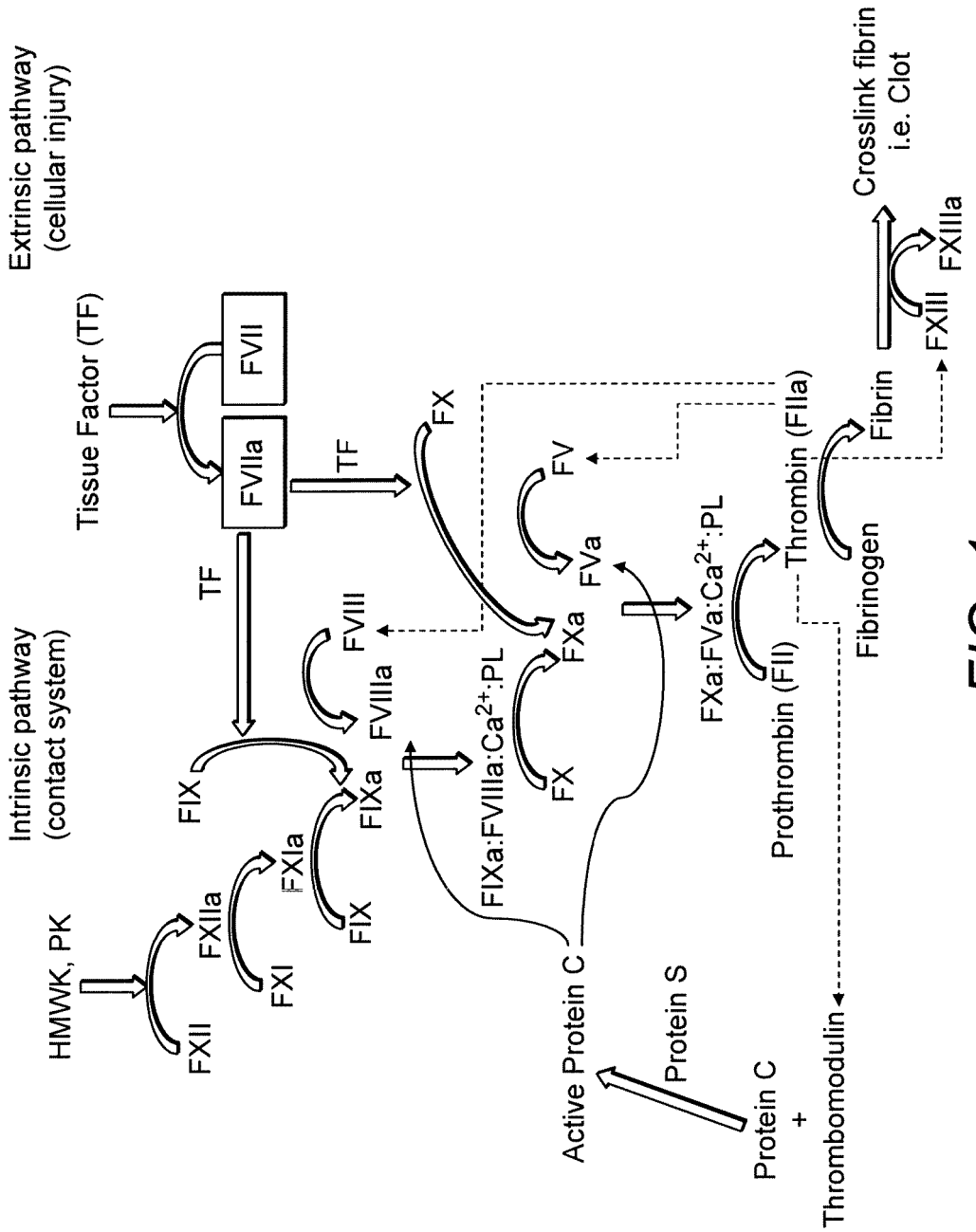

Extrinsic pathway
(cellular injury)
Tissue Factor (TF)
FVII
FVIIa
TF
TF
FX
FV
FVa
FVIII
FVIIIa
FIX
FIXa
FIXa:FVIIIa:Ca2+:PL
FXa
FX
FXa:FVa:Ca2+:PL
Thrombin (FIIa)
Fibrin
Crosslink fibrin
i.e. Clot
FXIII
FXIIIa
Intrinsic pathway
(contact system)
HMWK, PK
FXII
FXIIa
FXI
FXIa
FIX
Prothrombin (FII)
Fibrinogen
Active Protein C
Protein S
Protein C
+
Thrombomodulin

