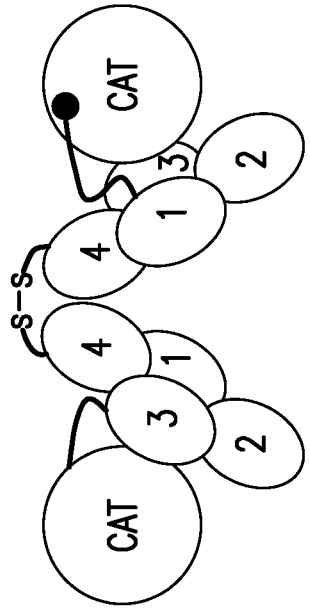
CAT
2
3
1
4
S–S
4
1
3
2
CAT

FIG.1B

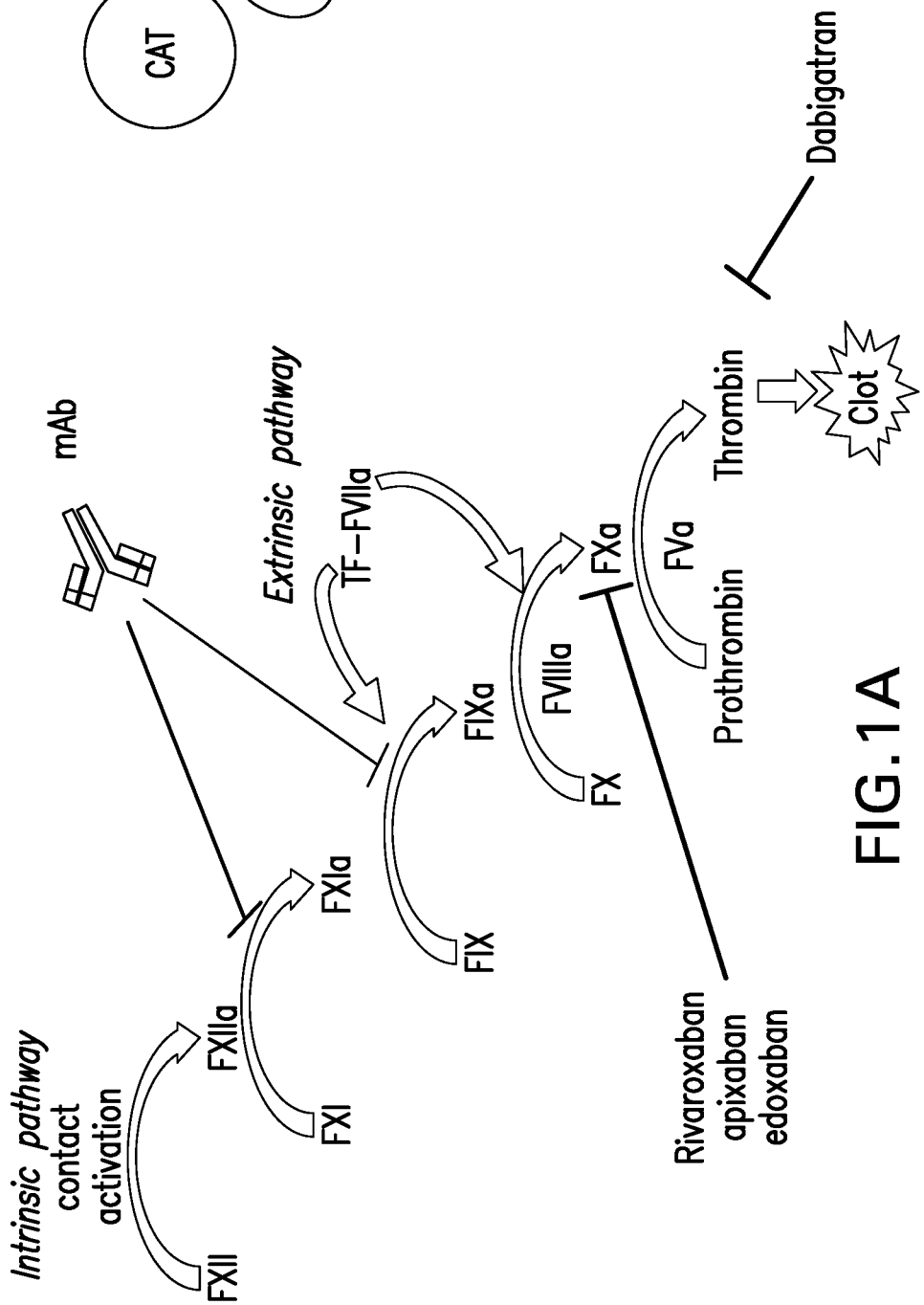
Intrinsic pathway
contact activation
FXII
FXIIa
FXI
FXIa
FIX
FIXa
Extrinsic pathway
TF–FVIIa
mAb
FX
FVIIIa
FXa
Prothrombin
FVa
Thrombin
Clot
Dabigatran
Rivaroxaban
apixaban
edoxaban

