OR13

Long-Term Efficacy of Marstacimab in Adults and Adolescents With Severe Hemophilia A or B Without Inhibitors Who Completed the BASIS Trial

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Disclosure for David Matino

In compliance with COI policy, EAHAD requires the following disclosures to the session audience:

Shareholder	**No relevant conflicts of interest to declare**
Grant / Research Support	**Bayer, Novo Nordisk, Octapharma, Pfizer, Roche Sanofi, Spark Therapeutics**
Consultant	**No relevant conflicts of interest to declare**
Employee	**No relevant conflicts of interest to declare**
Paid Instructor	**No relevant conflicts of interest to declare**
Speaker bureau	**No relevant conflicts of interest to declare**
Other	**Honoraria: Bayer, Novo Nordisk, Octapharma, Pfizer, Sanofi, Sobi**

Presentation includes discussion of the following off-label use of a drug or medical device:

NA

Background

- Marstacimab is a monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), preventing interactions with FXa and TF/FVIIa to improve hemostasis.
  - Currently approved for patients with severe HA and HB, without inhibitors.
- BASIS (NCT03938792) is the pivotal phase 3 trial assessing the safety and efficacy of marstacimab for people with severe HA (FVIII <1%) or moderately severe to severe HB (FIX ≤2%), with or without inhibitors.
  - Marstacimab 150 mg SC QW resulted in a significant reduction in annualized bleeding rate (ABR) up to 12 months compared with previous factor replacement therapy in participants without inhibitors.[1]
  - The trial is ongoing for participants with inhibitors.

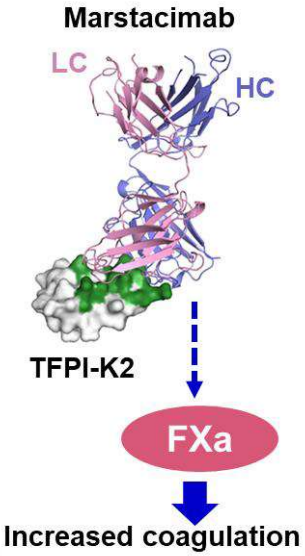
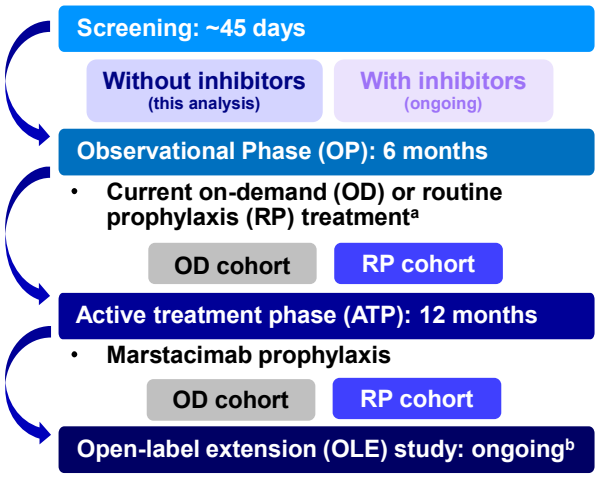


Figure adapted from Apgar et al. 2020[2]

FIX=factor IX; FIXa=activated factor IX; FVIIa=activated factor VII; ; FVIII=factor VIII; HA=hemophilia A; HB=hemophilia B; HC=heavy chain; K=Kunitz domain; LC=light chain; QW=once weekly; SC=subcutaneous; TF=tissue factor

1. Matino D, et al. Blood 2023;2023:285. **2.** Apgar J, et al. Res Pract Thromb Haemost 2020;4(suppl 1) [ISTH abstract PB0240].