FIG. 1

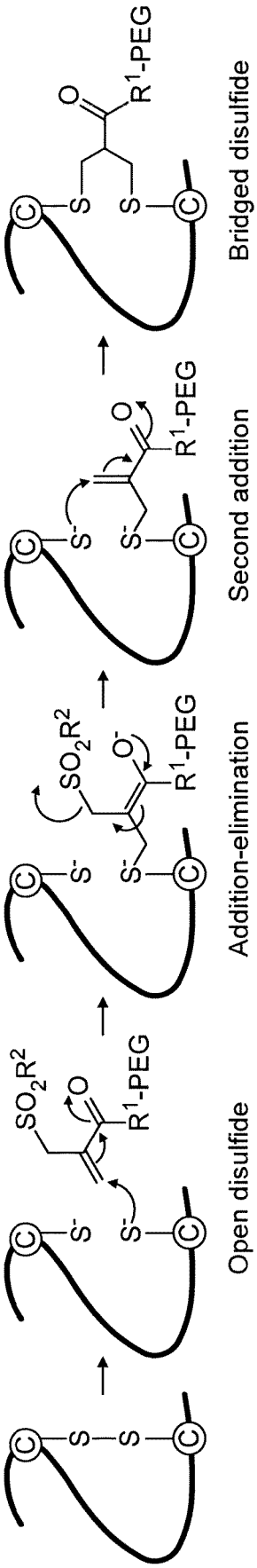

Open disulfide
Addition-elimination
Second addition
Bridged disulfide
R1-PEG
SO2R2

FIG. 2

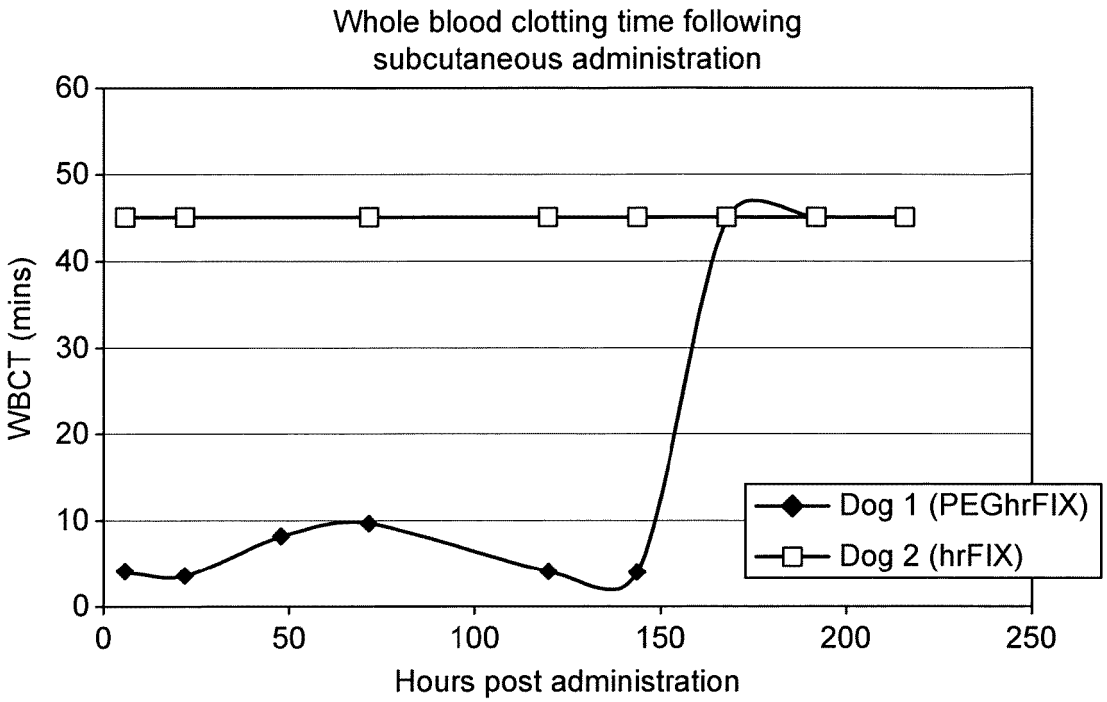

Whole blood clotting time following subcutaneous administration
WBCT (mins)
60
50
40
30
20
10
0
0
50
100
150
200
250
Hours post administration
Dog 1 (PEGhrFIX)
Dog 2 (hrFIX)

