SerpinPC in persons with severe haemophilia (PwH): updated results from a multicentre multi-part, first-in-human study

T Baglin*, A Koch[f], I Mocanu[+], L Makhaldiani[$], J Huntington*

*Centessa Pharmaceuticals plc, 1 Ashley Road, Altrincham, Cheshire, United Kingdom, WA14 2DT, [f]Simbec-Orion Clinical Pharmacology, Merthyr Tydfil, CF48 4DR, United Kingdom, [+]Arensia Exploratory Medicine, Testemitanu Str. 30, Chisinau, Republic of Moldova, [$]Arensia Exploratory Medicine, 13a Tevdore Mgvdeli Str. 0112, Tbilisi, Georgia

Disclosures for Trevor Baglin

Employee	Centessa Pharmaceuticals
Shareholder	Centessa Pharmaceuticals
Grant / Research Support	No relevant conflicts of interest to declare
Consultant	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	No relevant conflicts of interest to declare

Presentation includes discussion of the following off-label use of a drug or medical device:
<N/A>

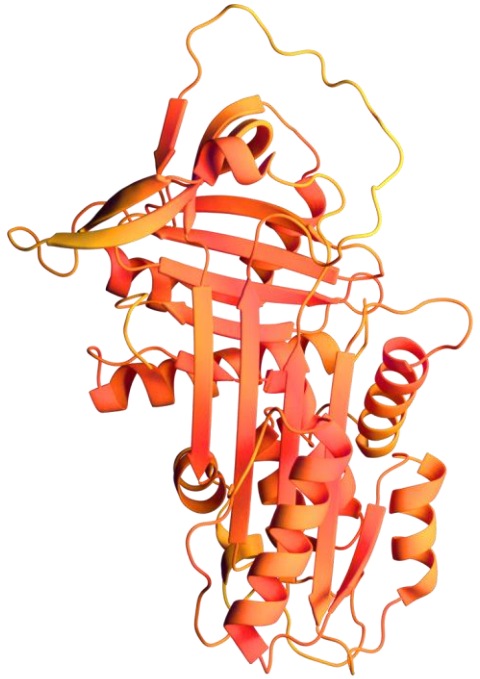
Disclaimer

This presentation has been prepared by Centessa Pharmaceuticals plc (the "Company") for informational purposes only and not for any other purpose. This presentation does not contain all the information that is or may be material to investors or potential investors and should not be considered as advice or a recommendation to investors or potential investors in respect of the holding, purchasing or selling of securities or other financial instruments and does not take into account any investor's particular objectives, financial situation or needs. The communication of this presentation may be restricted by law; it is not intended for distribution to, or use by any person in, any jurisdiction where such distribution or use would be contrary to local law or regulation. This presentation is not directed to or intended for distribution, or transfer, either directly or indirectly to, or use by, any person or entity that is a citizen or resident or located in any locality, state, country or other jurisdiction where such distribution, transfer, publication, availability or use would be contrary to law or regulation or which would require any registration or licensing within such jurisdiction.

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; our current expectations concerning, amongst other things, the development and therapeutic potential and benefits of our product candidates, including SerpinPC; the commencement, continuation and conclusion of new studies or clinical trials or clinical and preclinical data related to SerpinPC, and other Company programs (if any); the Company's ability to continue to meet the criteria for Fast Track designation; its ability to be eligible for Accelerated Approval, Priority Review, or Rolling Review; its ability to identify, screen, recruit, register and retain a sufficient number of or any subjects in its existing or anticipated new studies or clinical trials including PRESent-2, PRESent-3 and PRESent-5; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; enroll subjects in clinical trials; market size and opportunity for our product candidates; and our anticipated cash runway. Words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," and variations of these words or similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including, without limitation, risks related to our ability to protect and maintain our intellectual property position; business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oberland, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and risks related to the COVID-19 pandemic including the effects of the Delta, Omicron and any other variants, geo-political risks such as the Russia-Ukraine conflict and other risk factors contained in our filings with the U.S. Securities and Exchange Commission. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. All projections, valuations and statistical analyses are provided for information purposes only. **We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based, except as may be required by law. They** may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, they should not be relied upon as an accurate prediction of future performance.

