Attaining New Goals in Hemophilia

Exploring the Clinical Utility of Emerging Treatments

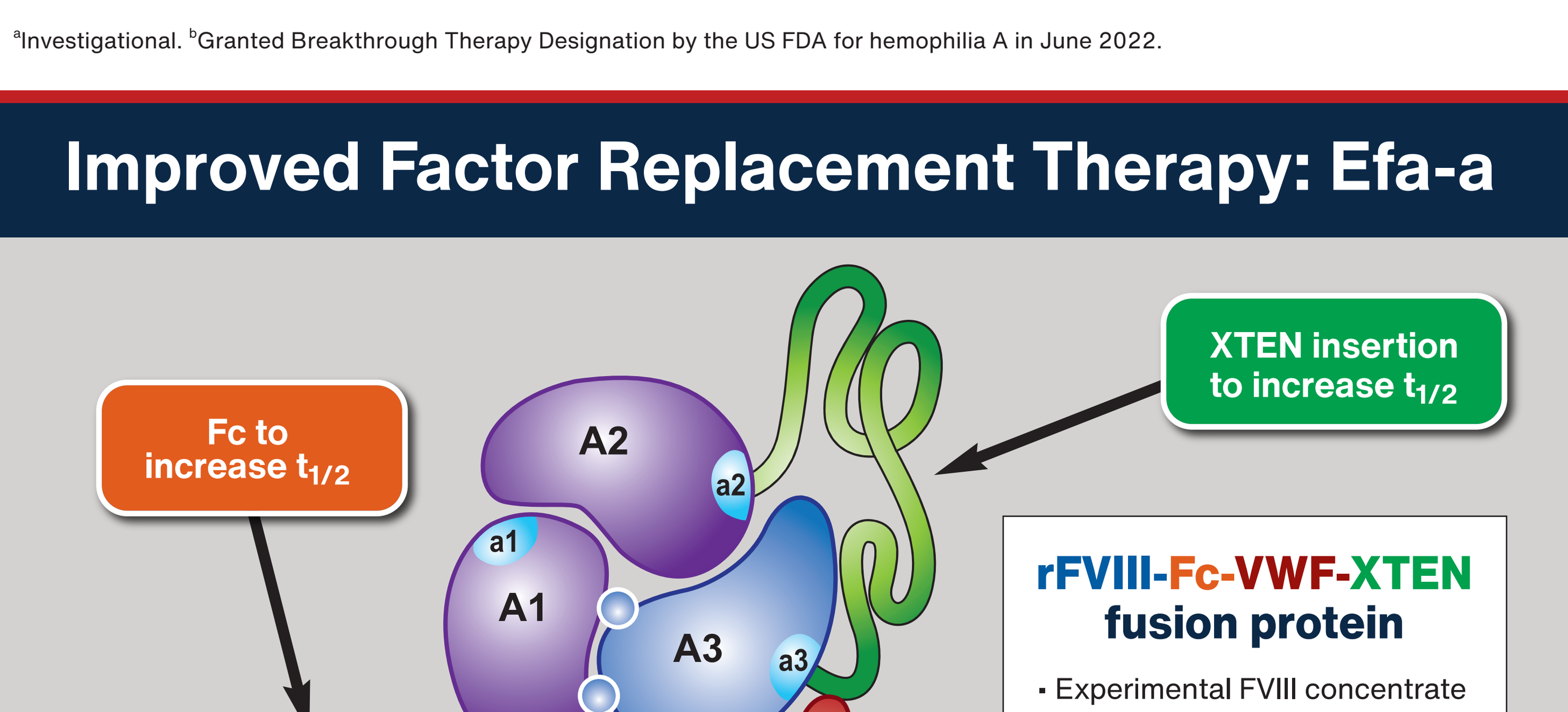
Factor Replacement Therapy

Although factor replacement therapy is an effective method for restoring factor levels to within normal range when at peak, it has many disadvantages, resulting in the need for new therapies.