Study design



- **Screening:**
  - Males aged ≥12 to <75 years with severe HA or moderately severe to severe HB.
  - No detection or history of FVIII or FIX inhibitors.
  - OD cohort: ≥6 acute bleeding episodes (spontaneous or traumatic) that required factor infusion prior to enrollment
  - RP cohort: ≥80% compliance with FVIII/FIX regimen 6 months prior to enrollment.
- **Observational phase:**
  - Current OD or RP treatment SOC treatment.
- **Active treatment phase:**
  - A single loading dose of marstacimab 300 mg (2× 150 mg SC) followed by marstacimab 150 mg SC QW.
  - Could escalate to 300 mg SC QW after 6 months, based on breakthrough bleeding.
- **Open-label extension:**
  - Participants who successfully completed BASIS could continue marstacimab treatment (150 mg or 300 mg SC QW)

We present interim long-term efficacy data (**ABR for treated bleeds**) for BASIS participants without inhibitors who continued treatment up to an additional 18 months in the OLE study

[a] eg, factor replacement therapy.
[b] OLE data cutoff: April 13, 2024.
FVIII=factor VIII; FIX=factor IX; HA=hemophilia A; HB=hemophilia B; OD=on-demand; OLE-open-label extension; QW=once weekly; RP=routine prophylaxis; SC=subcutaneous; SOC=standard of care

Baseline characteristics of OLE participants

	Baseline treatment		
	On-demand n=32	Routine prophylaxis n=75	Overall N=107
Age, median (range), y	28.5 (15–58)	29.0 (13–66)	29.0 (13–66)
Adolescent (≥12 to <18 y), n (%)	2 (6.3)	16 (21.3)	18 (16.8)
Adult (≥18 to <75 y), n (%)	30 (93.8)	59 (78.7)	89 (83.2)
Hemophilia A, n (%)	25 (78.1)	58 (77.3)	83 (77.6)
Hemophilia B, n (%)	7 (21.9)	17 (22.7)	24 (22.4)
Target joints present at baseline, n (%)	32 (100.0)	40 (53.3)	72 (67.3)
Race, n (%)			
White	10 (31.3)	43 (57.3)	53 (49.5)
Asian	22 (68.8)	30 (40.0)	52 (48.6)
Black	0	1 (1.3)	1 (0.9)
Not reported	0	1 (1.3)	1 (0.9)

- 128 (OD=37, RP=91) participants entered the 6-month OP
- 116 (OD=33, RP=83) received ≥1 dose of marstacimab in the ATP
- 111 (95.7%) completed the ATP
- 107 (92.2%) continued to receive marstacimab in the OLE

ATP=active treatment phase; OD=on-demand; OP=observational phase; OLE=open-label extension; QW=once weekly; RP=routine prophylaxis; SC=subcutaneous; SOC=standard of care

Summary of marstacimab exposure in BASIS and the OLE

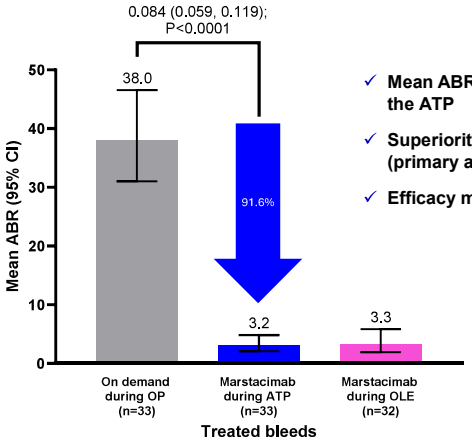
Duration of treatment, months[a]	Baseline treatment		
	On-demand	Routine prophylaxis	Overall
BASIS, n	33	83	116
Median (range)	12.1 (11.5–13.1)	12.1 (0.9–12.8)	12.1 (0.9–13.1)
OLE, n	32	75	107
Median (range)	19.9 (1.2–28.0)	17.5 (4.9–29.4)	18.9 (1.2–29.4)

The combined median exposure (BASIS and OLE) was 30 (range 0.9–41.5) months

[a] A month is defined as 30 days.
OLE data cutoff: April 13, 2024.
OLE=open-label extension study

Estimated mean ABR for treated bleeds in BASIS and the OLE (up to an additional 30 months)

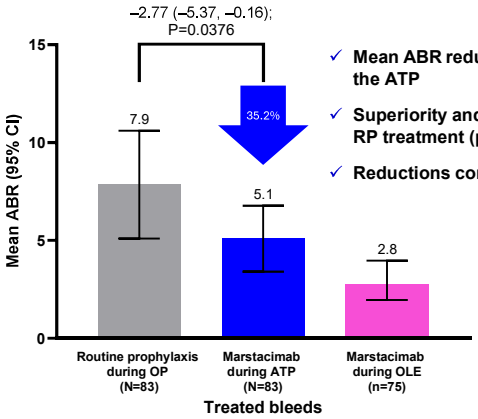
On-Demand



- ✓ **Mean ABR reduced by 91.6% in the ATP**
- ✓ **Superiority to OD treatment (primary analysis)**
- ✓ **Efficacy maintained in the OLE**

