SerpinPC in persons with severe hemophilia (PwH): long-term treatment from a multi-center, multi-part, first-in-human study

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Disclosure for **Trevor Baglin**

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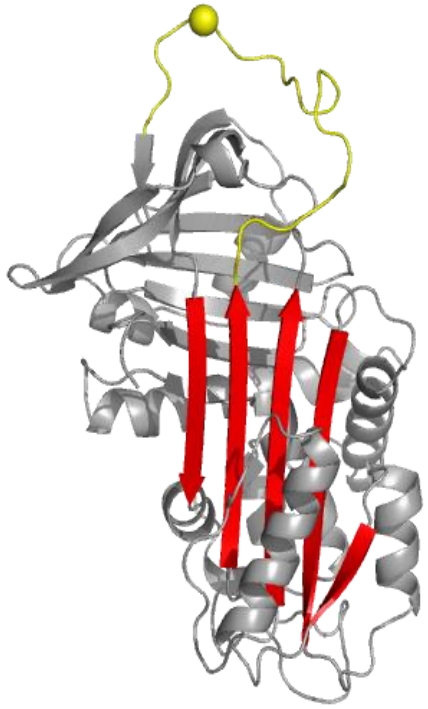
SerpinPC: a subcutaneously administered biologic inhibitor of APC