✓		✗
• Decades of data and experience • Lower risk for inhibitors based on SIPPET study	**Plasma-derived Products**	• High treatment burden • Refrigeration needed • Larger volume • IV administration
• Decades of data and experience • Safe (other than inhibitors) • Generally effective for prophylaxis, treatment, and surgery	**SHL Products**	• High treatment burden • Cannot fully prevent arthropathy • Inhibitors • Cost • IV administration
• Fewer infusions needed for outcomes similar to those with SHL factors • Safe (other than inhibitors) • Effective for prophylaxis, treatment, and surgery	**EHL Products**	• Lower (but still high) treatment burden • Cannot fully prevent arthropathy • Inhibitors (data emerging, but likely similar to SHL) • Cost (higher than SHL) • IV administration

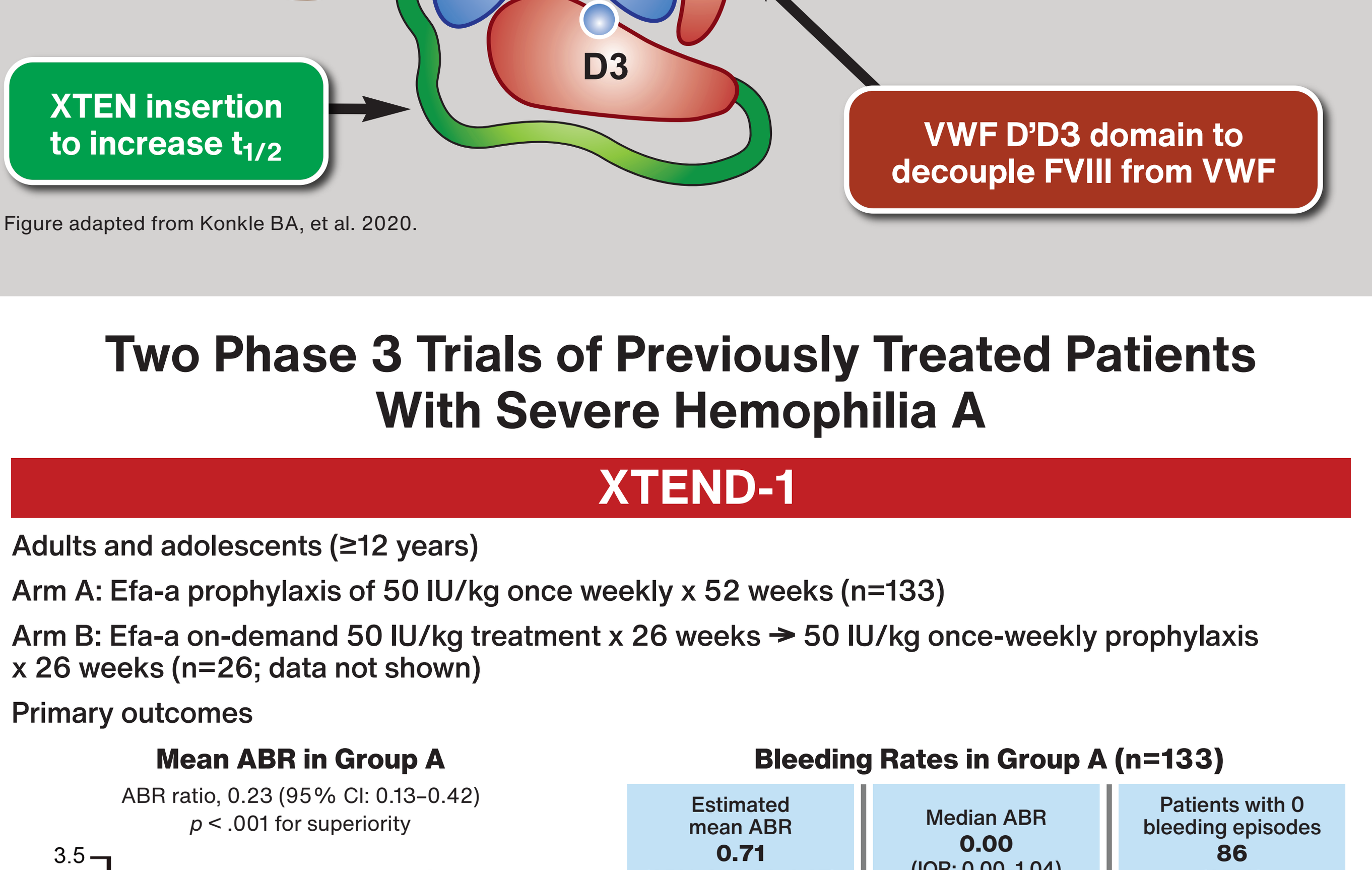
New and Emerging Therapies Target Different Aspects of Hemostasis

IMPROVED REPLACEMENT THERAPY	SUBSTITUTION THERAPY	REBALANCING AGENTS
Adds novel structural modifications to replacement factor therapy to increase $t_{1/2}$ and reduce administration frequency	Non–factor-based therapy that mimics the action of missing FVIII	Inhibit coagulation inhibitors to restore the balance of procoagulation and anticoagulation
EXAMPLES Efanesocotog alfa (Efa a)[a,b]	**EXAMPLES** Bispecific mAbs: emicizumab and Mim8[a]	**EXAMPLES** Antithrombin siRNA: fitusiran[a] TFPI inhibitors: concizumab[a] and marstacimab[a] APC inhibitor: serpin PC[a]



[a]Investigational. [b]Granted Breakthrough Therapy Designation by the US FDA for hemophilia A in June 2022.