Median	35.73	2.02	1.56
Q1, Q3	18.47, 55.21	0, 4.25	0, 5.28
Min, max	0, 83.43	0, 16.48	0, 50.73

Routine Prophylaxis



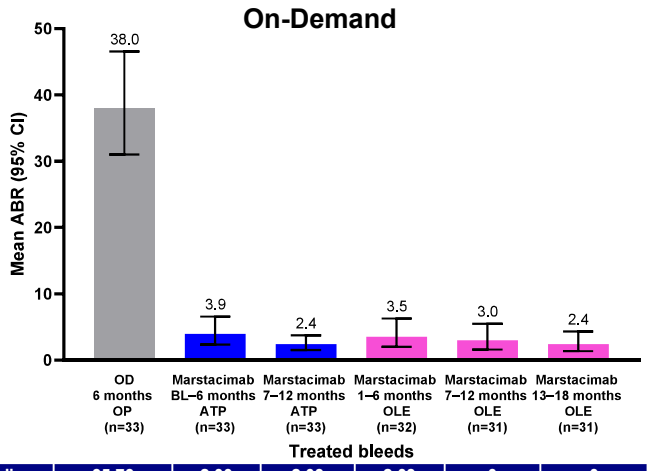
- ✓ **Mean ABR reduced by 35.2% in the ATP**
- ✓ **Superiority and non-inferiority to RP treatment (primary endpoint)**
- ✓ **Reductions continued in the OLE**

Median	2.16	2.02	0.94
Q1, Q3	0, 9.87	0, 6.09	0, 3.83
Min, max	0, 59.51	0, 35.51	0, 39.76

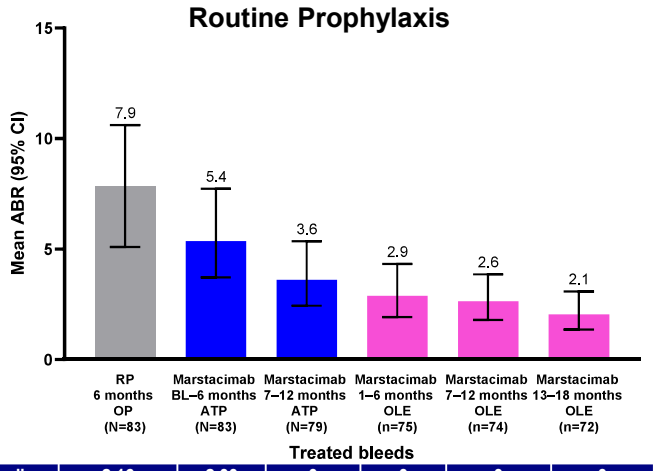
Model-based. P values for the null hypothesis that the ratio = 0.5 for all bleed related parameters.
Ratio estimate, 95% CI and P values are shown for marstacimab vs OD; difference estimate and 95% CI are shown for marstacimab vs prior RP.
OLE data cutoff: April 13, 2024.
ABR=annualized bleeding rate; ATP=active treatment phase; min, max=minimum, maximum; OD=on-demand; OLE=open-label extension study; OP=observational phase; Q=quartile; RP=routine prophylaxis

Time course of ABR for treated bleeds in BASIS and the OLE

Marstacimab lowered ABR over the first 6 months, which continued to Month 12 of the ATP. Bleed rates for up to an additional 18 months of the OLE were consistent with OD and continued to reduce for RP



