

Rebalancing the Coagulation Cascade

Emerging Strategies To Restore Hemostasis In Hemophilia

Balancing the Hemostatic System by Blocking Coagulation Inhibitors



Pros

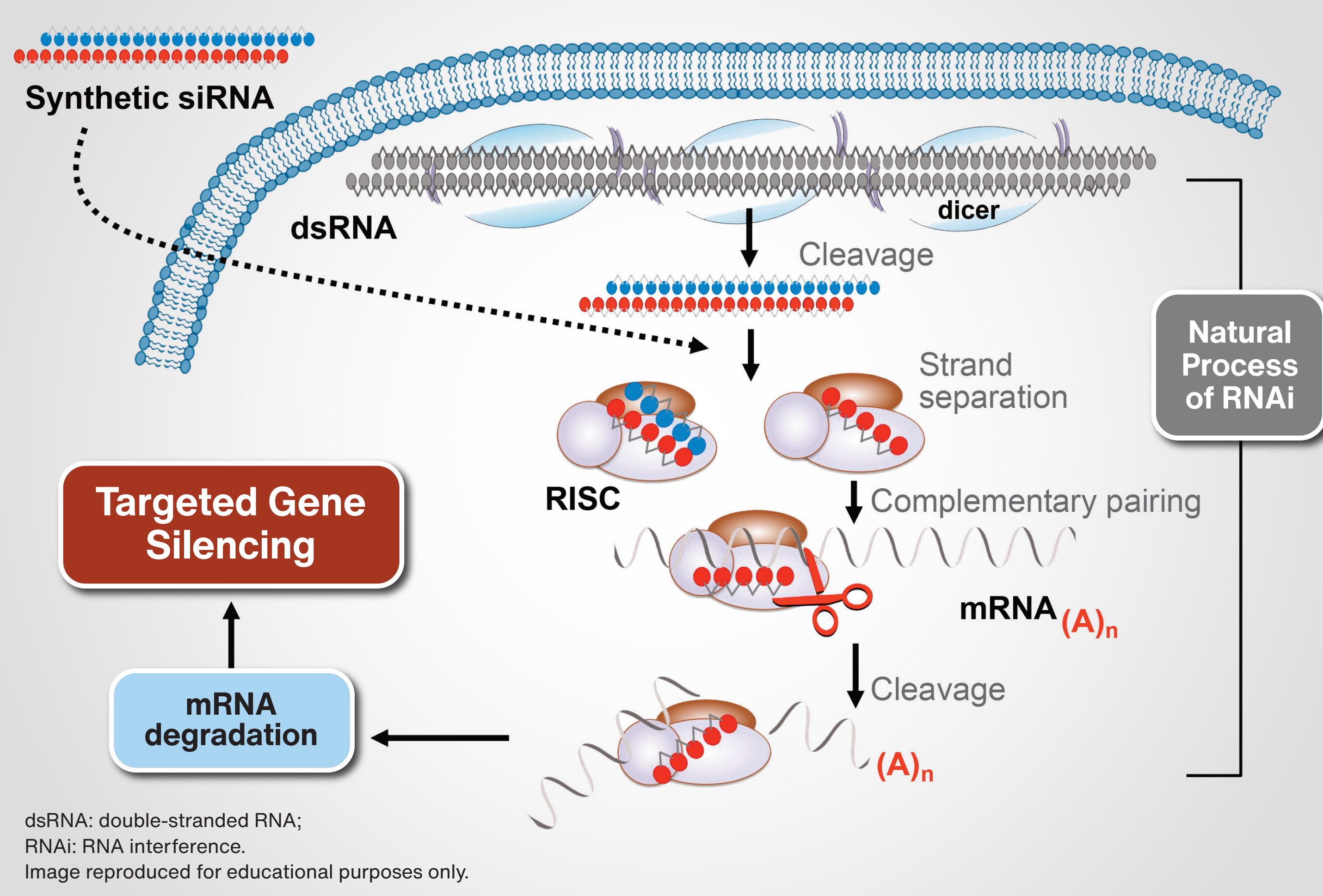
- Same medication for hemophilia A and B with/without inhibitors
- Several mechanisms of action
- Can be used in different types of patients
- Efficacious
- Safe (mostly)
- Subcutaneously administered
- Potential to be used in other bleeding disorders



