FIG. 1

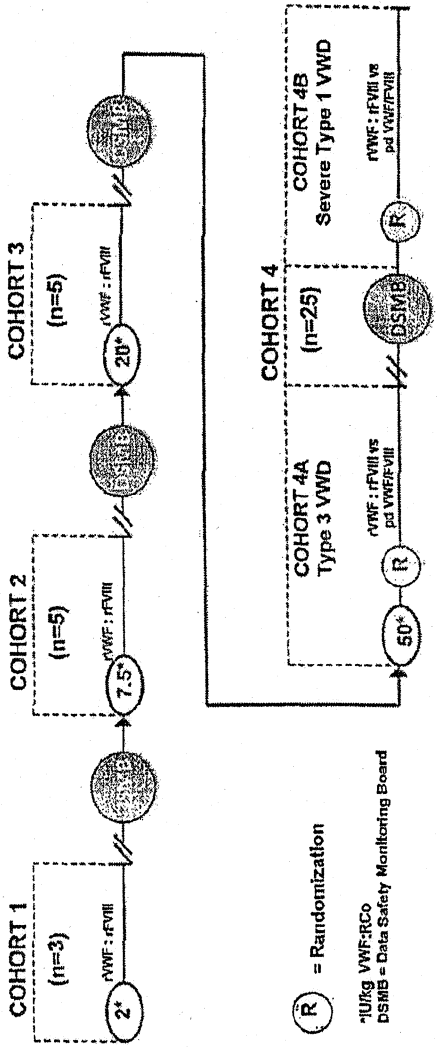
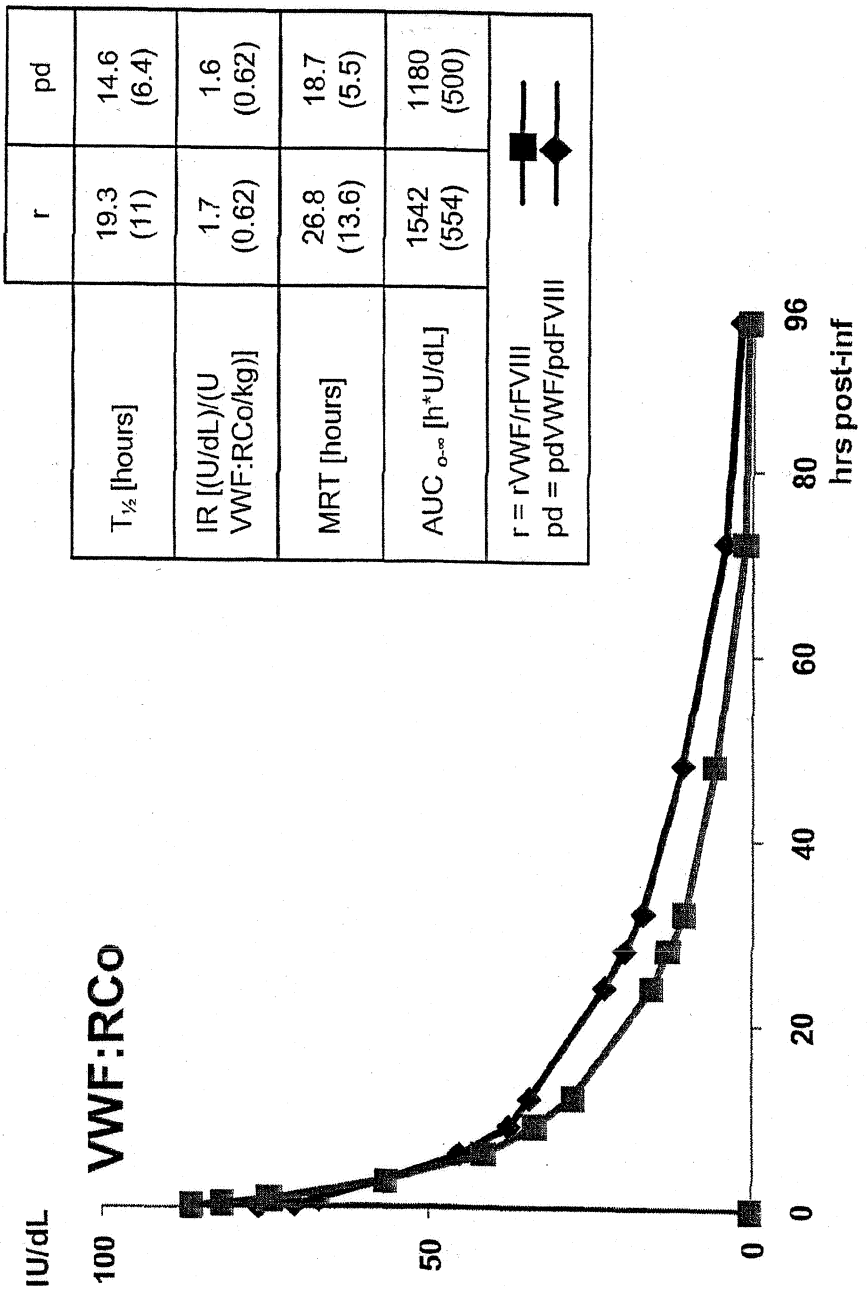

COHORT 1
(n=3)
rVWF : rFVIII
2*
COHORT 2
(n=5)
rVWF : rFVIII
7.5*
COHORT 3
(n=5)
rVWF : rFVIII
20*
COHORT 4
COHORT 4A
Type 3 VWD
(n=25)
rVWF : rFVIII vs pd VWF/FVIII
50*
COHORT 4B
Severe Type 1 VWD
rVWF : rFVIII vs pd VWF/FVIII
DSMB
R = Randomization
*IU/kg VWF:RCo
DSMB = Data Safety Monitoring Board

FIG. 2A



	r	pd
$T_{½}$ [hours]	19.3 (11)	14.6 (6.4)
IR [(U/dL)/(U VWF:RCo/kg)]	1.7 (0.62)	1.6 (0.62)
MRT [hours]	26.8 (13.6)	18.7 (5.5)
$AUC_{0-\infty}$ [h*U/dL]	1542 (554)	1180 (500)
r = rVWF/rFVIII pd = pdVWF/pdFVIII		

FIG. 2B

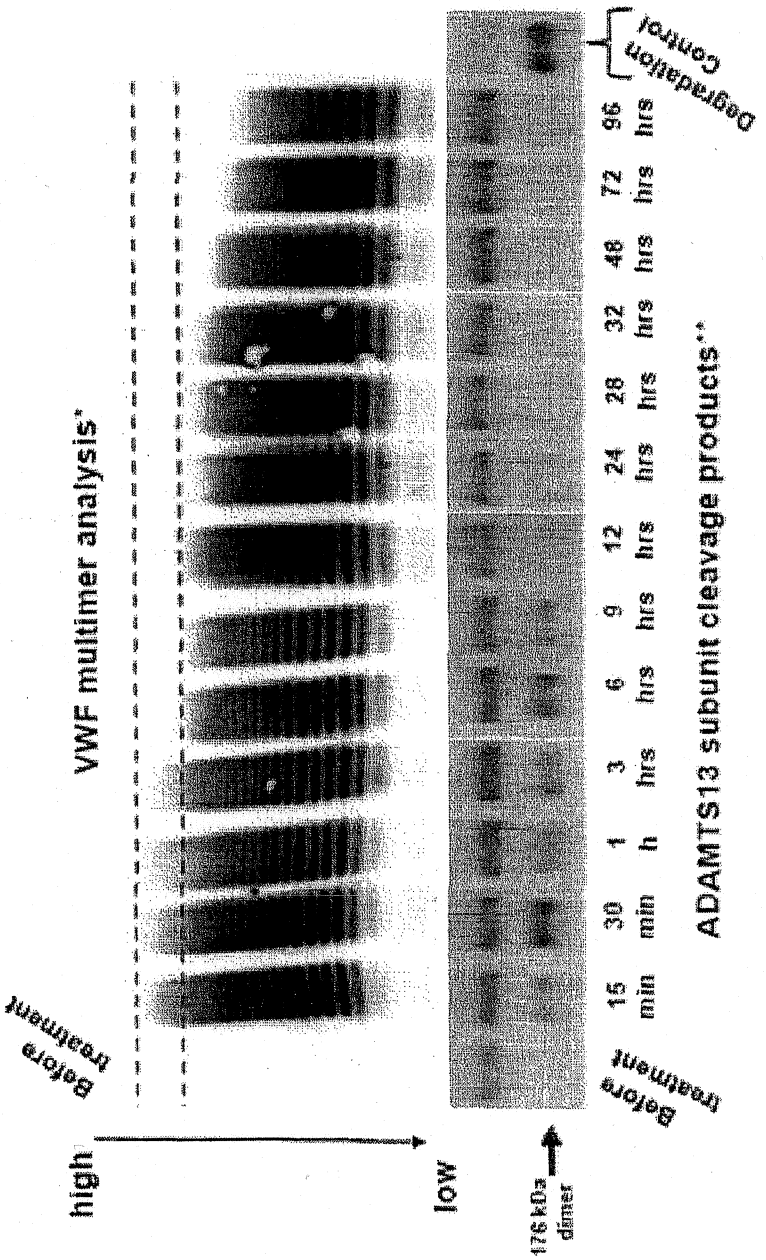

VWF multimer analysis*
Before treatment
high
low
ADAMTS13 subunit cleavage products**
Before treatment
176 kDa dimer
15 min
30 min
1 h
3 hrs
6 hrs
9 hrs
12 hrs
24 hrs
28 hrs
32 hrs
48 hrs
72 hrs
96 hrs
Degradation Control