Improved Factor Replacement Therapy: Efa-a



rFVIII-Fc-VWF-XTEN fusion protein

- Experimental FVIII concentrate
- Aims to reduce treatment burden with a weekly infusion schedule
- Aims to increase trough levels

Figure adapted from Konkle BA, et al. 2020.

Two Phase 3 Trials of Previously Treated Patients With Severe Hemophilia A

XTEND-1

Adults and adolescents (≥12 years)

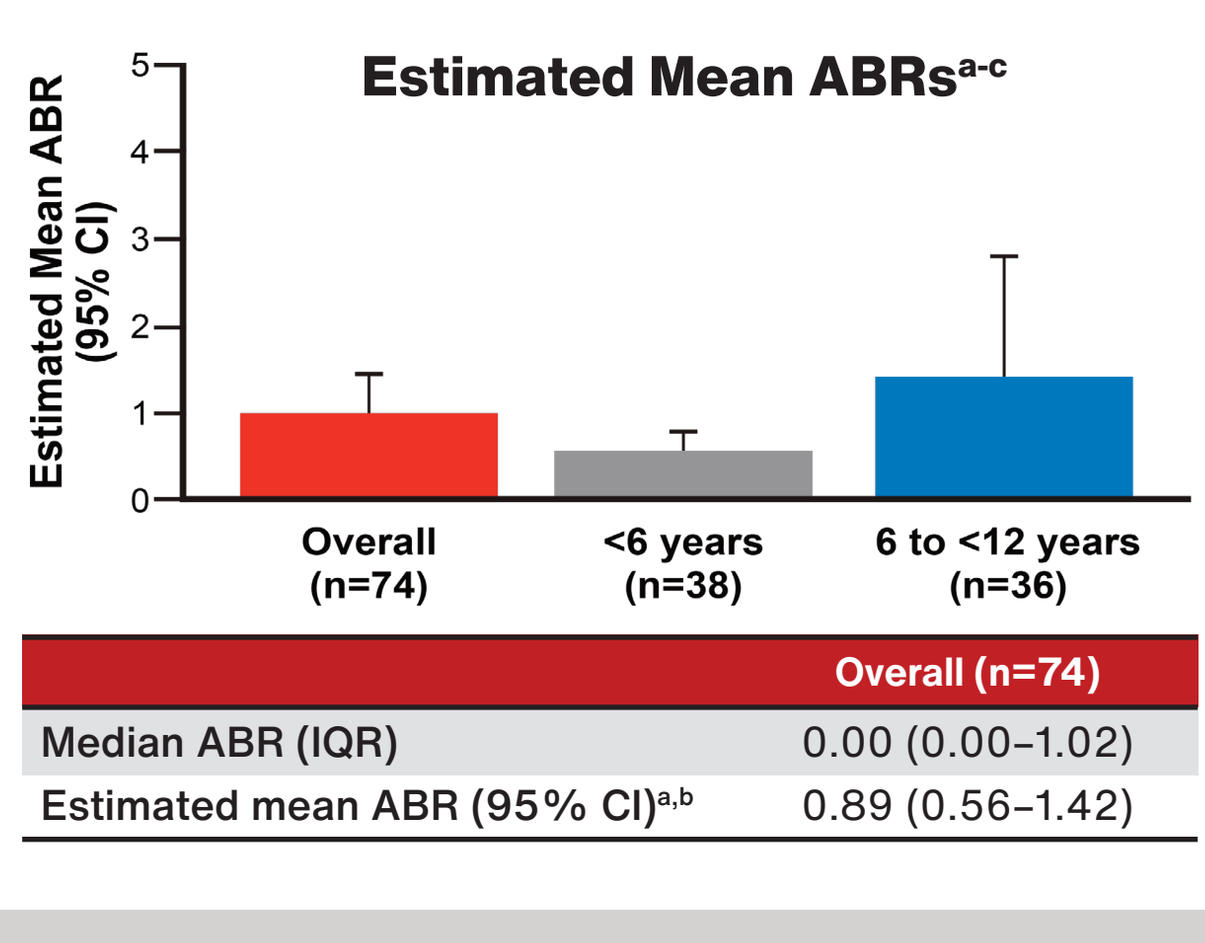
Arm A: Efa-a prophylaxis of 50 IU/kg once weekly x 52 weeks (n=133)