Cons

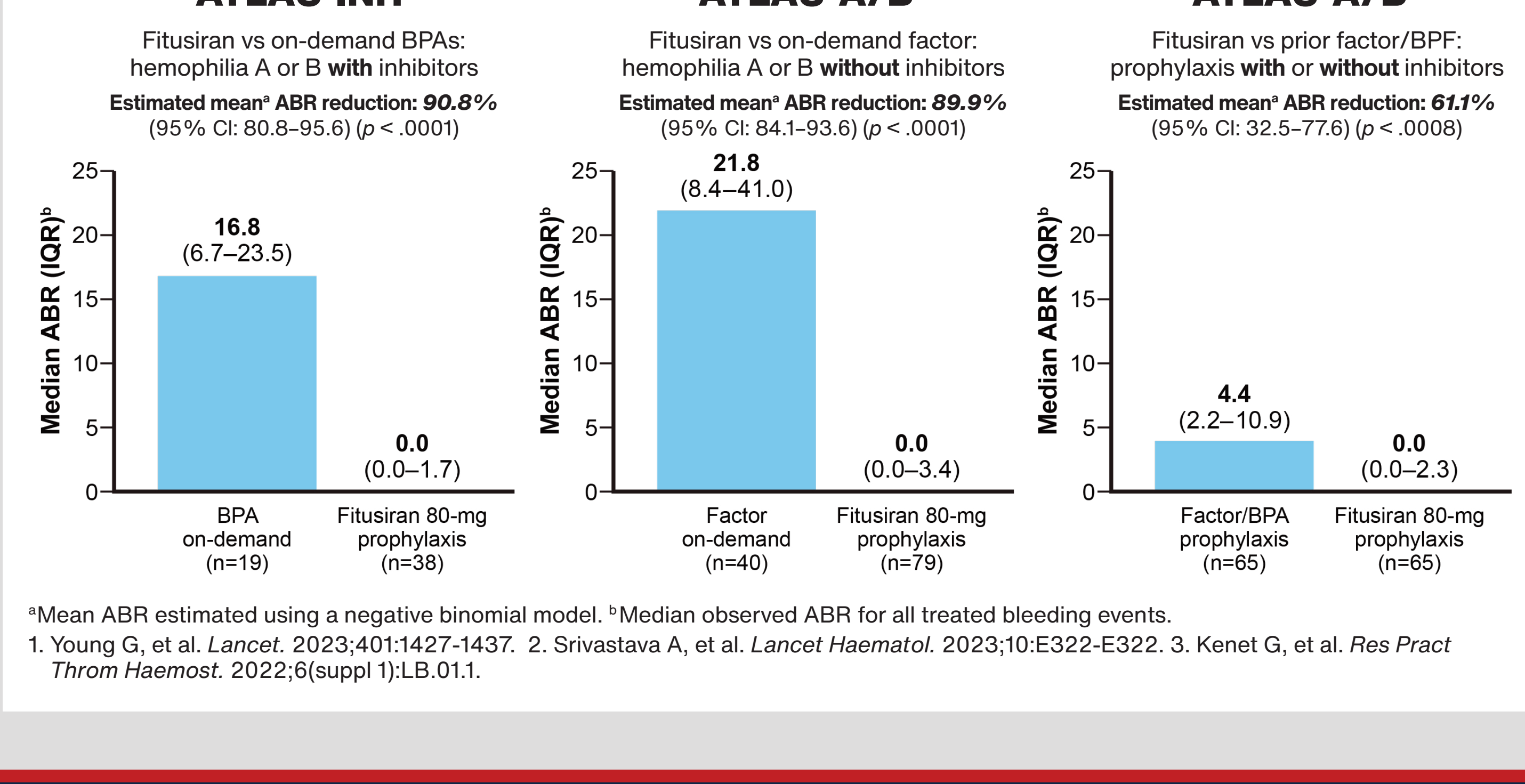
- Novel mechanisms of action
 - Treaters/patients must learn about another part of the coagulation cascade
- Therapeutic drug monitoring with dose adjustments will be required (at least for some)
- Safety concerns (thrombosis)
- Lack of antidote for some