FIG. 3

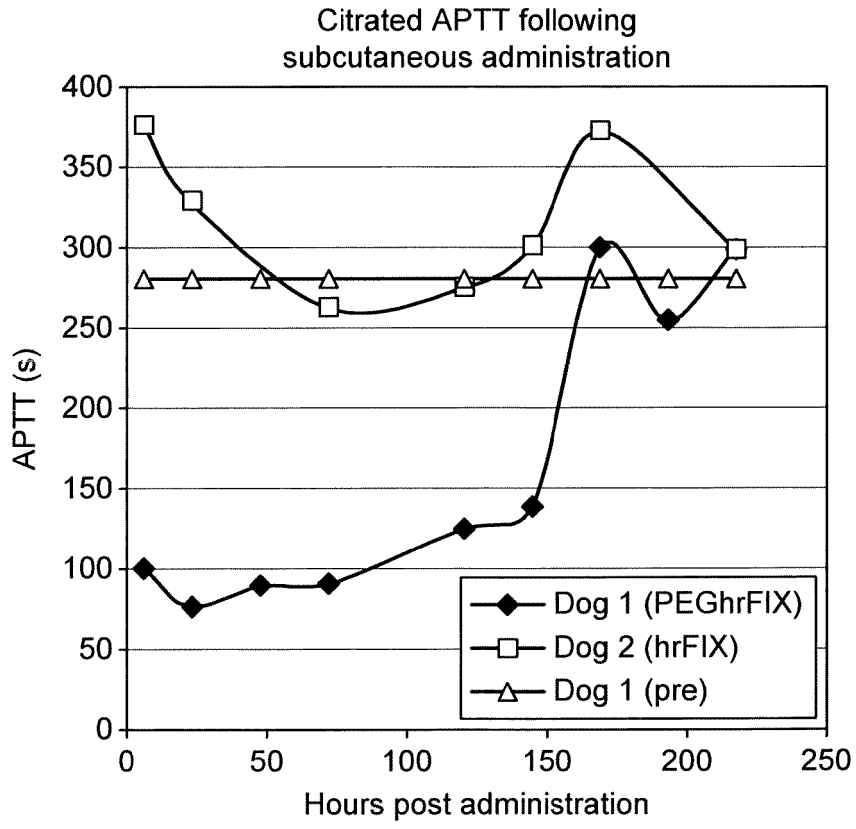

Citrated APTT following subcutaneous administration
APTT (s)
400
350
300
250
200
150
100
50
0
0
50
100
150
200
250
Hours post administration
Dog 1 (PEGhrFIX)
Dog 2 (hrFIX)
Dog 1 (pre)

FIG. 4

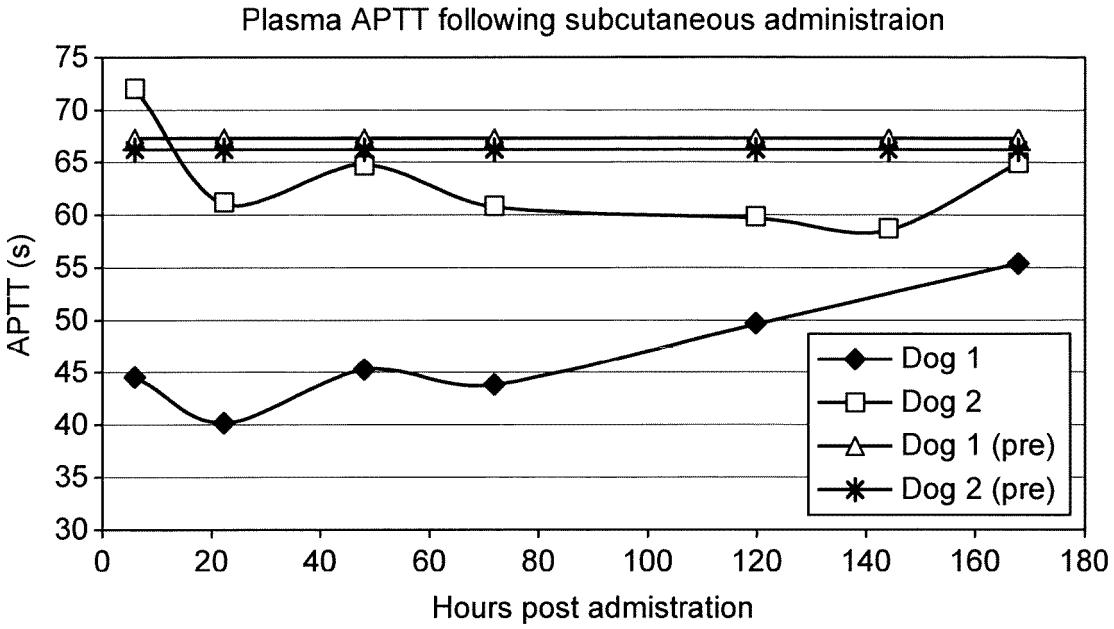

Plasma APTT following subcutaneous administraion
APTT (s)
75
70
65
60
55
50
45
40
35
30
0
20
40
60
80
100
120
140
160
180
Hours post admistration
Dog 1
Dog 2
Dog 1 (pre)
Dog 2 (pre)

