia A with factor VIII inhibitors[2]

HAVEN 3
Prophylaxis with HEMLIBRA® (emicizumab) in adult and adolescent patients (aged ≥12 years-old) who have severe haemophilia A without factor VIII inhibitors[3]

HAVEN 4
Prophylaxis with HEMLIBRA® (emicizumab) given as maintenance every 4 weeks in adult and adolescent patients (aged ≥12 years-old) who have haemophilia A with or without factor VIII inhibitors[4]

Long-term efficacy of emicizumab: pooled data from HAVEN 1 to 4[5]

Integrated safety analysis
Including an analysis of surgical experience in patients taking emicizumab

1. Oldenburg J, et al. N Engl J Med. 2017;377:809-18.
2. Young G, et al. ASH. 2018:632 [oral presentation].
3. Mahlangu J, et al. N Engl J Med. 2018;379:811-22.
4. Pipe S, et al. The Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].
5. Callaghan M, et al. ISTH. 2019: OC60.2

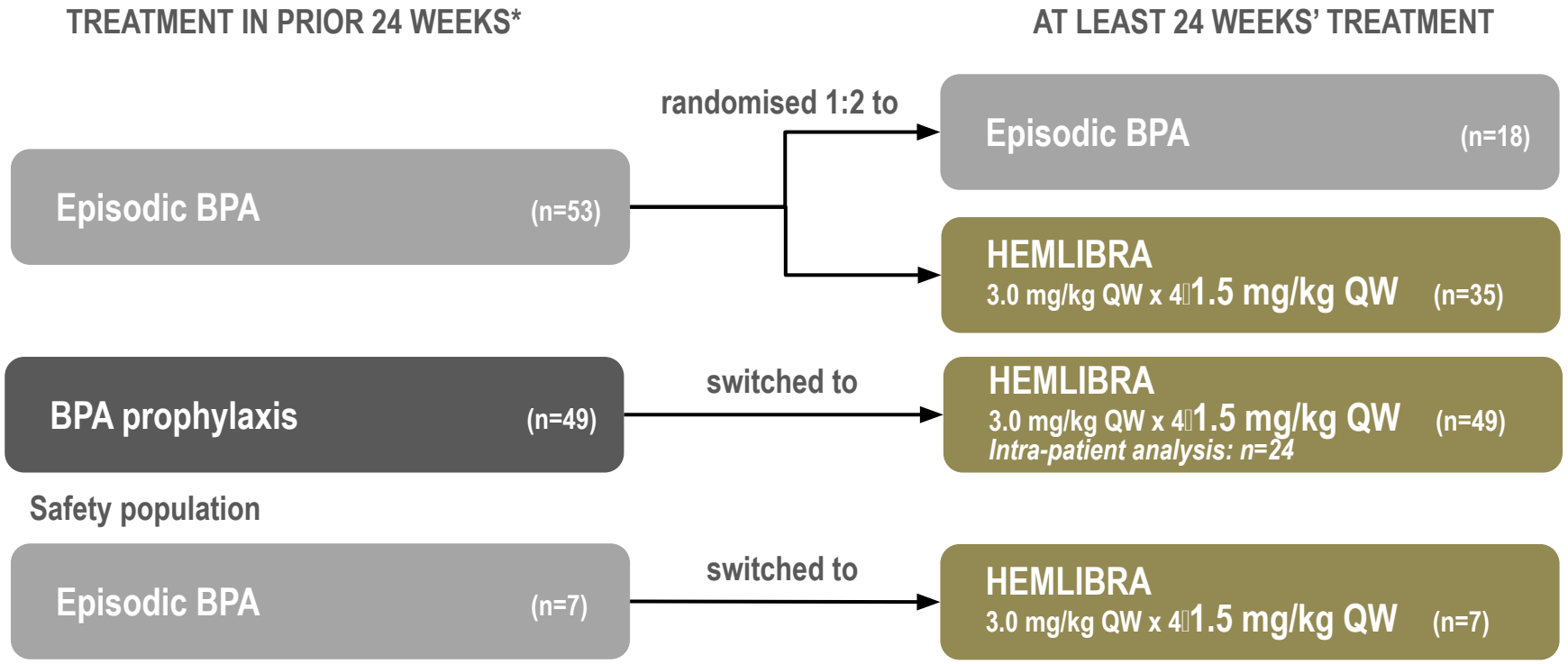
HAVEN 1

Prophylaxis with HEMLIBRA (emicizumab) in adult and adolescent patients who have haemophilia A with factor VIII inhibitors

Oldenburg J, et al. N Engl J Med. 2017;377:809-18.

HAVEN 1: trial design

- A multicentre, open-label, randomised, phase III clinical trial[1,2]
- Adults and adolescent patients (≥12 years old and ≥40 kg) with haemophilia A with factor VIII inhibitors[1,2]



1. Oldenburg J, et al. N Engl J Med. 2017;377:809-18.
2. Oldenburg J, et al. N Engl J Med. 2017;377:809-18 (supplementary appendix).

BPA=bypassing agent; NIS=non-interventional study; QW=every week
*Stratified by prior 24 week bleed rate (<9 or ≥9 bleeds).

HAVEN 1: endpoints

Primary endpoint:

- Difference in annualised rate of treated bleeds (treated ABR) at 24 weeks with HEMLIBRA prophylaxis vs. no prophylaxis (episodic BPA)

Secondary endpoints:

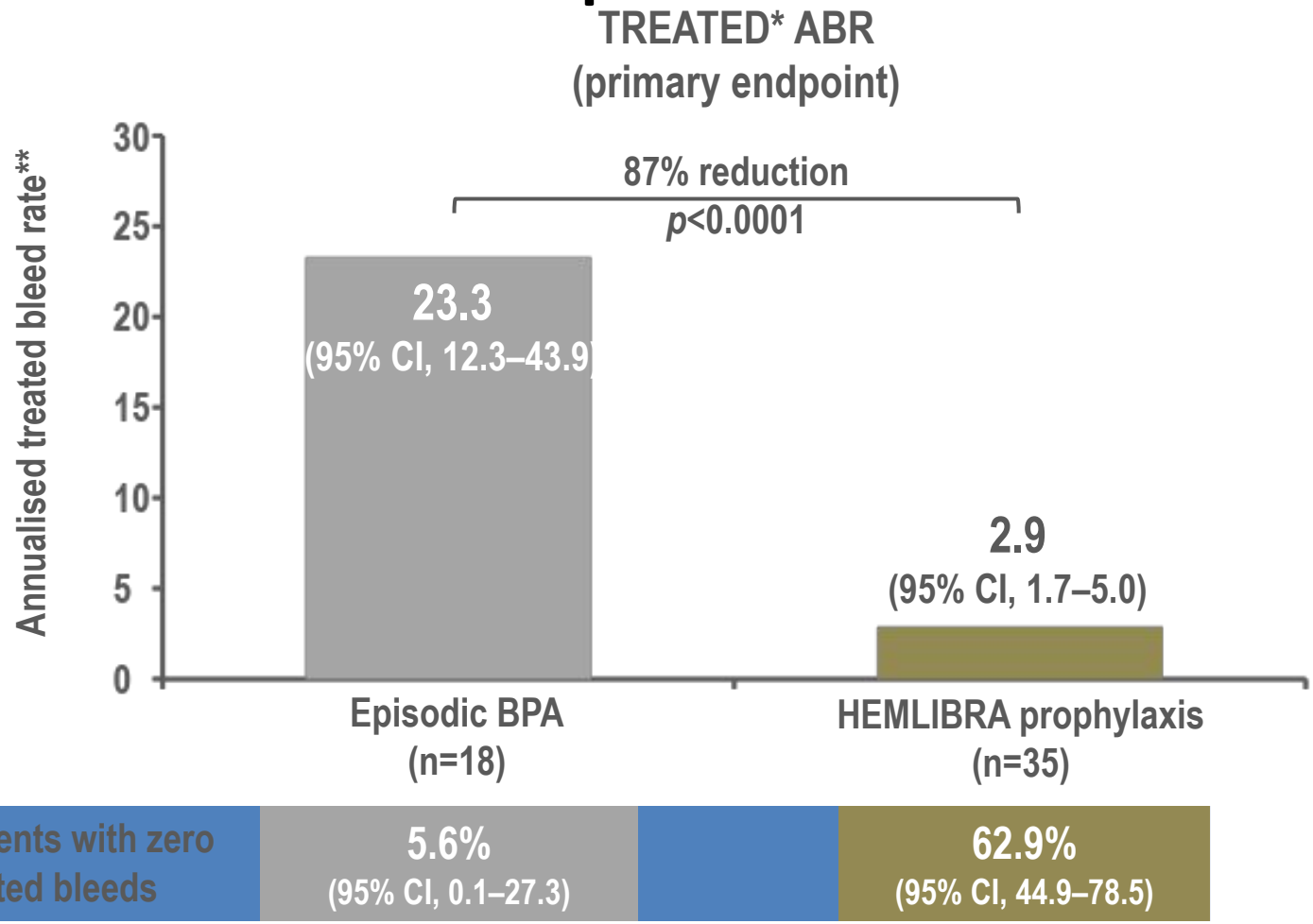
- Treated target joint bleeds
- Treated joint bleeds
- Treated spontaneous bleeds
- All bleeds*
- Intra-patient analysis
- Health-related quality of life
- Pharmacokinetics
- Safety

Oldenburg J, et al. N Engl J Med. 2017;377:809-18.

ABR=annualised bleed rate; BPA=bypassing agent

*All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not.

HEMLIBRA reduced treated bleeds vs. episodic BPA

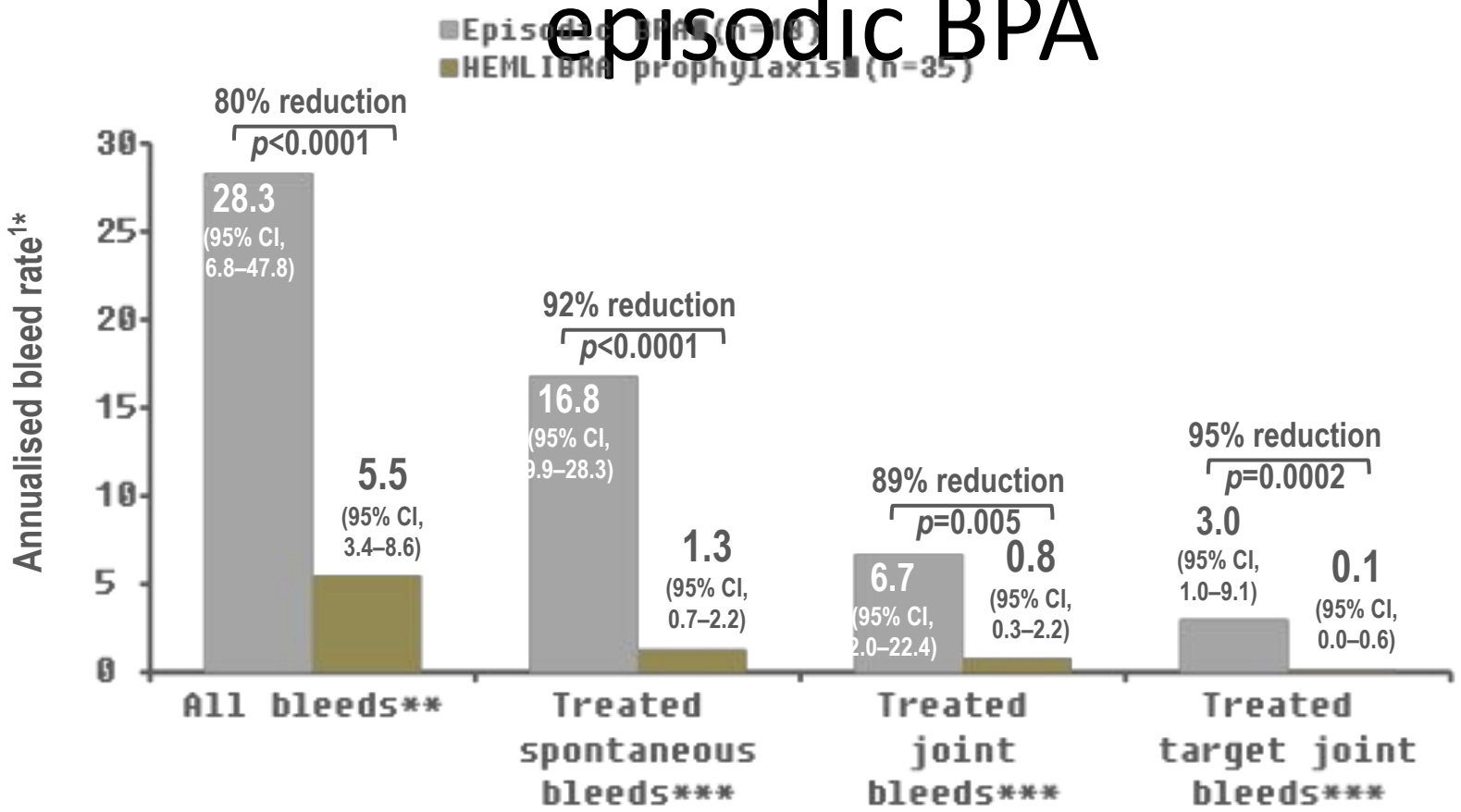


ABR=annualised bleed rate; BPA=bypassing agent; CI=confidence interval

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times.

Oldenburg J, et al. N Engl J Med. 2017;377:809-18).

HEMLIBRA: significant reductions in all other bleeding endpoints vs. episodic BPA

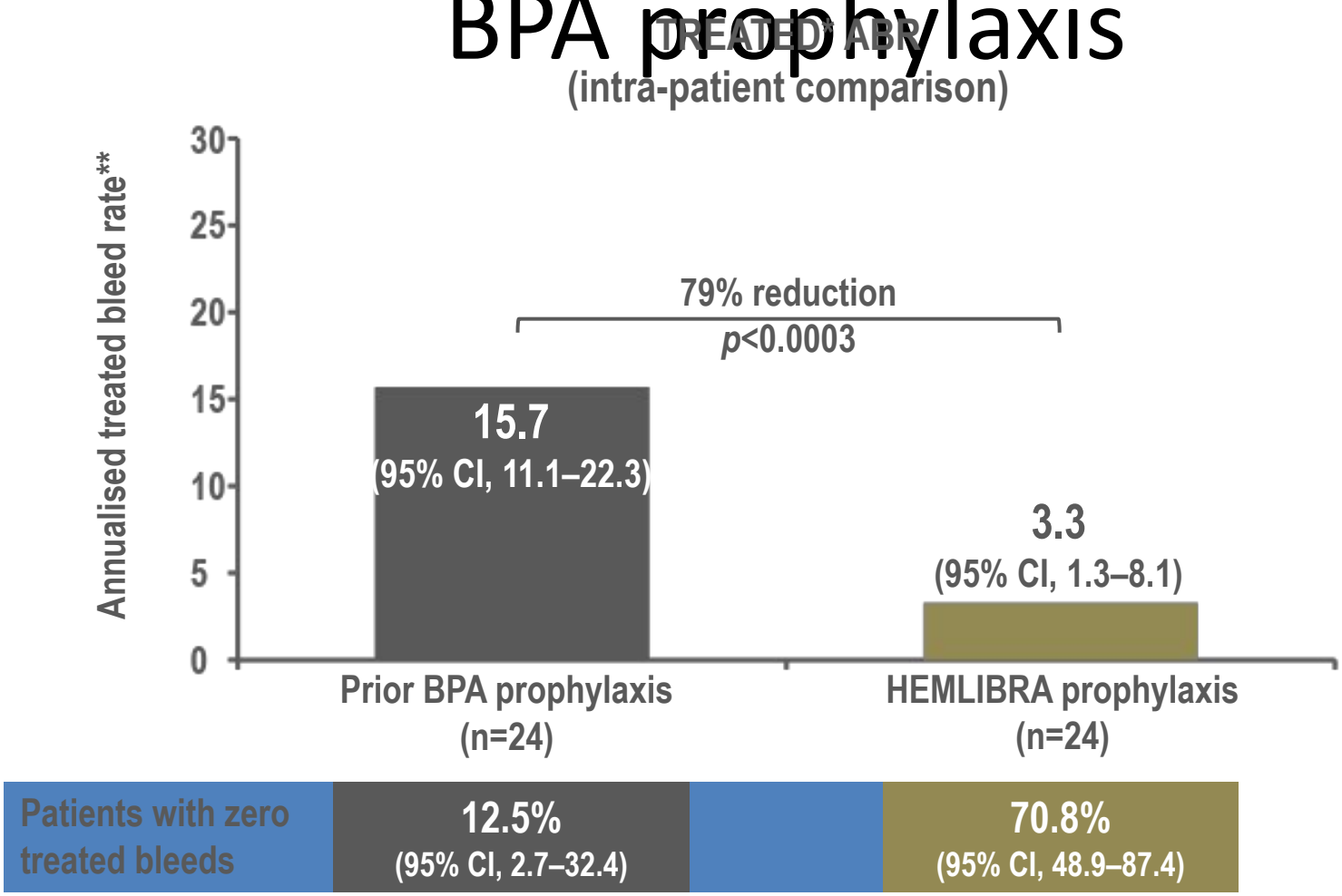


Patients with zero bleeds[2]	5.6% (95% CI, 0.1–27.3)	37.1% (95% CI, 21.5–55.1)	11.1% (95% CI, 1.4–34.7)	68.6% (95% CI, 50.7–83.1)	50.0% (95% CI, 26.0–74.0)	85.7% (95% CI, 69.7–95.2)	50.0% (95% CI, 26.0–74.0)	94.3% (95% CI, 80.8–99.3)

1. *Adapted from Oldenburg J, et al. N Engl J Med. 2017;377:809-18 (including Supplementary Appendix).*
2. *HEMLIBRA Summary of Product Characteristics.*

ABR=annualised bleed rate; BPA=bypassing agent CI=confidence interval; *ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. **All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not. ***Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed.