RNA Interference: Fitusiran

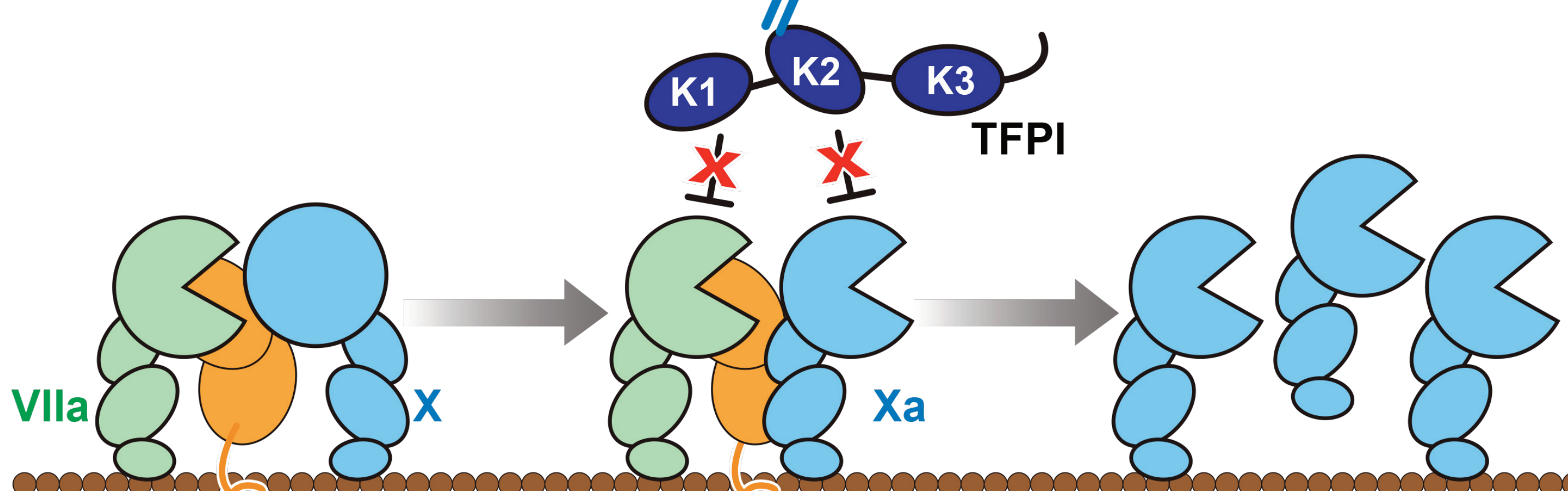


Fitusiran: phase 3 efficacy data

- Significant reductions in bleeding outcomes in studied patient groups
 - ATLAS-INH: adults and adolescents with hemophilia A or B with inhibitors who previously used on-demand BPAs
 - ATLAS-A/B: adults and adolescents with hemophilia A or B without inhibitors who previously used on-demand factor therapy
 - ATLAS-PPX: adults and adolescents with severe hemophilia A or B who previously used on-demand factor therapy
- Treatment-related adverse events consisted of ALT and AST elevations, cholecystitis, cholelithiasis, and thrombosis, which were consistent with previously identified risks