FIG.1A

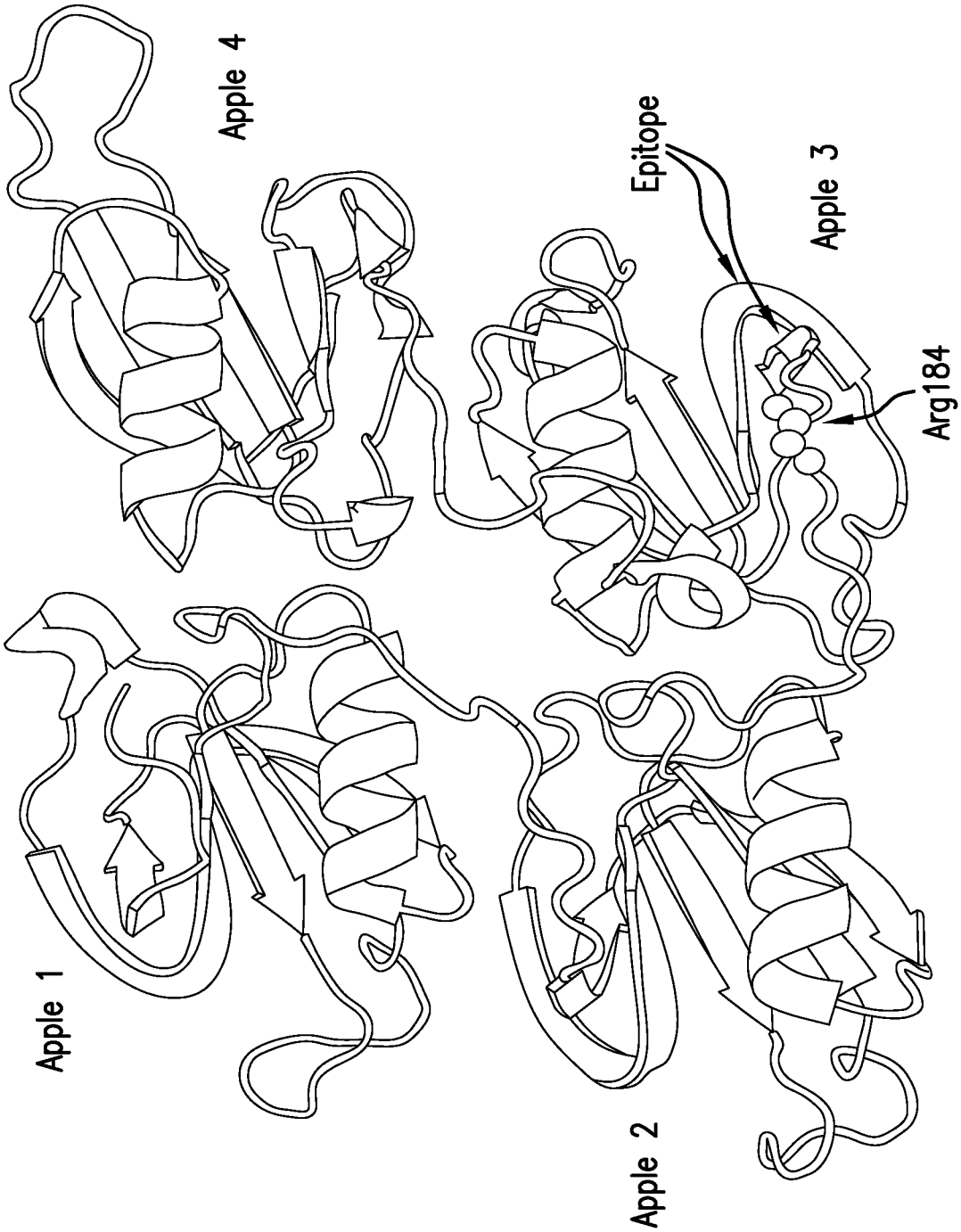

FIG.2

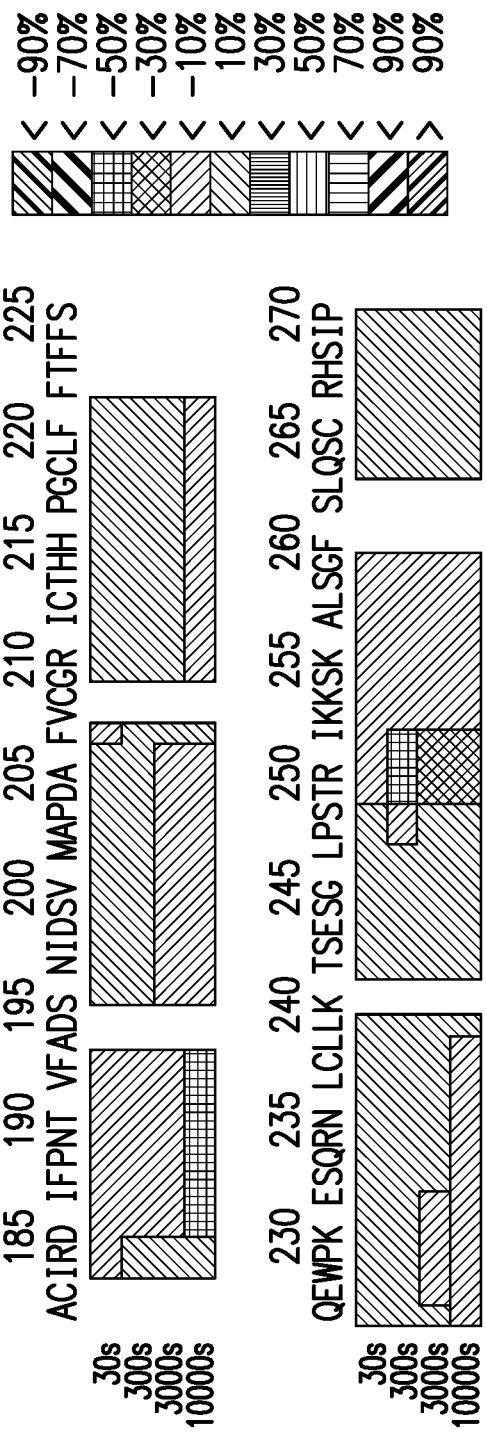
< -90%
< -70%
< -50%
< -30%
< -10%
< 10%
< 30%
< 50%
< 70%
< 90%
> 90%
185 190 195 200 205 210 215 220 225
ACIRD IFPNT VFADS NIDSV MAPDA FVCGR ICTHH PGCLF FTFFS
230 235 240 245 250 255 260 265 270
QEWPK ESQRN LCLLK TSESG LPSTR IKKSK ALSGF SLQSC RHSIP
30s
300s
3000s
10000s

FIG.3A

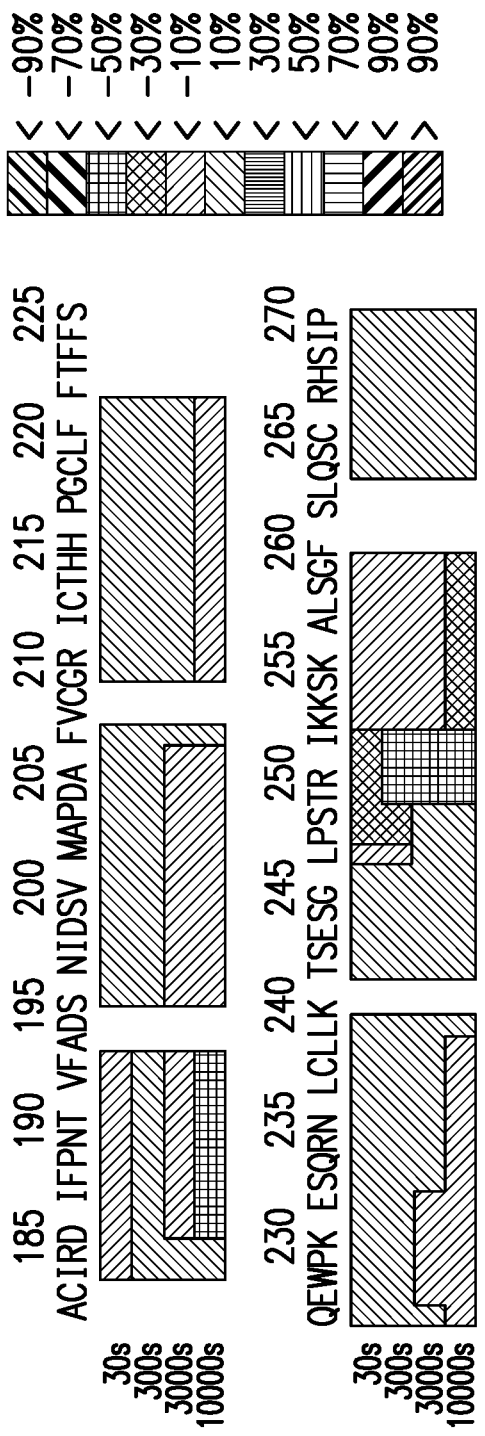
< -90%
< -70%
< -50%
< -30%
< -10%
< 10%
< 30%
< 50%
< 70%
< 90%
> 90%
185 190 195 200 205 210 215 220 225
ACIRD IFPNT VFADS NIDSV MAPDA FVCGR ICTHH PGCLF FTFFS
230 235 240 245 250 255 260 265 270
QEWPK ESQRN LCLLK TSESG LPSTR IKKSK ALSGF SLQSC RHSIP
30s
300s
3000s
10000s