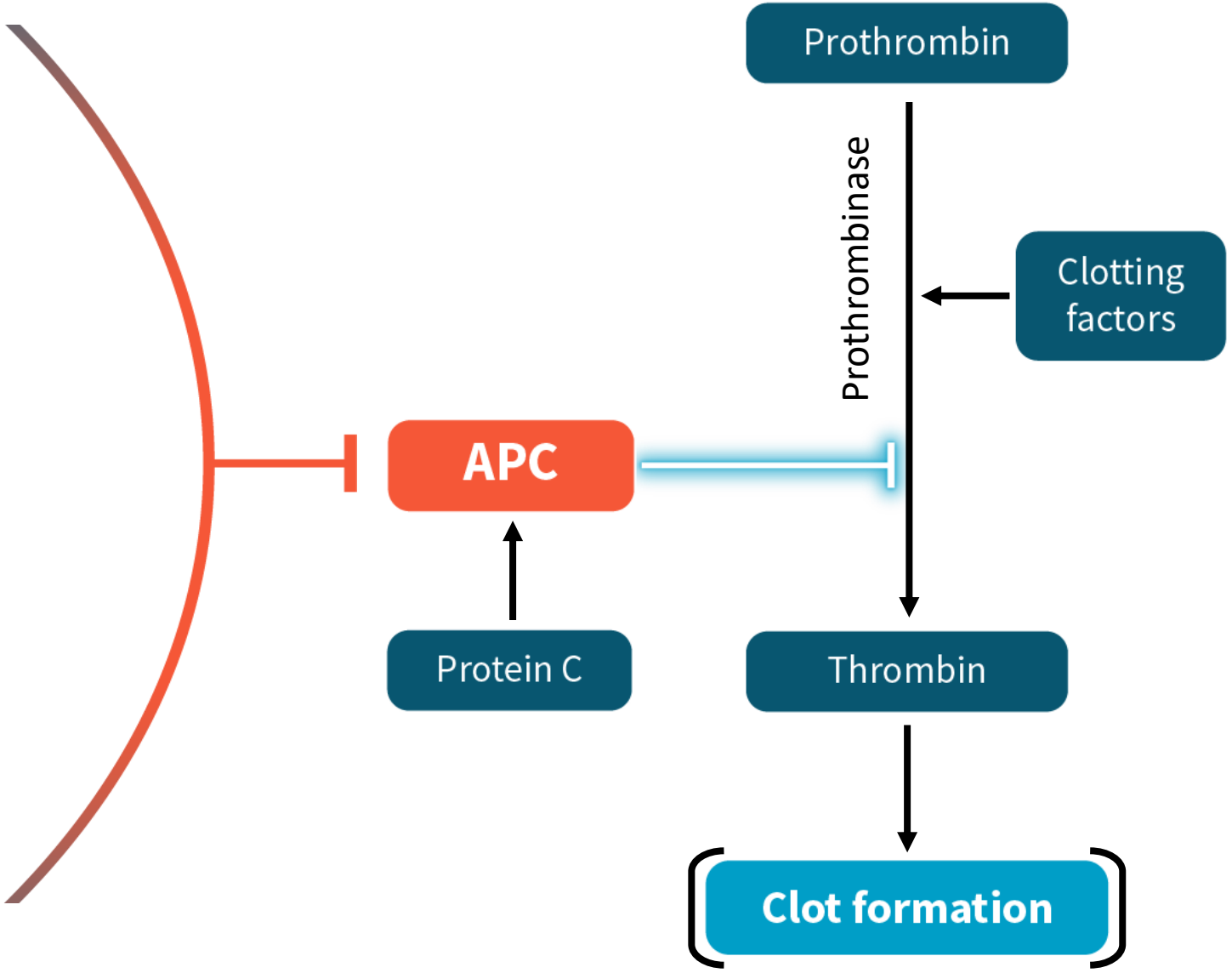
This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the U.S. Food and Drug Administration or any other regulatory agency. No representation or warranty, express or implied, is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third party sources and the Company's own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation or warranty, express or implied, as to the adequacy, fairness, accuracy or completeness of, any information obtained from third party sources. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