Arm B: Efa-a on-demand 50 IU/kg treatment x 26 weeks → 50 IU/kg once-weekly prophylaxis x 26 weeks (n=26; data not shown)

Primary outcomes

Mean ABR in Group A

ABR ratio, 0.23 (95% CI: 0.13–0.42)
$p < .001$ for superiority



Bleeding Rates in Group A (n=133)

Estimated mean ABR	Median ABR	Patients with 0 bleeding episodes
0.71 (95% CI: 0.52–0.97)	**0.00** (IQR: 0.00–1.04)	**86** (65%)

Safety Summary

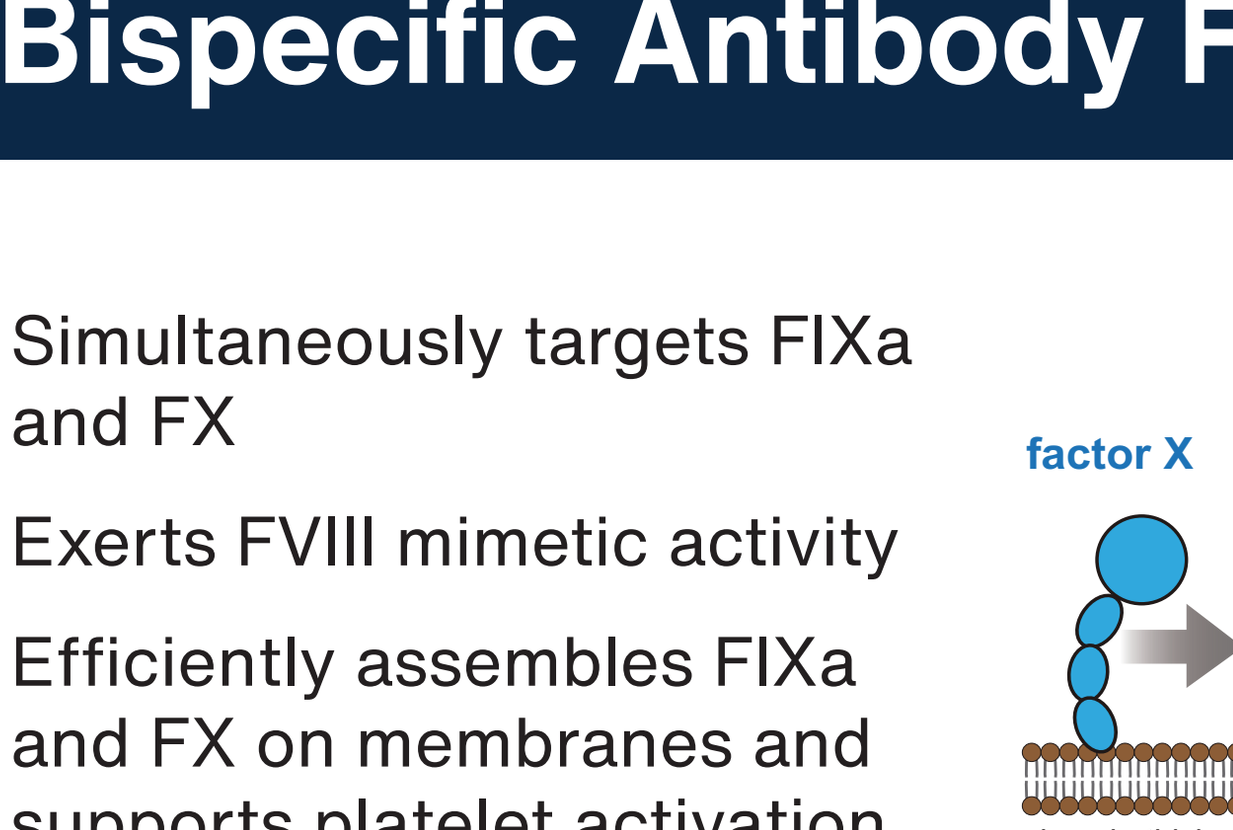
- 362 bleeding events during the study
  - 74% in Arm B during on-demand treatment
  - Single injection sufficient for bleed resolution in 97% of bleeds
- 14 major surgeries (n=13) —> all hemostatic responses deemed excellent
- Most common AEs: headache and arthalgia
- No hypersensitivity reactions, anaphylaxis, or vascular thrombotic events
- No inhibitors were detected