FIG.3B

Heavy Chain variable domain of αFXI-18611p(E1)(M105) (SEQ ID NO:22)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
EVQLQESGPGLVKPSETLSLTCAVSGYSISSGYFWGWIRQPPGKGLEWIGSILHSGVTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                    789012345a                    012345678901234                    HC-CDR1
                                                                    HC-CDR2

          1         1
          0         1
567890abcde1234567890123
DRTTVSMIEYFQHWGQGTLVTVSS
HC-CDR3
```

Heavy Chain variable domain of αFXI-18611(E1)(L105) (SEQ ID NO:24)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
EVQLQESGPGLVKPSETLSLTCAVSGYSISSGYFWGWIRQPPGKGLEWIGSILHSGVTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                    789012345a                    012345678901234                    HC-CDR1
                                                                    HC-CDR2

          1         1
          0         1
567890abcde1234567890123
DRTTVSLIEYFQHWGQGTLVTVSS
HC-CDR3
```

FIG.4A

Heavy Chain variable domain of αFXI-18611p(Q1)(M105) (SEQ ID NO:21)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
QVQLQESGPGLVKPSETLSLTCAVSGYSISSGYFWGWIRQPPGKGLEWIGSILHSGVTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                                  HC-CDR1                                 HC-CDR2
          1         1
          0         1
567890abcde12345678901234
DRTTVSMIEYFQHWGQGTLVTVSS
    HC-CDR3
```

Heavy Chain variable domain of αFXI-18611(Q1)(L105) (SEQ ID NO:23)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
QVQLQESGPGLVKPSETLSLTCAVSGYSISSGYFWGWIRQPPGKGLEWIGSILHSGVTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                                  HC-CDR1                                 HC-CDR2
          1         1
          0         1
567890abcde12345678901234
DRTTVSLIEYFQHWGQGTLVTVSS
    HC-CDR3
```

FIG.4B

Light Chain variable domain of αFXI-18611p and αFXI-18611 families (SEQ ID NO:25)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678
DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQFHLLPITF
                    HC-CDR1             HC-CDR2                                 HC-CDR3
  1
  0
890123456
GGGTKVEIK
```

FIG.4C

Heavy Chain variable domain of αFXI-18623p(Q1) (SEQ ID NO:28)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
QVQLQESGPGLVKPSQTLSLTCTVSGGSIYSGAYYWSWIRQHPGKGLEWIGSIHYSGLTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                                  HC-CDR1                 HC-CDR2
          1         1
0         0
567890abcdefg12345678901234567890123
DVDDSSGDEHYGMDVWGQGTTVTVSS
HC-CDR3
```

Heavy Chain variable domain of αFXI-18623p(E1) (SEQ ID NO:29)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012abc345678901234
EVQLQESGPGLVKPSQTLSLTCTVSGGSIYSGAYYWSWIRQHPGKGLEWIGSIHYSGLTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR
                                  HC-CDR1                 HC-CDR2
          1         1
0         0
567890abcdefg12345678901234567890123
DVDDSSGDEHYGMDVWGQGTTVTVSS
HC-CDR3
```

FIG.5A

Light Chain variable domain of the αFXI-18623p family (SEQ ID NO:30)