FIG. 3

	r	pd
$T_{½}$ [hours]	24.3 (6.5)	19 (5.1)
IR [(U/dL)/(U VWF:RCo/kg)]	2.1 (0.8)	1.3 (0.3)
MRT [hours]	38.9 (12.4)	32.7 (7.5)
AUC $_{0-\infty}$ [h*U/dL]	5376 (2380)	3361 (1350)

r = rVWF/rFVIII
pd = pdVWF/pdFVIII

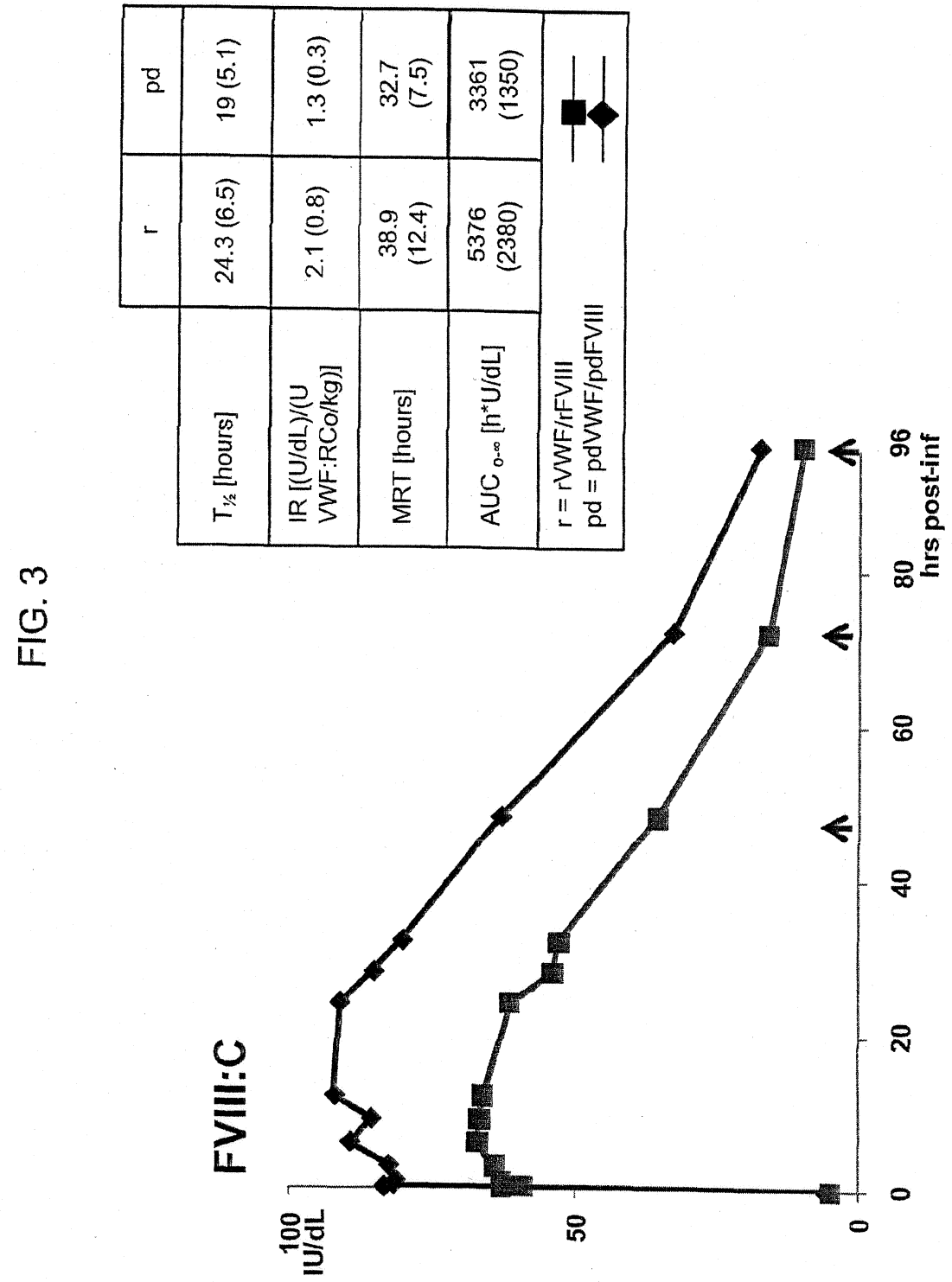
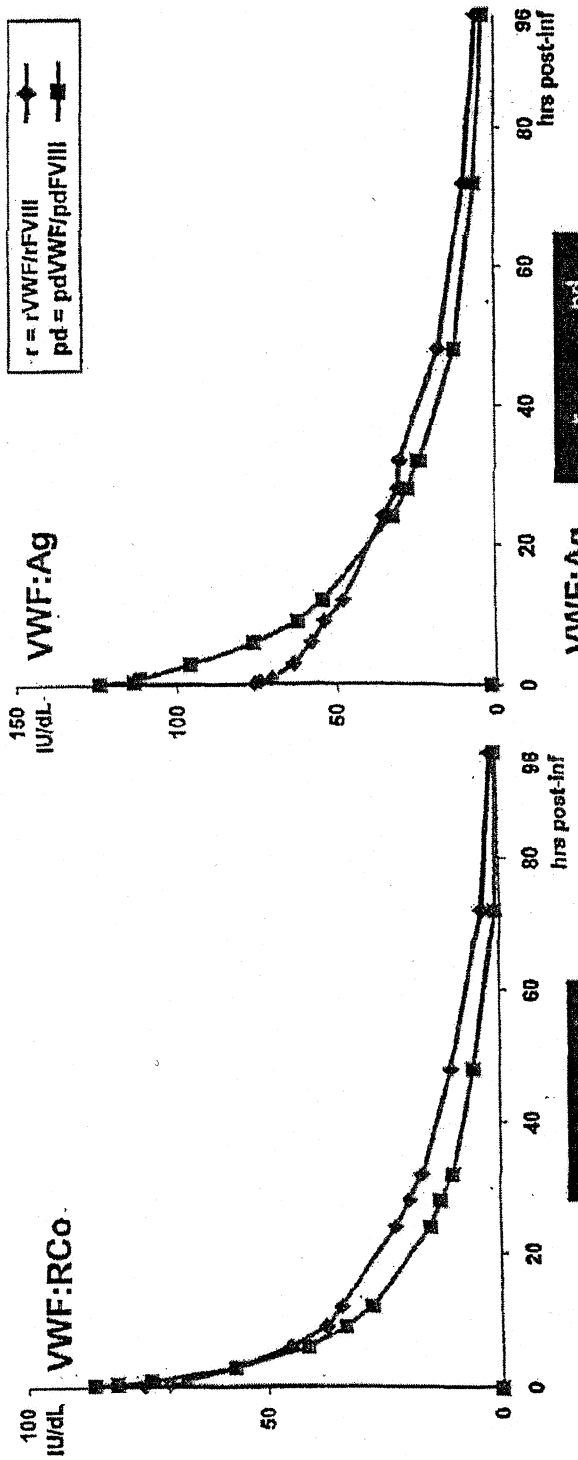


FIG. 4

COHORT	# of patents	Gender (Female/Male)	Age (years) Median (range)	Weight (kg) Median	Ethnicity
1 (Type 3)	3	1/2	38 (26-44)	130	Caucasian
2 (Type 3)	5	2/3	26 (21-39)	86.2	Caucasian
3 (Type 3)	5	0/5	34 (19-55)	79	4 Caucasian 1 Asian
4A (Type 3) (50 IU/kg VWF:RCo)	22	11/11	33 (18-60)	74.8	Caucasian
4B (Severe Type 1)	3	2/1	25 (19-47)	82.1	Caucasian
Total	32*	15/17	33 (18-60)	81.1	31 Caucasian 1 Asian

*Six subjects from cohort 1-3 were re-enrolled in cohort 4A

FIG. 5



VWF:Ag	r	pd
IR [(U/dL)/(U VWF:RCo/kg)]	1.7 (0.55)	2.3 (0.67)
$T_{1/2}$ [hours]	25.3 (6.3)	18.2 (3.3)
MRT [hours]	33.6 (10.7)	22.4 (5.2)
AUC $_{0-\infty}$ [h*U/dL]	2245 (683)	2254 (1012)

VWF:RCo	r	pd
IR [(U/dL)/(U VWF:RCo/kg)]	1.7 (0.62)	1.6 (0.62)
$T_{1/2}$ [hours]	19.3 (10.9)	14.6 (6.4)
MRT [hours]	26.8 (13.6)	18.7 (5.5)
AUC $_{0-\infty}$ [h*U/dL]	1542 (554)	1180 (500)

All values are "means" () Standard Deviation.