HEMLIBRA prophylaxis significantly reduced treated bleeds vs. prior BPA prophylaxis

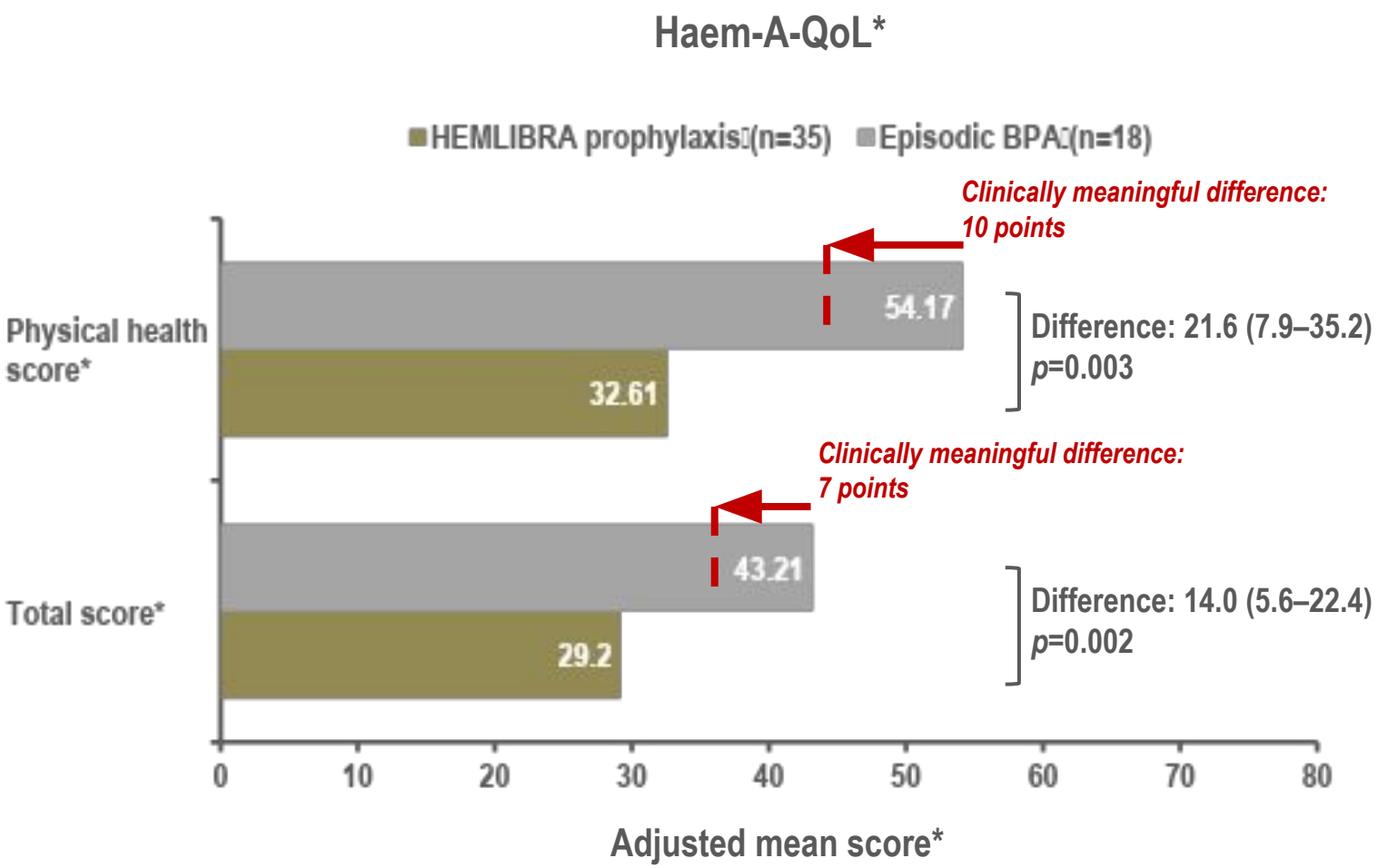


ABR=annualised bleed rate; BPA=bypassing agent; CI=confidence interval

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM which takes into account number of bleeds and different treatment and follow-up times.

Oldenburg J, et al. N Engl J Med. 2017;377:809-18.

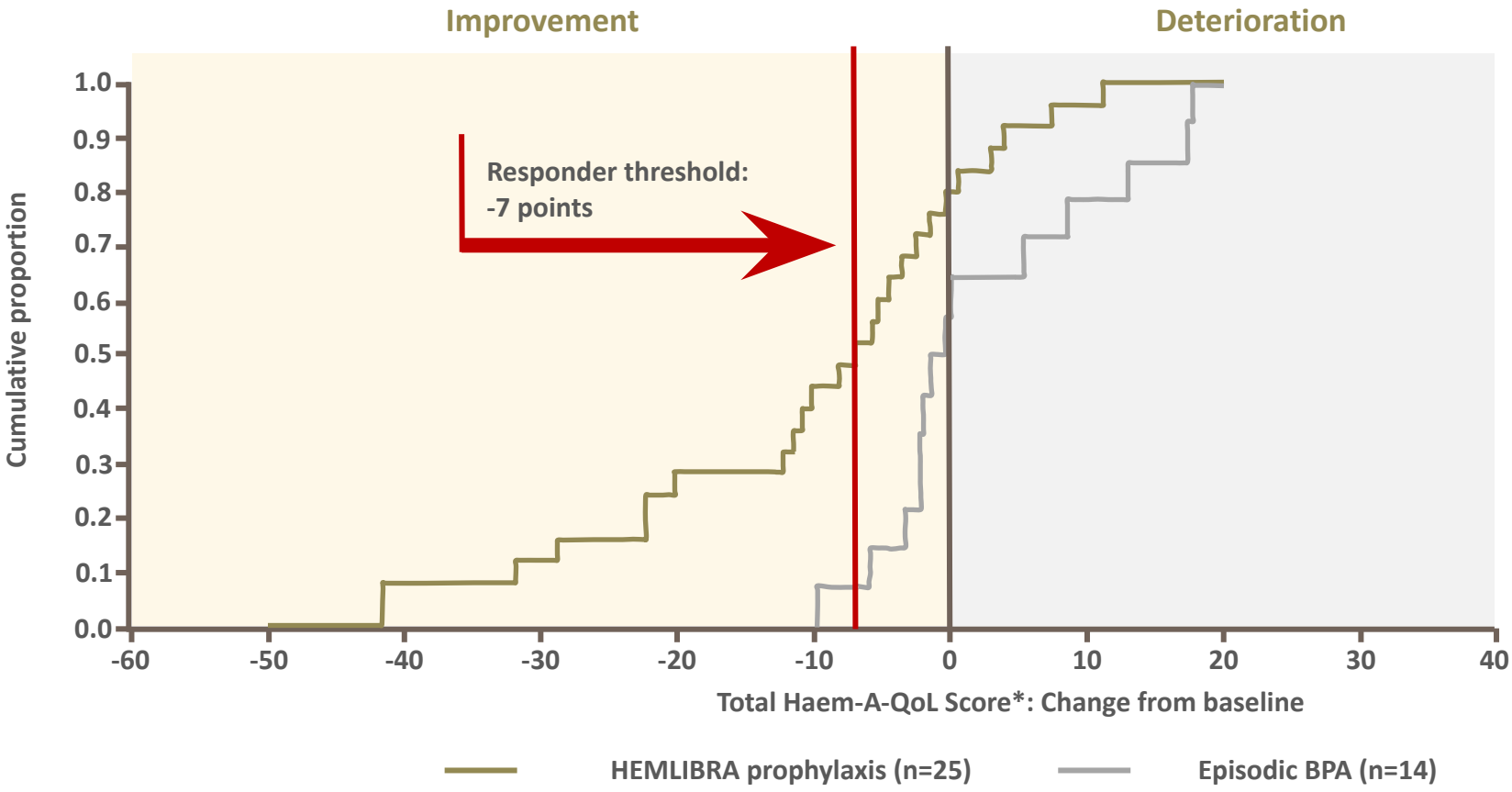
Statistically significant, clinically meaningful differences in health-related quality of life after 24 weeks with HEMLIBRA prophylaxis (vs. episodic BPA)



Oldenburg J, et al. N Engl J Med. 2017;377:809-18.
HEMLIBRA Summary of Product Characteristics.

BPA=bypassing agent; CI=confidence interval
*Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better health-related quality of life

Changes in health-related quality of life after 24 weeks with HEMLIBRA prophylaxis (vs. episodic BPA): Haem-A-QoL

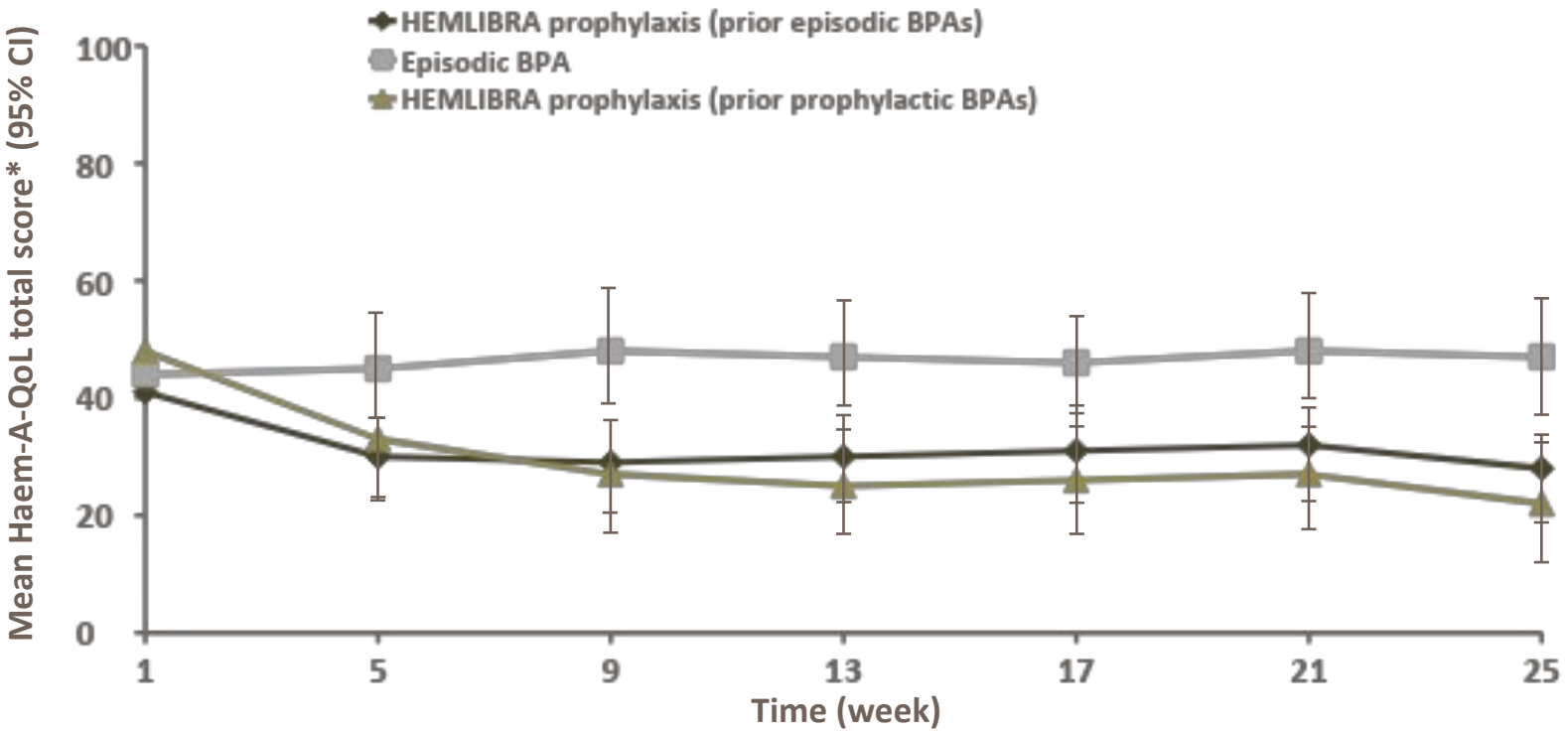


Oldenburg J, et al. Haemophilia. 2019;25:33-44.

BPA=bypassing agent

*Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better health-related quality of life

Effect of HEMLIBRA on quality of life (total Haem-A-QoL score) over time

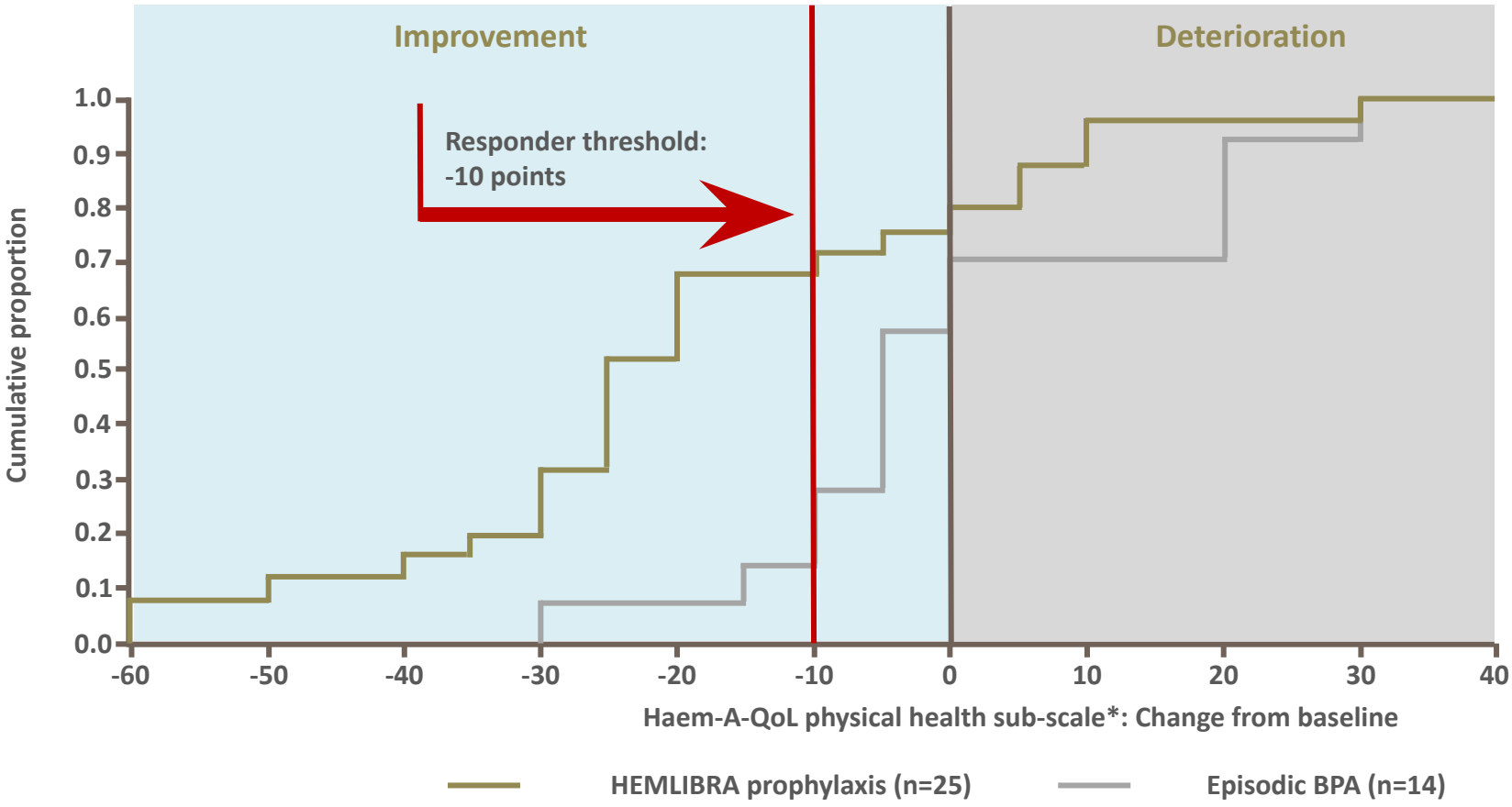


N=	29	27	27	28	28	28	26
N=	16	16	14	15	15	14	14
N=	21	19	15	12	10	9	8

Oldenburg J, et al. Haemophilia. 2019;25:33-44.