```
          1         2         3         4         5         6         7         8         9
1234567890123456789012345678901234567890123456789012345678901234567890123456789012345678
DIQMTQSPSSVSASVGDRVTITCRASQGIDSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYHIVPITF
                    HC-CDR1                 HC-CDR2                                 HC-CDR3
```

1
0
890123456
GGGTKVEIK

FIG.5B

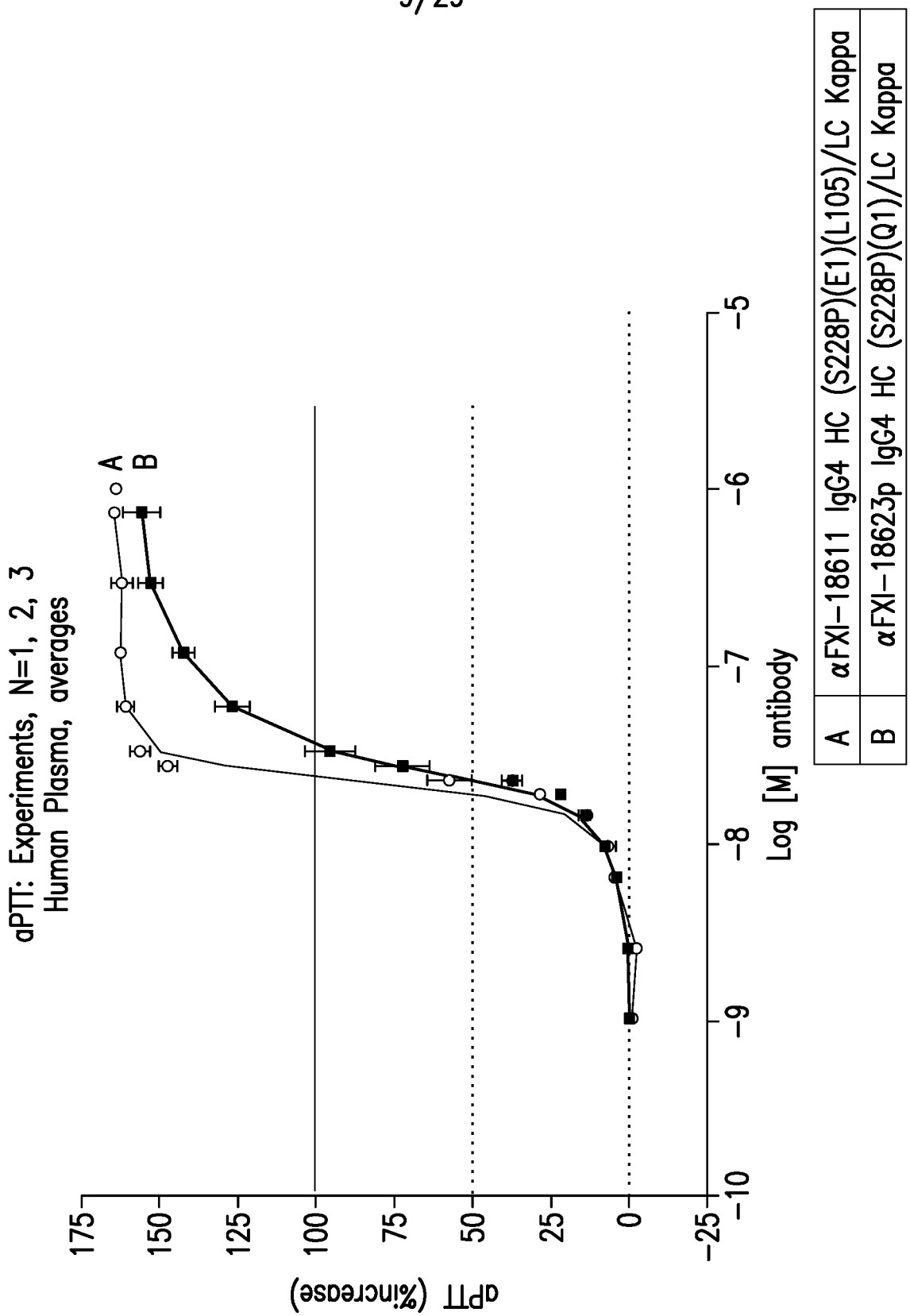
aPTT: Experiments, N=1, 2, 3
Human Plasma, averages
A
B
aPTT (%increase)
175
150
125
100
75
50
25
0
−25
−10
−9
−8
−7
−6
−5