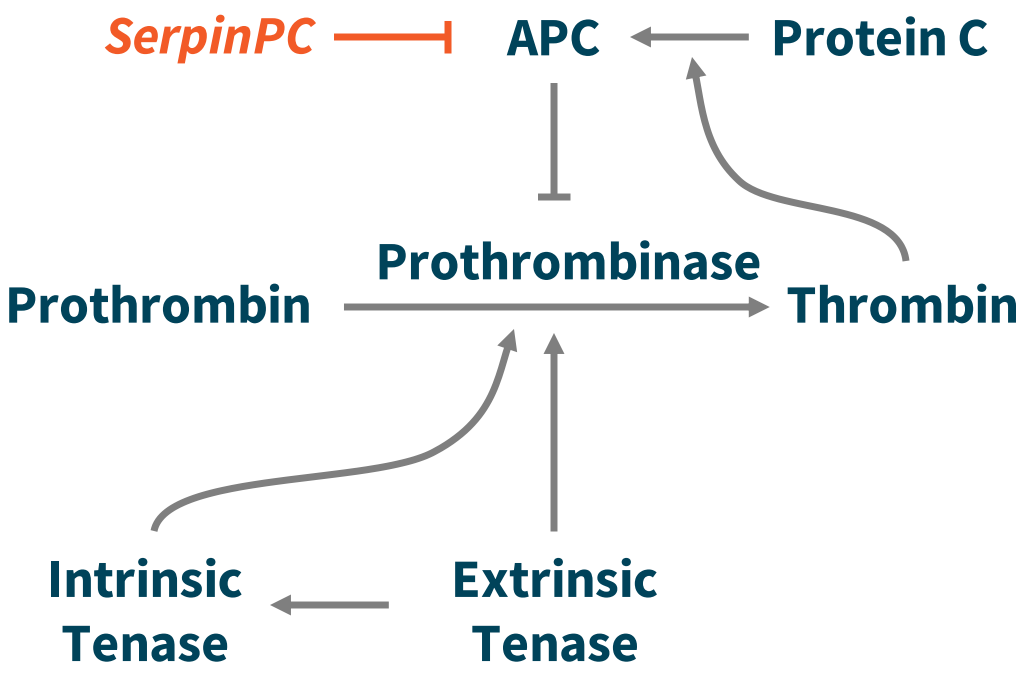


3D-model of SerpinPC*

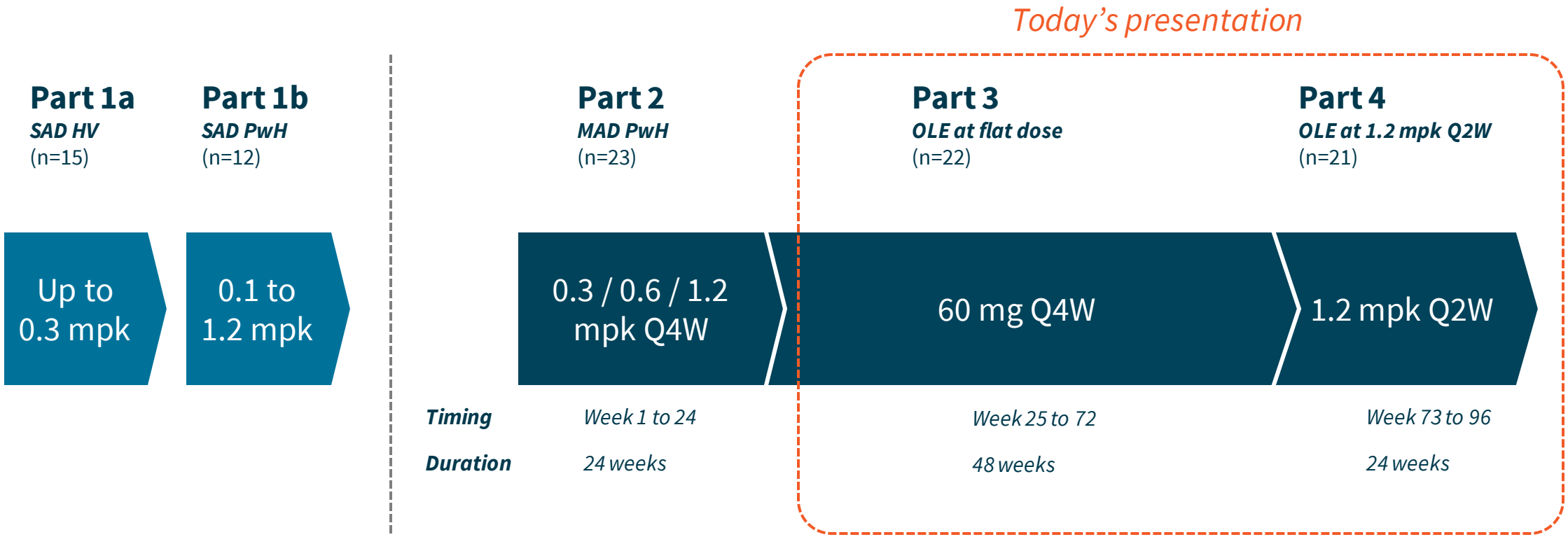
- Unprecedented biology with novel pharmacology
- Intended for subcutaneous prophylaxis across hemophilia subtypes
- Modified α1 anti-trypsin with 3 substitution mutations to confer selective inhibition of activated protein C (APC)
- Prevents bleeds by inhibiting APC to prolong prothrombinase activity and allow sufficient thrombin generation in the absence of intrinsic tenase

* SerpinPC is an investigational agent that has not been approved by the FDA or any other regulatory authority

SerpinPC and thrombin generation



AP-0101 study design: adaptive first-in-human study to investigate the safety, tolerability, efficacy and PK of SerpinPC



AP-0101 Parts 2-4: demographics, baseline characteristics and early terminations

Demographics and baseline characteristics

Characteristic	Value
Age, median (min to max)	**39** (21 to 56)
Number of subjects	**23** (including 12 from Part 1b SAD)
Prospective baseline Annualized Bleed Rate (ABR)[1], median (min to max)	**34.1** (22.8 to 53.0)
% subjects receiving previous prophylaxis	**0%**
% subjects with target joints[2]	**100%**
No. of target joints, median (min. to max.)	**2.5** (1 to 4)

Early terminations

Part	Early termination
Part 2	**1 subject** due to skin-rash – treatment-related[3]
Part 3	**1 subject** due to emigration to another country
Part 4	**1 subject** due to recto-sigmoid cancer – not related to treatment[3]

[1] Values for Part 3 subjects

[2] "Target joint" = joint with >3 bleeds in any 6-month period

[3] Determined by Safety Review Group

AP-0101 Parts 3 and 4: no observations of treatment-related adverse events

	Part 3 (n=22)		**Part 4** (n=21)	
Treatment Emergent Adverse Events	**Subjects with event** No. (%)	**Treatment-related***	**Subjects with event** No. (%)	**Treatment-related***
Elevated ALT	3 (14%)	0	3 (14%)	0
Elevated gamma-GT	0	NA	2 (10%)	0
COVID-19 infection	2 (9%)	0	1	0
Hepatic fibrosis	1	0	1	0
Chronic hepatitis C	0	NA	1	0
Fever	0	NA	1	0
Urinary tract infection	0	NA	1	0
Fracture	1	0	1	0
Radiculopathy	1	0	1	0
Elevated creatinine phosphokinase	1	0	0	NA
Anemia	1	0	1	0
Elevated sodium	0	NA	1	0
Rectosigmoid cancer	0	NA	1	0
Low neutrophil count	1	0	0	NA

* Determined by Safety Review Group

AP-0101 Parts 3 and 4: no observations of treatment-related, non-transient elevations in D-dimer