XTEND-Kids

Pediatric (<12 years)

Efa-a prophylaxis of 50 IU/kg once weekly x 52 weeks (n=74)

Estimated Mean ABRs[a-c]



	Overall (n=74)
Median ABR (IQR)	0.00 (0.00–1.02)
Estimated mean ABR (95% CI)[a,b]	0.89 (0.56–1.42)

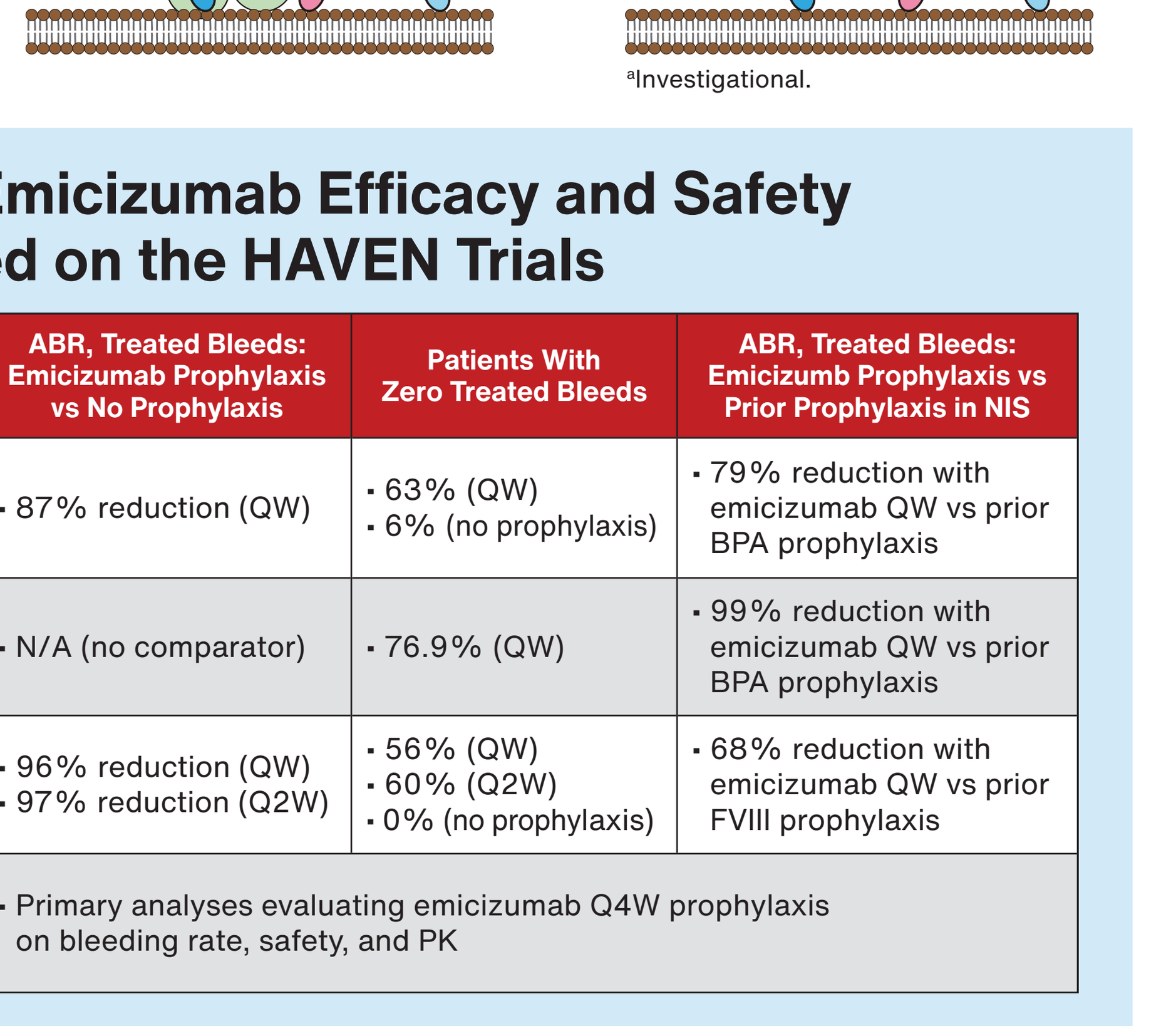
Values After the First Dose, PK Subgroup, Mean (SD)	<6 Years (n=19)	6 to <12 Years (n=18)
$t_{1/2}$, h	38.0 (3.72)	42.4 (3.70)
CL, mL/h/kg	0.742 (0.121)	0.681 (0.139)
IR, IU/dL per IU/kg	2.81 (1.10)	2.24 (0.437)
C_{max}, IU/dL	143 (57.8)	113 (22.7)
Mean ED	51.2 ± 8.6	53.9 ± 4.9