SerpinPC: a subcutaneously administered biologic inhibitor of APC

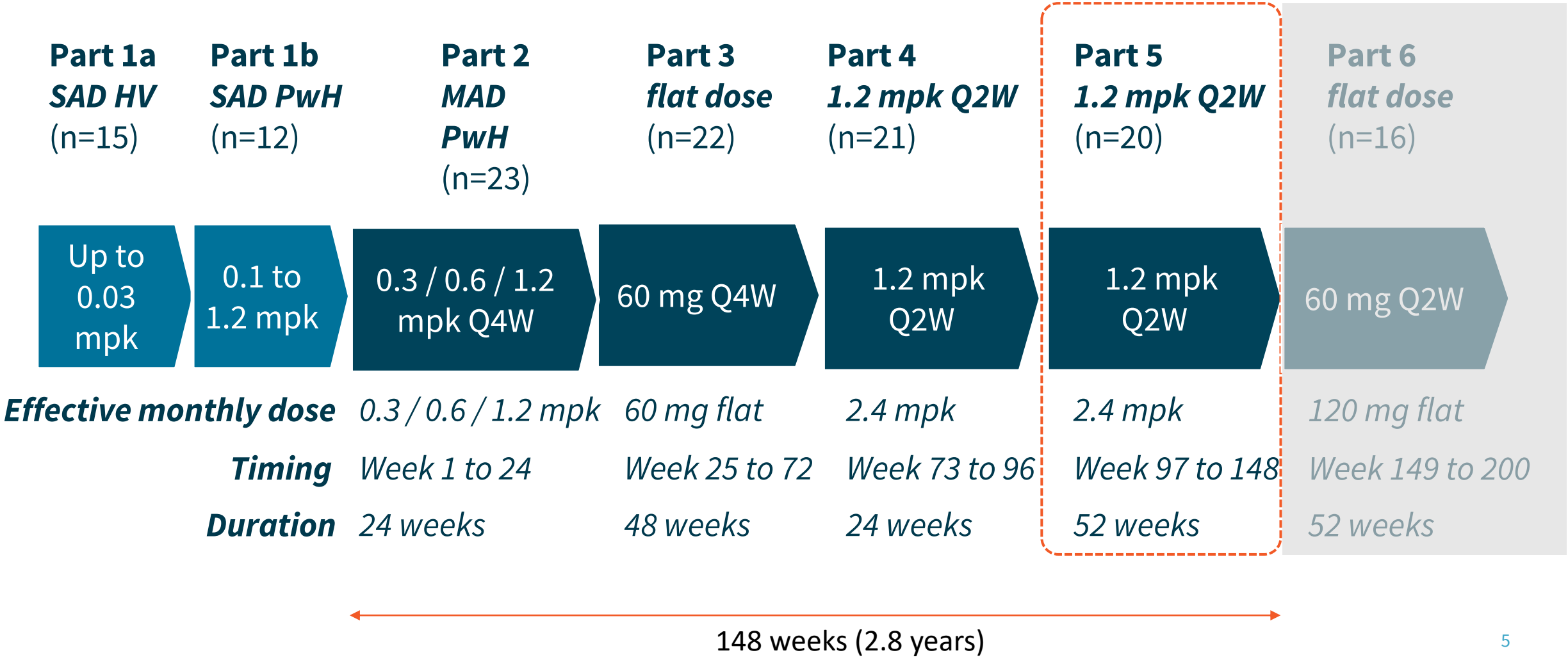


SerpinPC

Inhibits circulating activated protein C (APC)