FIG. 5

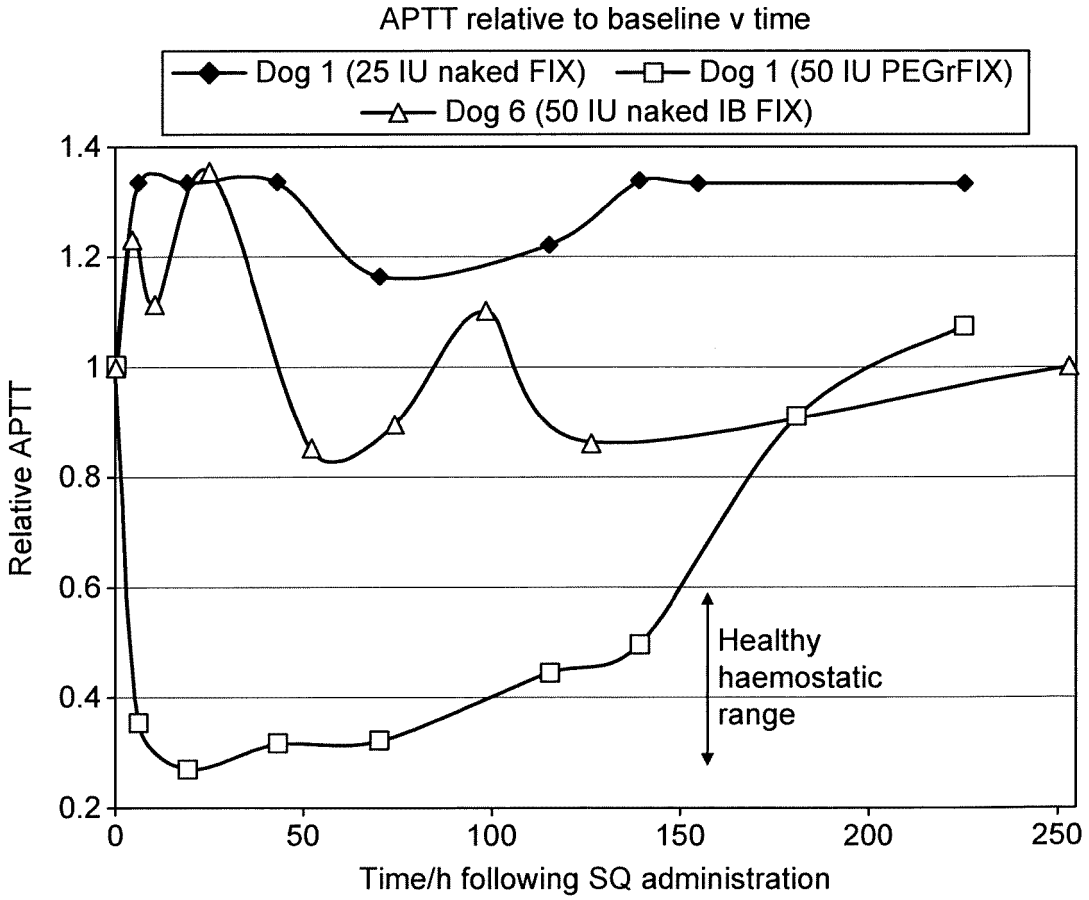

APTT relative to baseline v time
Dog 1 (25 IU naked FIX)
Dog 1 (50 IU PEGrFIX)
Dog 6 (50 IU naked IB FIX)
Relative APTT
1.4
1.2
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
Time/h following SQ administration
Healthy
haemostatic
range