Safety Summary

- No antidrug antibodies
- No hypersensitivity reactions, anaphylaxis, or vascular thrombotic events

Non-factor Therapy: Bispecific Antibody FVIII Substitution Therapy

- Simultaneously targets FIXa and FX
- Exerts FVIII mimetic activity
- Efficiently assembles FIXa and FX on membranes and supports platelet activation
- Not affected by FVIII inhibitors
- Subcutaneous absorption
- $t_{1/2}$ = 4-5 weeks



[a]Investigational.

Summary of Emicizumab Efficacy and Safety Based on the HAVEN Trials

Clinical Trial	Population	ABR, Treated Bleeds: Emicizumab Prophylaxis vs No Prophylaxis	Patients With Zero Treated Bleeds	ABR, Treated Bleeds: Emicizumb Prophylaxis vs Prior Prophylaxis in NIS
HAVEN 1	Patients with hemophilia A aged ≥12 years with FVIII inhibitors	• 87% reduction (QW)	• 63% (QW) • 6% (no prophylaxis)	• 79% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 2	Patients with hemophilia A aged <12 years with FVIII inhibitors	• N/A (no comparator)	• 76.9% (QW)	• 99% reduction with emicizumab QW vs prior BPA prophylaxis
HAVEN 3	Patients with hemophilia A aged ≥12 years without FVIII inhibitors	• 96% reduction (QW) • 97% reduction (Q2W)	• 56% (QW) • 60% (Q2W) • 0% (no prophylaxis)	• 68% reduction with emicizumab QW vs prior FVIII prophylaxis
HAVEN 4	Patients with hemophilia A aged ≥12 years with or without FVIII inhibitors	• Primary analyses evaluating emicizumab Q4W prophylaxis on bleeding rate, safety, and PK		

	Thrombosis	TMA	Antidrug Antibody	Other
Frequency	3% in HAVEN 1 Additional reports of MI in patients with risk factors	2% in HAVEN 1 1 other case when aPCC given at high doses (personal communication)	Rare 4 reported cases, all in patients with inhibitors (3 neutralizing, 1 clearance)	Rare (1 case of lupus nephritis that resolved)
Identification	Clinical examination, imaging	Laboratory testing	Prolonged PTT Additional testing	Hematuria
Mitigation	Avoid aPCC at doses >100 IU/kg/d for >24 hours	Avoid aPCC at doses >100 IU/kg/d for >24 hours	None identified	

Rebalancing Agent: Fitusiran

- Novel siRNA therapy
- Reduces antithrombin production
- Administered subcutaneously