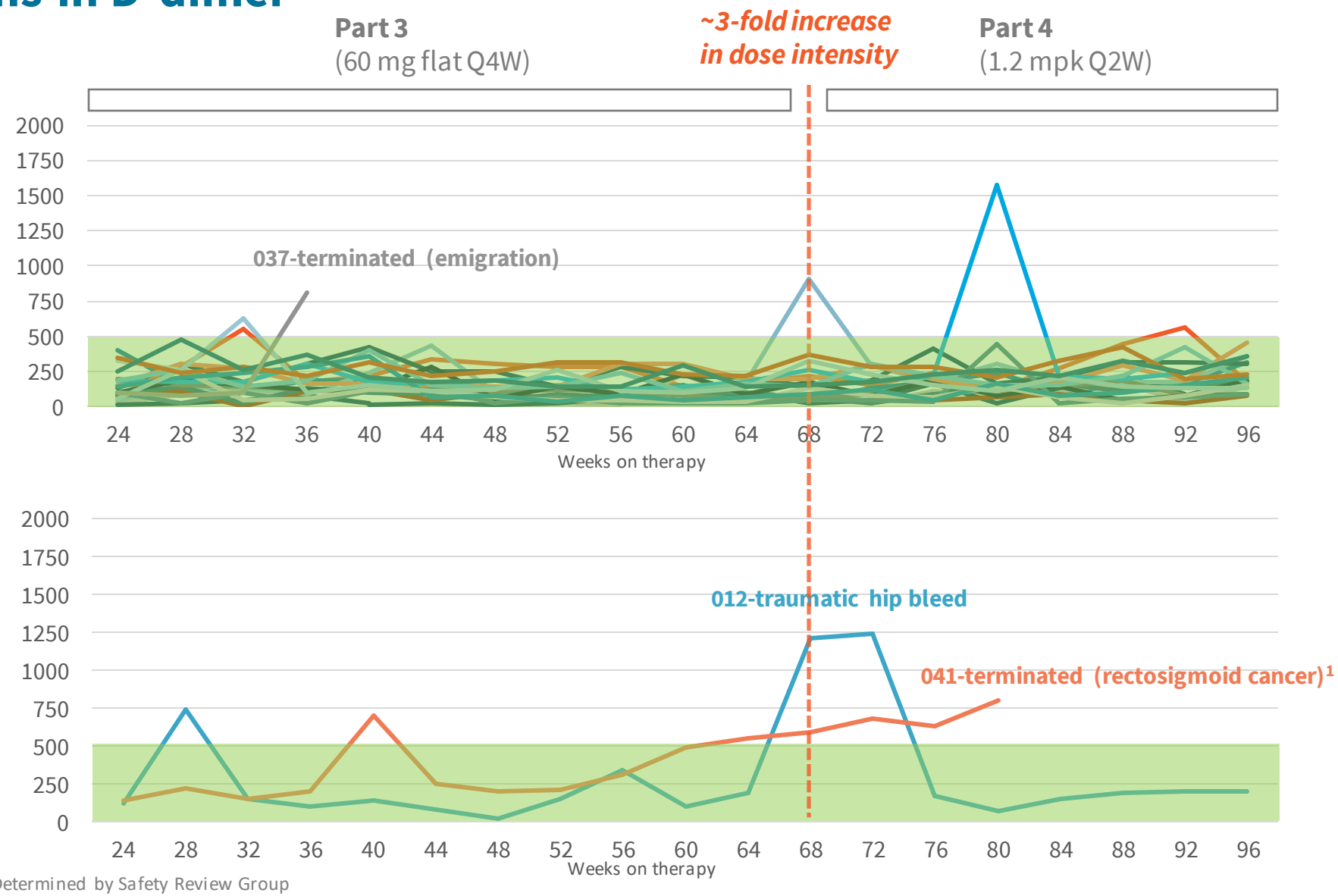
Result	Subjects in Part 3 (n=22) No. (%)	Subjects in Part 4 (n=21) No. (%)
Any result ≥ 500 ng/ml	5 (23%)	3 (14%)
2 consecutive results ≥ 500 ng/ml	2 of 5*	1 of 3**
Unexplained sustained elevation of D-dimer	**0 of 5**	**0 of 3**

>96% of D-dimer measurements were ≤ 500 ng/ml
(384 of 398 measurements)

* For Part 3, one subject with rectosigmoid cancer and one subject with traumatic hip bleed

**For Part 4, one subject with rectosigmoid cancer

AP-0101 Parts 3 and 4: no observations of treatment-related, non-transient elevations in D-dimer



[1] Not related to treatment - Determined by Safety Review Group

AP-0101: Anti-drug Antibodies (ADAs)

- **Samples were taken at trough (when there is least drug concentration) to increase likelihood of ADA detection**
  - Sensitivity 100 ng/mL at baseline dilution of 1:100
  - No ADA drug interference
- **Transient defined as**
  - i) positive on only one sample timepoint, or
  - ii) two or more sample timepoints separated by less than 16 weeks and negative at last timepoint
- **Persistent defined as**
  - i) positive at two or more sample timepoints during the treatment period and
  - ii) first and last positives (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer