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



AP-0101 Part 5: demographics, baseline characteristics and early terminations

Patient Characteristics	Value
Number of subjects (Hemophilia A / B)	**20** (16 / 4)
Age in years, median (min to max)	**40** (21 to 56)
Weight kg (min to max)	**74** (54 to 91)
Prospective ABR, median (min to max)	**35.6** (23 to 53)
% subjects receiving previous prophylaxis	**0%**
% subjects with target joints	**100%**
No. of target joints*, median (min to max)	**3** (1 to 4)
Total number of target joints	**53**
Early terminations in Part 5	**4****

* "Target joint" is defined as any joint with >3 bleeds in 6 months prior to SerpinPC exposure

** Early terminations were not related to study drug. Subject 300-027 suffered a femur fracture and discontinued treatment on Day 126 of Part 5. Subject 300-034 emigrated and discontinued treatment on Day 182. Subject 300-038 left the country for an extended period and discontinued treatment on Day 388. Subject 300-040 moved a distance away from the site and discontinued treatment on Day 102. For early terminations, ABR and target joints are calculated based on the treatment period.

AP-0101 Part 5: No observation of treatment-related adverse events

Treatment Emergent Adverse Events (TEAEs)	Number of subjects (%) n=20
All TEAEs (total 41 events)	16 (80%)
Related to SerpinPC	**0**
Leading to discontinuation	1 (5%)
Leading to death	0
AEs of special interest	0
Serious adverse events	2 (10%)*
Thromboembolic events	0
Injection site reactions	0
Anti-drug antibodies	1#
Neutralizing anti-drug antibodies	0#

*Two SAEs occurred and were considered unrelated to study drug: (1) traumatic fracture of femur (led to discontinuation) (2) traumatic epididymitis
Preliminary finding

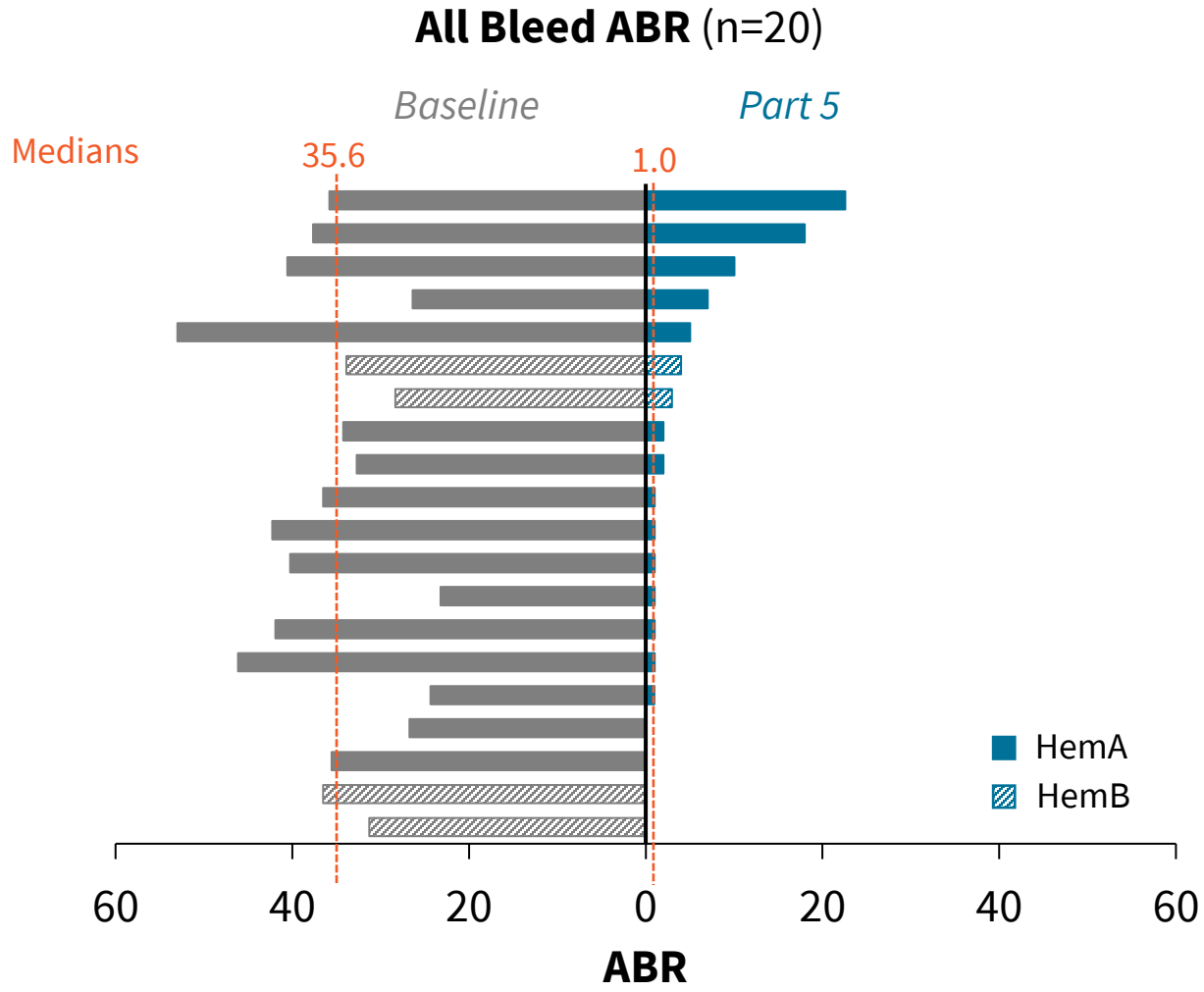
AP-0101 Part 5: Reduction in Annualized Bleed Rate (ABR) & Target Joints