BPA=bypassing agent; CI=confidence interval
*Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better health-related quality of life

Changes in physical health after 24 weeks with HEMLIBRA prophylaxis (vs. episodic BPA): Haem-A-QoL sub-scale vs. episodic BPA

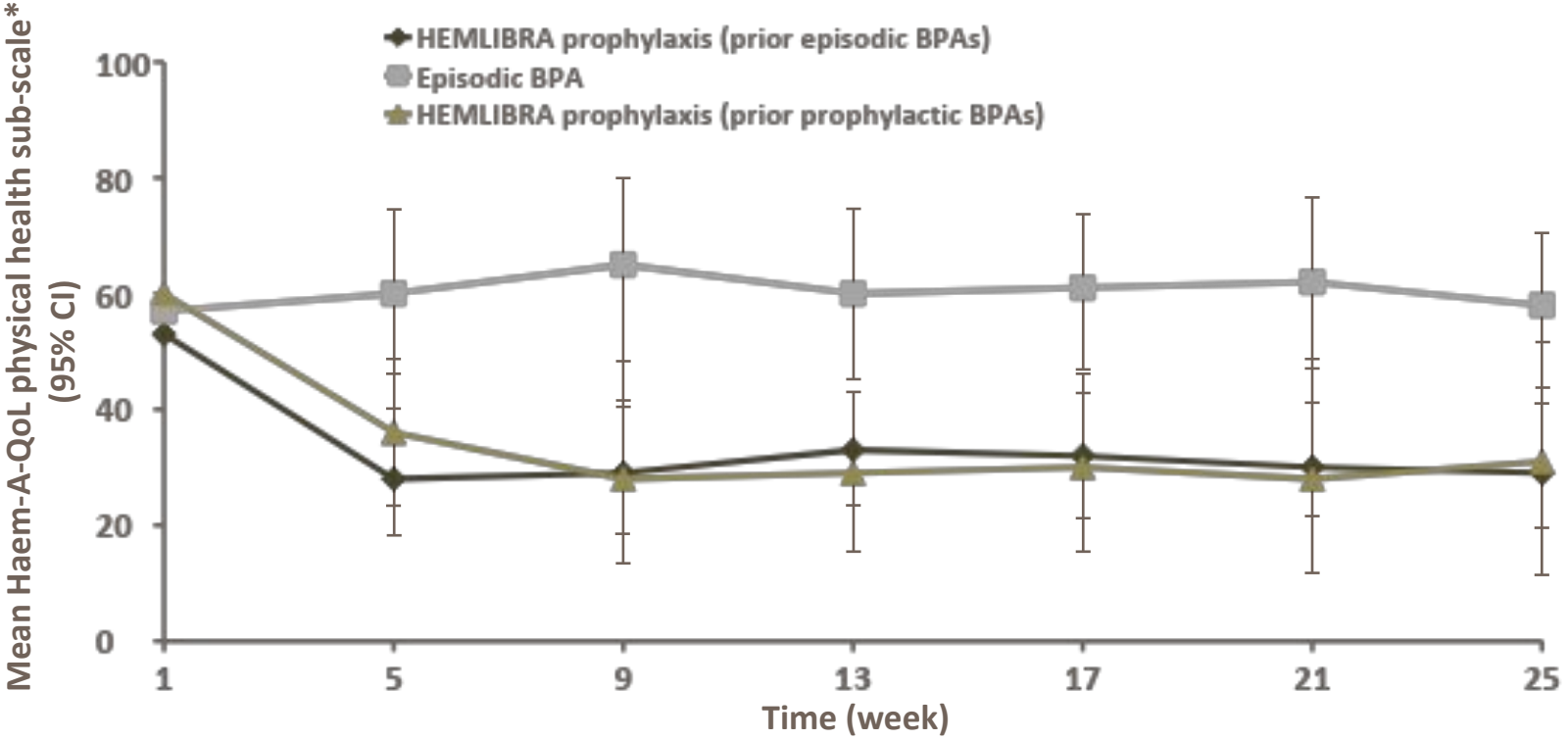


Oldenburg J, et al. Haemophilia. 2019;25:33-44.

BPA=bypassing agent

*Haem-A-QoL sub-scales were normalised to range from 0 to 100; lower scores are reflective of better health-related quality of life

Effect of HEMLIBRA on physical health sub-score of Haem-A-QoL over time



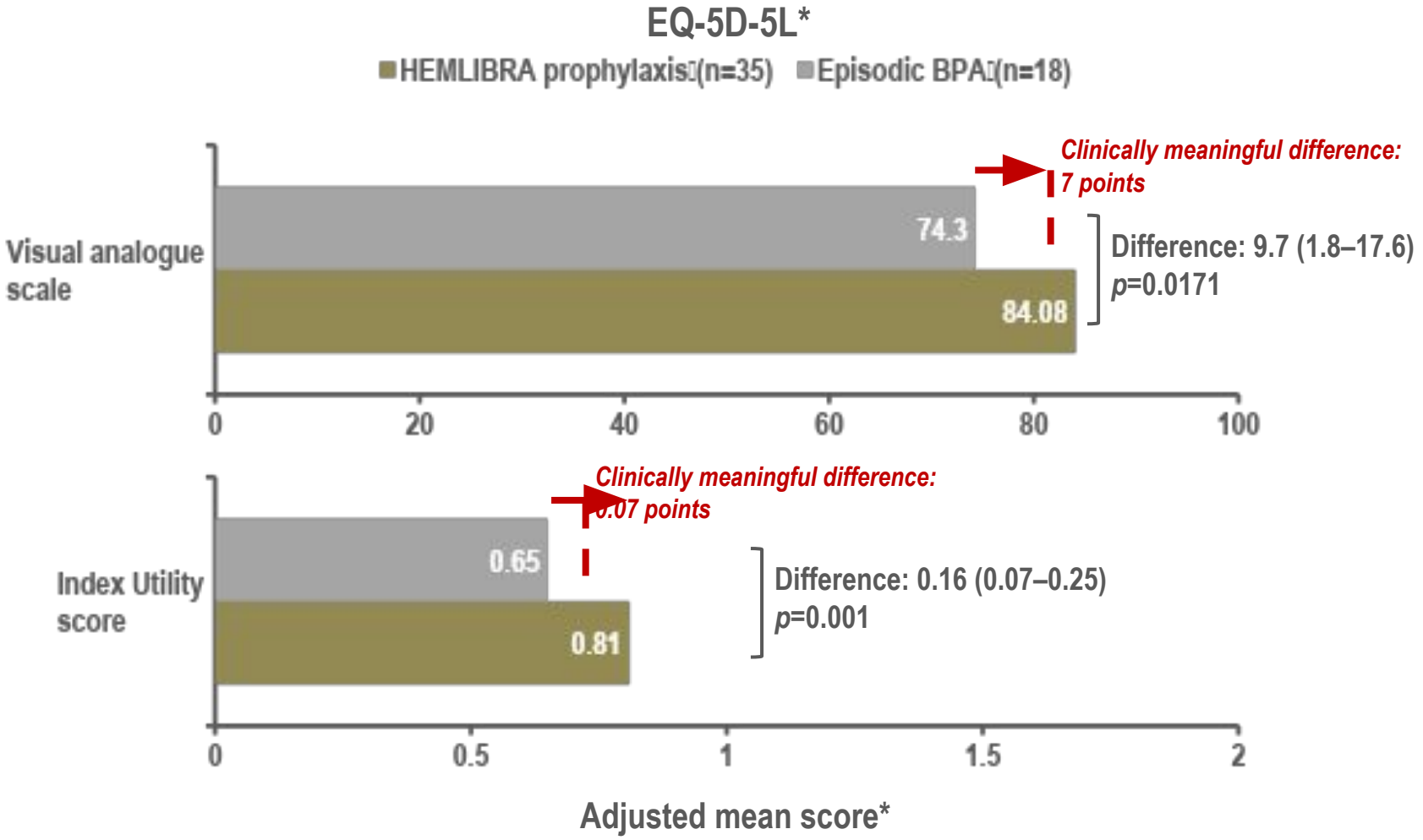
N=	29	27	27	28	28	28	26
N=	16	16	14	15	15	14	14
N=	21	19	15	12	10	9	8

Oldenburg J, et al. Haemophilia. 2019;25:33-44.

BPA=bypassing agent; CI=confidence interval

*Haem-A-QoL sub-scales were normalised to range from 0 to 100; lower scores are reflective of better health-related quality of life

Statistically significant, clinically meaningful differences in health-related quality of life after 24 weeks with HEMLIBRA prophylaxis (vs. episodic BPA)



Oldenburg J, et al. N Engl J Med. 2017;377:809-18.
HEMLIBRA Summary of Product Characteristics.

BPA=bypassing agent; CI=confidence interval
*Higher scores indicate better quality of life.

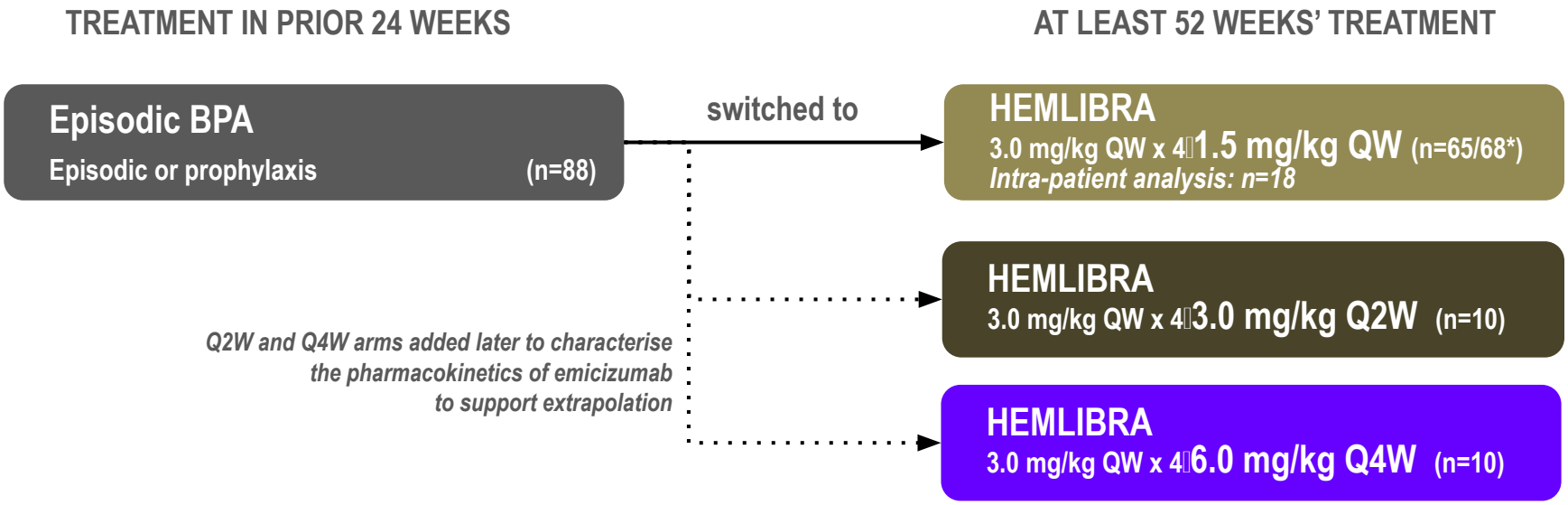
HAVEN 2

Prophylaxis with HEMLIBRA (emicizumab) in children who have haemophilia A with factor VIII inhibitors

Young G, et al. ASH. 2018:632 [oral presentation].

HAVEN 2: trial design

- A single-arm, multicentre, open-label, phase III trial
- Paediatric patients aged <12 years (or 12–17 years and weighing <40kg) with haemophilia A with inhibitors
  - Note, efficacy analysis undertaken only in children aged <12 years (n=65)



Young G, et al. ASH. 2018:632 [oral presentation].

BPA=bypassing agent; PK=pharmacokinetics' QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks
*68 patients included in safety analysis, 65 in the efficacy analysis.

HAVEN 2: endpoints

Primary endpoint:*

- Treated bleeds over time (up to 52 weeks)

Secondary endpoints:*

- Treated joint bleeds
- Treated target joint bleeds
- Treated spontaneous bleeds
- All bleeds**
- Pharmacokinetics
- Safety
- Health-related quality of life
- Intra-patient analysis (reduction vs. baseline) in:
  - Treated bleeds
  - Treated joint bleeds
  - Treated target joint bleeds
  - Treated spontaneous bleeds
  - All bleeds**

CinicalTrials.gov (NCT02795767). Accessed 2/5/2019

ABR=annualised bleed rate; BPA=bypassing agent
*In this single-arm study, there is no formal hypothesis testing as there is no comparator treatment.
**All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not.

HEMLIBRA once-weekly provided effective bleed control across all bleed endpoints

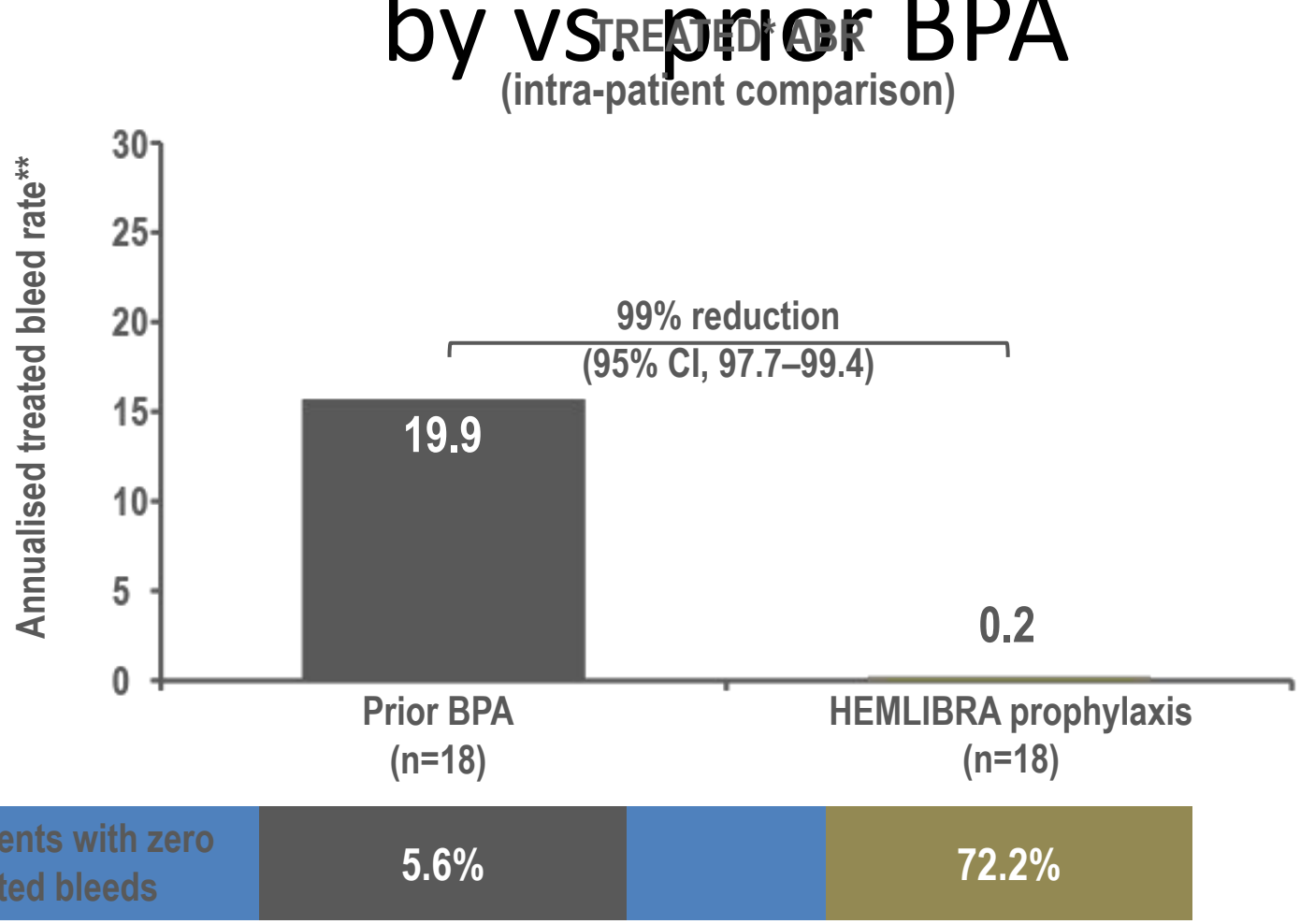
- 76.9% (50/65*) patients reported zero treated bleeds** (95%CI, 64.8–86.5)
  - Median efficacy period: 58 (17.9–92.6) weeks

	HEMLIBRA QW prophylaxis (n=65*)	
	Mean ABR† (95% CI)	Median ABR (95% CI)
Treated bleeds**	0.3 (0.17–0.50)	0.0 (0.00–0.00)
Treated joint bleeds**	0.2 (0.08–0.29)	0.0 (0.00–0.00)
Treated target joint bleeds**	Not estimable	0.0 (0.00–0.00)
Treated spontaneous bleeds**	0.0 (0.01–0.10)	0.0 (0.00–0.00)
All bleeds††	3.2 (1.94–5.22)	0.6 (0.00–2.92)

ABR=annualised bleed rate; CI=confidence intervals;
*Excludes 3 patients aged >12 years. **Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. †ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. ††All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not.