FIG. 6

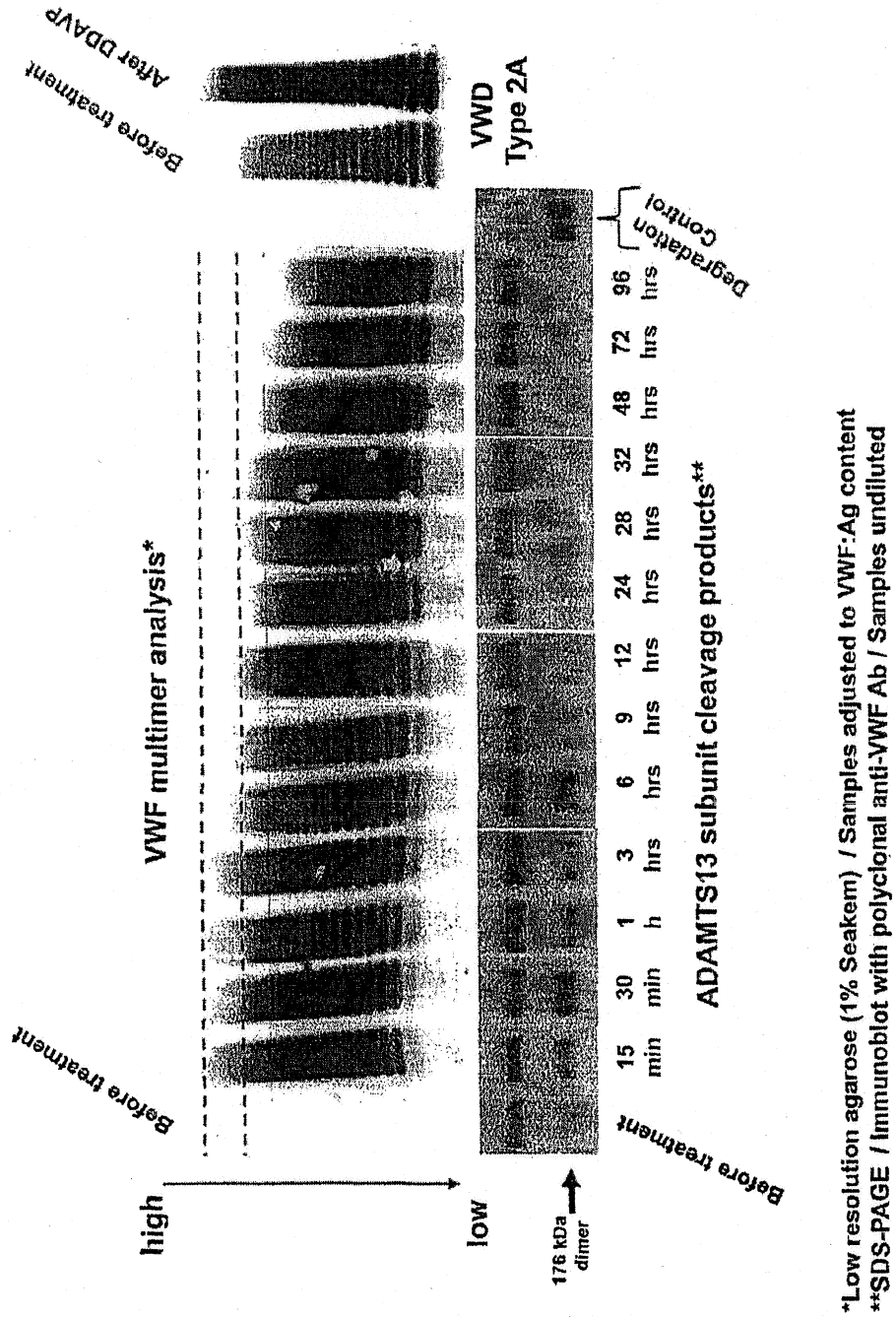
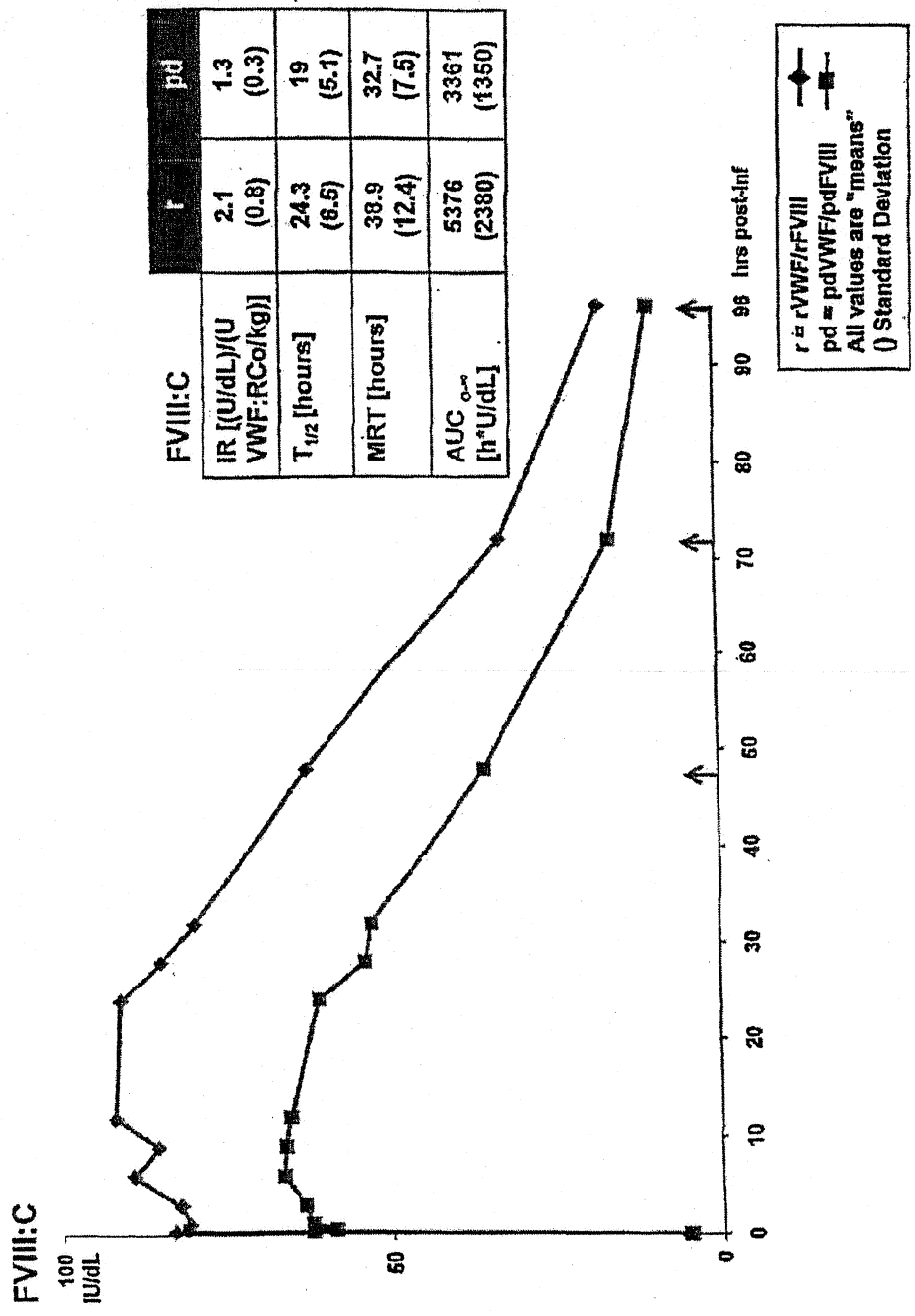

After DDAVP
Before treatment
VWD
Type 2A
VWF multimer analysis*
Before treatment
high
low
ADAMTS13 subunit cleavage products**
15 min
30 min
1 h
3 hrs
6 hrs
9 hrs
12 hrs
24 hrs
28 hrs
32 hrs
48 hrs
72 hrs
96 hrs
Degradation Control
Before treatment
176 kDa dimer
*Low resolution agarose (1% Seakem) / Samples adjusted to VWF:Ag content
**SDS-PAGE / Immunoblot with polyclonal anti-VWF Ab / Samples undiluted

FIG. 7



FVIII:C	r	pd
IR [(U/dL)/(U VWF:RCo/kg)]	2.1 (0.8)	1.3 (0.3)
$T_{1/2}$ [hours]	24.3 (6.6)	19 (5.1)
MRT [hours]	38.9 (12.4)	32.7 (7.5)
$AUC_{0-\infty}$ [h*U/dL]	5376 (2380)	3361 (1350)

FIG. 8

Cohort		
Cohort 1 (Type 3) n=3	Hypertension**	
Cohort 2 (Type 3) n=5	Tremor, generalized pruritus	
Cohort 4A (Type 3) n=22	rVWF/rFVIII	pdVWF/pdFVIII
	Nausea, sP-selectin increase, dizziness, psychomotor hyperactivity, hypertension**	Low titer anti-VWF Ab, dizziness (n=2), headache