Annualized Bleed Rate (ABR)			
	Baseline (n=20)	**Part 5** (n=20)	**Change*** (%)
All bleeds (median) Interquartile range	35.6 29.8 to 40.4	1.0 1.0 to 4.5	**-96%** -89% to -98%
Spontaneous joint bleeds (median) Interquartile range	30.3 24.0 to 35.2	1.0 0.0 to 3.0	**-95%** -90% to -100%

Target Joints			
	Baseline (n=20)	**Part 5** (n=20)	**Change** (%)
Target joints per patient (median)	3	0	**-100%**
Total number of target joints in cohort	53	3	**-94%**

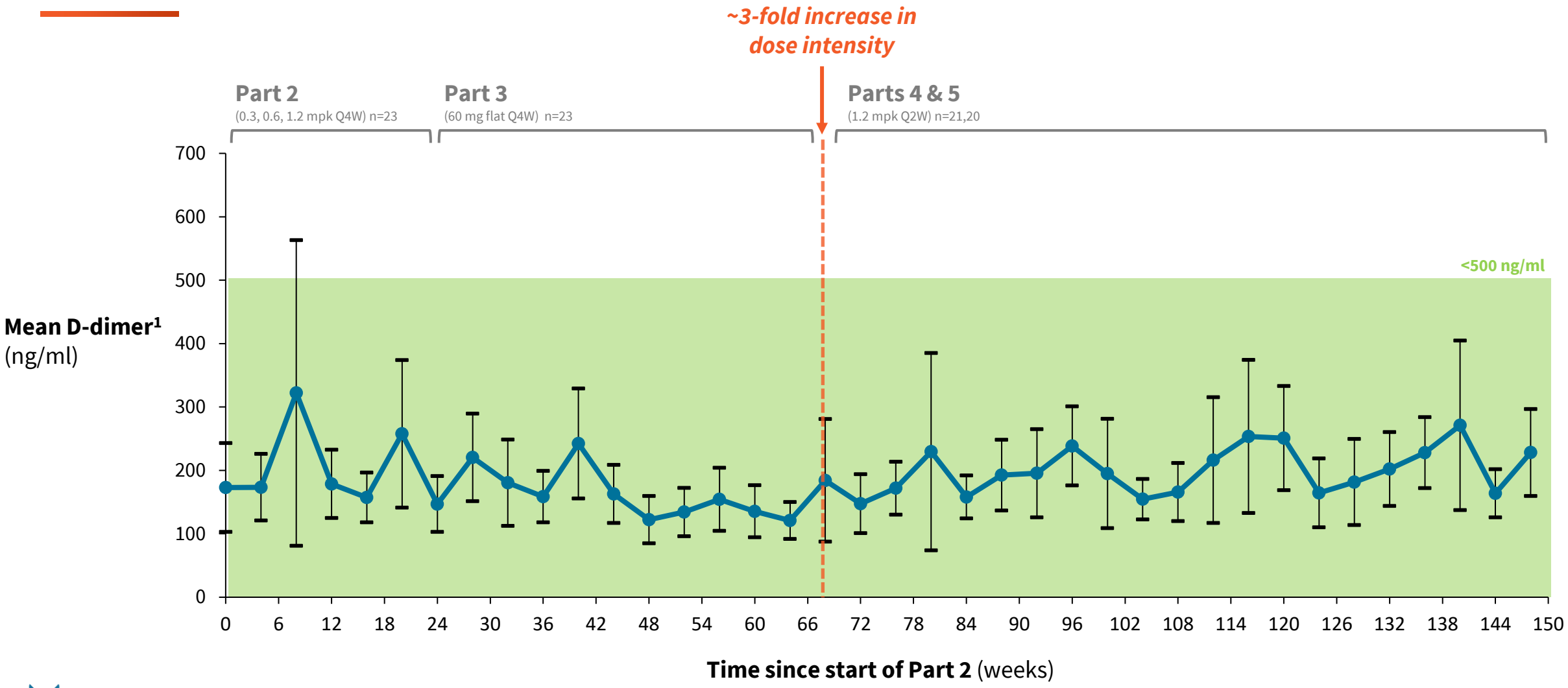
*Median of individual changes calculated by comparing the baseline value from each subject with the Part 5 value from the same subject.