Young G, et al. ASH. 2018:632 [oral presentation].

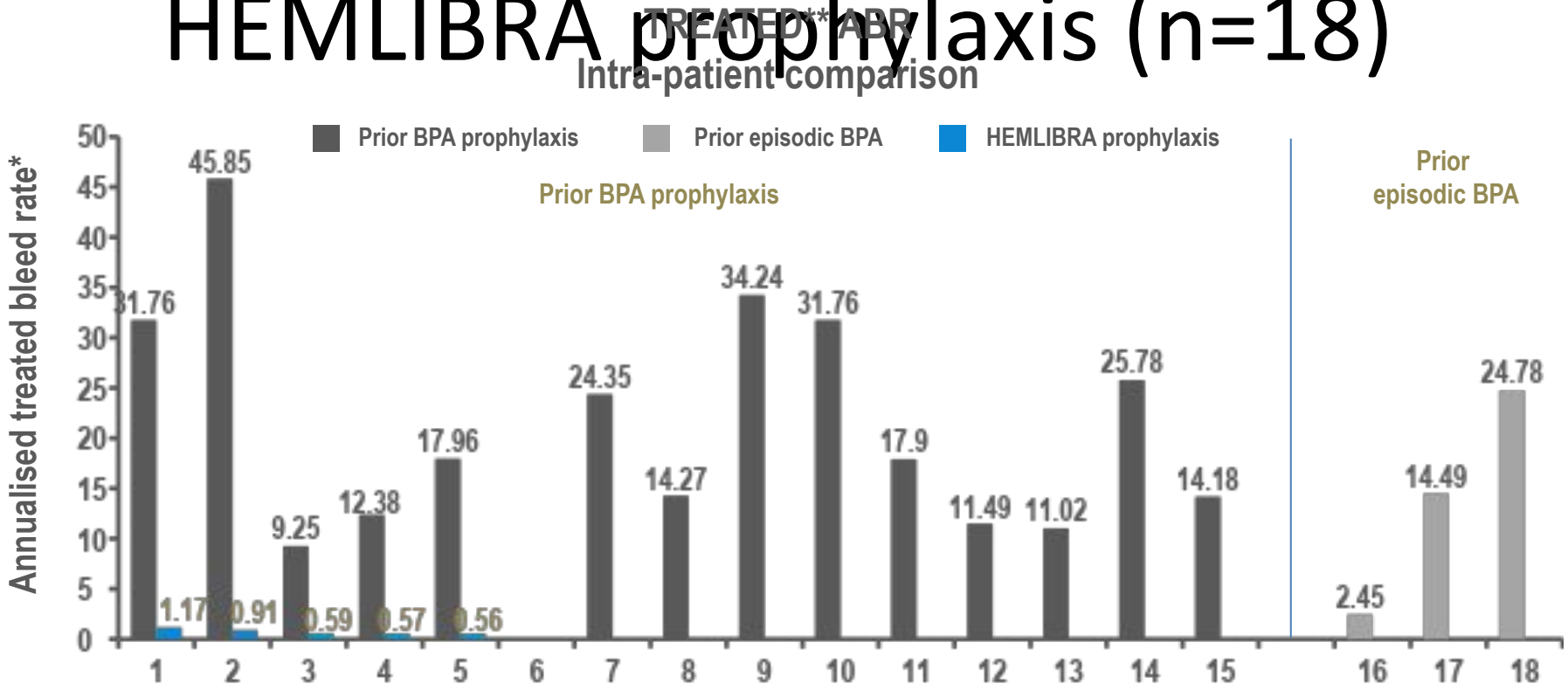
HEMLIBRA prophylaxis reduced treated bleeds by vs. prior BPA



ABR=annualised bleed rate; BPA=bypassing agent; 95% CI=95% confidence interval
*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times.

Young G, et al. ASH. 2018:632 [oral presentation].

Intra-patient comparison comparing prior BPA with HEMLIBRA prophylaxis (n=18)



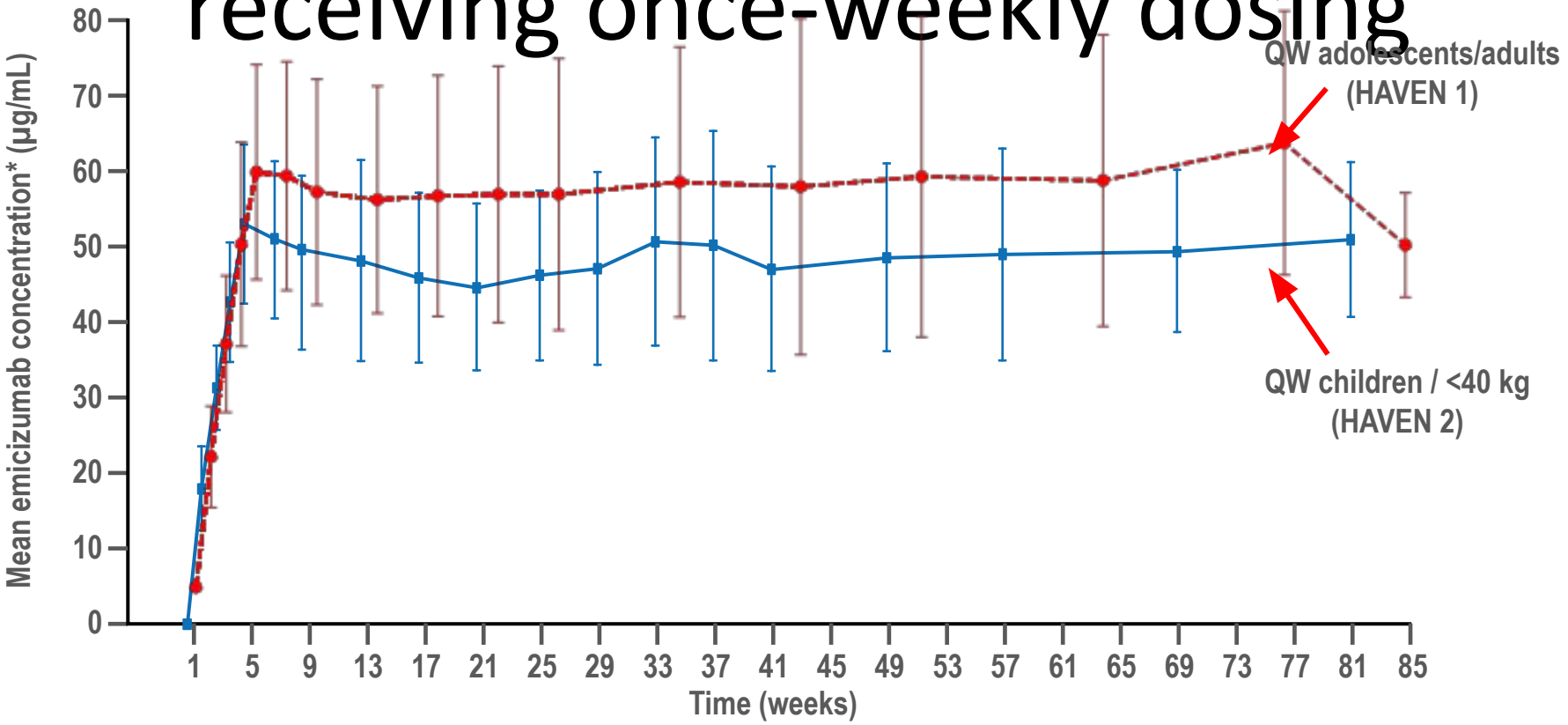
Duration of efficacy period (days)	115	239	79	118	122	61	120	128	128	138	102	159	232	255	309	149	252	280
	624	403	616	638	648	648	635	634	634	634	616	599	463	405	392	648	433	391
Number of treated bleeds	10	30	2	4	6	0	8	5	12	12	5	5	7	18	12	1	10	19
	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

ABR=annualised bleed rate; BPA=bypassing agent

*ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times; **Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed.

Young G, et al. ASH. 2018:632 [oral presentation].

Pharmacokinetics of HEMLIBRA were stable in adults and children receiving once-weekly dosing



Adapted from; Young G, et al. ASH. 2018:632 [oral presentation].

QW=every week

In children with factor VIII inhibitors, HEMLIBRA Q2W and Q4W provided effective bleed control

	HEMLIBRA Q2W (n=10)	HEMLIBRA Q4W (n=10)
Treated bleeds*: Mean ABR† (95% CI)	0.2 (0.03–1.72)	2.2 (0.69–6.81)
Treated bleeds*: Median ABR (95% CI)	0.0 (0.00–0.00)	0.0 (0.00–3.26)
Patients with zero treated bleeds* (%, 95%CI)	90.0% (55.5–99.7)	60.0% (26.2–87.8)
Duration of efficacy assessment (median)	21.3 (18.6–24.1) weeks	19.9 (8.9–24.1) weeks

ABR=annualised bleed rate; CI=confidence intervals;
*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. †ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times.

Young G, et al. ASH. 2018:632 [oral presentation].

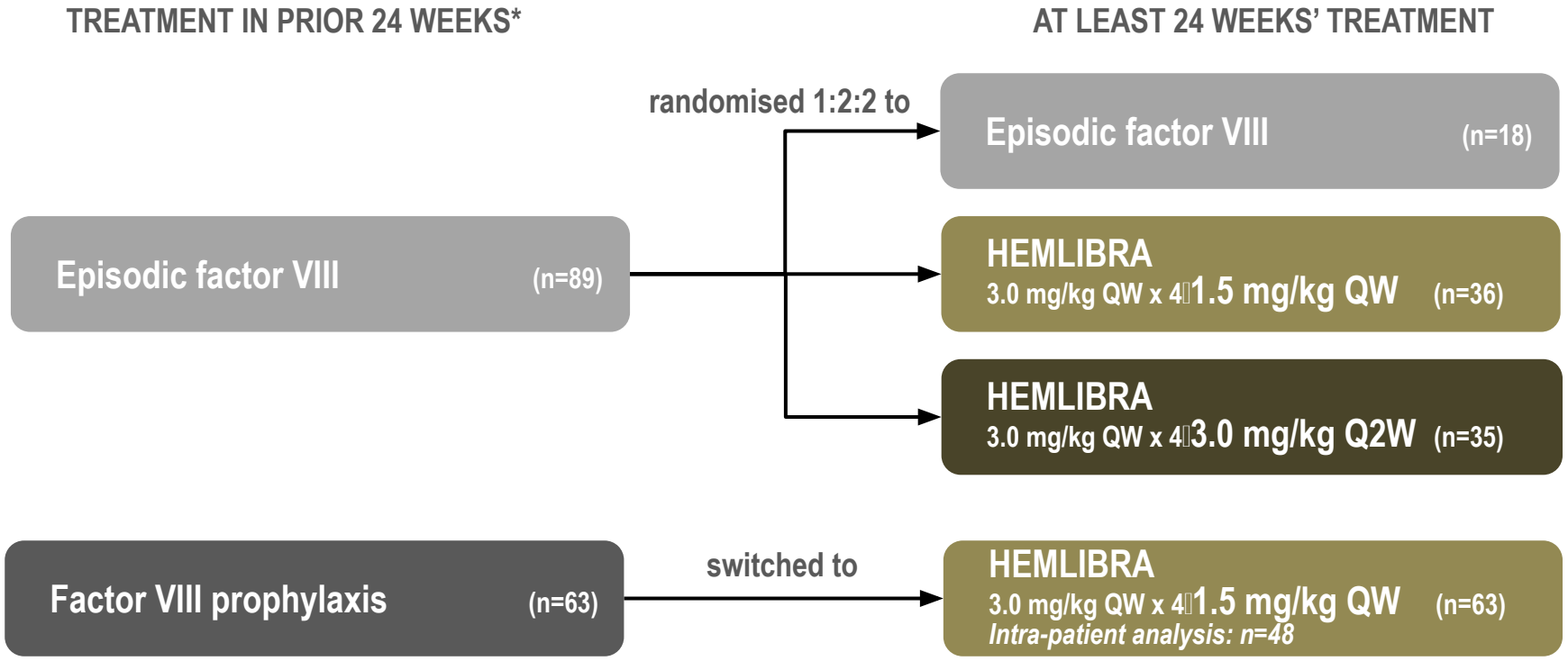
HAVEN 3

Prophylaxis with HEMLIBRA (emicizumab) in patients who have severe haemophilia A without factor VIII inhibitors

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.

HAVEN 3: trial design

- A multicentre, open-label, randomised, phase III clinical study
- Adults and adolescents (≥12 years-old and body weight ≥40 kg) with severe haemophilia A without current factor VIII inhibitors



Mahlangu J, et al. N Engl J Med. 2018;379:811-22.
Mahlangu J, et al. N Engl J Med. 2018;379:811-22 (supplementary appendix).

QW=every week; Q2W=every 2 weeks
*Stratified by prior 24 week bleed rate (<9 or ≥9 bleeds).

HAVEN 3: additional entry criteria

- Age 12 years or older, weight ≥40 kg
- Severe haemophilia A (FVIII <1%) without current inhibitors (<0.6 Bethesda units/mL)
- Documentation of ≥24 weeks' treatment with:
  - Episodic factor VIII therapy and ≥5 bleeding events in prior 24 weeks
  - Prophylactic factor VIII (no bleed requirements)

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.
Mahlangu J, et al. N Engl J Med. 2018;379:811-22 (supplementary appendix).