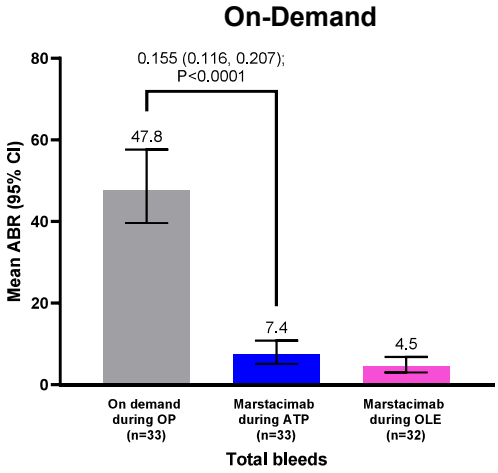
Median	35.73	2.00	2.03	2.03	0	0
Q1, Q3	18.47, 55.21	0, 5.99	0.00, 4.10	0, 6.09	0, 6.09	0, 4.06
Min, max	0, 83.43	0, 35.93	0, 10.15	0, 50.73	0, 14.20	0, 12.18



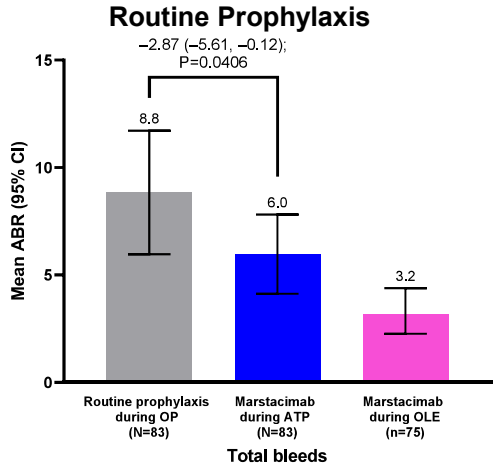
Median	2.16	2.00	0	0	0	0
Q1, Q3	0, 9.87	0, 7.98	0, 4.08	0, 4.06	0, 4.06	0, 3.55
Min, max	0, 59.51	0, 39.92	0, 30.95	0, 39.76	0, 28.41	0, 52.18

Model-based. P values for the null hypothesis that the ratio = 0.5 for all bleed related parameters.
Ratio estimate, 95% CI and P values are shown for marstacimab vs OD; difference estimate and 95% CI are shown for marstacimab vs prior RP.
OLE data cutoff: April 13, 2024;
ABR=annualized bleeding rate; ATP=active treatment phase; min, max=minimum, maximum; OD=on-demand; OLE=open-label extension study; OP=observational phase; Q=quartile; RP=routine prophylaxis

Estimated mean ABR for total bleeds in BASIS and the OLE (up to an additional 30 months)



Median	41.69	5.03	3.23
Q1, Q3	27.06, 63.18	2.01, 9.01	0.78, 7.05
Min, max	5.56, 135.9	0, 36.12	0, 50.73



Median	3.91	2.89	0.96
Q1, Q3	0, 11.66	0, 7.04	0, 4.69
Min, max	0, 59.51	0, 37.54	0, 39.76

Model-based. P values for the null hypothesis that the ratio = 0.5 for all bleed related parameters.
Ratio estimate, 95% CI and p-values are shown for marstacimab vs OD; difference estimate and 95% CI are shown for marstacimab vs prior RP.
OLE data cutoff: April 13, 2024.
ABR=annualized bleeding rate; ATP=active treatment phase; OLE=open-label extension study; OP=observational phase; RP=routine prophylaxis

BASIS and OLE safety

	Baseline treatment					
	On-demand			Routine prophylaxis		
	OP n=37	ATP n=33	OLE n=32	OP n=91	ATP n=83	OLE n=75
Serious AEs[a]	1 (2.7)	0	0	2 (2.2)	7 (8.4)	6 (8.0)
Treatment-related	NA	0	0	NA	1 (1.2)	0
Discontinued due to AEs	0	0	0	0	1 (1.2)[b]	0
Patients with an AESI, n (%)	9 (24.3)	14 (42.4)	1 (3.1)	15 (16.5)	46 (55.4)	21 (28.0)
AESIs (≥5%)[c], n (%)						
COVID-19	0	2 (6.1)	0	3 (3.3)	19 (22.9)	5 (6.7)
Hemorrhage	1 (2.7)	0	0	5 (5.5)	13 (15.7)	6 (8.0)
Hepatic disorders	7 (18.9)	7 (21.2)	0	3 (3.3)	4 (4.8)	1 (1.3)
Hypersensitivity	0	2 (6.1)	1 (3.1)	2 (2.2)	6 (7.2)	6 (8.0)
Hypertension	1 (2.7)	2 (6.1)	0	2 (2.2)	5 (6.0)	3 (4.0)
Injection site reactions	0	2 (6.1)	0	0	9 (10.8)	6 (8.0)
Deaths or serious AEs related to thromboembolism	0	0	0	0	0	0