96% median reduction in annualized bleeding rates at 1.2 mpk Q2W after continuous treatment with SerpinPC



- **Median all bleed ABR of 1.0**
- **96% median reduction from baseline in all bleed ABR**
- **Only 2 subjects with target joints at end of Part 5** vs. all 20 patients with target joints at baseline

No observations of unexplained, sustained elevations of D-dimer values over 148-weeks of treatment



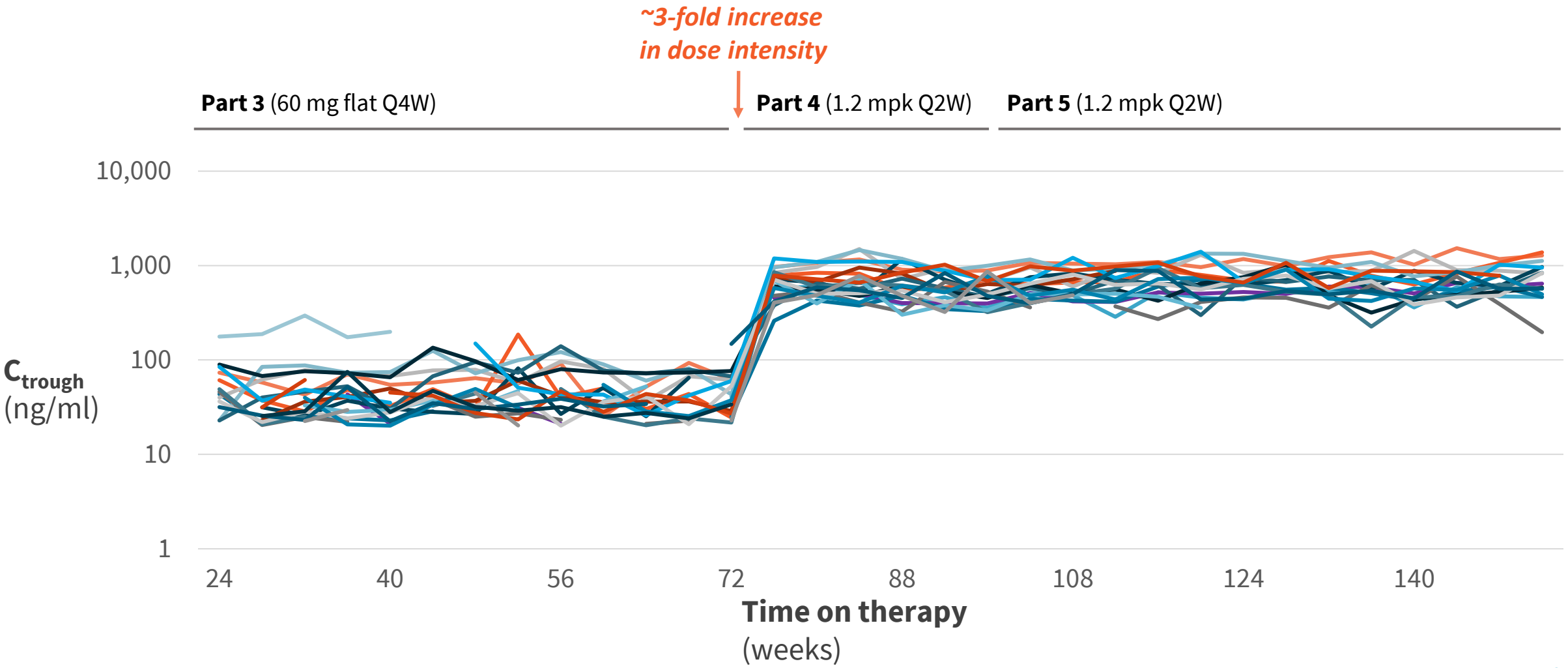
1. Error bars represent 95% confidence interval