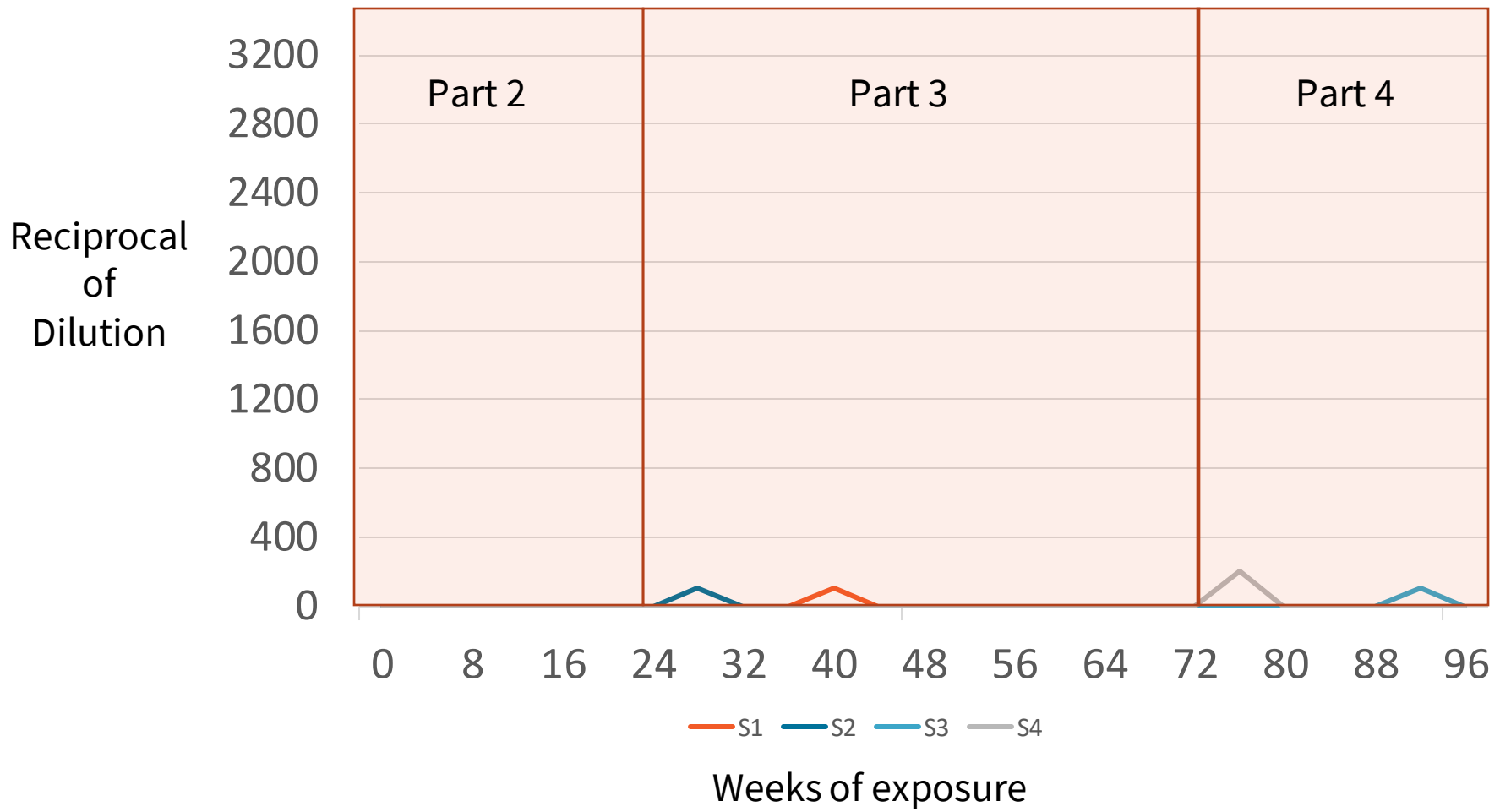
Harmonized Recommendations, Shankar et al. The APSS Journal 2014

AP-0101: Anti-drug Antibodies (ADAs)