[a] Number of participants with serious AEs.
[b] Discontinued after surgical resection for non–treatment-related serious AE of atypical meningioma.
[c] AESIs are listed by event type by standardized MedDRA query. (MedDRA v25.1 coding dictionary was applied.)
OLE data cutoff: April 13, 2024.
AE=adverse event; AESI=adverse event of special interest; ATP=active treatment phase; NA=not applicable; OLE=open-label extension; OP=observational phase

BASIS and OLE safety update (October 2024)

- A non-life-threatening deep vein thrombosis (DVT) originating in the subclavian vein was reported in a 24-year-old participant with HA after ~3 years of treatment with marstacimab.
- Several thrombosis and cardiovascular risk factors, some of which were unknown at time of study entry:
  - Heterozygous factor V Leiden mutation (conferring a 6- to 8-fold increased risk of venous thromboembolism).
  - Lifestyle risks (sedentary, alcohol consumption, smoking).
  - Family history of acute coronary syndrome.
- Marstacimab was discontinued, and the participant received treatment CFC and with anticoagulation, and is currently doing well.

HA=hemophilia A; SC=subcutaneous

Conclusions

- In this long-term, OLE of the BASIS trial, treatment with marstacimab SC QW demonstrated sustained or improved efficacy for treated and total ABR in adults and adolescents with HA or HB without inhibitors.
  - These findings were consistent across participants who had received either on-demand or routine prophylaxis factor replacement therapy at baseline.
- 92.2% of the non-inhibitor participants from the BASIS study have transitioned to the OLE (at time of data cutoff: April 2024).
- Marstacimab is safe and well tolerated in patients with hemophilia in BASIS and OLE.
  - There was a single report of DVT in one participant with heterozygeous factor V Leiden mutation.
  - The overall benefit–risk profile of marstacimab remains favorable.

ABR=annualized bleeding rate; DVT=deep vein thrombosis; HA=hemophilia A; HB=hemophilia B; OLE=open-label extension; QW=once weekly; SC=subcutaneous

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Back-up slides

Statistical methods

- ABR (annualized bleeding rate)

The ABR of treated bleeding events (primary efficacy endpoint in the BASIS study) is derived for each participant for each treatment period by using the following formula:

ABR = number of bleeds requiring treatments/(days on treatment period / 365.25)

If participant does not complete a treatment period, days on treatment ends at last dosing date + 6 days.

- Model-derived mean estimate of ABR

Based on a negative binomial regression model without treatment and with a log link function, the model uses the number of bleeds as a response variable and log time on treatment as an offset variable to account for different duration on treatment

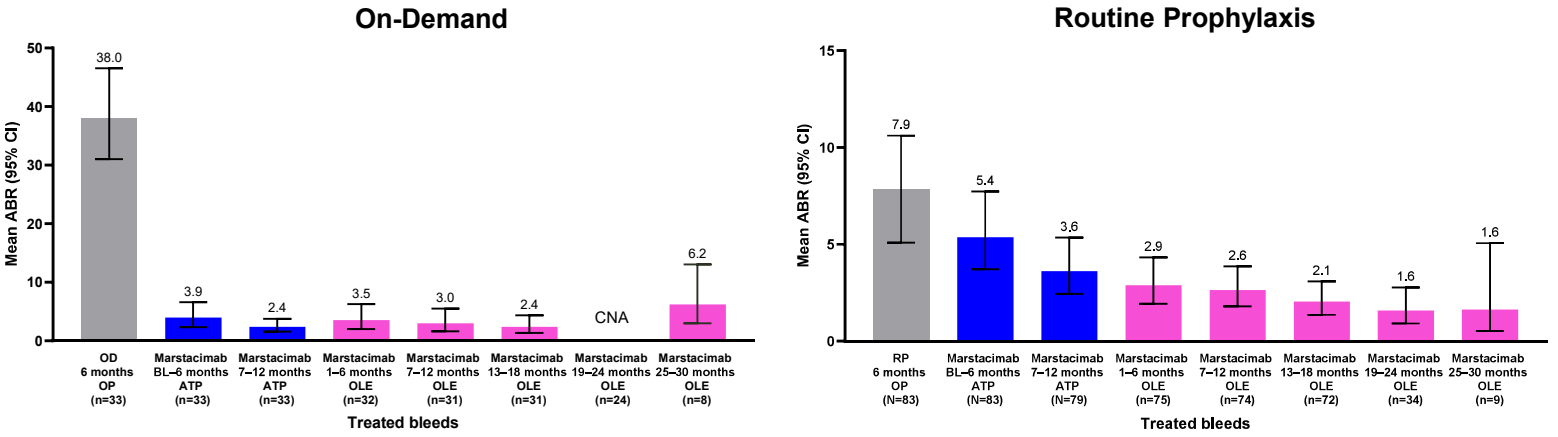
- Methods used for statistical analysis for the ABR of treated bleeds in the BASIS study