*All reported related adverse events were mild, no related adverse events were reported for cohort 3 and 4B
**Same patient

FIG. 9

Patient 1

02-0001

Time (hours)	VWF:RCo (IU/mL)	VWF:Ag (IU/mL)	FVIII activity (IU/mL)	VWF:CBA (IU/mL)
screening	<0.007	<0.01	0.03	<0.01
0	<0.007	<0.01	0.03	<0.01
0.25	0.043	0.05	0.10	0.04
0.5	0.036	0.06	0.08	0.04
1	0.036	0.05	0.09	0.04
3	0.030	0.05	0.11	0.03
6	0.028	0.04	0.13	0.03
9	0.021	0.03	0.13	0.02
12	0.020	0.04	0.13	0.02
24	<0.007	0.03	0.13	<0.01
28	<0.007	0.02	0.12	<0.01
32	<0.007	0.03	0.09	<0.01
48	<0.007	0.02	0.07	<0.01
72	<0.007	0.01	0.05	<0.01
96	<0.007	0.01	0.04	<0.01

Manual Test Baxter

Data from the Central Laboratory

Patient 2

02-0002

Time (hours)	VWF:RCo (IU/mL)	VWF:Ag (IU/mL)	FVIII activity (IU/mL)	VWF:CBA (IU/mL)
screening	<0.007	<0.01	0.03	<0.01
0	<0.007	<0.01	0.03	<0.01
0.25	0.044	0.04	0.12	0.04
0.5	0.041	0.04	0.13	0.04
1	0.041	0.03	0.14	0.05
3	0.031	0.03	0.18	0.03
6	0.022	0.02	0.18	0.02
9	0.015	0.02	0.16	0.02
12	0.007	0.02	0.14	0.01
24	<0.007	0.01	0.08	<0.01
28	<0.007	0.01	0.09	<0.01
32	<0.007	0.02	0.07	<0.01
48	<0.007	0.01	0.05	<0.01
72	<0.007	0.01	0.03	<0.01
96	<0.007			

Manual Test Baxter

Data from the Central Laboratory

Patient 3

07-0001

Time (hours)	VWF:RCo (IU/mL)	VWF:Ag (IU/mL)	FVIII activity (IU/mL)	VWF:CBA (IU/mL)
screening	<0.007	<0.01	0.02	<0.01
0	<0.007	<0.01	0.02	<0.01
0.25	0.044	0.05	0.08	0.04
0.5	0.037	0.05	0.09	0.04
1	0.033	0.05	0.09	0.04
3	0.029	0.05	0.11	0.04
6	0.026	0.04	0.13	0.04
9	0.022	0.03	0.12	0.03
12	0.015	0.03	0.12	0.02
24	0.007	0.03	0.04	<0.01
28	<0.007	0.02	0.12	<0.01
32	<0.007	0.02	0.06	<0.01
48	<0.007	0.02	0.06	<0.01
72	<0.007	<0.01	0.04	<0.01
96	<0.007	<0.01	0.02	<0.01

Manual Test Baxter

Data from the Central Laboratory

FIG. 10

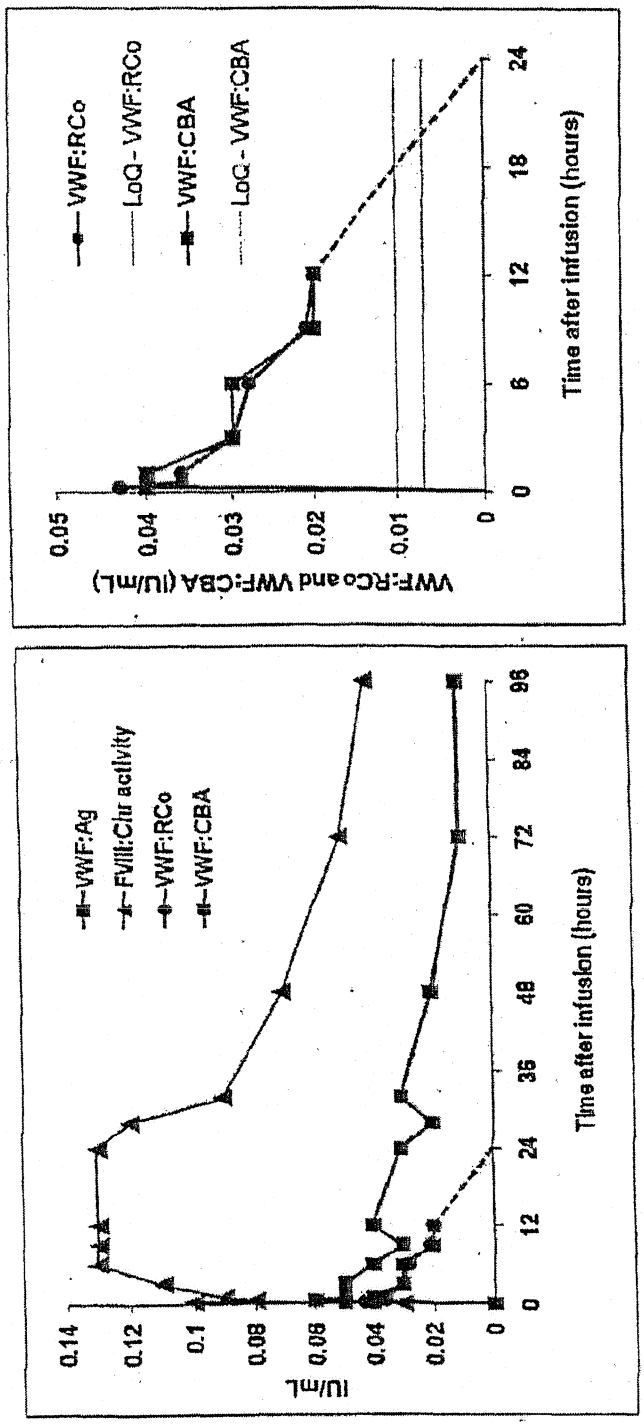

VWF:Ag
FVIII:Chr activity
VWF:RCo
VWF:CBA
IU/mL
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
12
24
36
48
60
72
84
96
Time after infusion (hours)
VWF:RCo
LoQ - VWF:RCo
VWF:CBA
LoQ - VWF:CBA
VWF:RCo and VWF:CBA (IU/mL)
0.05
0.04
0.03
0.02
0.01
0
0
6
12
18
24
Time after infusion (hours)

FIG. 11

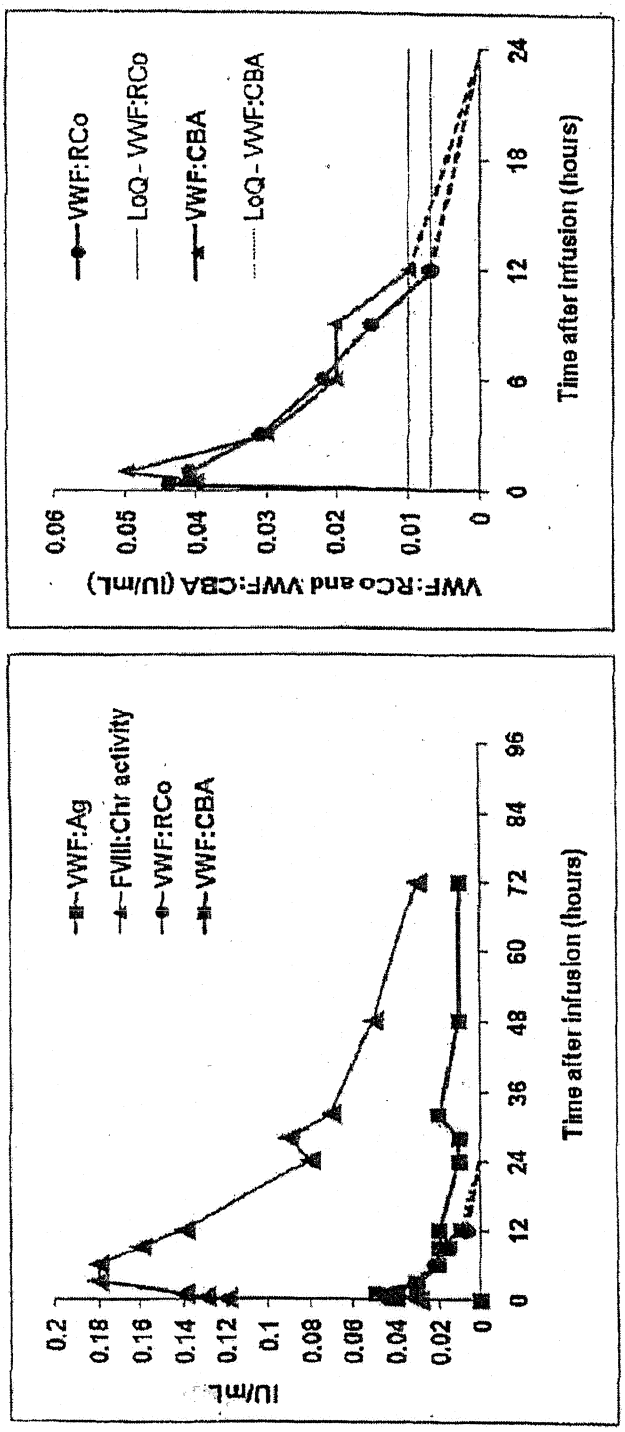

VWF:Ag
FVIII:Chr activity
VWF:RCo
VWF:CBA
IU/mL
Time after infusion (hours)
VWF:RCo
LoQ - VWF:RCo
VWF:CBA
LoQ - VWF:CBA
VWF:RCo and VWF:CBA (IU/mL)
Time after infusion (hours)