Log [M] antibody
A αFXI−18611 IgG4 HC (S228P)(E1)(L105)/LC Kappa
B αFXI−18623p IgG4 HC (S228P)(Q1)/LC Kappa

FIG.6

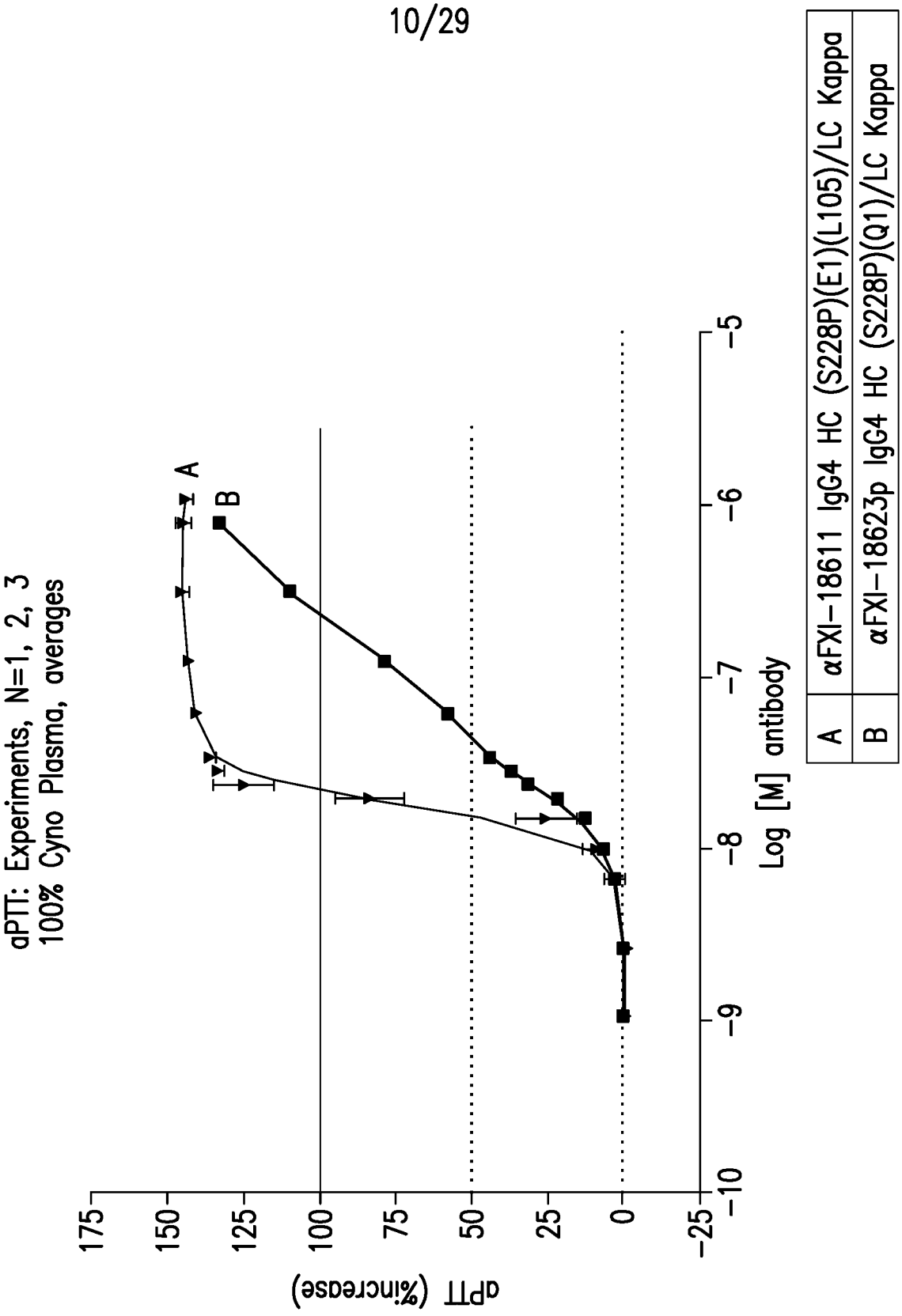
aPTT: Experiments, N=1, 2, 3
100% Cyno Plasma, averages
aPTT (%increase)
175
150
125
100
75
50
25
0
−25
−10
−9
−8
−7
−6
−5
Log [M] antibody
A
B
A αFXI−18611 IgG4 HC (S228P)(E1)(L105)/LC Kappa
B αFXI−18623p IgG4 HC (S228P)(Q1)/LC Kappa

FIG. 7

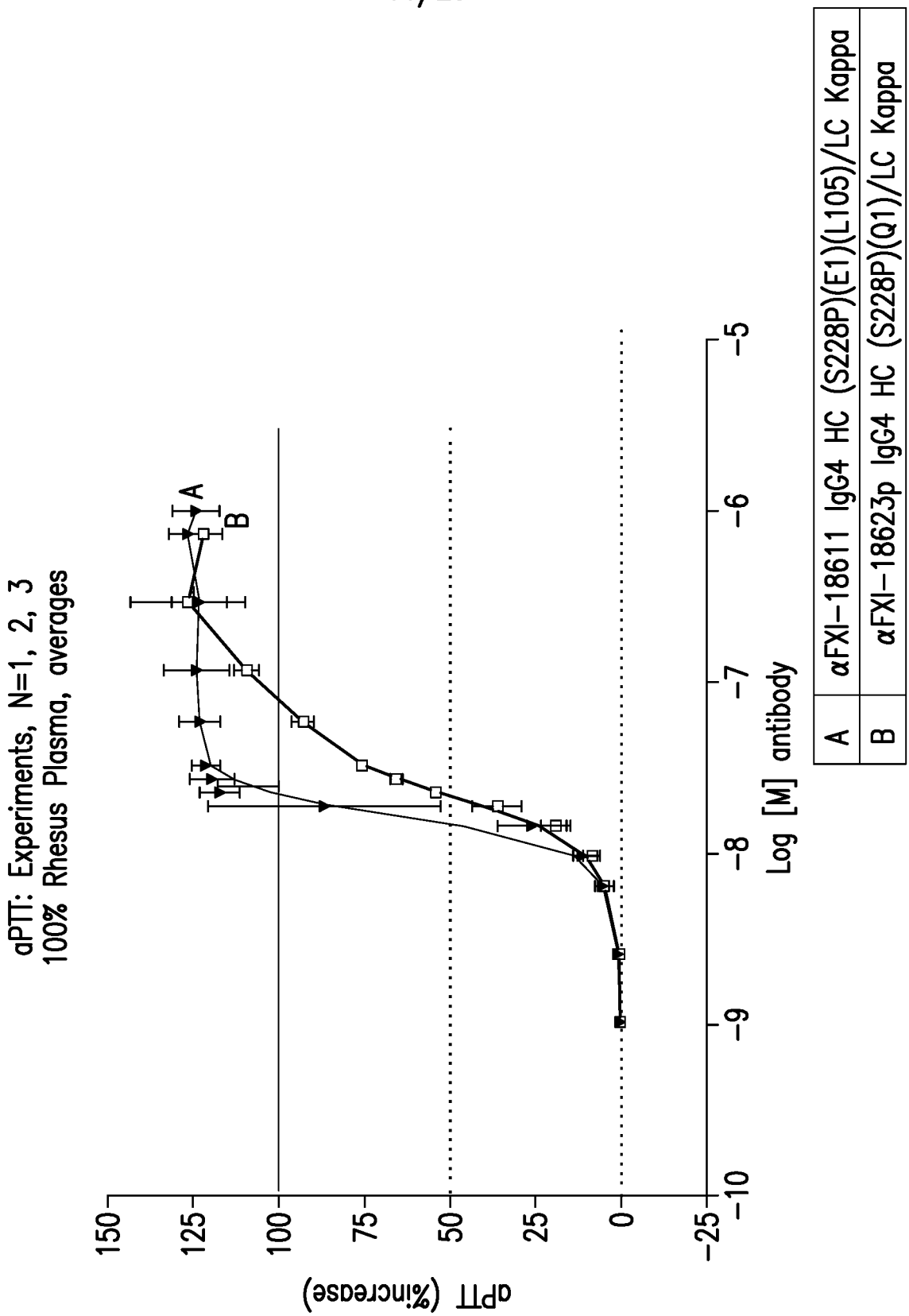
aPTT: Experiments, N=1, 2, 3
100% Rhesus Plasma, averages
aPTT (%increase)
150
125
100
75
50
25
0
−25
−10
−9
−8
−7
−6
−5
Log [M] antibody
A
B