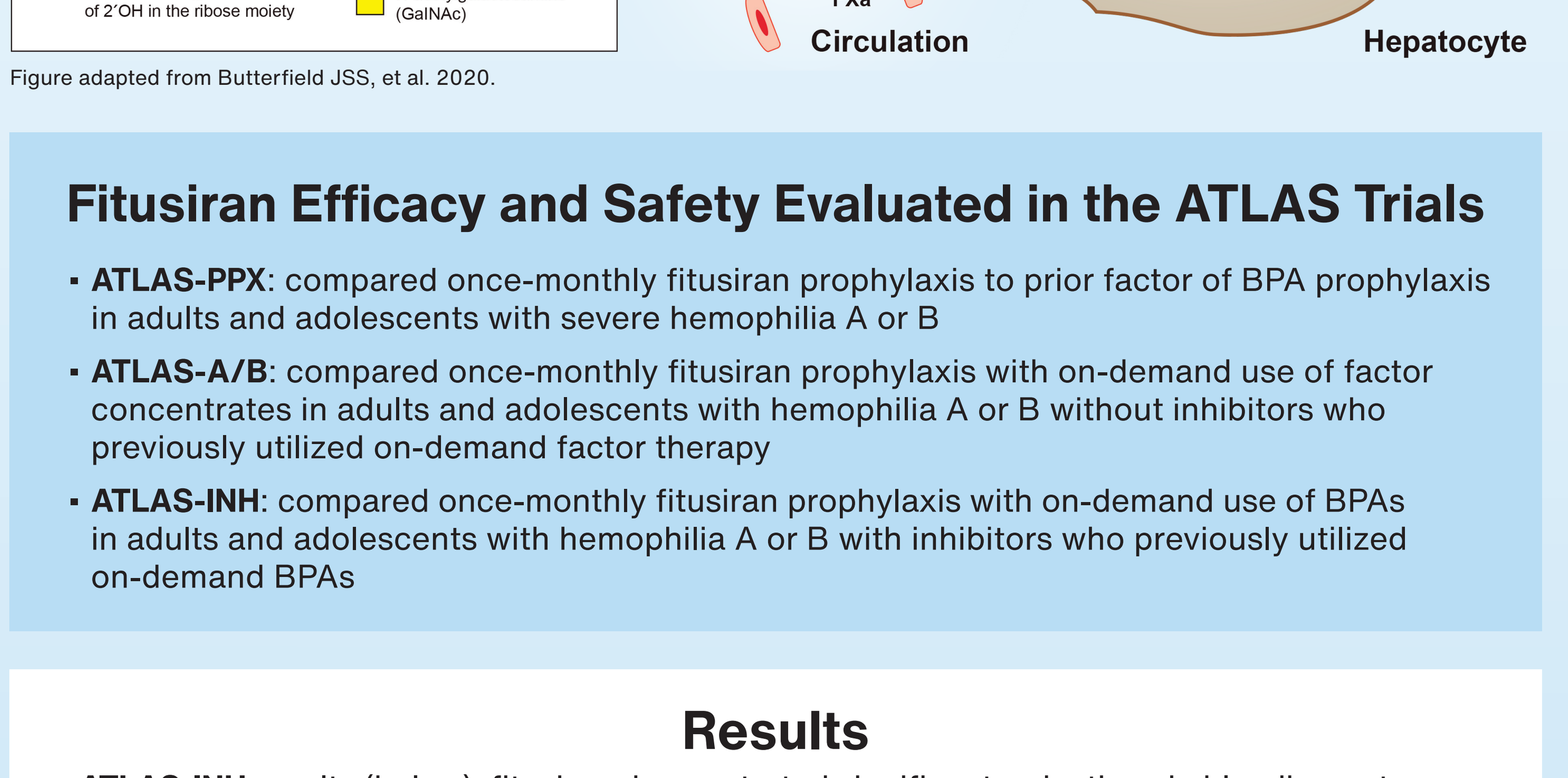


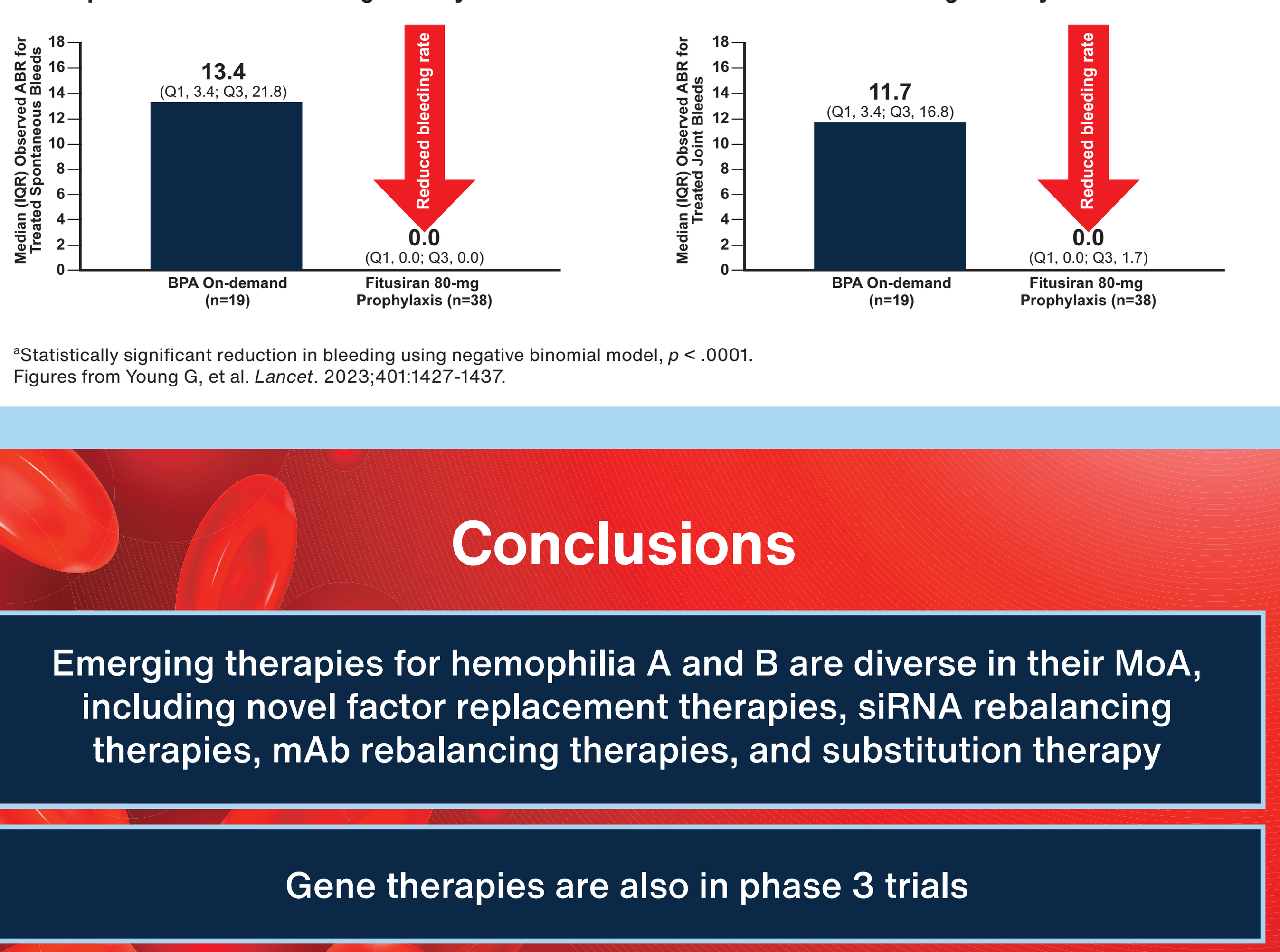
Figure adapted from Butterfield JSS, et al. 2020.