HAVEN 3: endpoints

Primary endpoint:

- Annualised rate of treated bleeds* (treated ABR) over ≥24 weeks with HEMLIBRA QW or Q2W vs. episodic FVIII

Secondary endpoints:

- All bleeds (treated and untreated)
- Treated spontaneous bleeds
- Treated joint bleeds
- Treated target joint bleeds
- Intra-patient analysis
- Safety
- Pharmacokinetics
- Health-related quality of life

Exploratory endpoints:

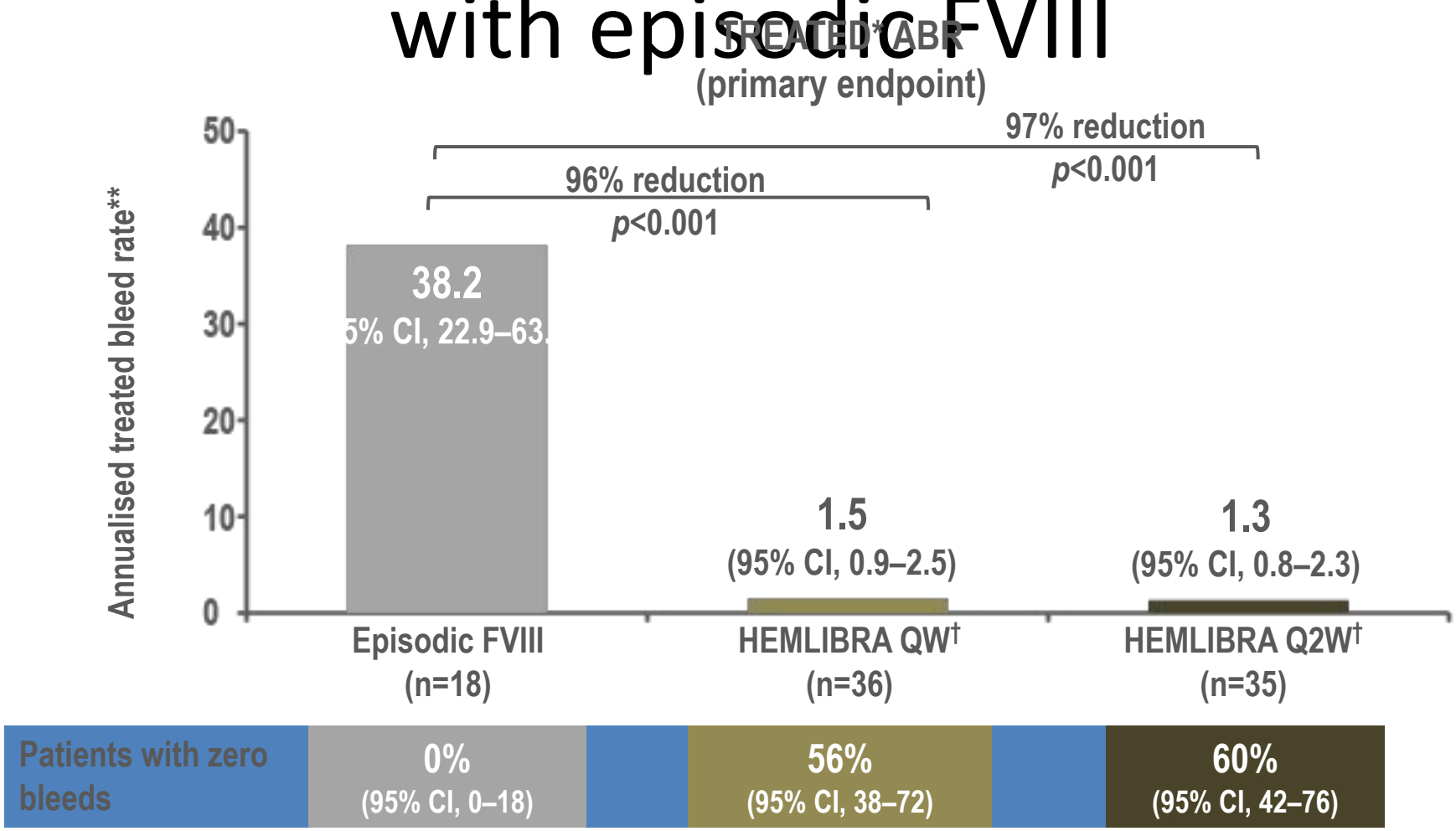
- EmiPref (exploratory endpoint)

1. *Mahlangu J, et al. N Engl J Med. 2018;379:811-22.*
2. *Oldenburg J, et al. N Engl J Med. 2017;377:809-18 (supplementary appendix).*

ABR=annualised bleed rate; FVIII=factor VIII therapy; QW=every week; Q2W=every 2 weeks

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed

HEMLIBRA prophylaxis significantly reduced treated bleeds compared with episodic FVIII

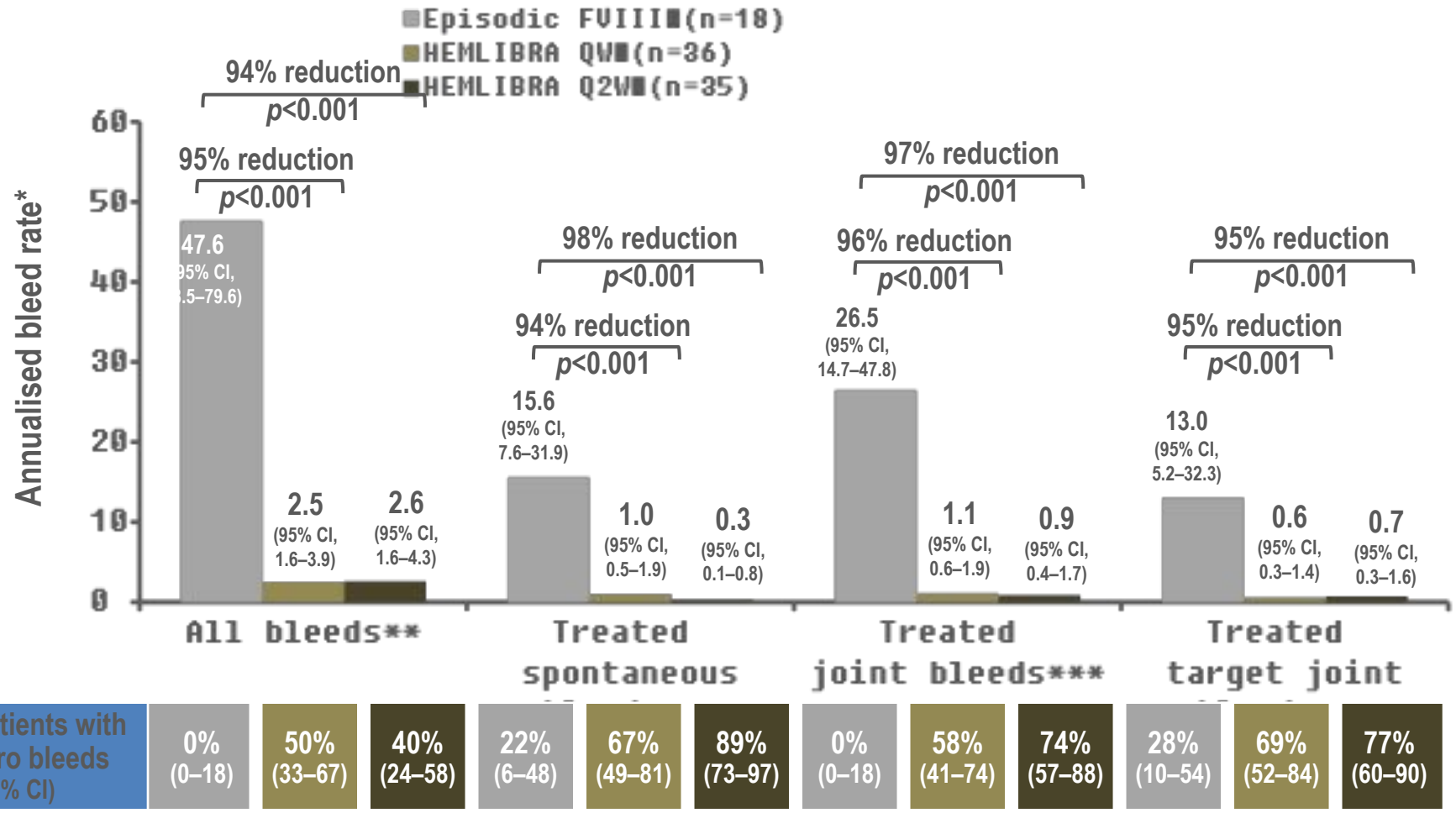


ABR=annualised bleed rate; CI=confidence interval; FVIII=factor VIII therapy; QW=every week; Q2W=every 2 weeks

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. †Patients received 4 loading doses of 3.0 mg/kg QW

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.

Significant reduction in all other measures of bleeding episodes with HEMLIBRA vs. episodic factor VIII therapy

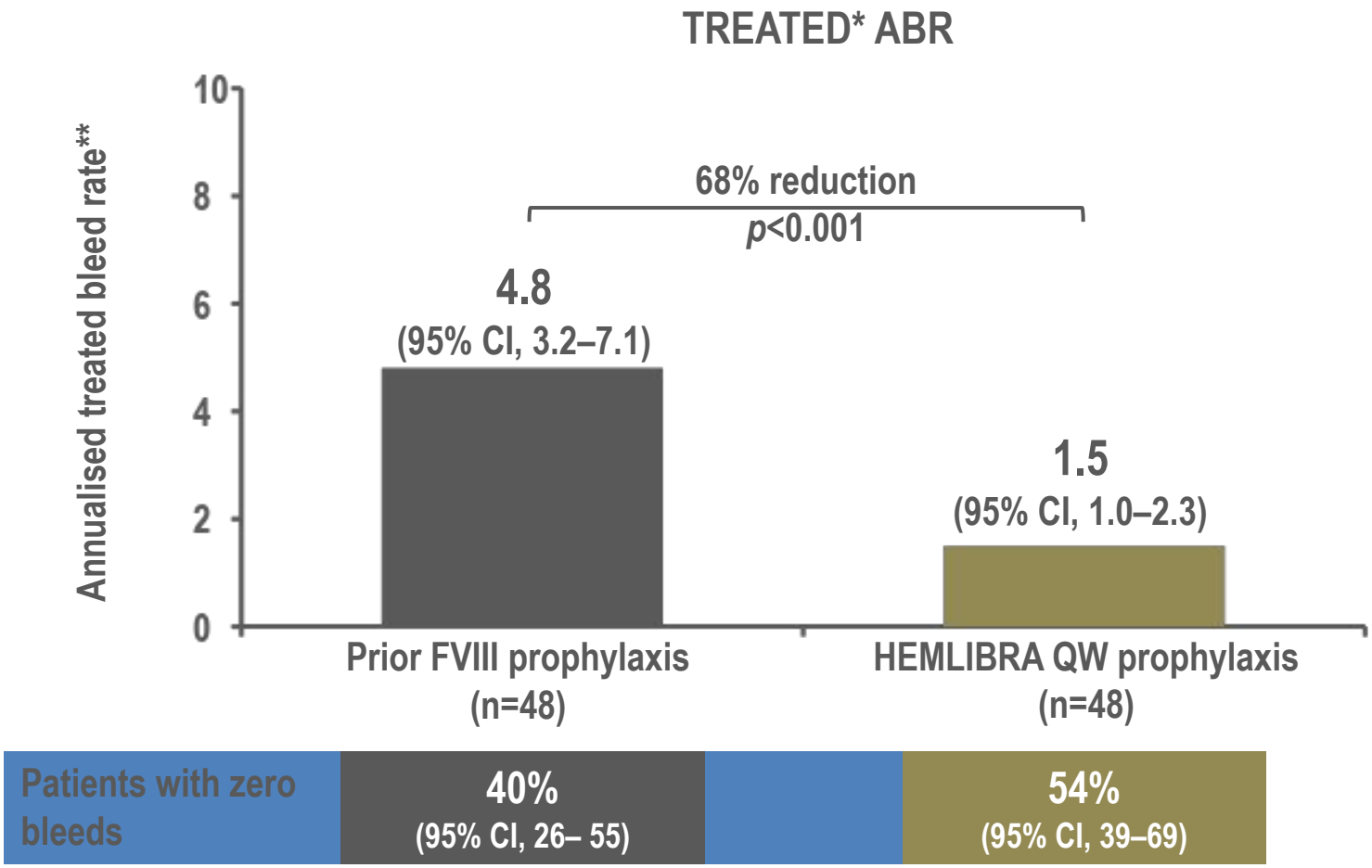


ABR=annualised bleed rate; CI=confidence interval; FVIII=factor VIII therapy; QW=every week; Q2W=every 2 weeks

*ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. **All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not. ***Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed.

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.

HEMLIBRA reduced treated bleeds compared with prior FVIII prophylaxis



ABR=annualised bleed rate; CI=confidence interval; FVIII=factor VIII therapy

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. . †Patients received 4 loading doses of 3.0 mg/kg QW

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.

The effects of HEMLIBRA on health-related quality of life (Haem-A-QoL) in HAVEN 3

- Observed differences in the physical health subscore at Week 25 (vs. episodic FVIII)
  - HEMLIBRA QW: 12.5 points (95% CI, -2.0 to 27.0), p=0.09
  - HEMLIBRA Q2W: 16.0 points (95% CI, 1.2 to 30.8)
- In the hierarchical testing framework HEMLIBRA QW vs. episodic FVIII was ranked first; due to this hierarchy, all other endpoints were considered non-significant

Mahlangu J, et al. N Engl J Med. 2018;379:811-22.

CI=confidence interval; FVIII=factor VIII therapy; QW=every week; Q2W=every 2 weeks
Haem-A-QoL scales range from 0 to 100; lower scores are reflective of better health-related quality of life.

HAVEN 3: EmiPref survey (exploratory endpoint)

- The EmiPref survey was an exploratory endpoint to evaluate patient preference for therapy[1,2]
- Patients were asked to indicated their preference:[2]
  - New treatment
  - Previous treatment
  - No preference
- In addition, the reasons for their choice were selected from a drop-down list[2]
- In HAVEN 3, 95/134 patients completed the EmiPref survey at 17 weeks[1]
- Of these, 94% (89/95) preferred HEMLIBRA vs. prior factor VIII[1]
  - Including 98% (45/46) who preferred HEMLIBRA to their prior factor VIII prophylaxis
- The most frequent reasons selected were:[1]

"Lower frequency of treatment"

"Route of administration easier"

"Worries about bleeds was less"

1. Mahlangu J, et al. N Engl J Med. 2018;379:811-22.
2. Jimenez-Yuste V, et al. ASH, 2018:11878 [poster].

CI=confidence interval; FVIII=factor VIII therapy; QW=every week; Q2W=every 2 weeks

Use of factor VIII therapy in HAVEN 3

- Most breakthrough bleeds (138/215) were treated with FVIII <50 IU/kg/day for <24 hours

	FVIII <50 IU/kg/day	FVIII ≥50 IU/kg/day
<24 hours treatment	138 (64%)	35 (16%)
24 to <48 hours treatment	22 (10%)	4 (2%)
≥48 hours treatment	12 (6%)	4 (2%)

Mahlangu J, et al. N Engl J Med. 2018;379:811-22 (supplementary appendix).

FVIII=factor VIII therapy

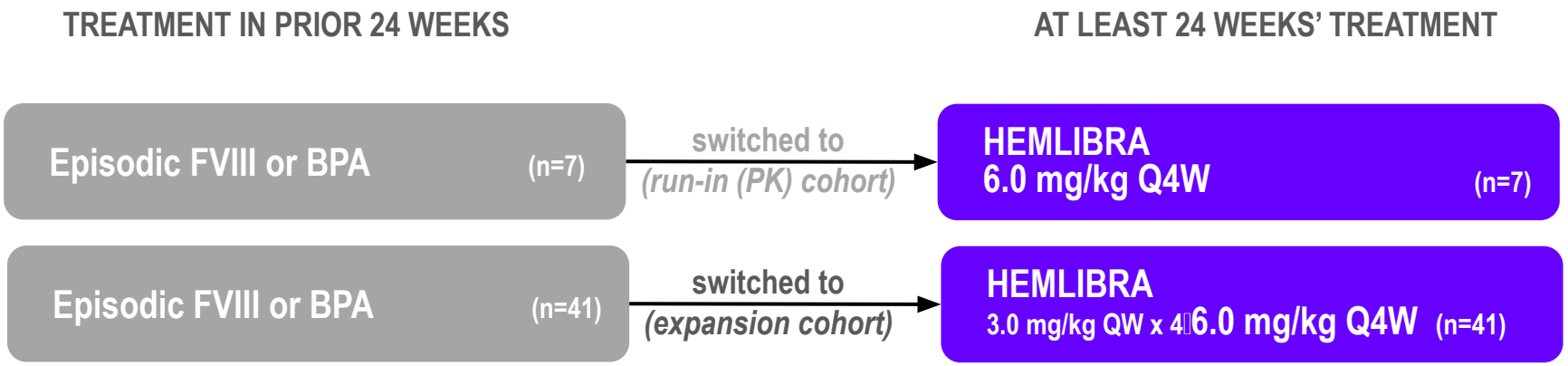
HAVEN 4

Prophylaxis with HEMLIBRA (emicizumab) given every 4 weeks in patients who have haemophilia A with or without factor VIII inhibitors

Pipe S, et al. The Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].