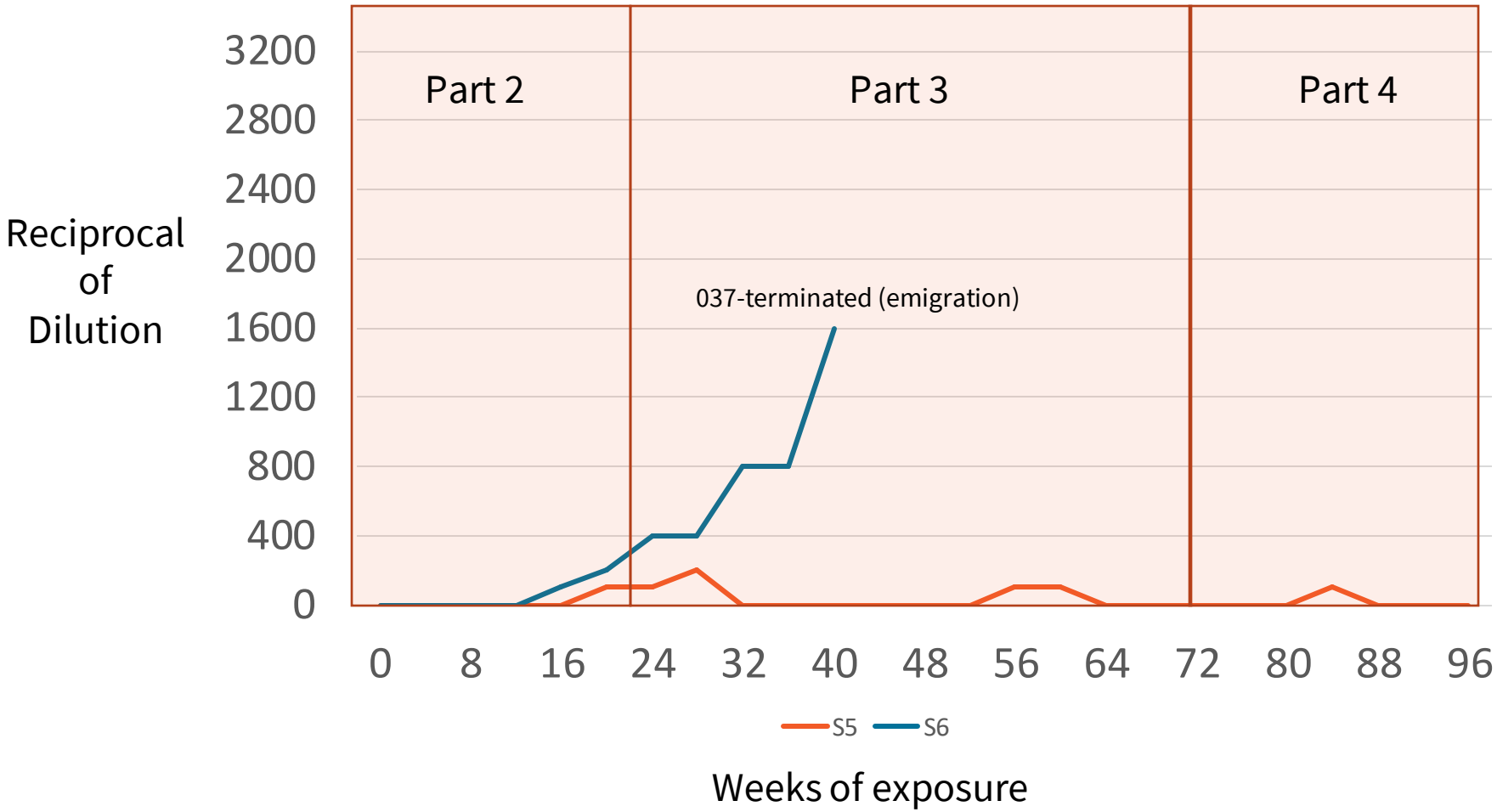
Result	Total duration Parts 1,2,3 & 4 (n=23) No.	Subjects in Part 3 (n=22) No.	Subjects in Part 4 (n = 21) No.
Any positive result	6	4	2
Transient	4	2	2
Persistent	2	2	1

>97% of ADA measurements were negative
(665 of 682 measurements)

AP-0101: Anti-drug Antibodies (ADAs) – transient titres



AP-0101: Anti-drug Antibodies (ADAs) - sustained titres



AP-0101 Parts 3 and 4: reduction in Annualized Bleed Rate (ABR)

All bleed ABR

Part	Median ABR from prospective baseline	Median ABR observed in this part	Median % change from baseline
Part 3 (n=22)	34.1	6.2	-83%
Part 4 (n=21)	35.5	2.2	-93%

Spontaneous joint bleed ABR

Part	Median ABR from prospective baseline	Median ABR observed in this part	Median % change from baseline
Part 3 (n=22)	27.5	4.3	-86%
Part 4 (n=21)	28.3	2.2	-93%

AP-0101 Parts 3 and 4: reduction in factor use

Factor VIII use (units/month)

Part	Median factor usage from prospective baseline	Median factor usage observed in this part	Median % change from baseline
Part 3 (n=22)	5,423	896	-74%
Part 4 (n=21)	5,382	535	-87%

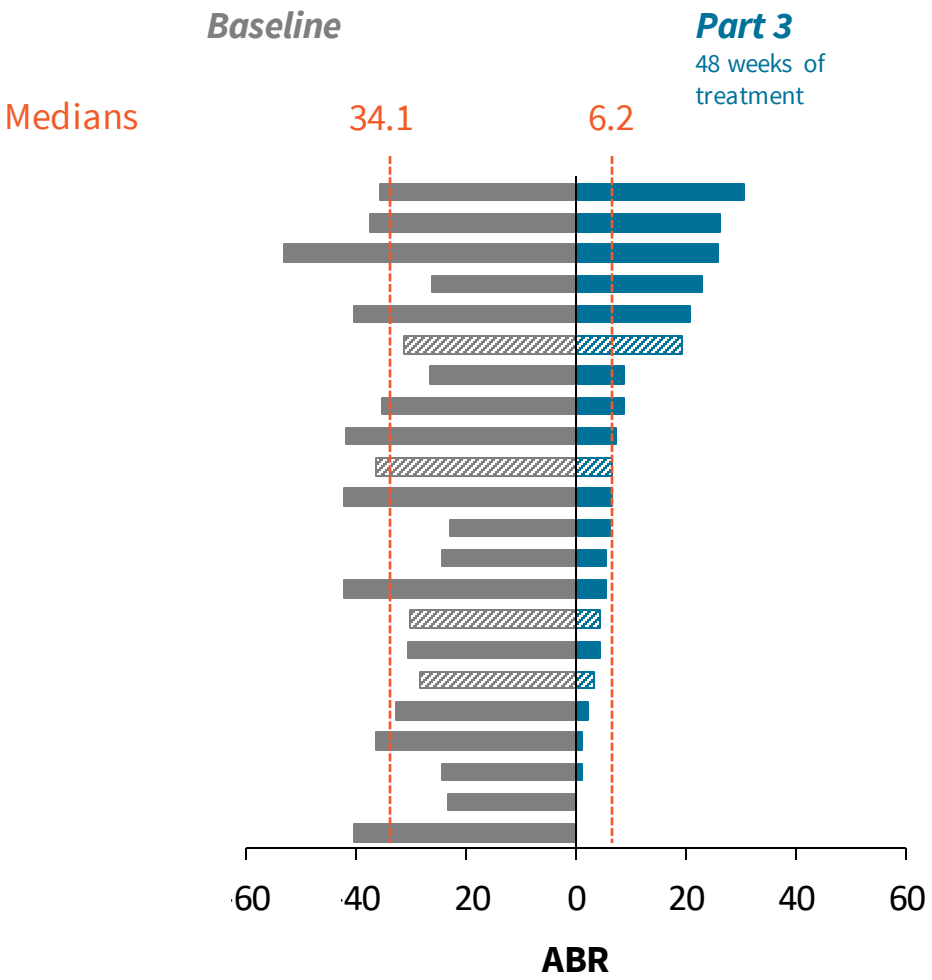
Factor IX use (units/month)