Fitusiran Efficacy and Safety Evaluated in the ATLAS Trials

- **ATLAS-PPX**: compared once-monthly fitusiran prophylaxis to prior factor of BPA prophylaxis in adults and adolescents with severe hemophilia A or B
- **ATLAS-A/B**: compared once-monthly fitusiran prophylaxis with on-demand use of factor concentrates in adults and adolescents with hemophilia A or B without inhibitors who previously utilized on-demand factor therapy
- **ATLAS-INH**: compared once-monthly fitusiran prophylaxis with on-demand use of BPAs in adults and adolescents with hemophilia A or B with inhibitors who previously utilized on-demand BPAs

Results

- **ATLAS-INH** results (below): fitusiran demonstrated significant reductions in bleeding outcomes
- Safety profile consistent with previously identified fitusiran risks (eg, ALT or AST elevations, thrombosis)
- **ATLAS-PPX** and **ATLAS-A/B** demonstrated similar efficacy and safety results (not shown)



Estimated Mean ABR (95% CI)	
18.1 (10.60-30.81)	1.7 (1.01-2.74)

[a]Statistically significant reduction in bleeding using negative binomial model, $p < .0001$.
Figures from Young G, et al. *Lancet*. 2023;401:1427-1437.

Conclusions

Emerging therapies for hemophilia A and B are diverse in their MoA, including novel factor replacement therapies, siRNA rebalancing therapies, mAb rebalancing therapies, and substitution therapy

Gene therapies are also in phase 3 trials

The availability of multiple therapeutic options may allow for enhanced treatment individualization and improved outcomes for those living with hemophilia

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Abbreviations

ABR: annualized bleed rate
ALT: alanine aminotransferase
APC: activated PC
aPCC: activated prothrombin complex concentrate
ASGPR: asialoglycoprotein receptor
AST: aspartate aminotransferase
AT: antithrombin
BPA: bypassing agent
Efa-a: efanesoctocog alfa
EHL: extended half-life
FIXa: activated factor IX
FVIII: factor VIII
FX: factor X
IQR: interquartile range
IV: intravenous
mAb: monoclonal antibody
MI: myocardial infarction
MoA: mechanism of action
N/A: not applicable
NIS: non-interventional study
PC: protein C
PK: pharmacokinetics
PS: protein S
PTT: partial thromboplastin time
Q2W: every 2 weeks
Q4W: every 4 weeks
QW: weekly
rFVIII: recombinant factor VIII
RISC: RNA-induced silencing complex
siRNA: small-interfering RNA
SHL: standard half-life
$t_{1/2}$: half-life
TFPI: tissue factor pathway inhibitor
TMA: thrombotic microangiopathy
VWF: von Willebrand factor