HAVEN 4: trial design

- A multicentre, open-label, two-stage clinical study
- Run-in cohort (n=7) to determine pharmacokinetics of HEMLIBRA 6.0 mg/kg Q4W
- The expansion cohort enrolled 41 patients to evaluate efficacy, safety and pharmacokinetics
  - Efficacy results based on the expansion cohort (n=41)



Pipe S, et al. Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].

PK=pharmacokinetics; QW=every week; Q4W=every 4 weeks

HAVEN 4: entry criteria

- Adults or adolescents (≥12 years-old)
- Severe haemophilia A (<1% FVIII activity) OR haemophilia A with factor VIII inhibitors
- Documentation of ≥24 weeks' treatment (bypassing agents or factor VIII therapy):
  - Episodic therapy and ≥5 bleeding events in prior 24 weeks
  - Prophylaxis (no bleed requirements)

Pipe S, et al. Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].

HAVEN 4: study population

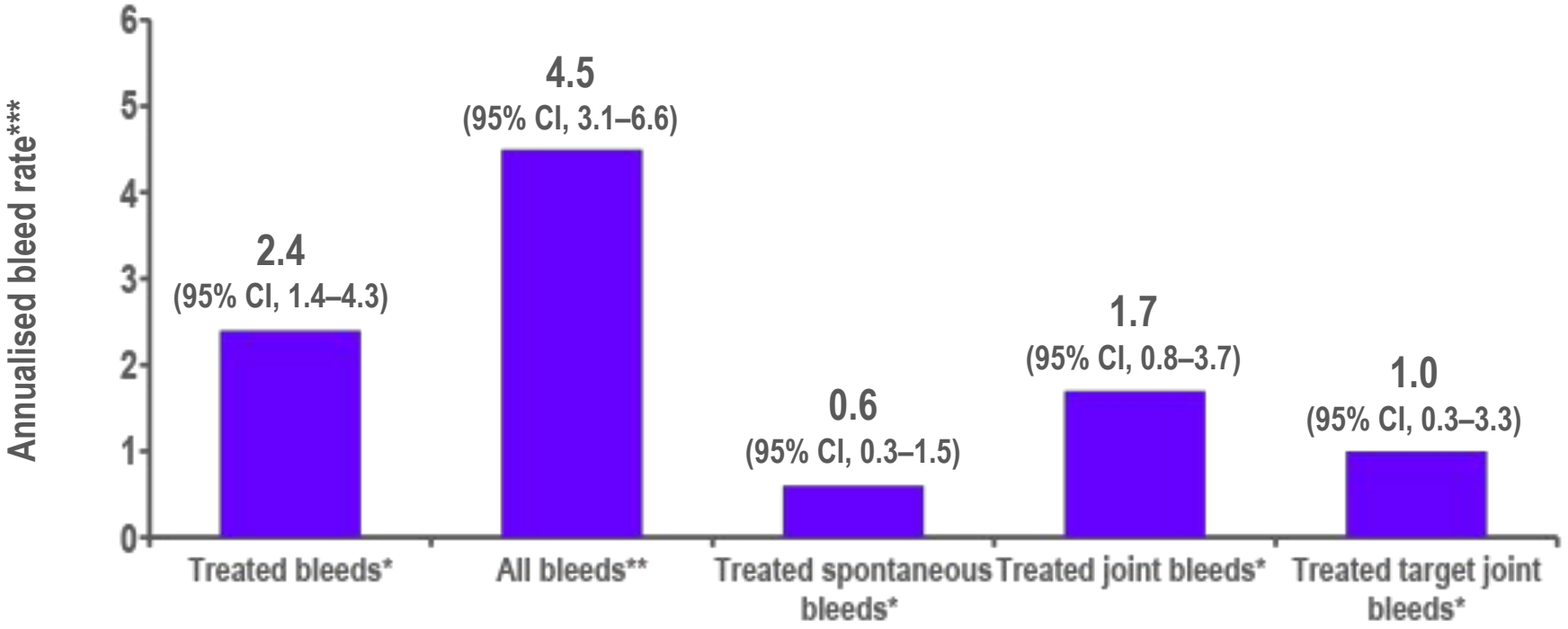
- Run-in cohort (n=7)
  - Severe haemophilia: 7/7 (100%)
  - Previous episodic treatment: 7/7 (100%)
  - Current FVIII inhibitors: 3/7 (43%)
- Expansion cohort (n=41)
  - Severe haemophilia: 40/41 (98%)
  - Previous episodic treatment: 11/41(27%)
  - Current FVIII inhibitors: 5/41 (12%)

Pipe S, et al. Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].

FVIII=factor VIII

HEMLIBRA maintenance every 4 weeks demonstrated efficacy across multiple bleed-related endpoints

- Expansion cohort (n=41) includes 5 patients with factor VIII inhibitors at study entry

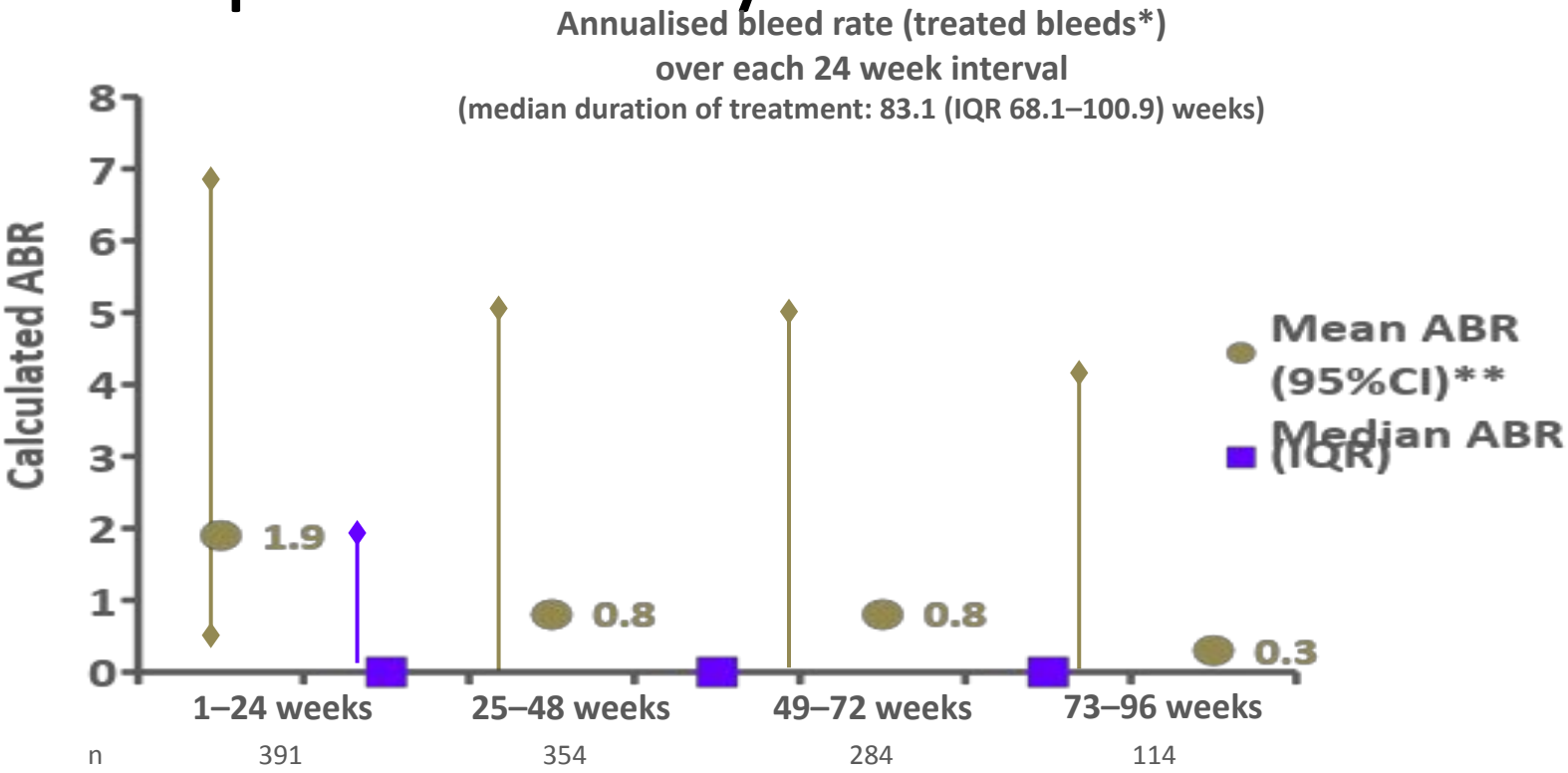


Pipe S, et al. Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].

ABR=annualised bleed rate; CI=confidence interval
*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times. ***All bleeds defined as any bleeding event, reported as such by the patient (including bruising, pain), whether treated with bypassing agents or not.

Long-term efficacy of emicizumab: pooled data from HAVEN 1 to 4

Efficacy of emicizumab for up to 96 weeks: pooled analysis of HAVEN 1–4

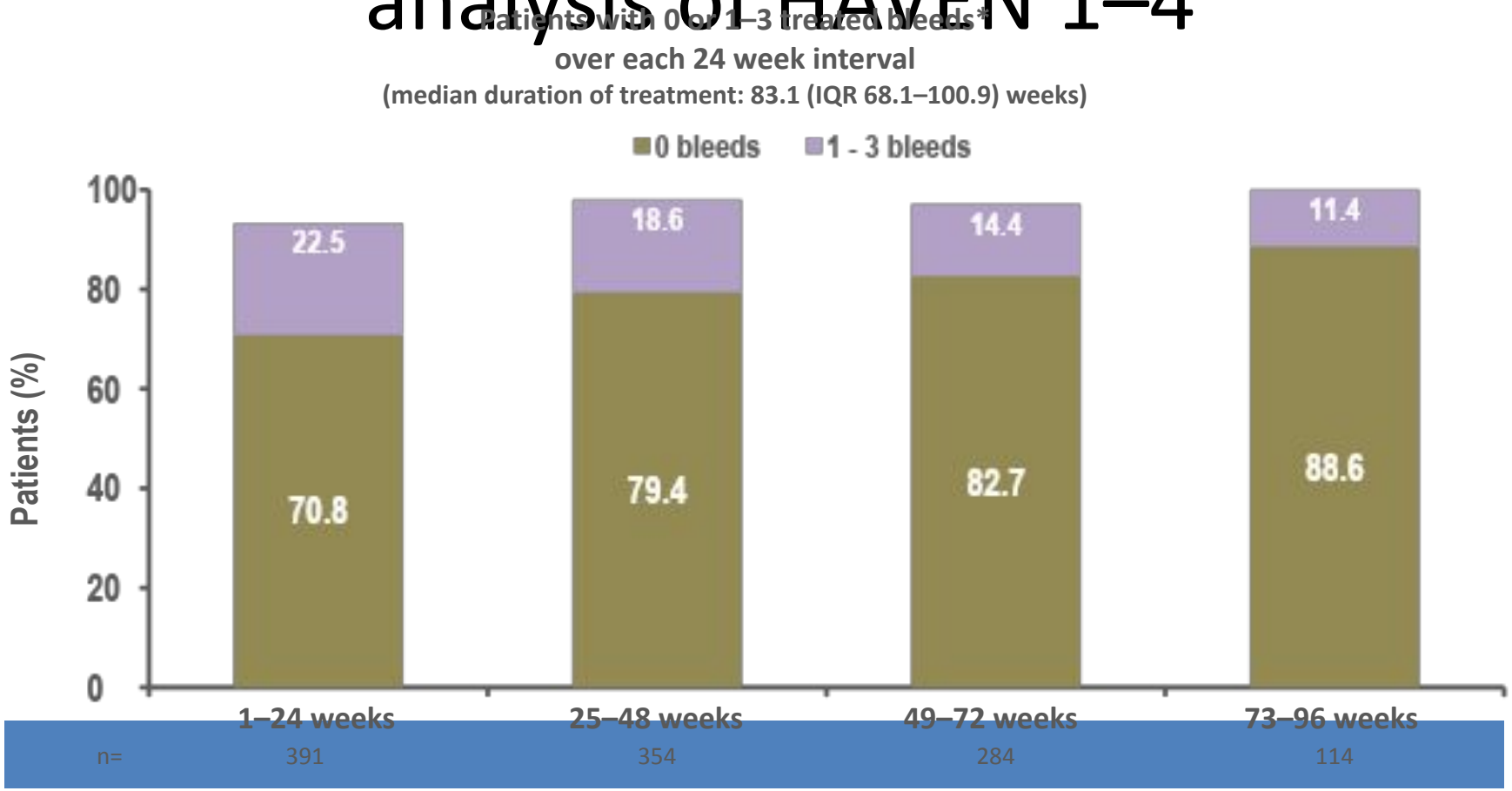


95%CI=95% confidence interval; ABR=annualised bleed rate; IQR=interquartile range

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times

Callaghan M, et al. ISTH. 2019: OC60.2..

Proportion of patients with zero treated bleeds over time: pooled analysis of HAVEN 1–4

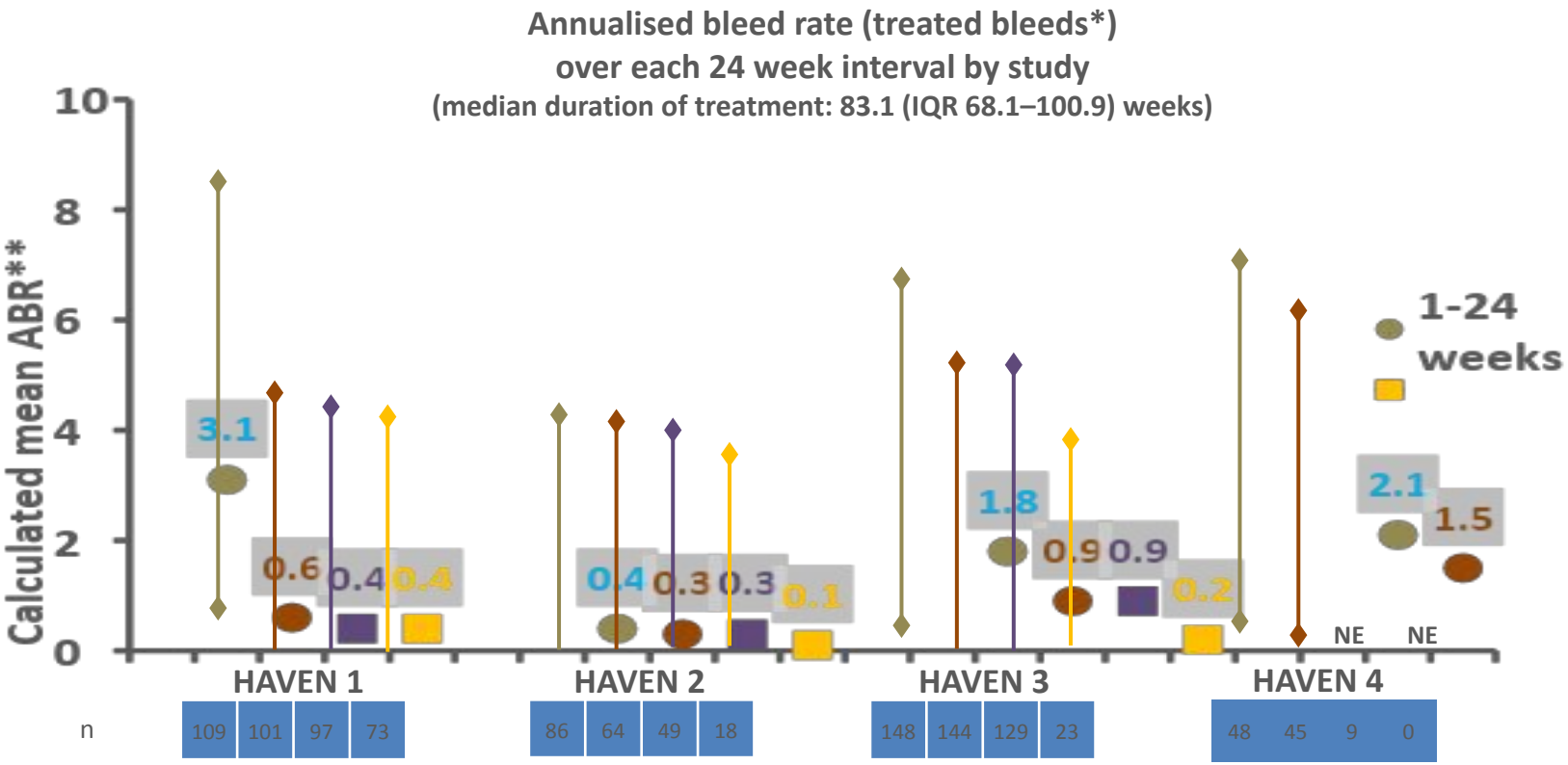


IQR=interquartile range

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed.