Superiority vs On-Demand Treatment: repeated measure negative binomial regression model via generalized estimating equation (GEE) approach with log link function

Non-inferiority vs Routine Prophylaxis: repeated measure negative binomial regression model via GEE approach with identity link function

Time course of ABR for treated bleeds in BASIS and the OLE

Marstacimab lowered ABR over the first 6 months, which continued to Month 12 of the ATP. Bleed rates for up to an additional 30 months of the OLE were consistent with OD and continued to reduce for RP



Median	35.73	2.00	2.03	2.03	0	0	0	0
Q1, Q3	18.47, 55.21	0, 5.99	0.00, 4.10	0, 6.09	0, 6.09	0, 4.06	0, 0	0, 10.15
Min, max	0, 83.43	0, 35.93	0, 10.15	0, 50.73	0, 14.20	0, 12.18	0, 14.20	0, 11.07

Median	2.16	2.00	0	0	0	0	0	0
Q1, Q3	0, 9.87	0, 7.98	0, 4.08	0, 4.06	0, 4.06	0, 3.55	0, 2.03	0, 0
Min, max	0, 59.51	0, 39.92	0, 30.95	0, 39.76	0, 28.41	0, 52.18	0, 7.07	0, 4.65

Model-based. P values for the null hypothesis that the ratio = 0.5 for all bleed related parameters. Ratio estimate, 95% CI, and P values are shown for marstacimab vs OD; difference estimate and 95% CI are shown for marstacimab vs prior RP.
OLE data cutoff: April 13, 2024.
ABR=annualized bleeding rate; ATP=active treatment phase; CNA=convergence not attained; min, max=minimum, maximum; OD=on-demand; OLE=open-label extension study; OP=observational phase; Q=quartile; RP=routine prophylaxis

Descriptive time course of ABR for total bleeds in BASIS and the OLE

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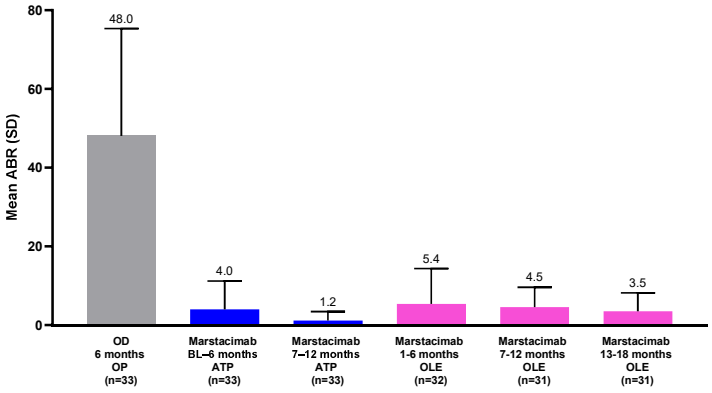
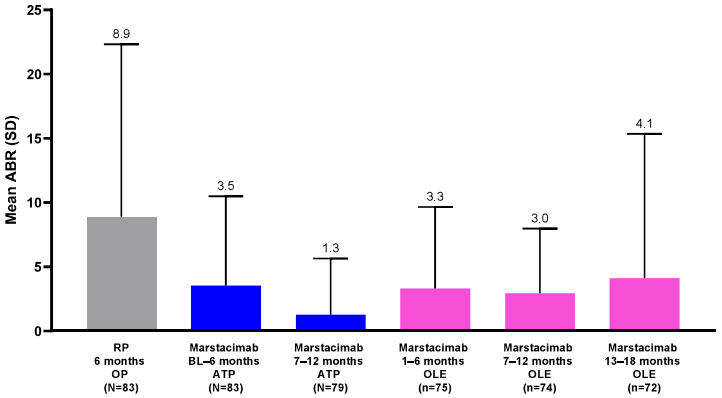
On-Demand