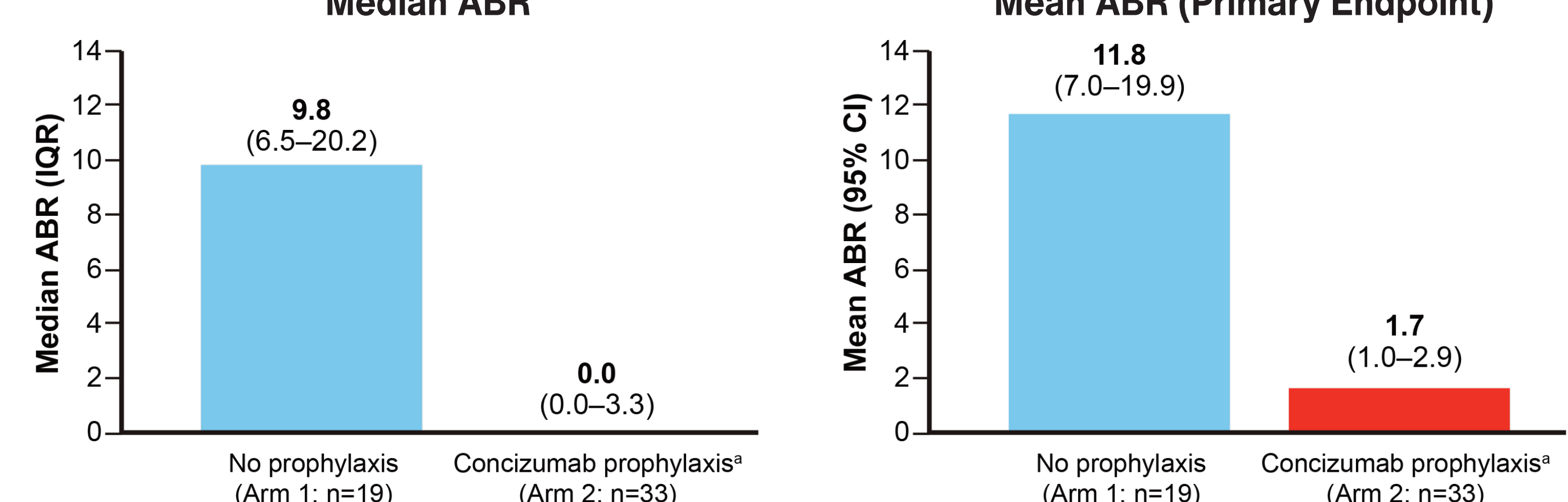
Anti-TFPIs: Concizumab and Marstacimab



Concizumab: explorer7 phase 3 efficacy data

- Mean ABR was 1.7, median ABR was 0, and 64% of participants who received concizumab (Arm 2; n=33) had zero treated bleeds at 24 weeks
- Efficacy results were consistent when split by hemophilia subtype (data not shown)
- Safety
 - Low rate of thromboembolic events on treatment period
 - No thromboembolic events occurred after treatment restart

ABR at primary analysis cutoff^a in people with hemophilia A or B with inhibitors



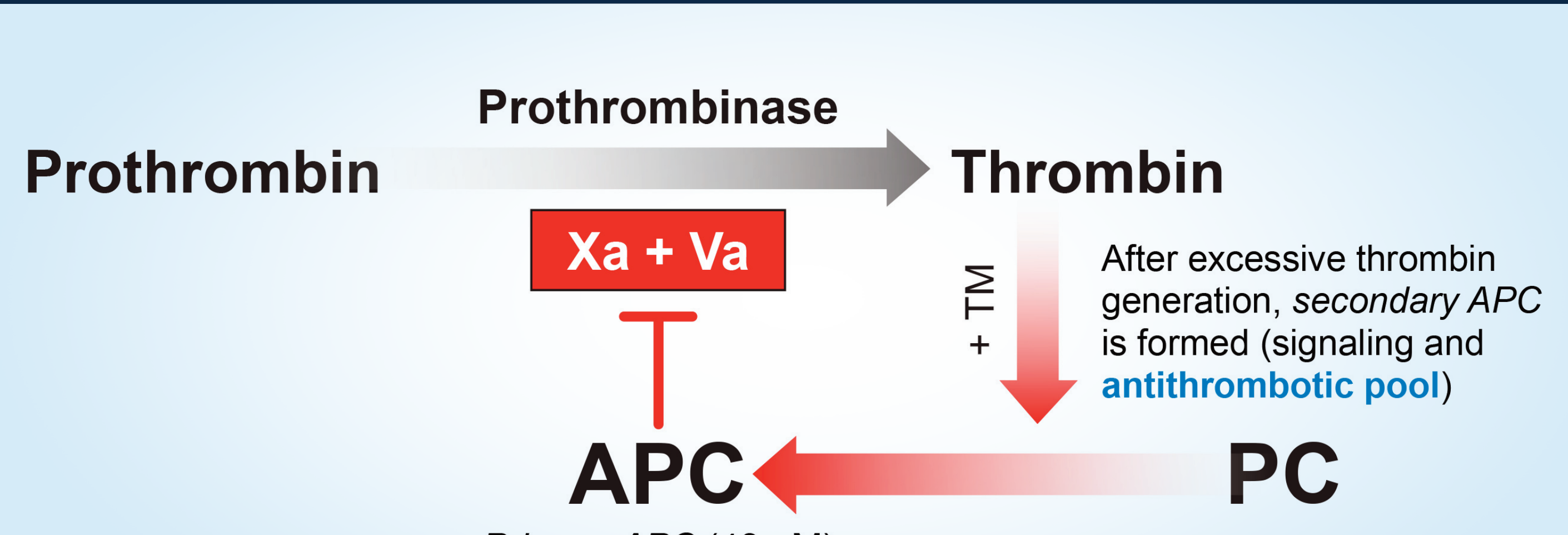
Marstacimab: phase 2 efficacy data

- 50% of participants who completed the study (n=18) had no bleeding events
- No serious treatment-related adverse events were observed