Callaghan M, et al. ISTH. 2019: OC60.2..

Efficacy of emicizumab for up to 96 weeks was consistent between studies

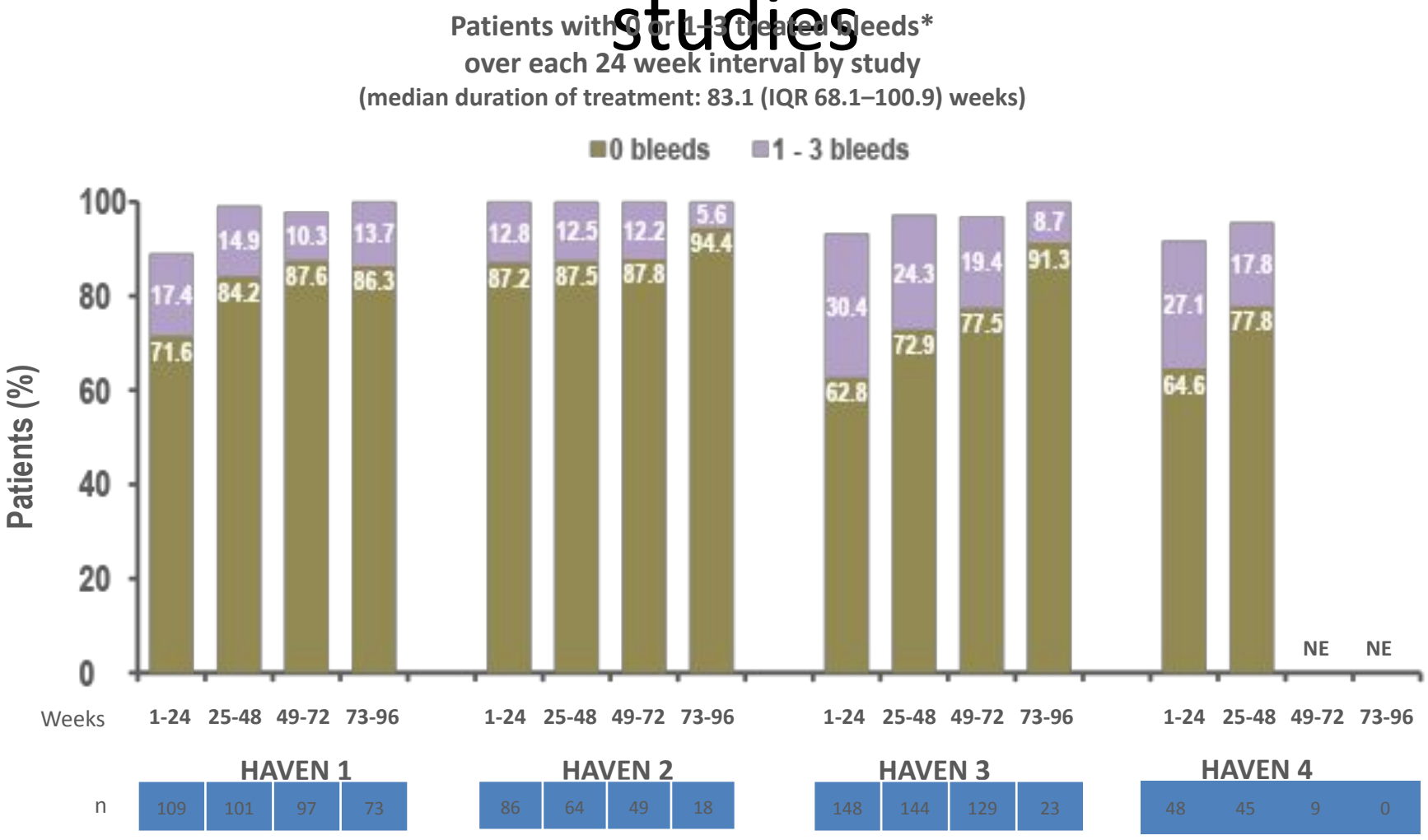


95%CI=95% confidence interval; ABR=annualised bleed rate;IQR=interquartile range; NE=not estimable

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times

Callaghan M, et al. ISTH. 2019: OC60.2..

Proportion of patients with zero treated bleeds was consistent between studies

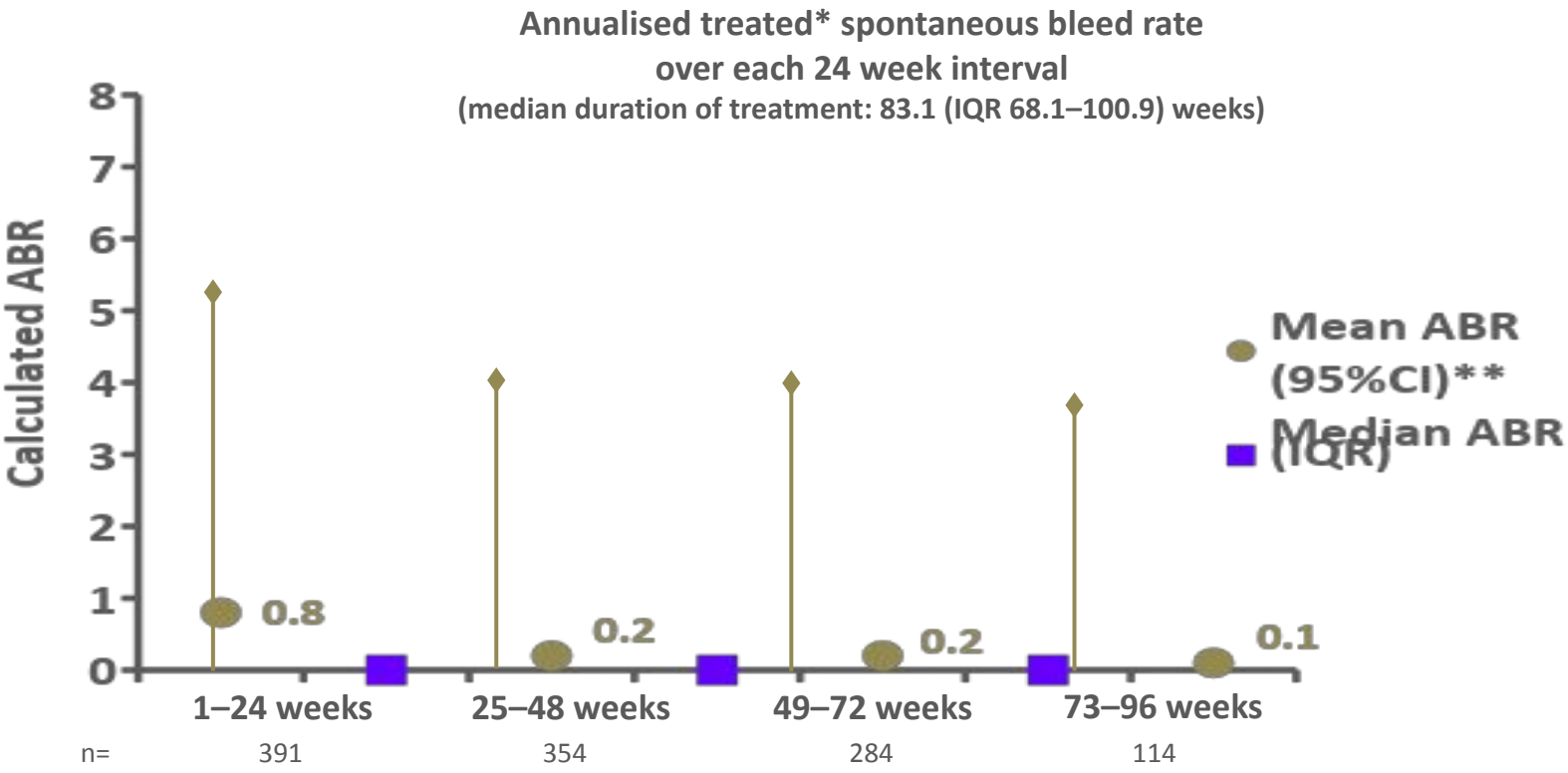


IQR=interquartile range; NE=notestimable

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed.

Callaghan M, et al. ISTH. 2019: OC60.2..

Low spontaneous bleed rates with up to 96 weeks of HEMLIBRA prophylaxis: pooled analysis of HAVEN 1–4



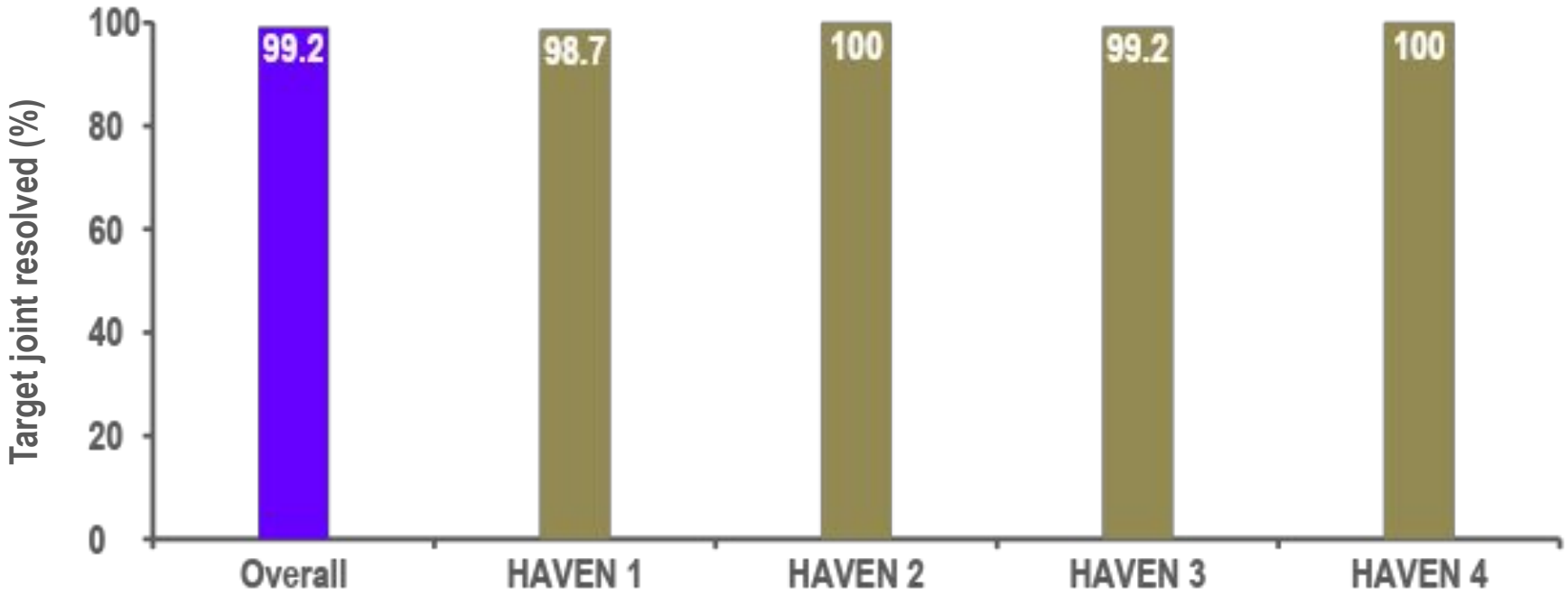
95%CI=95% confidence interval; ABR=annualised bleed rate; IQR=interquartile range

*Treated bleeds defined as a bleed that was directly followed by a haemophilia medication reported to be a "treatment for bleed", regardless of the time between the treatment and the preceding bleed. **ABR based on Negative Binomial Regression Model (NBRM) which takes into account number of bleeds and different treatment and follow-up times

Callaghan M, et al. ISTH. 2019: OC60.2..

Resolution of target joints with emicizumab prophylaxis for up to 96 weeks

Proportion of resolved target joints
(median duration of treatment: 83.1 (IQR 68.1–100.9) weeks)



	Overall	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4
Patients with target joints at baseline, n=	217	68	23	97	29
Target joints at baseline, n=	519	159	45	238	77

Callaghan M, et al. ISTH. 2019: OC60.2..

IQR=interquartile range

Integrated safety analysis

Integrated safety analysis

- Data on adverse drug reactions (ADRs) are based on pooled data from the four HAVEN trials and a total of 373 male patients
  - 266 adults
  - 47 adolescents
  - 55 children (aged 2–12 years)
  - 5 infants (aged 1 month to 2 years)
- In total 3 patients (0.8%) withdrew from treatment due to ADRs, which were TMA, superficial thrombophlebitis and headache

HEMLIBRA Summary of Product Characteristics.

TMA=Thrombotic microangiopathy

Integrated safety analysis

- The most common ADRs were:
  - Injection site reactions (20%); mostly mild to moderate in intensity
  - Arthralgia (15%)
  - Headache (14%)
- The most serious ADRs reported were:
  - Thrombotic events:
    - Cavernous sinus thrombosis (1 patient)
    - Superficial vein thrombosis contemporaneous with skin necrosis (1 patient)
  - TMA in 3 patients (<1%)
- The overall safety profile of HEMLIBRA was consistent between infants, children, adolescents, and adults

Please refer to the HEMLIBRA Summary of Product Characteristics for the full list of adverse events

HEMLIBRA Summary of Product Characteristics.

ADR=adverse drug reaction; aPCC=activated prothrombin complex concentrate; TMA=Thrombotic microangiopathy

Integrated safety analysis

Summary of adverse drug reactions from pooled clinical trials with HEMLIBRA (n=373)

System organ class	Adverse reaction	Frequency*
General disorders and administration site conditions	Injection site reaction	Very common
	Pyrexia	Common
Nervous system disorders	Headache	Very common
Gastrointestinal disorders	Diarrhoea	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Common
Skin and subcutaneous tissue disorders	Skin necrosis	Uncommon
Vascular disorders	Thrombophlebitis superficial	Uncommon
	Cavernous sinus thrombosis	Uncommon
Blood and lymphatic system disorders	Thrombotic microangiopathy	Uncommon

*The corresponding frequency categories for each ADR are based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100)

HEMLIBRA Summary of Product Characteristics.

Thrombotic microangiopathy (TMA)

- TMA events reported in <1% of patients (3/373) and in 9.7% of patients (3/31) who received at least one dose of aPCC while being treated with HEMLIBRA[1-3]
  - In all 3 cases patients had received, on average a cumulative aPCC dose of >100 U/kg/24 hours for 24 hours or more
  - One patient with a TMA also suffered a rectal haemorrhage which was fatal[2,3]
    - At the time of death, the TMA was recorded as improving. The Investigator deemed the death to be due to the rectal haemorrhage and was not attributed to HEMLIBRA
  - One patient resumed HEMLIBRA after resolution of TMA without recurrence[1]
- To-date, no cases of TMA have been reported in HAVEN 2, HAVEN 3, or HAVEN 4[1,4-6]

1. *HEMLIBRA Summary of Product Characteristics.*
2. *Oldenburg J, et al. N Engl J Med. 2017;377:809-18.*
3. *Oldenburg J, et al. N Engl J Med. 2017;377:809-18 (supplementary appendix).*
4. *Young G, et al. ASH. 2018:632 [oral presentation].*
5. *Mahlangu J, et al. N Engl J Med. 2018;379:811-22.*
6. *Pipe S, et al. The Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].*

aPCC=activated prothrombin complex concentrate; TMA=thrombotic microangiopathy

Thrombotic events

- Serious thrombotic events were reported in <1% of patients (2/373) and in 6.5% of patients (2/31) who received at least one dose of aPCC while being treated with HEMLIBRA[1-3]
  - In both cases patients had received, on average a cumulative aPCC dose of >100 U/kg/24 hours for 24 hours or more
  - One case of cavernous sinus thrombosis
  - One case of skin necrosis (thrombophlebitis superficial)
  - One patient resumed HEMLIBRA after resolution of thrombotic event without recurrence[1]

- To-date, no cases of thrombotic events have been reported in HAVEN 2, HAVEN 3 or HAVEN 4[1,4-6]

1. *HEMLIBRA Summary of Product Characteristics.*
2. *Oldenburg J, et al. N Engl J Med. 2017;377:809-18.*
3. *Oldenburg J, et al. N Engl J Med. 2017;377:809-18 (supplementary appendix).*
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6. *Pipe S, et al. The Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].*

aPCC=activated prothrombin complex concentrate

Surgical experience in the HAVEN clinical trial programme

- In the HAVEN 1–4 programme 126/399 (31.6%) of patients had one or more surgical procedure*
- Minor surgeries: 215 surgeries in 115 patients
  - 141/215 (66%) were managed without factor prophylaxis and of these, 128 (91%) did not result in treated post-operative bleeds:

	Dental	CVAD	Endoscopic	Joint	Other
Surgeries (n)	64	34	30	25	62
Procedures managed with no coagulation factor prophylaxis (n)	42	25	17	12	45
Treated post-operative bleed	9 (21%)	1 (4%)	0	1 (8%)	2 (4%)

- Major surgeries: 18 in 18 patients
  - 3/18 (17%) procedures were managed without factor prophylaxis: 3/3 (100%) had no post-operative bleeds
  - 15/18 (83%) procedures were manged with factor prophylaxis: 12/15 (80%) had no post-operative bleeds (1 patient had a treated post-operative bleed, 2 had untreated post-operative bleeds)
- There were no thromboembolic events / TMA

Santagostino E, et al. ISTH. 2019 [oral presentation].