A αFXI−18611 IgG4 HC (S228P)(E1)(L105)/LC Kappa
B αFXI−18623p IgG4 HC (S228P)(Q1)/LC Kappa

FIG.8

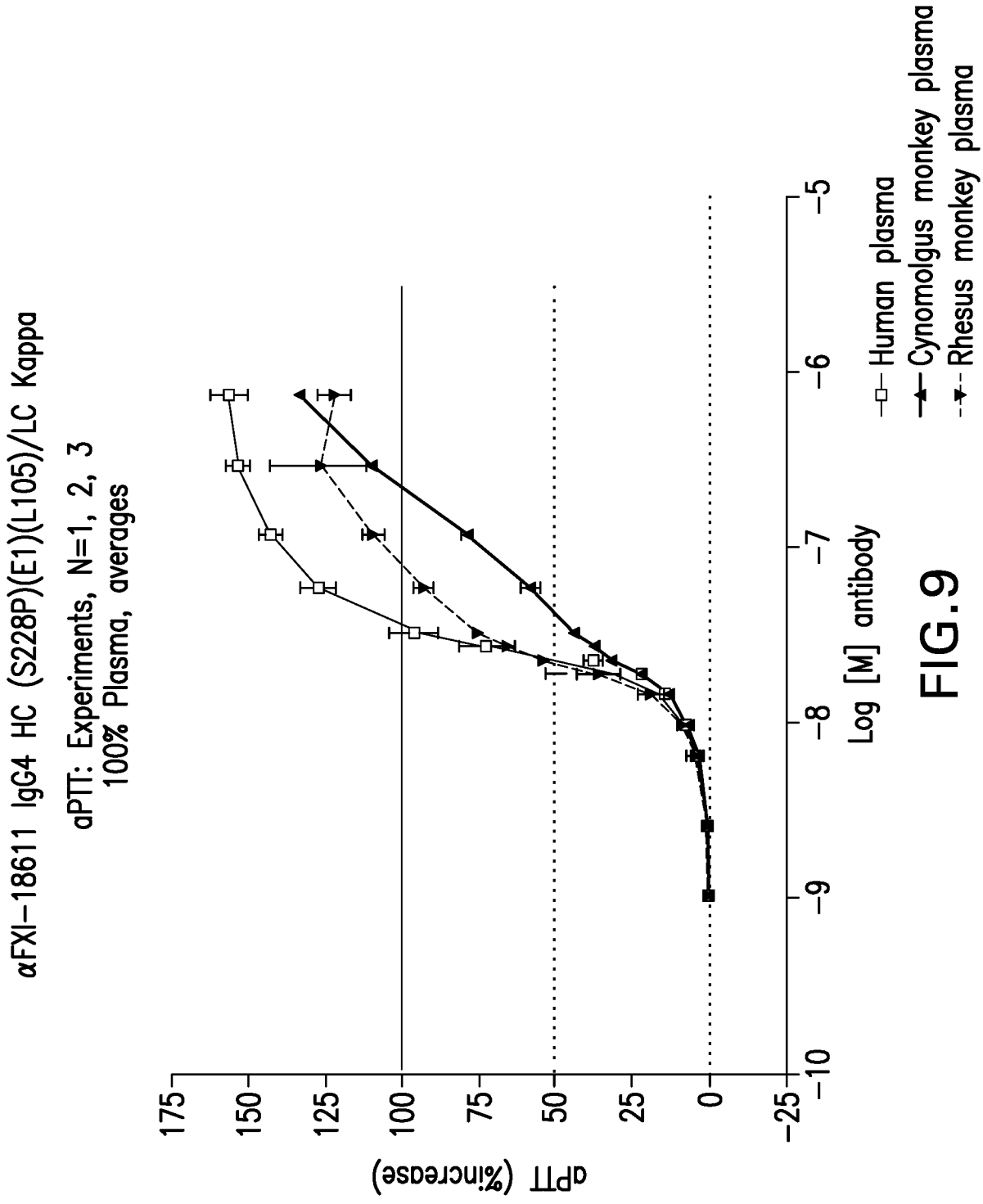
αFXI-18611 IgG4 HC (S228P)(E1)(L105)/LC Kappa
aPTT: Experiments, N=1, 2, 3
100% Plasma, averages
aPTT (%increase)
175
150
125
100
75
50
25
0
-25
-10
-9
-8
-7
-6
-5
Log [M] antibody
Human plasma
Cynomolgus monkey plasma
Rhesus monkey plasma

FIG.9

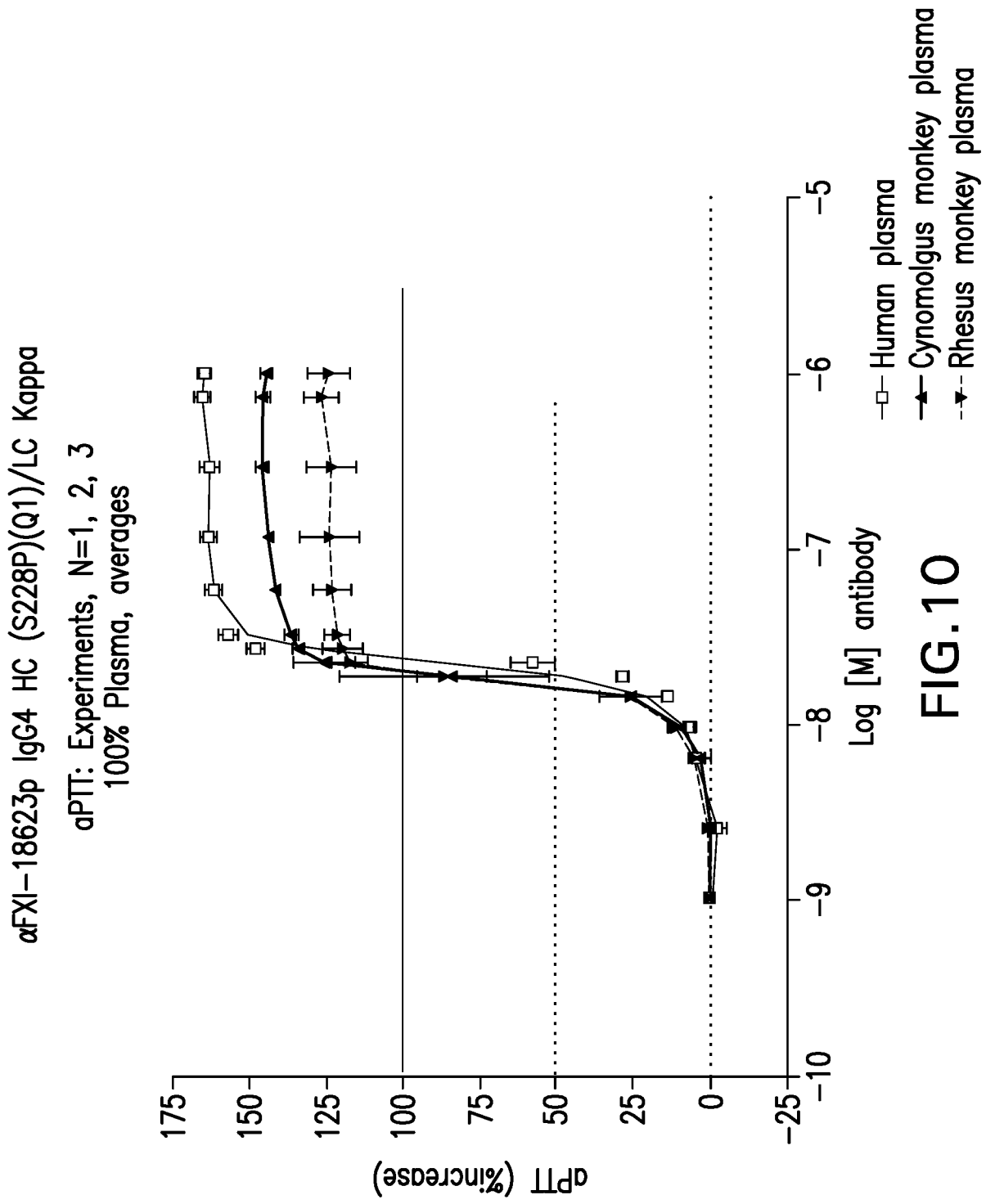
αFXI–18623p IgG4 HC (S228P)(Q1)/LC Kappa
aPTT: Experiments, N=1, 2, 3
100% Plasma, averages
aPTT (%increase)
175
150
125
100
75
50
25
0
–25
–10
–9
–8
–7