FIG. 6

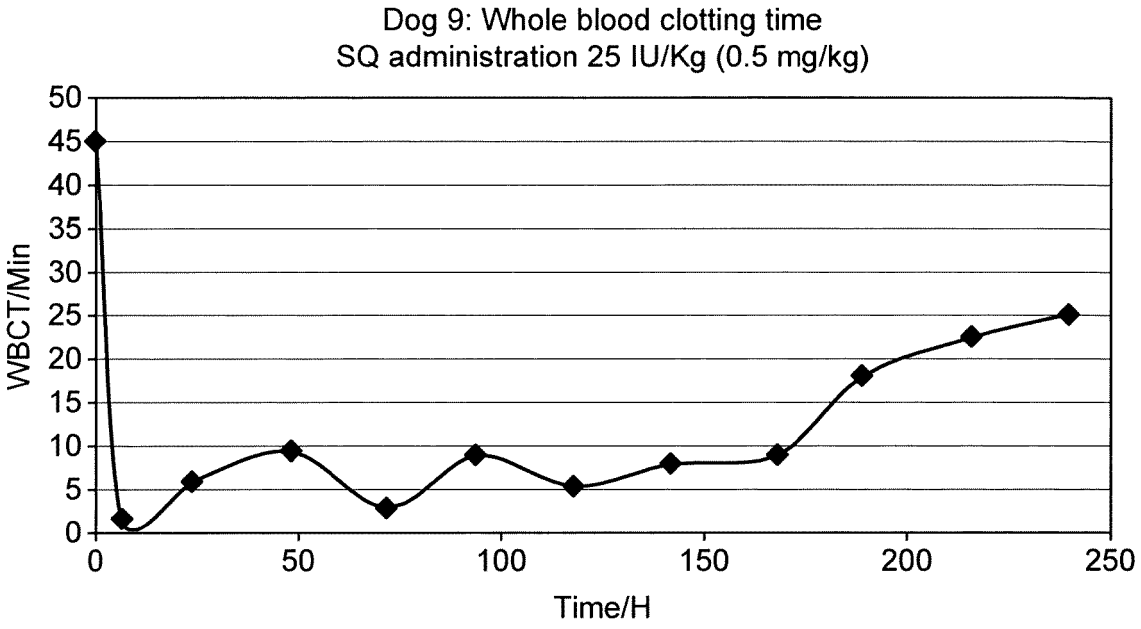

Dog 9: Whole blood clotting time
SQ administration 25 IU/Kg (0.5 mg/kg)
WBCT/Min
50
45
40
35
30
25
20
15
10
5
0
0
50
100
150
200
250
Time/H

FIG. 7

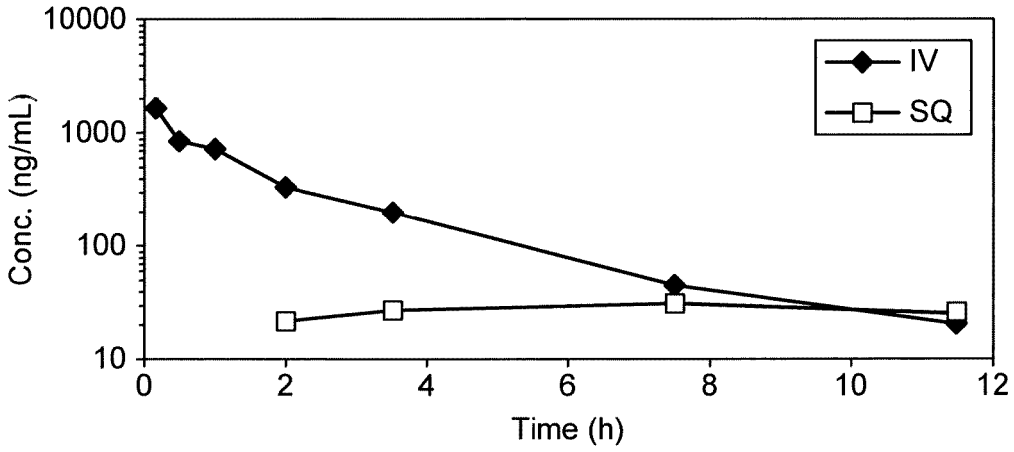

Conc. (ng/mL)
10000
1000
100
10
0
2
4
6
8
10
12
Time (h)
IV
SQ

FIG. 8

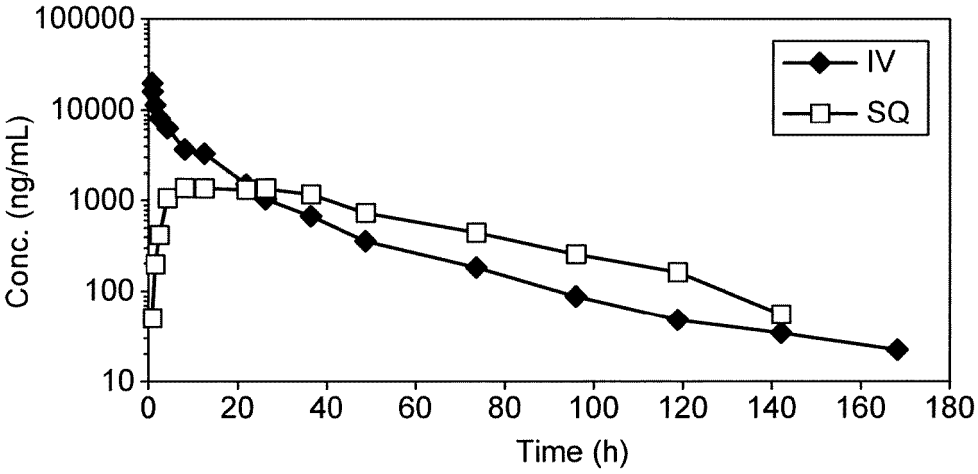

100000
10000
1000
100
10
Conc. (ng/mL)
0
20
40
60
80
100
120
140
160
180
Time (h)
IV
SQ