Part	Median factor usage from prospective baseline	Median factor usage observed in this part	Median % change from baseline
Part 3 (n=22)	5,241	905	-83%
Part 4 (n=21)	5,241	540	-90%

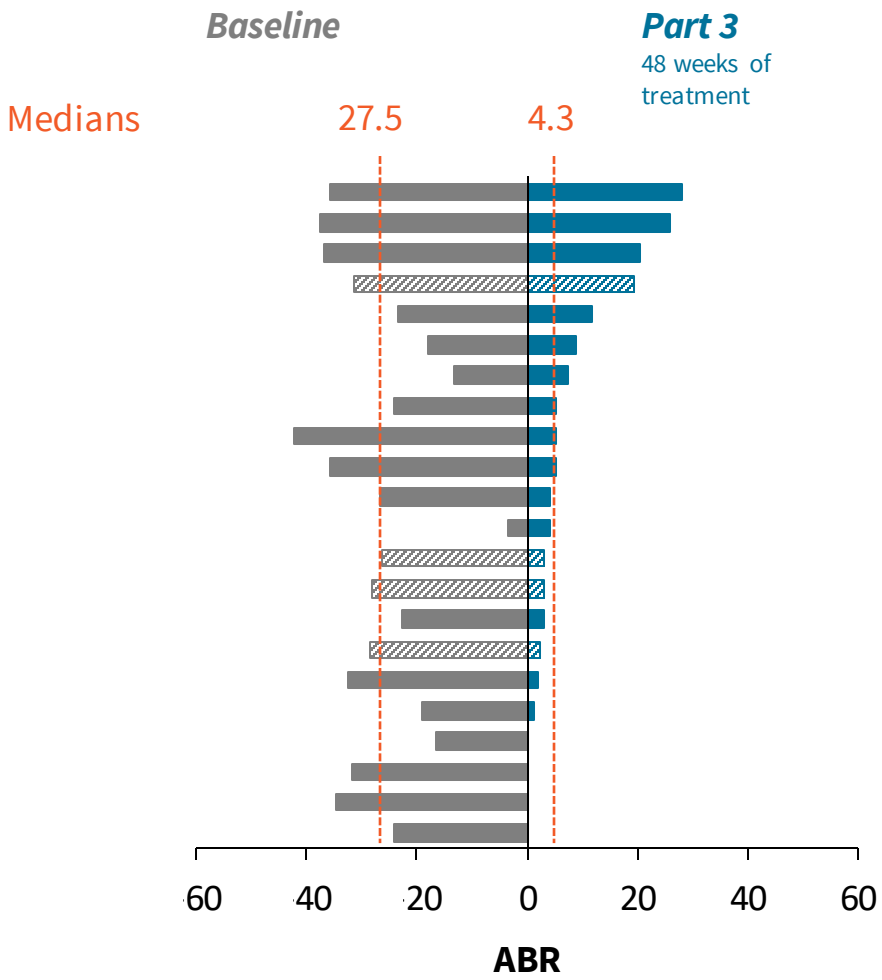
AP-0101 Part 3: ABR at 60mg Q4W flat dose