*Note patients may be counted twice if an individual underwent minor and major surgery
CVAD=central venous access device; TMA=thrombotic microangiopathy

Considerations for concurrent use of factor VIII with HEMLIBRA

- There is a possibility of hypercoagulability with FVIII with HEMLIBRA based on preclinical experiments[1]
- In HAVEN 3, 64 patients were co-exposed to FVIII in 215 treatment events[2,3]

	Average daily dose of FVIII (IU/kg)				
	<50	50–100	101–150	>150	Any dose
<24 hours	138 (64.2%)	35 (16.3%)	0	0	173 (80.5%)
24–48 hours	22 (10.2%)	3 (1.4%)	1 (0.5%)	0	26 (12.1%)
48–72 hours	3 (1.4%)	2 (0.9%)	0	0	5 (2.3%)
72–96 hours	1 (0.5%)	2 (0.9%)	0	0	3 (1.4%)
>96 hours	8 (3.7%)	0	0	0	8 (3.7%)
Total	172 (80%)	42 (19.5%)	1 (0.5%)	0	215 (100%)

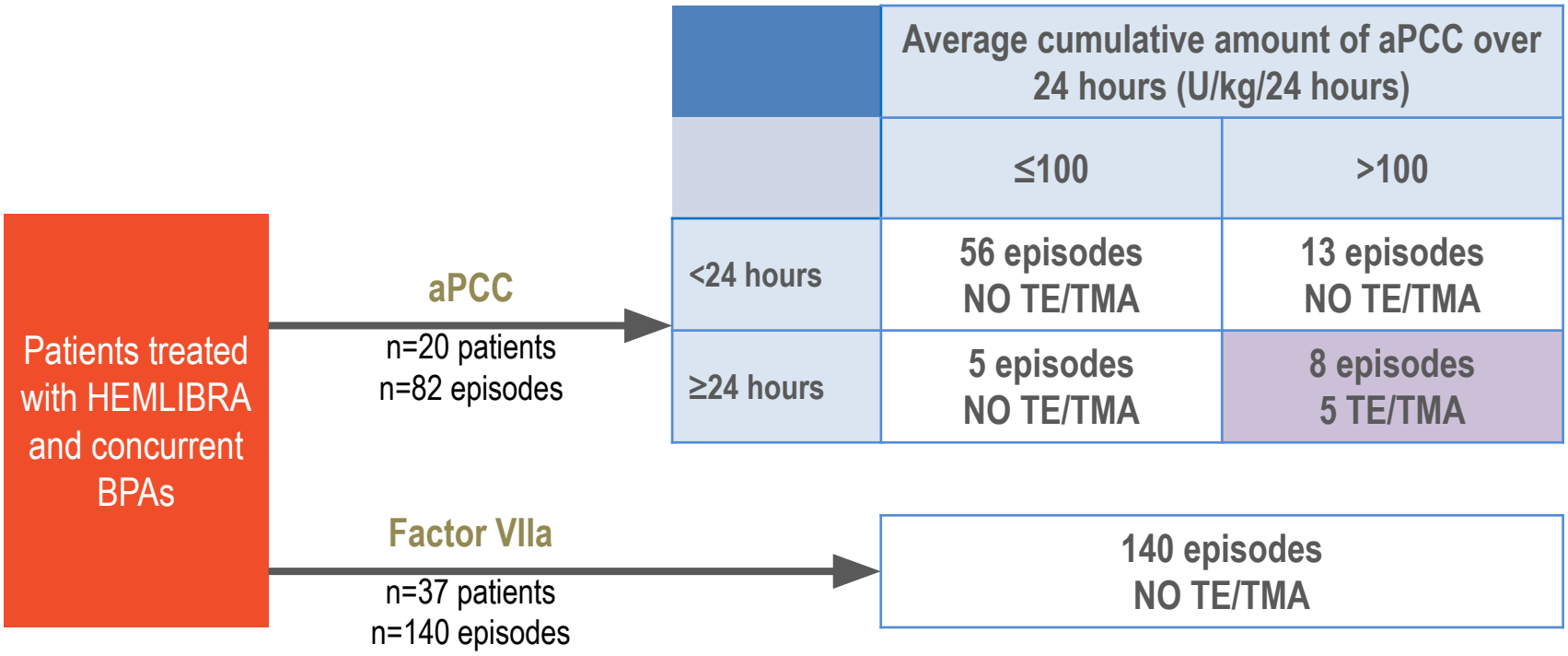
- No serious adverse events were reported; although HAVEN 3 was not specifically designed to evaluate the safety of concurrent FVIII and HEMLIBRA[2]

1. *HEMLIBRA Summary of Product Characteristics.*
2. *Mahlangu J, et al. N Engl J Med. 2018;379:811-22.*
3. *Mahlangu J, et al. N Engl J Med. 2018;379:811-22 (supplementary appendix).*

FVIII=factor VIII therapy

HEMLIBRA and concurrent activated prothrombin complex concentrate

- Instances of TE or TMA were reported in patients who had received multiple infusions of aPCC (total >100 U/kg/24 hours) while receiving HEMLIBRA prophylaxis



	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)	
	≤100	>100
<24 hours	56 episodes NO TE/TMA	13 episodes NO TE/TMA
≥24 hours	5 episodes NO TE/TMA	8 episodes 5 TE/TMA

140 episodes NO TE/TMA

HEMLIBRA Summary of Product Characteristics.

aPCC=activated prothrombin complex concentrate; BPA=bypassing agent; TE=thrombotic event; TMA=thrombotic microangiopathy

Considerations for concomitant use of bypassing agents with HEMLIBRA

Treatment with BPAs should be discontinued the day before initiating HEMLIBRA prophylaxis

- If BPAs are needed during HEMLIBRA prophylaxis:
  - Dose and duration will depend on the patient's clinical condition, the location and extent of bleeding
  - Dose may be lower than those used with BPAs alone
  - BPA dosing guidance should be followed for >6 months following discontinuation of HEMLIBRA prophylaxis
- Concomitant recombinant activated factor VII (rFVIIa):
  - No cases of TMA or thrombotic events were observed in clinical trials with rFVIIa alone, in patients receiving HEMLIBRA prophylaxis

HEMLIBRA Summary of Product Characteristics.

aPCC=activated prothrombin complex concentrate; BPA=bypassing agent; TMA=thrombotic microangiopathy

Considerations for concomitant use of aPCC with HEMLIBRA

Use of aPCC should be avoided, unless no other treatment options/alternatives are available

- If aPCC is indicated:
  - Initial dose should not exceed 50 U/kg; additional doses under medical supervision with laboratory monitoring recommended
  - Total dose should not exceed 100 U/kg in the first 24 hours of treatment; weigh risk of TMA and thrombotic events when considering >100 U/kg in the first 24 hours

Monitor patients for thrombotic events and TMA when administering concomitant aPCC

Please refer to the HEMLIBRA Summary of Product Characteristics for more information

HEMLIBRA Summary of Product Characteristics.

aPCC=activated prothrombin complex concentrate; BPA=bypassing agent; TMA=thrombotic microangiopathy

Laboratory monitoring requirements

- HEMLIBRA affects intrinsic pathway clotting-based laboratory tests. Therefore, they should not be used in patients treated with HEMLIBRA or to monitor its activity, determine its dosing for factor replacement of anticoagulation, or for the measurement of factor VIII (FVIII) inhibitor titres
- Effects of these coagulation assays may persist for up to 6 months after the last dose of HEMLIBRA

HEMLIBRA Summary of Product Characteristics.

*Patients receiving HEMLIBRA prophylaxis should be monitored for the development of TMA and thrombotic events when administering aPCC

aPCC=activated prothrombin complex concentrate; TMA=thrombotic microangiopathy

Laboratory tests affected in patients taking HEMLIBRA

Affected by HEMLIBRA	Unaffected by HEMLIBRA

• Activated partial thromboplastin time (aPTT)
• Clotting-based Bethesda assays for FVIII inhibitor titre
• One-stage, aPTT-based, single-factor assays
• aPTT-based activated protein C resistance (APC-R)
• Activated clotting time (ACT)
	• Thrombin time (TT)
	• Bovine chromogenic Bethesda assays for FVIII inhibitor titre
	• One-stage, prothrombin time (PT)-based, single-factor assays
	• Chromogenic-based single-factor assays, other than FVIII
	• Immuno-based assays
	  • e.g. ELISA, turbidimetric methods
	• Genetic tests of coagulation factors
	  • e.g. Factor V Leiden, Prothrombin 20210

HEMLIBRA Summary of Product Characteristics.

ELISA=enzyme-linked immunosorbent assay; FVIII=factor VIII

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with emicizumab[1]

In HAVEN 1–4:[2]

- Anti-emicizumab antibodies: 14/398 patients (3.5%)
- Anti-emicizumab antibodies with neutralising potential: 3 patients
  - Continued therapy for 48 weeks and remained bleed free: 1 patient
  - Discontinued due to loss of efficacy: 1 patient
  - Discontinued due to personal preference: 1 patient

1. *HEMLIBRA Summary of Product Characteristics.*
2. *Paz-Priel I, et al. ASH. 2018:633 [oral presentation].*

No new safety concerns were identified in the long-term extension of HAVEN 1–4: Pooled analysis

	Total (n=399)*
Total number of participants with ≥1 AE, n (%)	373 (93.5)
Total number of patients, n (%)	
AE with fatal outcome	1 (0.3)
Serious AE	71 (17.8)
AE leading to withdrawal from treatment	5 (1.3)
Grade ≥3 AE	73 (18.3)
Related AE	134 (33.6)
Local injection site reaction	107 (26.8)
Adverse events of special interest	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	1 (0.3)**
TMA event related to concomitant aPCC and emicizumab	3 (0.8)
TE related to concomitant aPCC and emicizumab	2 (0.5)
Other TE (grade 1 device occlusion)	1 (0.3)

- 103 serious AEs were reported in 71 participants
  - Serious AEs reported by ≥5 participants were haemorrhage (n=7, 1.8%) and haemarthrosis (n=5, 1.3%)
- The most common treatment-related AEs were injection site reactions (n=104; 26.1%)
- All injection site reactions were mild in severity

AE=adverse event; aPCC=activated prothrombin complex concentrate; TE=thromboembolic event; TMA=thrombotic microangiopathy
*The safety population only included those patients who received emicizumab. One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analyses. **Assessed using the Sampson Criteria and include all participants that experienced indicative symptoms

Callaghan M, et al. ISTH. 2019: OC60.2.

Conclusion

- In patients with FVIII inhibitors and in patients with severe haemophilia A, HEMLIBRA demonstrated control of bleeding episodes across multiple endpoints[1-4]
  - Intra-patient analyses demonstrated HEMLIBRA significantly reduced treated bleeds vs. bypassing agent prophylaxis (patients with inhibitors)[1] and vs factor VIII prophylaxis (patients without inhibitors)[3]
- Efficacy was also demonstrated in children with factor VIII inhibitors[2]
- HEMLIBRA does not induce inhibitors to factor VIII and is not affected by inhibitors[5]
  - Rates of anti-drug antibody formation to HEMLIBRA remain low
- HEMLIBRA was generally well-tolerated[5]
  - TE/TMA has been reported in patients also treated for a breakthrough bleed with aPCC at an average dose of >100 U/kg/24 hours for ≥24 hours[1]
  - TE/TMA has not been reported to-date with the concurrent administration of activated recombinant factor VII or factor VIII[2-5]
- HEMLIBRA can be given (maintenance dose) once-weekly, every 2 weeks, or every 4 weeks[5]

Oldenburg J, et al. N Engl J Med. 2017;377:809-18.
Young G, et al. ASH. 2018:632 [oral presentation].
Mahlangu J, et al. N Engl J Med. 2018;379:811-22.
4. Pipe S, et al. The Lancet Haematol. 2019. Apr 16 doi: 10.1016/S2352-3026(19)30054-7. [Epub ahead of print].
5. HEMLIBRA Summary of Product Characteristics.

aPCC=activated prothrombin complex concentrate ;FVIII=factor VIII; TE=thrombotic event; TMA= TMA=thrombotic microangiopathy

Prescribing Information

Hemlibra® (emicizumab) **30 mg/ml and 150 mg/ml solution for injection**

Please refer to Summary of Product Characteristics (SmPC) prior to use of Hemlibra

Indications: Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with: haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors; severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors. Hemlibra can be used in all age groups.
Dosage and Administration: Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. The recommended dose is 3 mg/kg once weekly for the first 4 weeks, followed by maintenance dose of either 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks, administered as a subcutaneous injection. Hemlibra is intended for long-term prophylactic treatment. Emicizumab has not been studied in patients with moderate or severe renal impairment or severe hepatic impairment. The safety and efficacy of emicizumab has not been established in patients receiving ongoing immune tolerance induction or in the surgical setting. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions:** Cases of thrombotic microangiopathy (TMA) have been reported in patients receiving Hemlibra when on average a cumulative amount of >100U/kg/24 hours of activated Prothrombin Complex Concentrate (aPCC) for 24 hours or more was administered. Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA when administering aPCC. Caution should be used when treating patients who are at high risk for TMA (e.g. have a medical or family history of TMA), or those who are receiving concomitant medications known to be a risk factor for the development of TMA. Serious thrombotic events have been reported in patients receiving Hemlibra when on average a cumulative amount of >100U/kg/24 hours of aPCC for 24 hours or more was administered. Patients receiving Hemlibra prophylaxis should be monitored for the development of thromboembolism when administering aPCC. Treatment with bypassing agents should be discontinued the day before starting Hemlibra therapy. Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving Hemlibra prophylaxis. In case a bypassing agent is indicated in a patient receiving Hemlibra, see SmPC for dosing guidance on the use of bypassing agents. Intrinsic pathway clotting-based laboratory test results in patients treated with Hemlibra should not be used to monitor its activity, or to determine dosing for factor replacement or anti-coagulation, or to measure factor VIII inhibitors titers. Caution should be taken if intrinsic pathway clotting based laboratory tests are used, as misinterpretation of their results may lead to under-treatment of patients experiencing bleeding episodes, which can potentially result in severe or life-threatening bleeds. There are no data in children <1 year of age. The developing hemostatic system in neonates and infants is dynamic and evolving, and the relative concentrations of pro- and anticoagulant proteins in these patients should be taken into consideration when making a benefit-risk assessment. Emicizumab increases coagulation potential, therefore the coagulation factor dose required to achieve haemostasis may be lower than when used without Hemlibra prophylaxis. In case of thrombotic complication, consider discontinuing rFVIIa or FVIII and interrupt Hemlibra prophylaxis as clinically indicated. *Immunogenicity:* <1% of patients developed anti-emicizumab antibodies with neutralising potential (based on declining pharmacokinetics). **Pregnancy and Lactation:** No data are available in humans. Women of childbearing potential receiving Hemlibra should use effective contraception during, and for at least 6 months after cessation of Hemlibra treatment.
Adverse reactions: *Very common:* headache, injection site reaction, arthralgia. *Common:* pyrexia, diarrhoea, myalgia. *Other serious adverse reactions: TMA* and thrombotic events, including cavernous sinus thrombosis and superficial vein thrombosis contemporaneous with skin necrosis. Prescribers should consult the SmPC for a full list of adverse reactions. **Legal Category:** POM
Presentation, Basic NHS Cost and Marketing Authorisation Numbers: 30 mg/ml, 1 vial of 1 n
EU/1/18/1271/002 150 mg/ml, 1 vial of 0.7 ml - £8,453.55 - EU/1/18/1271/003 150 mg/ml, 1
Supplied by: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW
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This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554. As Hemlibra is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number