FIG. 9

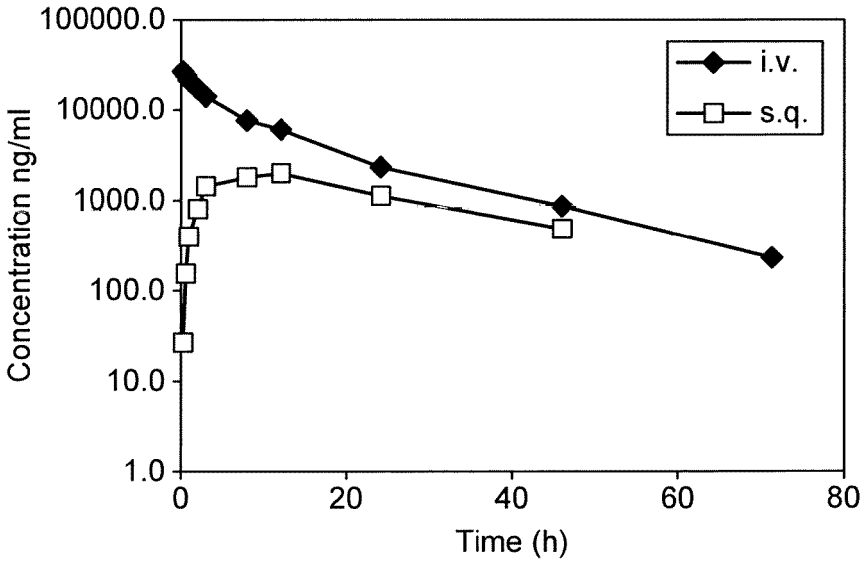

100000.0
10000.0
1000.0
100.0
10.0
1.0
Concentration ng/ml
0
20
40
60
80
Time (h)
i.v.
s.q.

FIG. 10

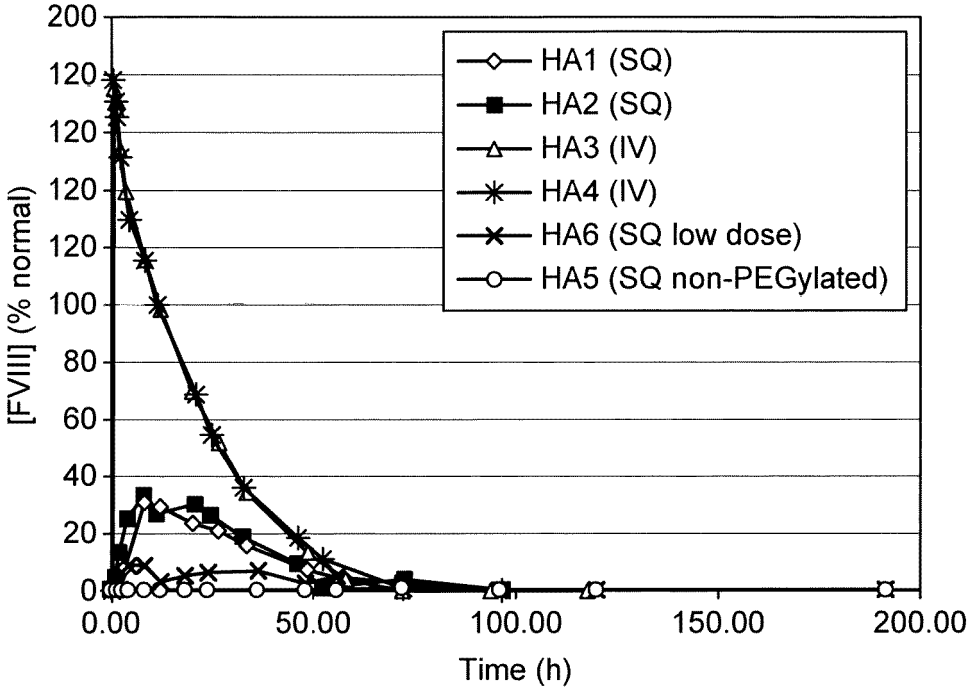

200
120
120
120
120
100
80
60
40
20
0
[FVIII] (% normal)
0.00
50.00
100.00
150.00
200.00
Time (h)
HA1 (SQ)
HA2 (SQ)
HA3 (IV)
HA4 (IV)
HA6 (SQ low dose)
HA5 (SQ non-PEGylated)

