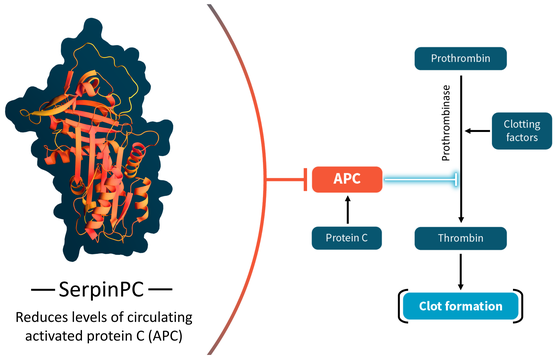
SERPINPC IN PERSONS WITH SEVERE HEMOPHILIA (PWH): UPDATED RESULTS FROM A MULTI-CENTER MULTI-PART FIRST-IN-HUMAN STUDY

T. BAGLIN[1], I. MOCANU[2] , L. MAKHALDIANI[3] , A.KOCH[4] , J. HUNTINGTON[1]

1. Centessa Pharmaceuticals plc, Altrincham, WA14 2DT, United Kingdom
2. Institute of Oncology, ARENSIA Exploratory Medicine, Testemitanu Str. 30, Chisinau, Republic of Moldova
3. Arensia Exploratory Medicine, 13a Tevdore Mgvdeli Str. 0112, Tbilisi, Georgia
4. Simbec-Orion Clinical Pharmacology, Merthyr Tydfil, CF48 4DR, United Kingdom

BACKGROUND

SerpinPC is an investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit Activated Protein C (APC) and facilitate thrombin generation.



APC is an endogenous protein with anticoagulant properties that breaks down prothrombinase and serves as a “brake” on the thrombin generation “engine”.

In hemophilia, deficiency of intrinsic Xase leads to a decrease in prothrombinase. This, along with the inhibitory action of APC, leads to a reduction in thrombin generation.

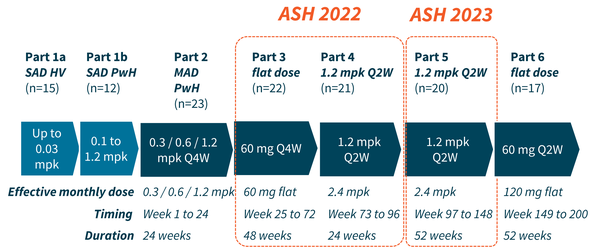
By inhibiting APC, SerpinPC is hypothesized to “release the brake,” preserving prothrombinase and restoring thrombin generation.

AP-0101 is a first-in-human Phase 1/2a open-label multicenter study utilizing an adaptive design to investigate the safety, tolerability, pharmacokinetics and efficacy of SerpinPC in subjects with severe hemophilia A and B.

Previously presented data showed that administration of SerpinPC was well tolerated and reduced bleeding in persons with severe hemophilia with no observations of unexplained chronic elevations in D-dimer, an indicator of excessive thrombin generation.

Here we present the results of Part 5, in which 20 subjects who completed Part 4 continued to receive 1.2 mg/kg of SerpinPC once every 2 weeks for 52 weeks.

STUDY DESIGN



Part 1 was a Single Ascending Dose Study of SerpinPC in 15 healthy male volunteers and 12 males with severe hemophilia. Part 2 enrolled 23 males with severe hemophilia (19 hemophilia A and 4 hemophilia B), who were not on replacement factor prophylaxis, to receive SerpinPC at 0.3, 0.6 or 1.2 mg/kg, administered as a subcutaneous (SC) injection once every 4 weeks over a 24-week period (6 total doses). Parts 3, 4 and 5 were sequential extensions in which subjects received either a flat dose of 60 mg once every 4 weeks (Part 3) or 1.2 mg/kg once every 2 weeks (Parts 4 & 5).

All self-reported treated bleeds were recorded in patient diaries. The baseline ABR was determined from a prospective observation period of 2 to 6 months before exposure to SerpinPC, during which time patients received usual on-demand clotting factor concentrate to treat breakthrough bleeds.

During treatment with SerpinPC all breakthrough bleeds were treated on-demand with usual clotting factor concentrate, without dose reduction and without limitation of number of infusions.

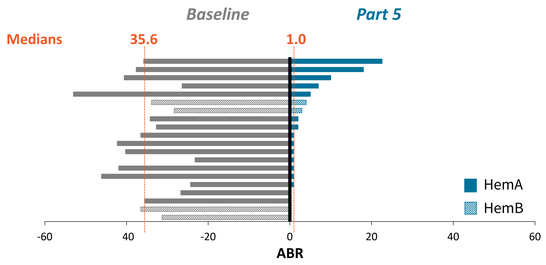
SUBJECTS

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 (30 to 40)
% subjects receiving previous prophylaxis	0%
% subjects with target joints	100%
No. of target joints, median (min to max) (>3 bleeds in 6 months prior to SerpinPC exposure)	3 (2 to 3.5)
Total number of target joints	53
Early terminations	3*

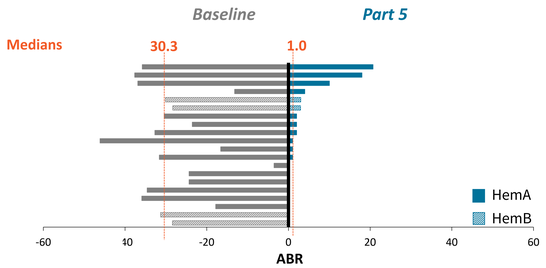
* All early terminations unrelated to study drug; two subjects emigrated (week 10 and week 22) and one subject exited after a femur fracture

EFFICACY

All bleed ABR



Spontaneous joint bleeds ABR



Individual baseline and Part 5 ABRs are shown above. Baseline ABRs in grey and ABRs during treatment with SerpinPC in blue. Subjects with hemophilia B shown by hatched bars.

Annualized Bleed Rate (ABR)			
	Baseline	Part 5	Change (%)
All bleeds (median)	35.63	1.00	-31.01 (-96%)
95% CI	31.85; 38.89	1.17; 7.00	-35.58; -26.99
Spont. joint bleeds (median)	30.28	1.00	-26.13 (-95%)
95% CI	23.59; 32.75	0.60; 6.17	-29.26; -20.30

All 20 patients had target joints before exposure to SerpinPC. At the end of Part 5 only 2 subjects still had a target joint. One subject still had 2 target joints and one subject who started with 3 had only 1. Total number of target joints was reduced by 94% from 53 to 3.

Target Joints			
	Baseline	Part 5	Change (%)
median	3.00	0.00	-2.50 (-100%)
95% CI	2.16; 3.14	-0.08; 0.38	-3.06; -1.94

SAFETY

Treatment Emergent Adverse Events (TEAEs)	Number of subjects (%)
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	
Transient	1 (5%)#
Persistent	0

D-Dimer	
% results < 500 ng/ml	**96%** (251/262)
No. of patients with sustained elevated D-dimer	1†
No. of patients with unexplained sustained elevated D-dimer	0

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

Preliminary finding

† One subject with periodontitis with jaw swelling. D-dimer reduced following commencement of antibiotics.

CONCLUSIONS

- **SerpinPC was shown to be well tolerated with exposures up to 3.8 years.**
- **No unexplained sustained D-dimer elevations were observed in Part 5, consistent with Parts 1-4.**
- **No SerpinPC-related AEs were observed in Part 5.**
- **Part 5 median all bleed ABR was 1.00, a 96% reduction from the pre-exposure baseline ABR.**
- **Data showed that 94% of target joints had resolved by the completion of Part 5.**

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