FIG. 12

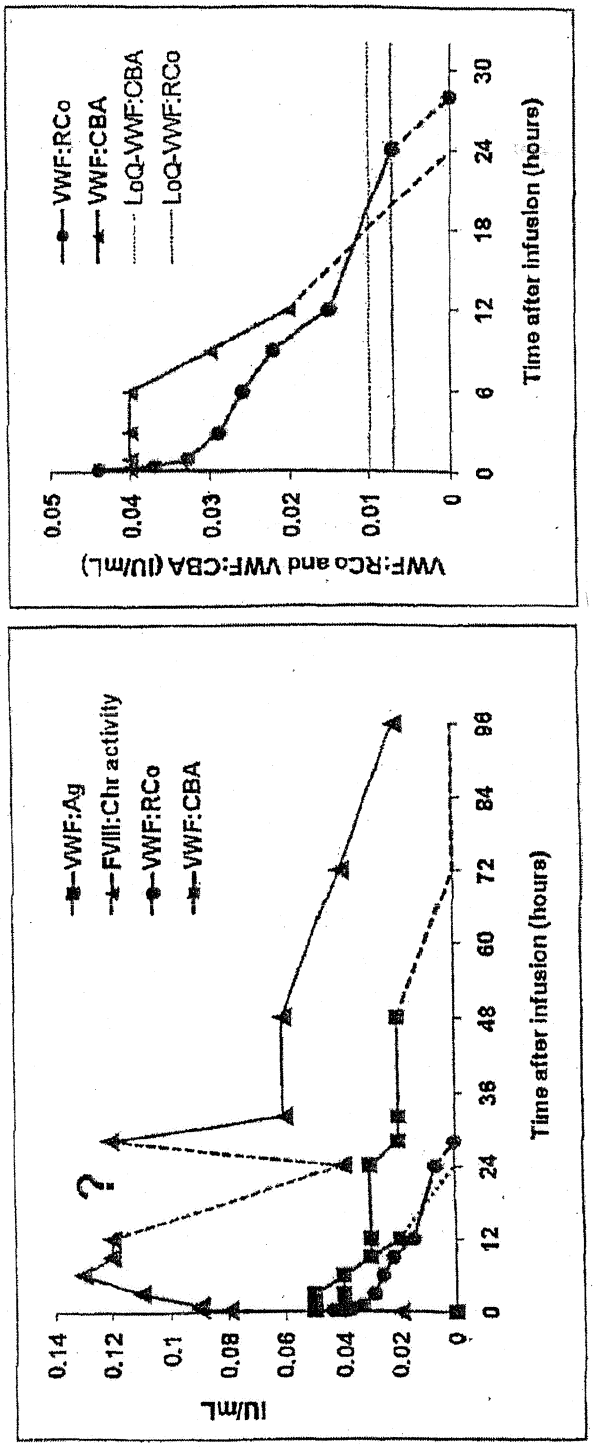

VWF:Ag
FVIII:Chr activity
VWF:RCo
VWF:CBA
?
IU/mL
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
12
24
36
48
60
72
84
96
Time after infusion (hours)
VWF:RCo
VWF:CBA
LoQ-VWF:CBA
LoQ-VWF:RCo
VWF:RCo and VWF:CBA (IU/mL)
0.05
0.04
0.03
0.02
0.01
0
0
6
12
18
24
30
Time after infusion (hours)

FIG. 13

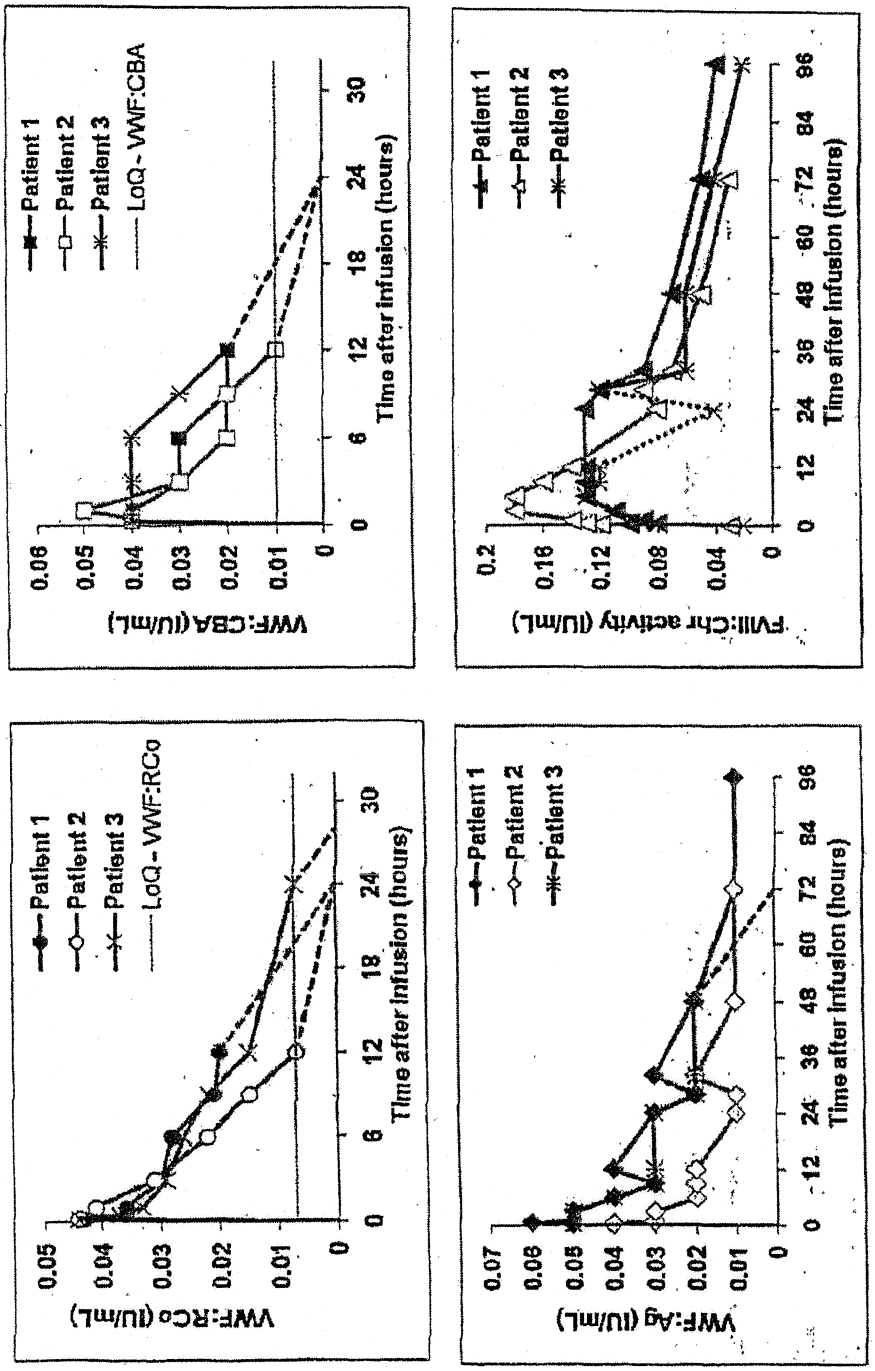

Patient 1
Patient 2
Patient 3
LoQ - VWF:CBA
VWF:CBA (IU/mL)
0.06
0.05
0.04
0.03
0.02
0.01
0
0 6 12 18 24 30
Time after infusion (hours)
Patient 1
Patient 2
Patient 3
FVIII:Chr activity (IU/mL)
0.2
0.16
0.12
0.08
0.04
0
0 12 24 36 48 60 72 84 96
Time after infusion (hours)
Patient 1
Patient 2
Patient 3
LoQ - VWF:RCo
VWF:RCo (IU/mL)
0.05
0.04
0.03
0.02
0.01
0
0 6 12 18 24 30
Time after infusion (hours)
Patient 1
Patient 2
Patient 3
VWF:Ag (IU/mL)
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0 12 24 36 48 60 72 84 96
Time after infusion (hours)