HemA
HemB

All bleeds ABR



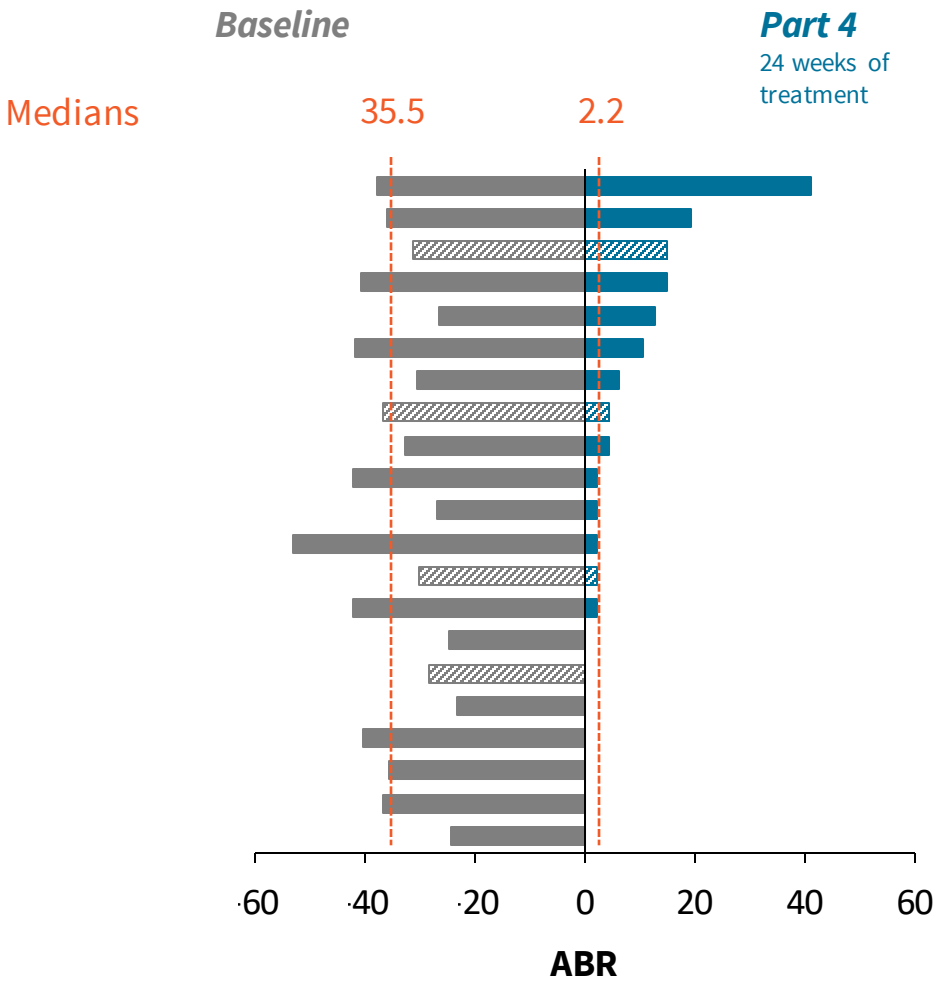
Spontaneous joint bleeds ABR



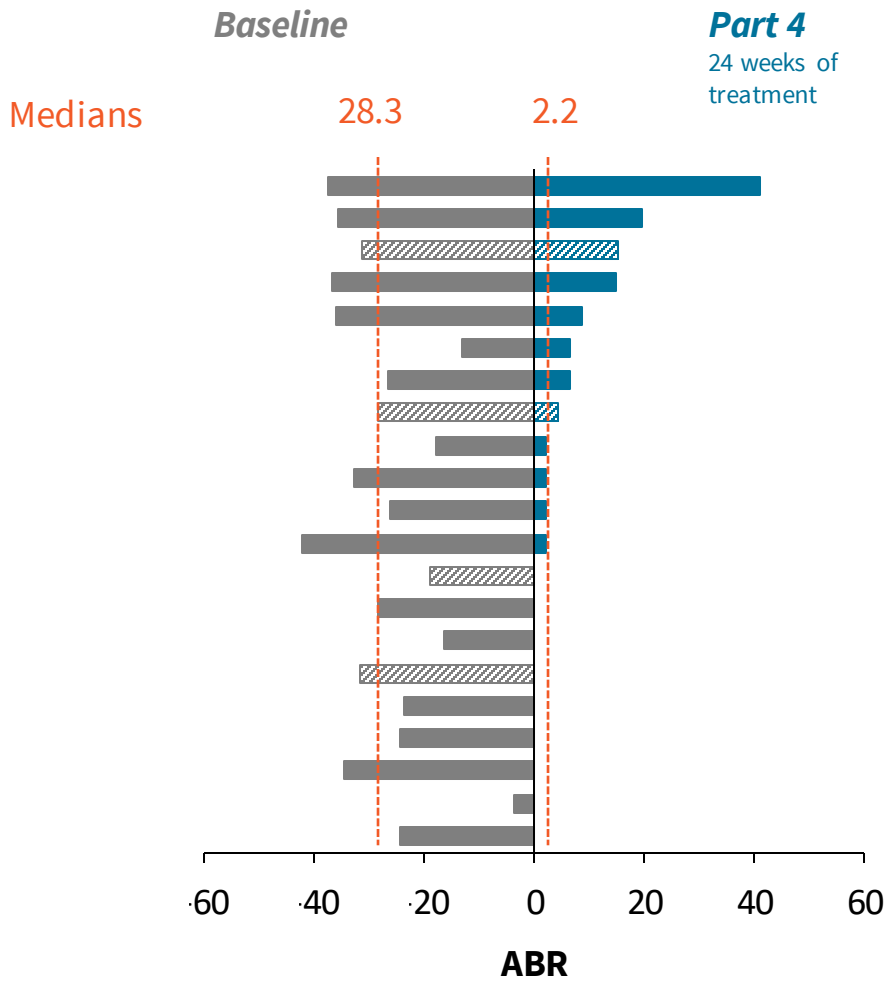
AP-0101 Part 4: ABR at 1.2 mpk Q2W

HemA
HemB

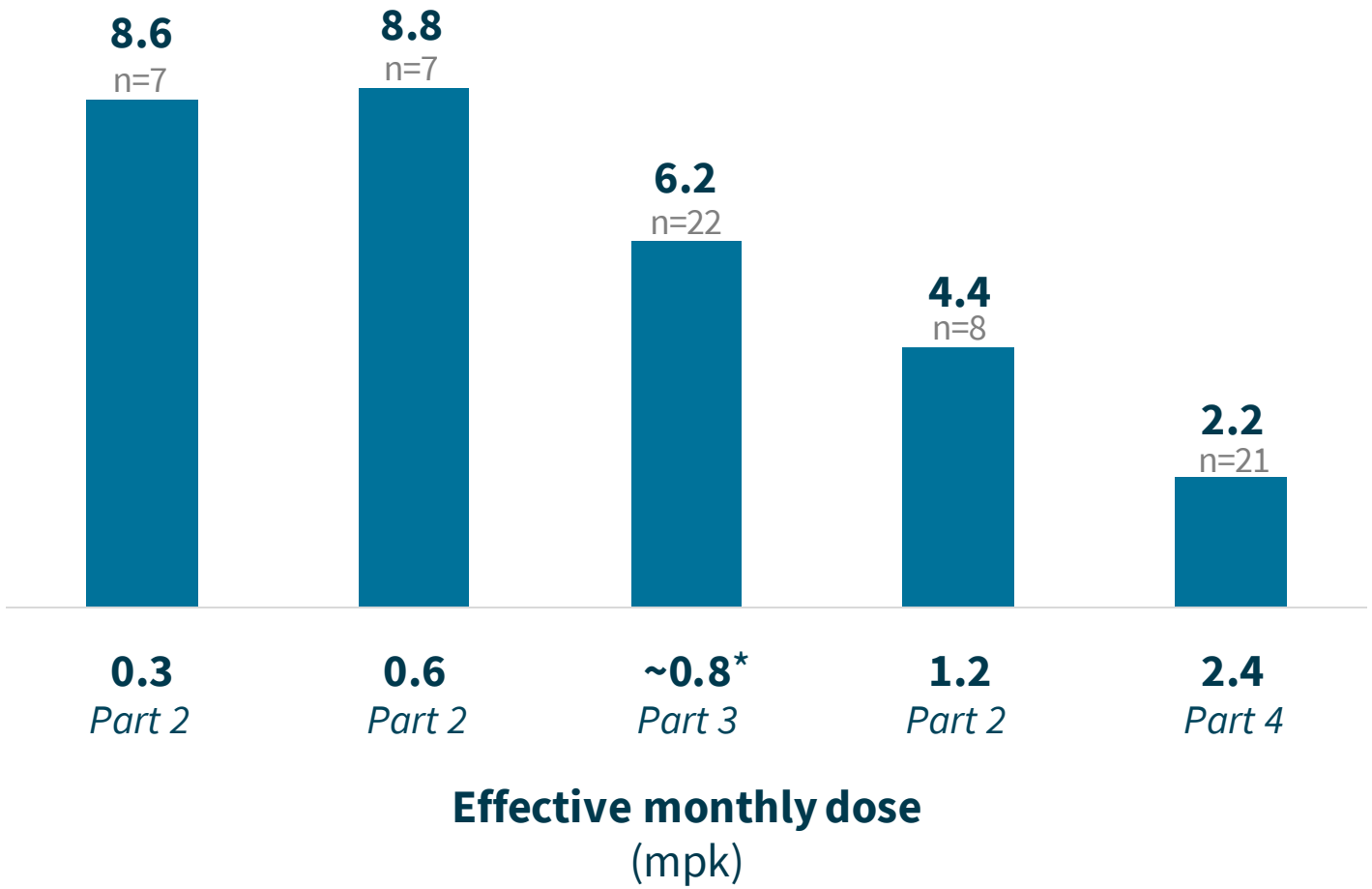
All bleeds ABR



Spontaneous joint bleeds ABR



AP-0101: All bleed median ABR by dose level



* 60 mg Flat dose which was equivalent to ~0.8 mpk

Summary

- **SerpinPC**
  - Novel MoA: inhibition of APC to rebalance coagulation
  - Potential to treat all subtypes of hemophilia
  - Subcutaneous route of administration

- **Results of Phase 2, Parts 3 and 4**
  - No observations of treatment-related adverse events
  - No observations of treatment-related sustained elevations of D-dimer
  - Low incidence of ADAs predominantly single weak positive transient results
  - All bleed median ABR of 2.2 (median percentage reduction from baseline of 93%) in Part 4

Thank you to all the persons who have and continue to participate in this study