–6
–5
Log [M] antibody
Human plasma
Cynomolgus monkey plasma
Rhesus monkey plasma

FIG.10

Scale:-10-140 RU
All Human unless indicated:
Cy- Cynomolgus
Rh - Rhesus

All plasma derived except:
Rec - Recombinant
His - Polyhistidine tag

FIG. 11

Scale:-10-140 RU
All Human unless indicated:
Cy – Cynomolgus
Rh – Rhesus

All plasma derived except:
Rec – Recombinant
His Polyhistidine tag

FIG.12

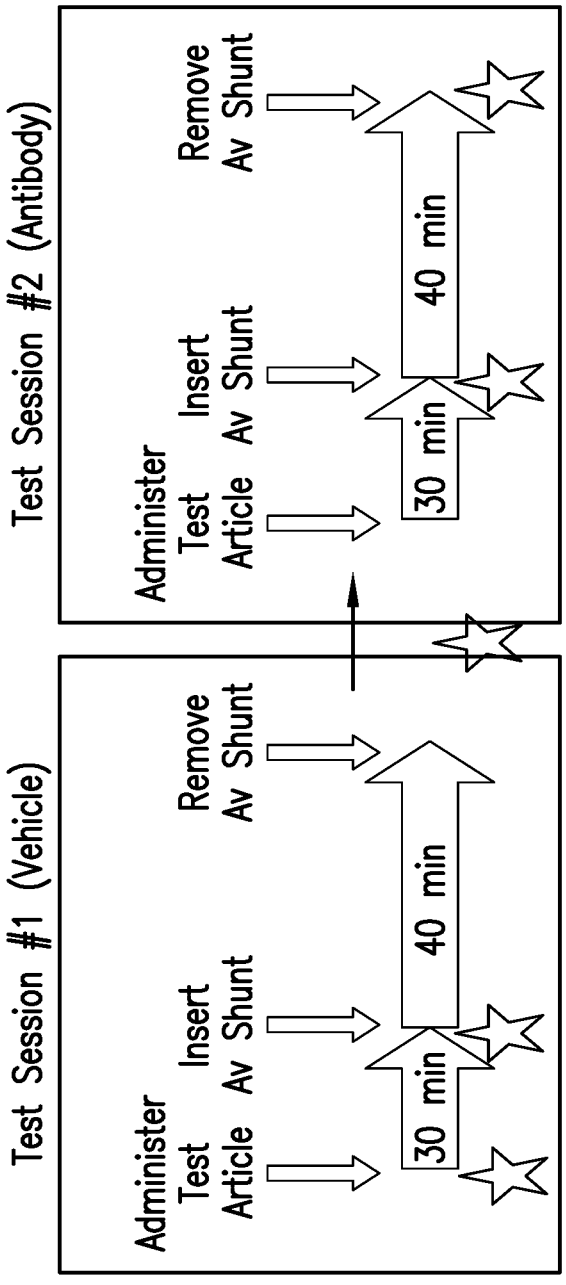
Test Session #1 (Vehicle)
Administer Test Article
Insert Av Shunt
30 min
40 min
Remove Av Shunt
Test Session #2 (Antibody)
Administer Test Article