FIG. 14

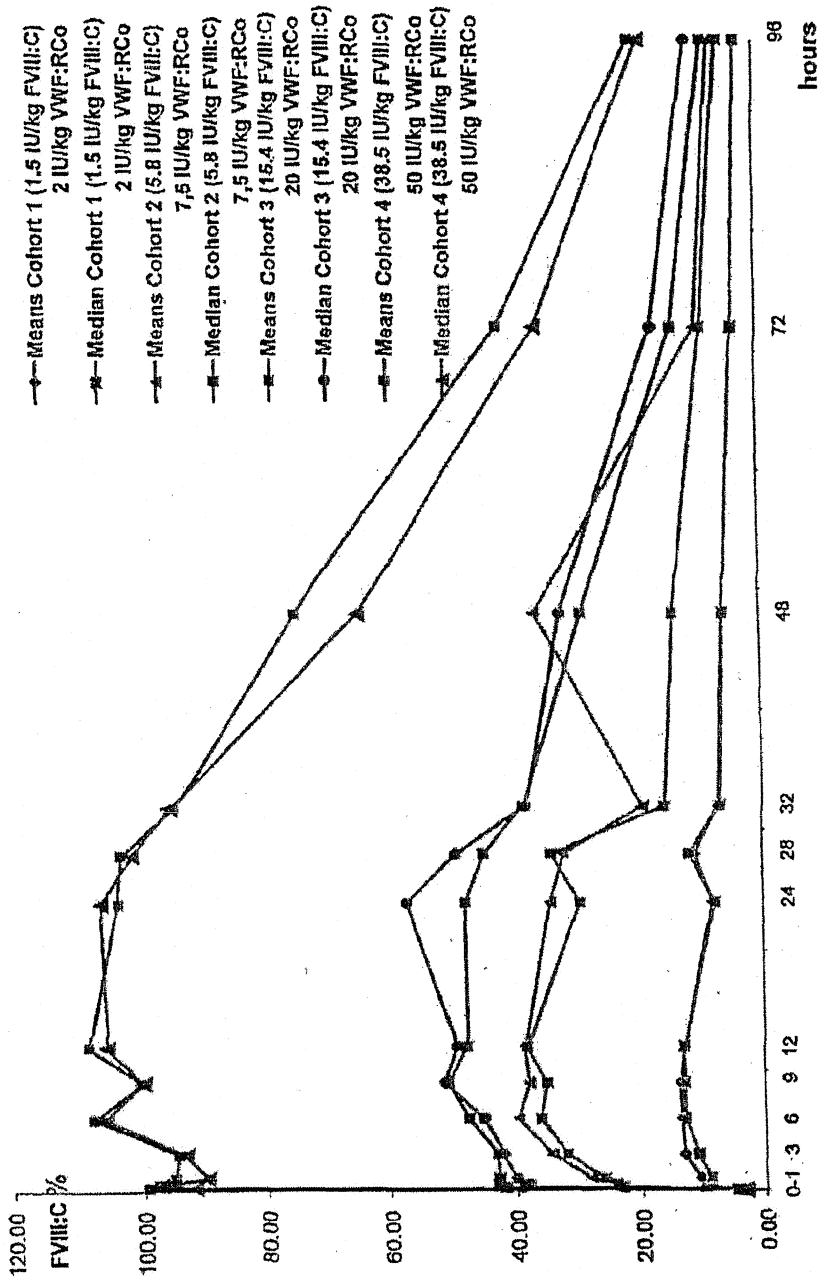

Means Cohort 1 (1.5 IU/kg FVIII:C) 2 IU/kg VWF:RCo
Median Cohort 1 (1.5 IU/kg FVIII:C) 2 IU/kg VWF:RCo
Means Cohort 2 (5.8 IU/kg FVIII:C) 7,5 IU/kg VWF:RCo
Median Cohort 2 (5.8 IU/kg FVIII:C) 7,5 IU/kg VWF:RCo
Means Cohort 3 (15.4 IU/kg FVIII:C) 20 IU/kg VWF:RCo
Median Cohort 3 (15.4 IU/kg FVIII:C) 20 IU/kg VWF:RCo
Means Cohort 4 (38.5 IU/kg FVIII:C) 50 IU/kg VWF:RCo
Median Cohort 4 (38.5 IU/kg FVIII:C) 50 IU/kg VWF:RCo
FVIII:C %
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0-1 3 6 9 12 24 28 32 48 72 96
hours

FIG. 15

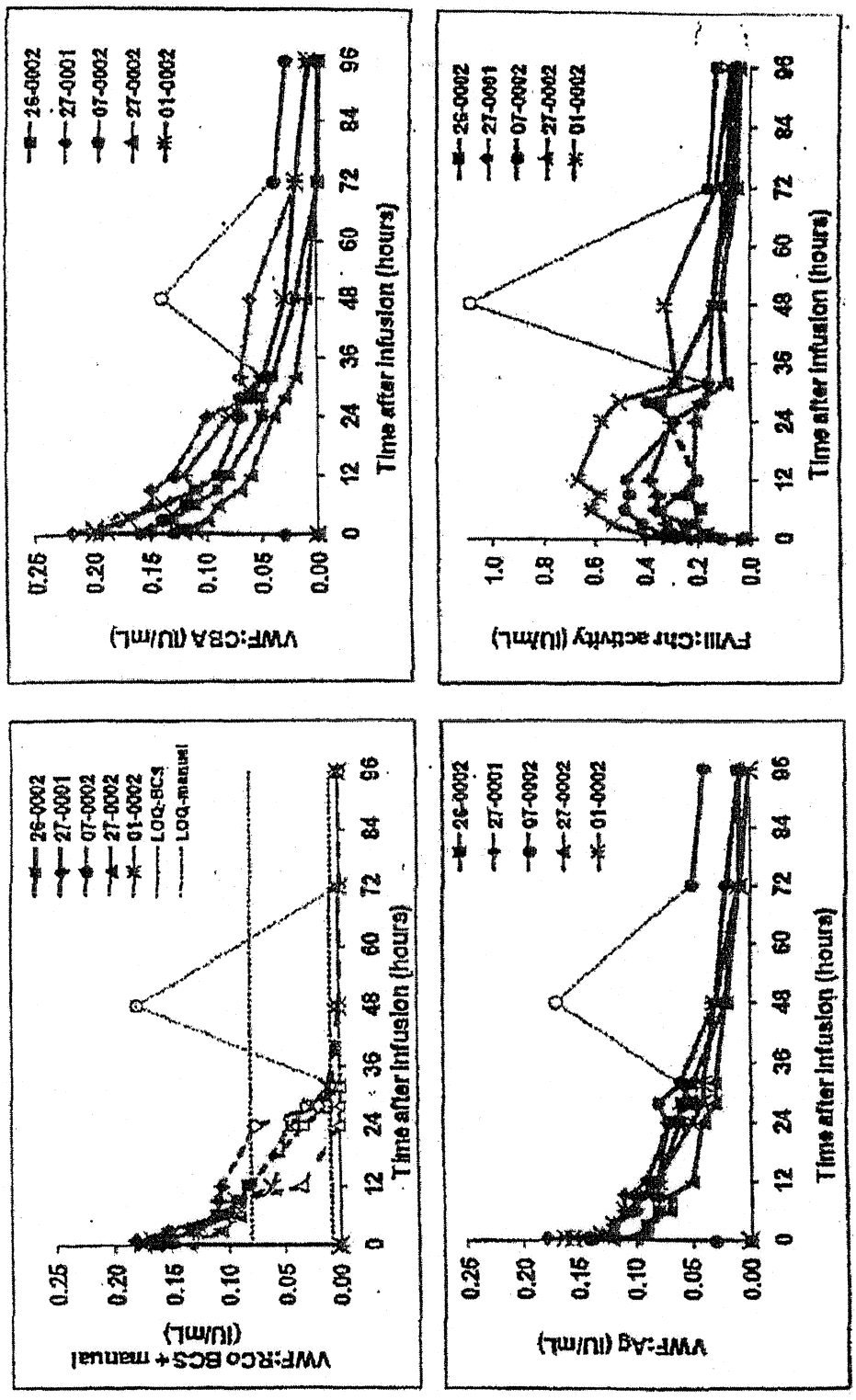

VWF:RCo BCS + manual (IU/mL)
VWF:CBA (IU/mL)
VWF:Ag (IU/mL)
FVIII:Chr activity (IU/mL)
Time after infusion (hours)
26-0002
27-0001
07-0002
27-0002
01-0002
LOQ-BCS
LOQ-manual

FIG. 16

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 2	rVFW/FVIII	$AUC_{0\text{-}96hrs}$ [h*U/dL]	5	1380.01	988.16; 3010.68	1860.05	942.5	50.67	1677.47
		$AUC_{0\text{-}inf}$ [h*U/dL]	5	1508.83	1056.99; 3072.84	1950.47	965.19	49.49	1766.01
		$AUMC_{0\text{-}inf}$ [h^2*U/dL]	5	64518.47	33186.37; 126406.6	72917.08	41521.23	56.94	63274.8
		$T_{1/2}$ [hours]	5	22.86	17.81; 24.48	21.93	2.54	11.56	21.8
		MRT [hours]	5	35.91	27.51; 42.73	36.22	6.08	16.78	35.79
		Cl [mL/kg/hours]	5	0.53	0.24; 0.71	0.47	0.21	44.92	0.43
		V_{ss} [mL/kg]	5	17.12	9.26; 24	16.63	6.91	41.52	15.4
		C_{max} [U/dL]	5	34	32; 98	51.8	28.99	55.96	46.39
		T_{max} [hours]	5	12.22	6.03; 48.07	21.15	17.1	80.87	16.27
		IR [(U/dL)/(U VWF: RCo/kg)]	5	4.53	3.98; 13.11	6.86	3.93	57.33	6.11
		T_{alpha} [hours]	1	32.57	NA	32.57	NA	NA	32.57
		T_{beta} [hours]	1	3207.83	NA	3207.83	NA	NA	3207.83