FIG. 11

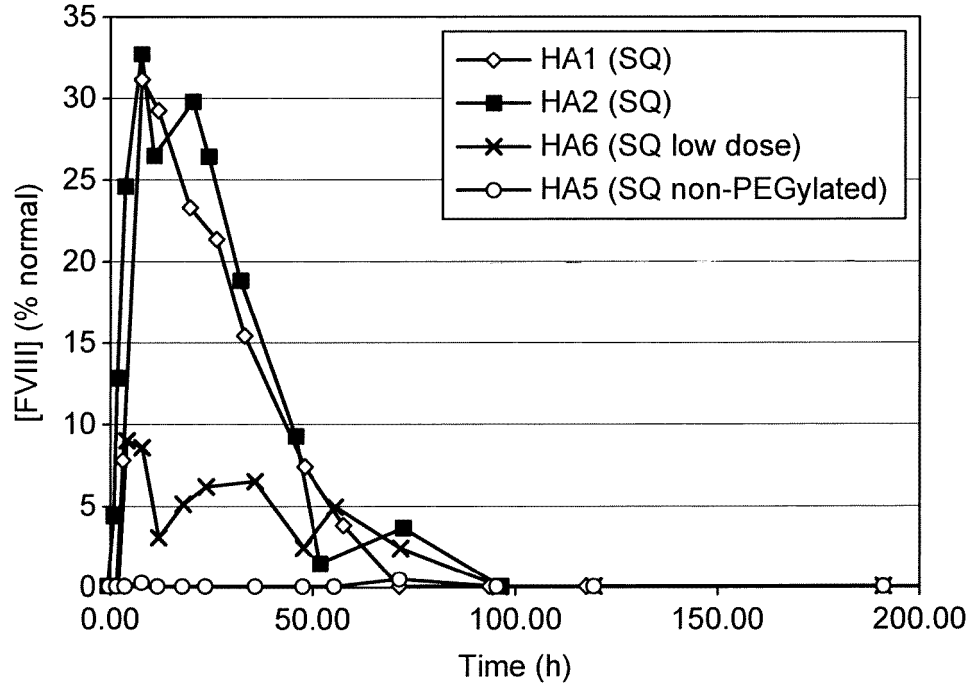

35
30
25
20
15
10
5
0
[FVIII] (% normal)
0.00
50.00
100.00
150.00
200.00
Time (h)
HA1 (SQ)
HA2 (SQ)
HA6 (SQ low dose)
HA5 (SQ non-PEGylated)