Note: Values from three instances of trauma, cancer and infection determined to represent explained D-dimer elevation and omitted from calculation (Subject 200-012 traumatic hip bleed, week 68 and 72; Subject 300-041 rectosigmoid cancer, Weeks 60-98; Subject 300-032 periodontitis, weeks 128 to 130

Pharmacokinetic parameters measured in Part 5

Parameter	**Mean value** (std. dev.)
$\mathbf{T_{max}}$ (n=20)	**74 hr** (28)
$\mathbf{t_{1/2}}$ (n=17)	**99 hr** (10)
$\mathbf{C_{max}}$ (n=20)	**3184 ng/ml** (1122)
$\mathbf{AUC_{0\text{-}t}}$ (n=19)	**564 hr*µg/ml** (148)
$\mathbf{AUC_{0\text{-}inf}}$ (n=17)	**673 hr*µg/ml** (21)

Consistent C_{trough} with no evidence of accumulation (Parts 3, 4, 5)



Summary of Part 5 Anti-Drug Antibody (ADA) results

- **In Part 5, 1 transient ADA response observed out of 20 subjects**
  - Subject had a single instance of an ADA at the limit of detection (1:100 dilution). Same sample was negative in the neutralizing anti-drug antibody test
  - Subject had an ABR of 0.99 in Part 5
  - Subject had an average C_{trough} of 619 ng/ml (min 422 to max 911 ng/ml in Part 5) vs. mean of 681 ng/ml for all subjects in Part 5
- **No anti-drug antibody cross-reactive to α1-antitrypsin* observed in any subject**

CENTESSA PHARMACEUTICALS

*SerpinPC is derived from α1-anti-trypsin, whose amino acid sequence is 99% identical

Summary

- **SerpinPC was shown to have a safe and well tolerated profile after repeat dose exposure for 2.8 years**
  - No observations of SerpinPC-related AE's in Parts 2 through 5, except for 1 resolved, moderate injection site reaction in a subject with a pre-existing skin condition
  - No observations of unexplained, sustained D-dimer elevations
  - PK parameters were observed to be stable and consistent
- **2.8 years of continuous treatment with SerpinPC reduced ABR and target joint bleeds**
  - Median all bleed ABR of 1.0 in Part 5
  - 96% reduction in all bleed ABR from baseline
  - 94% reduction in target joints across the study population

CENTESSA PHARMACEUTICALS