FIG. 17

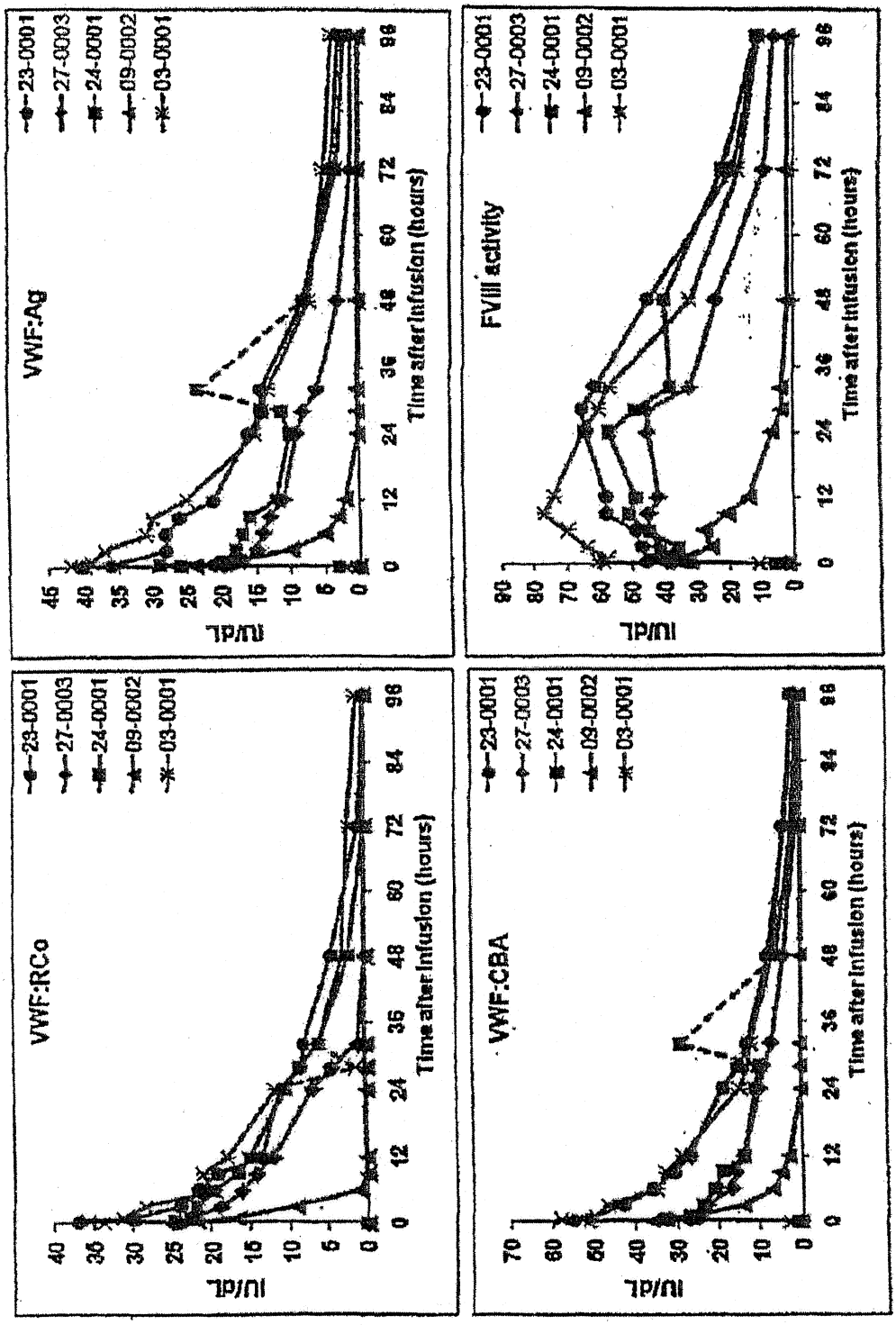

VWF:Ag
VWF:RCo
FVIII activity
VWF:CBA
IU/dL
Time after infusion (hours)
23-0001
27-0003
24-0001
09-0002
03-0001

FIG. 18

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 3	rVFW/FVIII	$AUC_{0\text{-}96hrs}$ [h*U/dL]	4	2745.17	2093.62; 3639.65	2805.91	635.05	22.63	2752.8
		$AUC_{0\text{-}inf}$ [h*U/dL]	4	2858.66	2172.08; 3947.87	2959.32	740.27	25.01	2892.1
		$AUMC_{0\text{-}inf}$ [h^2*U/dL]	4	100089.53	71254.38; 168025.02	109864.62	47247.29	43.01	102450.33
		$T_{1/2}$ [hours]	4	20.72	14.43; 25.93	20.45	5.19	25.36	19.94
		MRT [hours]	4	37.53	25.97; 43.16	36.05	8.21	22.77	35.3
		Cl [mL/kg/hours]	4	0.7	0.51; 0.95	0.72	0.18	25.34	0.7
		V_{ss} [mL/kg]	4	25.32	18.9; 31.12	25.16	5.82	23.11	24.65
		C_{max} [U/dL]	4	57	42; 66	55.5	11.09	19.98	54.63
		T_{max} [hours]	4	16.45	6.1; 28.48	16.87	10.9	64.6	13.95
		IR [(U/dL)/(U VWF: RCo/kg)]	4	2.84	2.04; 3.31	2.75	0.58	20.9	2.71
		T_{alpha} [hours]	0	NA					
		T_{beta} [hours]	0	NA					