FIG. 12

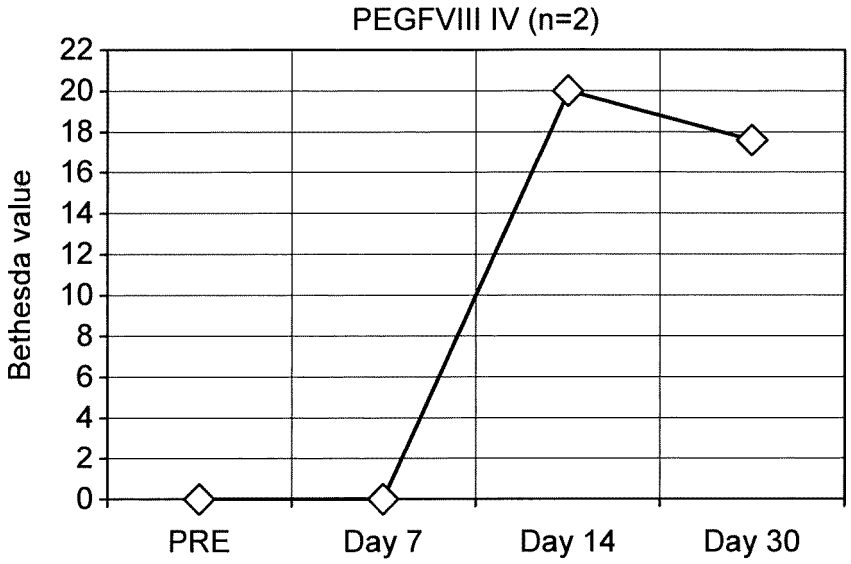


FIG. 13a

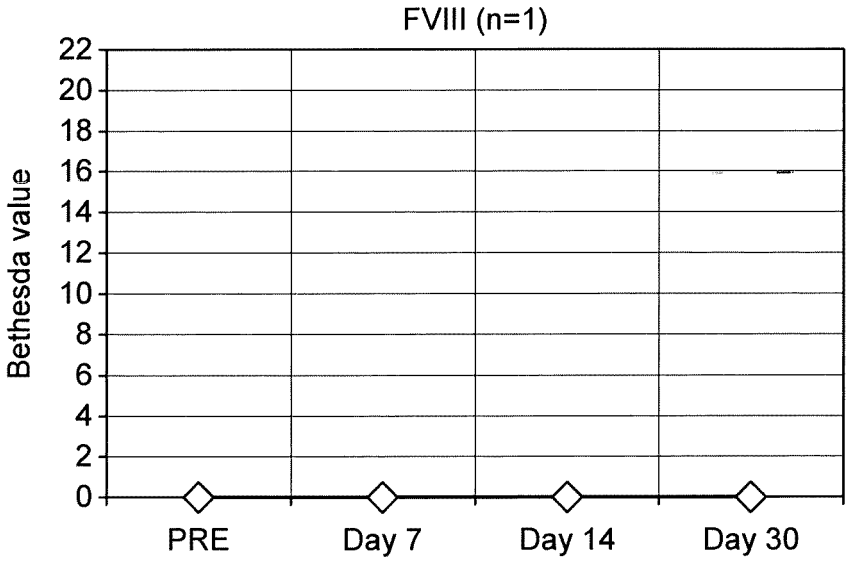


FIG. 13b

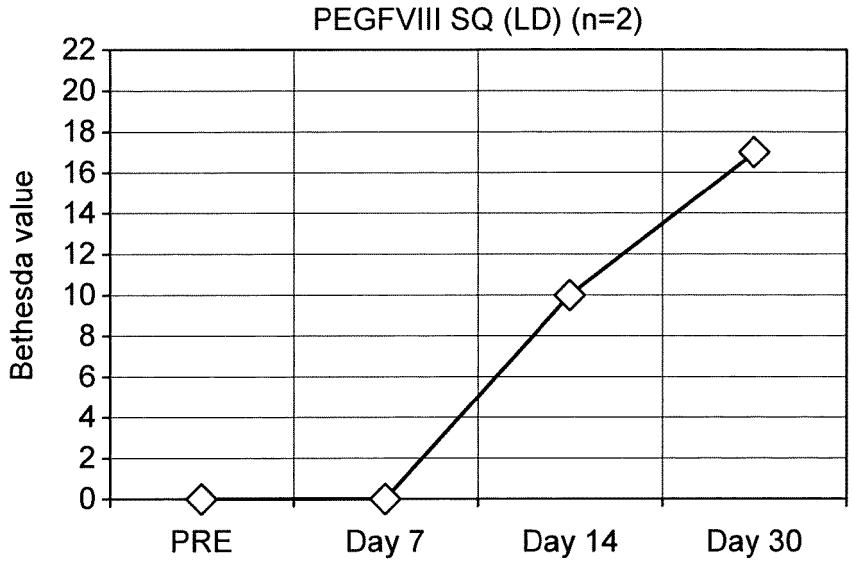


FIG. 13c

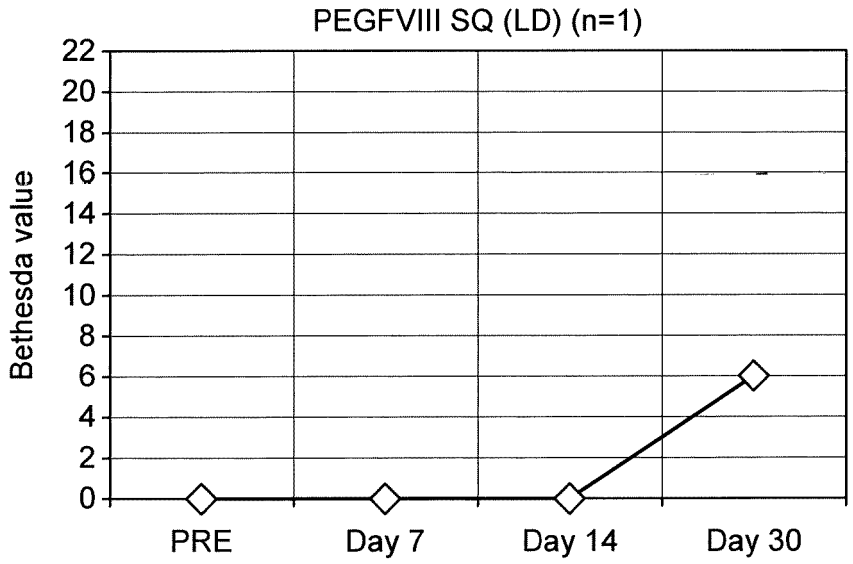


FIG. 13d