Median	**41.69**	**2.00**	**0**	**4.06**	**2.03**	**2.03**
Q1, Q3	27.06, 63.18	0, 5.99	0, 2.03	1.02, 6.09	0, 8.12	0, 6.09
Min, max	5.56, 135.9	0, 35.93	0, 10.15	0, 50.73	0, 16.23	0, 16.23

Routine Prophylaxis



Median	**3.91**	**0**	**0**	**2.03**	**0**	**0**
Q1, Q3	0, 11.66	0, 3.99	0, 0	0, 4.06	0, 4.06	0, 4.06
Min, max	0, 59.51	0, 39.92	0, 24.76	0, 39.76	0, 28.41	0, 78.27

OLE data cutoff: April 13, 2024.
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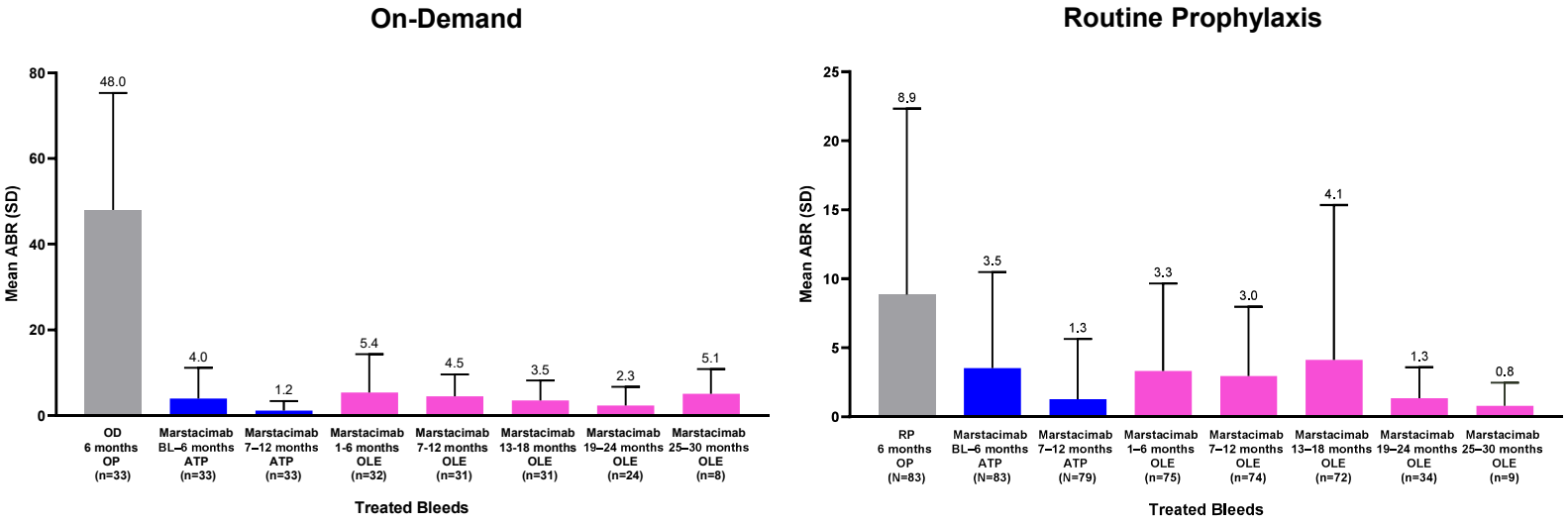

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