	Total 300 mg (n=10)	Total 300-mg Loading + 150 mg (n=10)
Pre-treatment ABR, mean (SD)	20.2 (5.7)	17.4 (9.0)
Median (range)	19.1 (12.0–30.0)	15.0 (12.0–42.0)
On-study ABR, mean (SD)	1.5 (2.4)	2.7 (4.5)
Median (range)	0 (0–6.0)	1.0 (0–14.4)

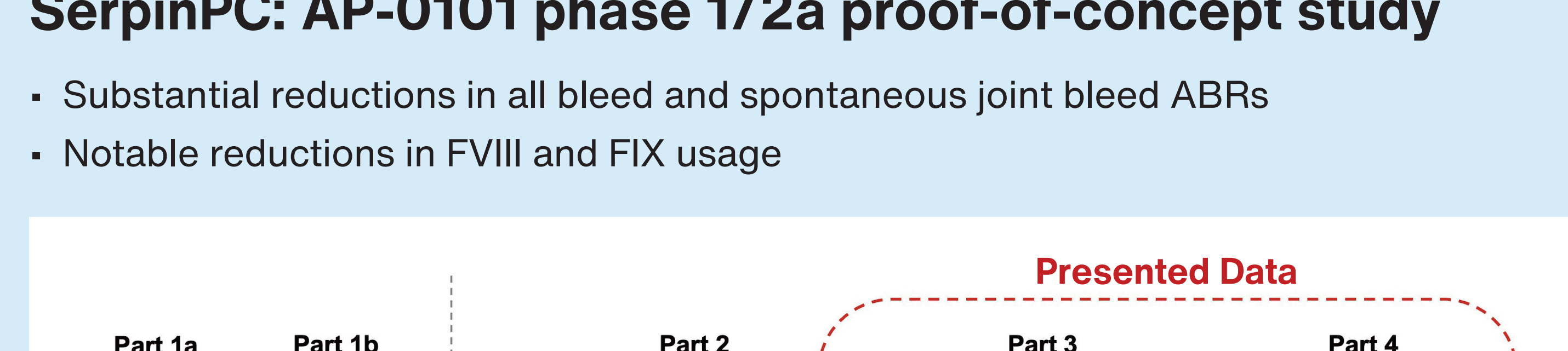
Mahlangu J, et al. *Br J Haematol*. 2023;200:240-248.

Anti-APC: SerpinPC



SerpinPC: AP-0101 phase 1/2a proof-of-concept study

- Substantial reductions in all bleed and spontaneous joint bleed ABRs
- Notable reductions in FVIII and FIX usage



	Median ABR From Prospective Baseline	Median ABR Observed In This Part	Median % Change From Baseline
All Bleed ABR			
Part 3 (n=22)	34.1	6.2	-83%
Part 4 (n=21)	35.5	2.2	-93%
Spontaneous Joint Bleed ABR			
Part 3 (n=22)	27.5	4.3	-86%
Part 4 (n=21)	28.3	2.2	-93%
FVIII Use (units/mo)			
Part 3 (n=22)	5,432	896	-74%
Part 4 (n=21)	5,382	535	-87%
FIX Use (units/mo)			
Part 3 (n=22)	5,241	905	-83%
Part 4 (n=21)	5,241	540	-90%

Baglin T, et al. Presented at 16th Annual Congress of European Association for Haemophilia and Allied Disorders; February 7-10, 2023; Manchester, England.

References

- Baglin T, et al. Presented at 16th Annual Congress of European Association for Haemophilia and Allied Disorders; February 7-10, 2023; Manchester, England.
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Abbreviations

- ABR: annualized bleeding rate
ALT: alanine aminotransferase
AST: aspartate aminotransferase
APC: activated PC
dsRNA: double-stranded RNA
FVIII: factor VIII
FIX: factor IX
HV: healthy volunteers
IQR: interquartile range
MAD: multiple ascending doses
mRNA: messenger RNA
OLE: open-label extension
PC: protein C
PwH: people with hemophilia
Q2W: every 2 weeks
Q4W: every 4 weeks
RISC: RNA-induced silencing complex
RNAi: RNA interference
SAD: single ascending dose
siRNA: small interfering RNA
TFPI: tissue factor pathway inhibitor