FIG. 19

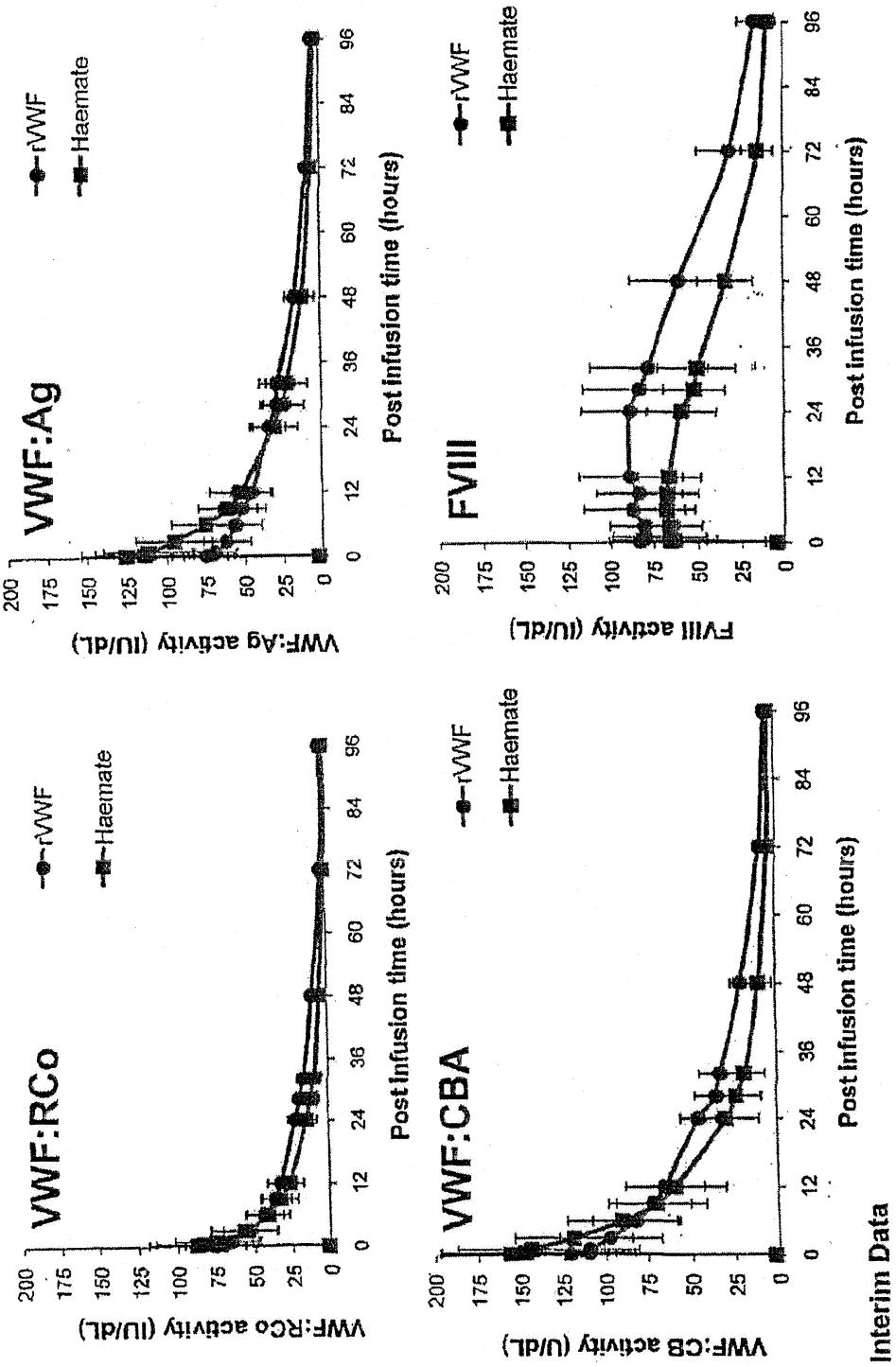
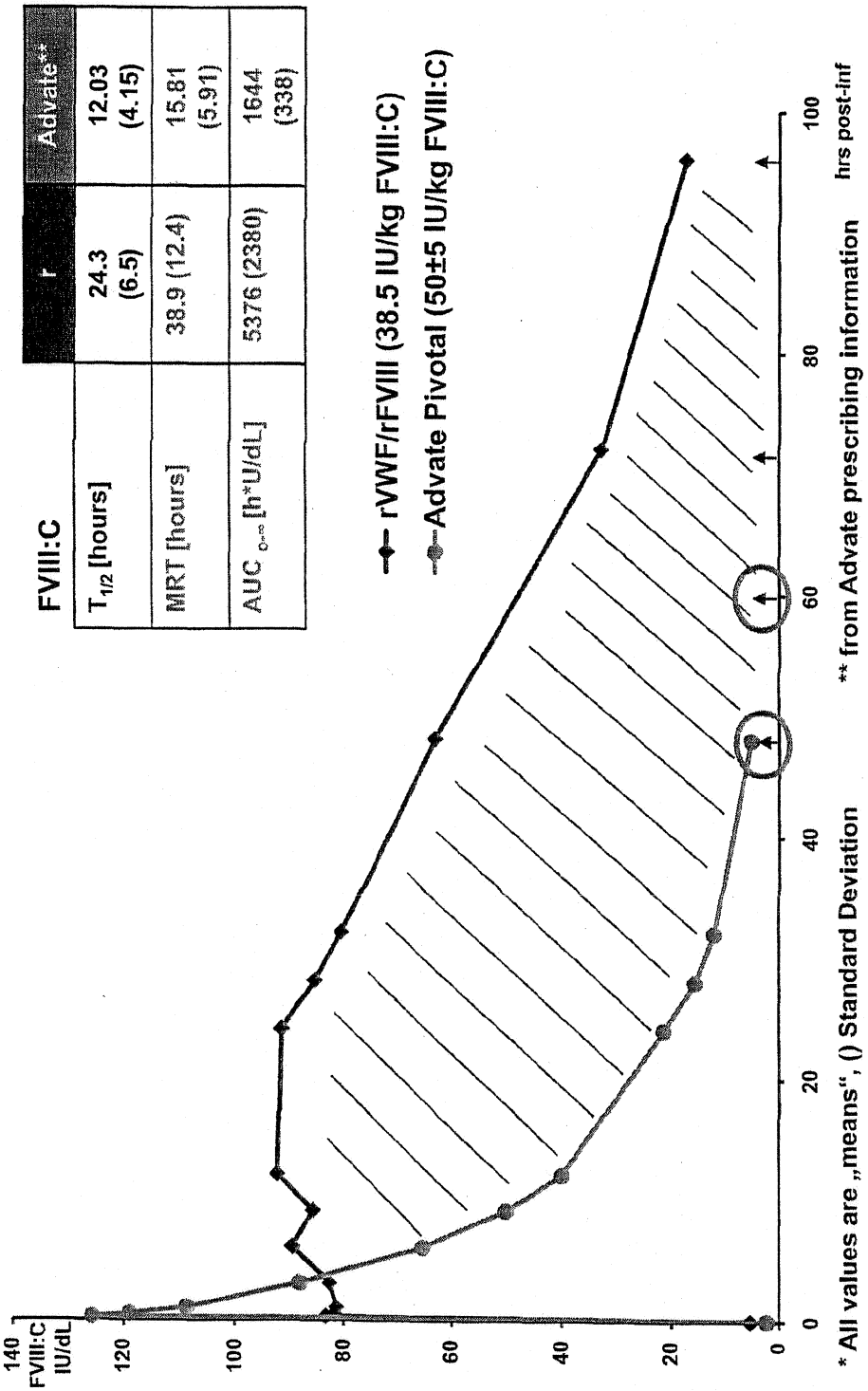

VWF:Ag
rVWF
Haemate
VWF:Ag activity (IU/dL)
Post infusion time (hours)
FVIII
FVIII activity (IU/dL)
VWF:RCo
VWF:RCo activity (IU/dL)
VWF:CBA
VWF:CB activity (U/dL)
Interim Data

FIG. 20

Cohort	Investigational Product	Parameter	N	Median	90% CI for Median	Mean	SD	CV (%)	GM
Cohort 4A	rVFW/FVIII	$AUC_{0\text{-}96hrs}$ [h*U/dL]	19	4895.54	4049.13; 5239.58	4882.21	1993.76	40.84	4162.04
		$AUC_{0\text{-}inf}$ [h*U/dL]	19	5287.34	4321.1; 5913.43	5375.56	2380.4	44.28	4520.61
		$AUMC_{0\text{-}inf}$ [h^2*U/dL]	19	198560.36	157848.13; 259396.51	233248.57	157945.3	67.72	155532.14
		$T_{1/2}$ [hours]	18	24.39	21.41; 25.78	24.3	6.47	26.64	23.48
		MRT [hours]	19	39.56	36.69; 43.32	38.92	12.43	31.93	34.06
		Cl [mL/kg/hours]	19	0.95	0.85; 1.16	1.57	2.67	169.59	1.04
		V_{ss} [mL/kg]	19	37.27	32.42; 38.84	37.12	11.63	31.34	35.28
		C_{max} [U/dL]	19	90	85; 99	94.53	22.68	24	92.07
		T_{max} [hours]	19	12.3	8.73; 24.22	15.94	11.01	69.07	9.14
		IR [(U/dL)/(U VWF: RCo/kg)]	19	1.83	1.74; 2.01	2.07	0.82	39.39	1.97
		T_{alpha} [hours]	1	36.66	NA	36.66	NA	NA	36.66
		T_{beta} [hours]	1	182.27	NA	182.27	NA	NA	182.27
	pdVWF/FVIII	$AUC_{0\text{-}96hrs}$ [h*U/dL]	17	3061.61	2911.05; 4270.87	3185.02	1219.32	38.28	2943.65
		$AUC_{0\text{-}inf}$ [h*U/dL]	17	3209.44	3026.55; 4394.81	3361.13	1350.1	40.17	3092.1
		$AUMC_{0\text{-}inf}$ [h^2*U/dL]	17	100993.49	83515.77; 149061.17	118375.88	72364.04	61.13	99238.4
		$T_{1/2}$ [hours]	17	18.07	17.52; 21.59	19.1	5.13	26.84	18.46
		MRT [hours]	17	30.33	27.68; 38.41	32.7	7.47	22.83	31.94
		Cl [mL/kg/hours]	17	1.73	1.56; 2.37	1.89	0.75	39.96	1.75
		V_{ss} [mL/kg]	17	59.01	45.8; 67.85	58.24	17.15	29.44	55.94
		C_{max} [U/dL]	17	71	58; 80	70.59	15.87	22.48	68.92
		T_{max} [hours]	17	6.63	3.25; 12.08	9.83	9.6	97.74	5.96
		IR [(U/dL)/(U VWF: RCo/kg)]	17	1.17	1.14; 1.5	1.31	0.33	24.99	1.27
		T_{alpha} [hours]	5	26.03	0.66; 42.02	20.5	18.95	92.42	7.05
		T_{beta} [hours]	5	81.94	24.3; 668.45	291.55	337.7	115.83	121.36

FIG. 21

FVIII:C	r	Advate**
$T_{1/2}$ [hours]	24.3 (6.5)	12.03 (4.15)
MRT [hours]	38.9 (12.4)	15.81 (5.91)
$AUC_{0-\infty}$ [h*U/dL]	5376 (2380)	1644 (338)



* All values are „means“, () Standard Deviation

** from Advate prescribing information

FIG. 22

Timepoint	Pre-Inf pdVWF/pdFVIII	Post-Inf pdVWF/pdFVIII	Post-Inf rVWF/rFVIII Study End
Binding Antibodies			
Binding anti-VWF Ab	Pos	Pos	Pos
Titer binding anti-VWF Ab	1/1280	1/5120	1/5120
Confirmation anti-VWF Ab	Specific	Specific	Specific
Inhibiting Antibodies			
Ab to VWF: RCo (BU/mL)	<1	<1	<1
Ab to VWF:CB (BU/mL)	<1	<1	<1
Ab to VWF:FVIII -B(BU/mL)	<1	<1	<1
Ab to FVIII (BU/mL)	<0.4	<0.4	<0.4