Insert Av Shunt
30 min
40 min
Remove Av Shunt

FIG.13

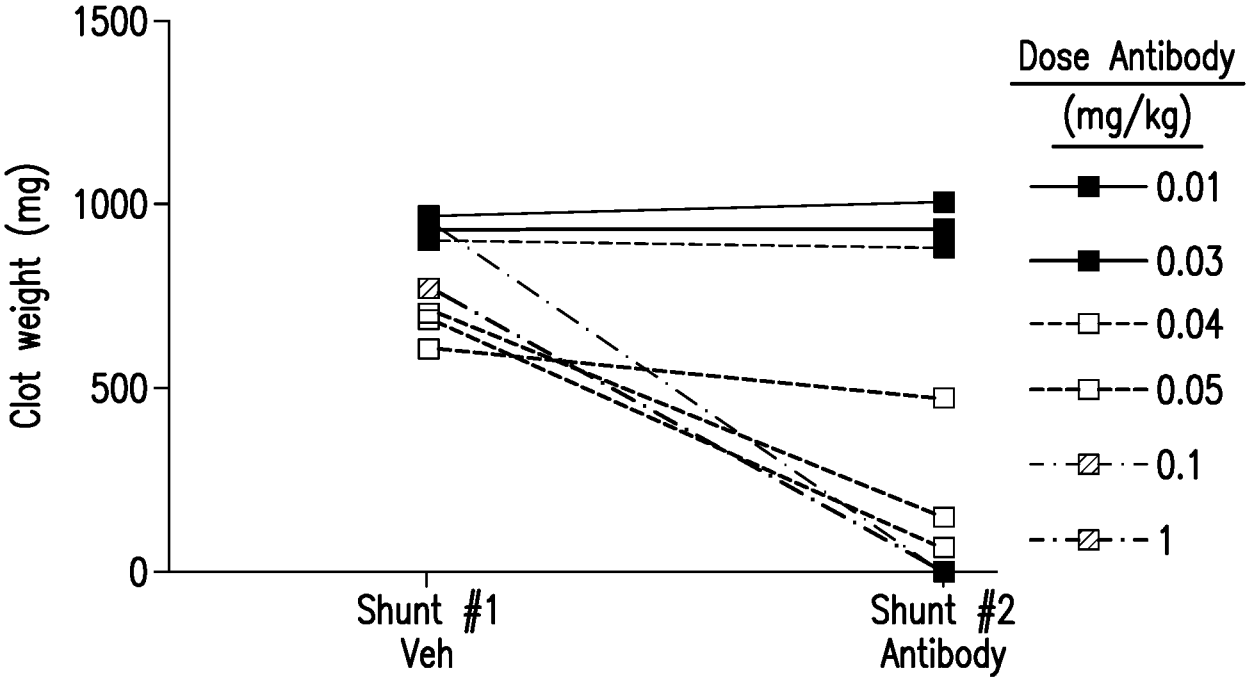
1500
1000
500
0
Clot weight (mg)
Shunt #1
Veh
Shunt #2
Antibody
Dose Antibody
(mg/kg)
0.01
0.03
0.04
0.05
0.1
1

FIG.14A

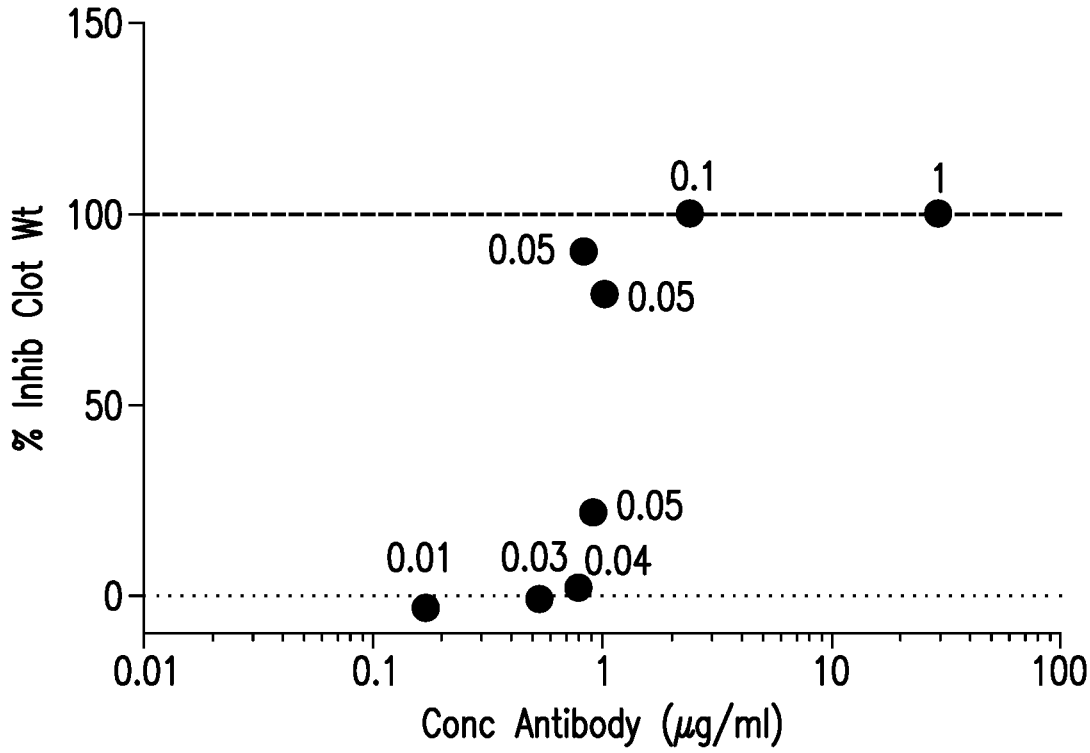
150
100
50
0
% Inhib Clot Wt
0.1
1
0.05
0.05
0.05
0.01
0.03
0.04
0.01
0.1
1
10
100
Conc Antibody (μg/ml)

FIG. 14B

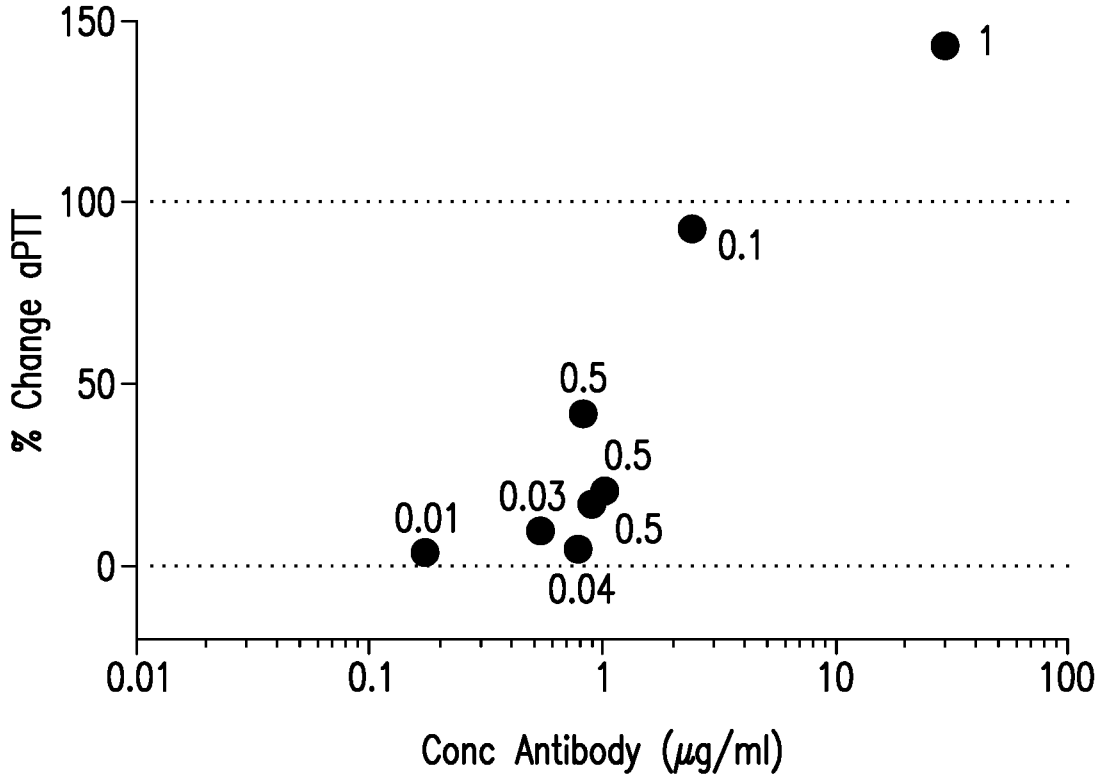
150
100
50
0
% Change aPTT
1
0.1
0.5
0.5
0.03
0.01
0.5
0.04
0.01
0.1
1
10
100
Conc Antibody (μg/ml)

FIG.14C

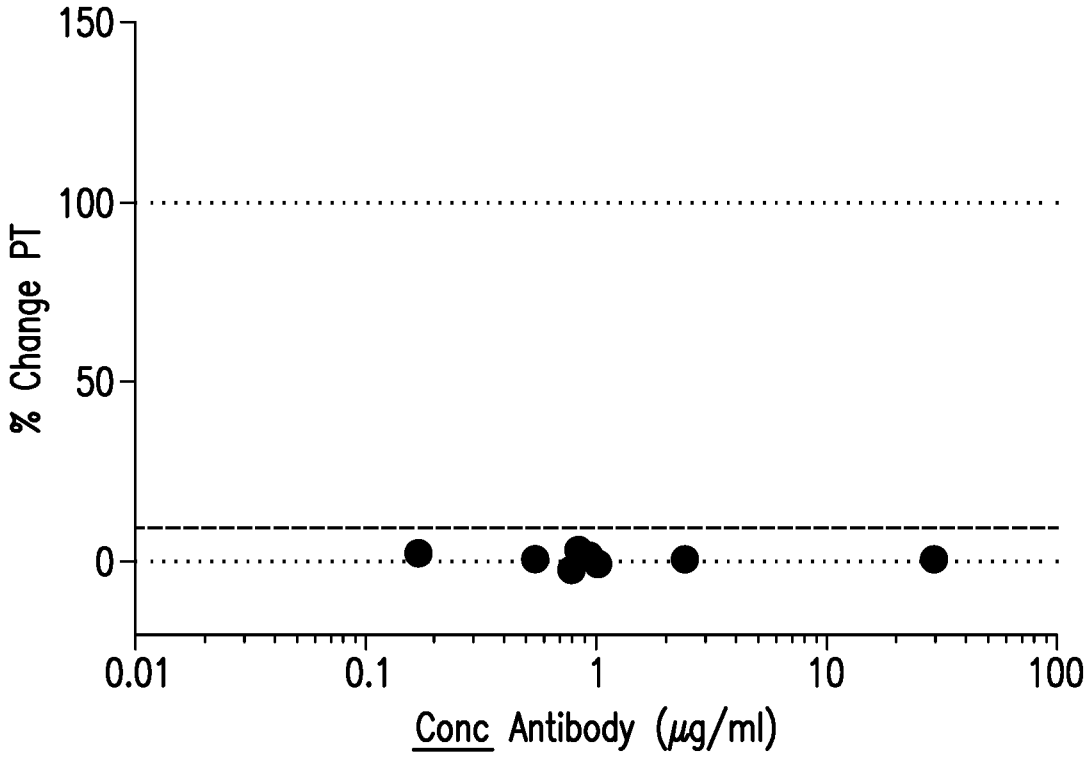

FIG.14D

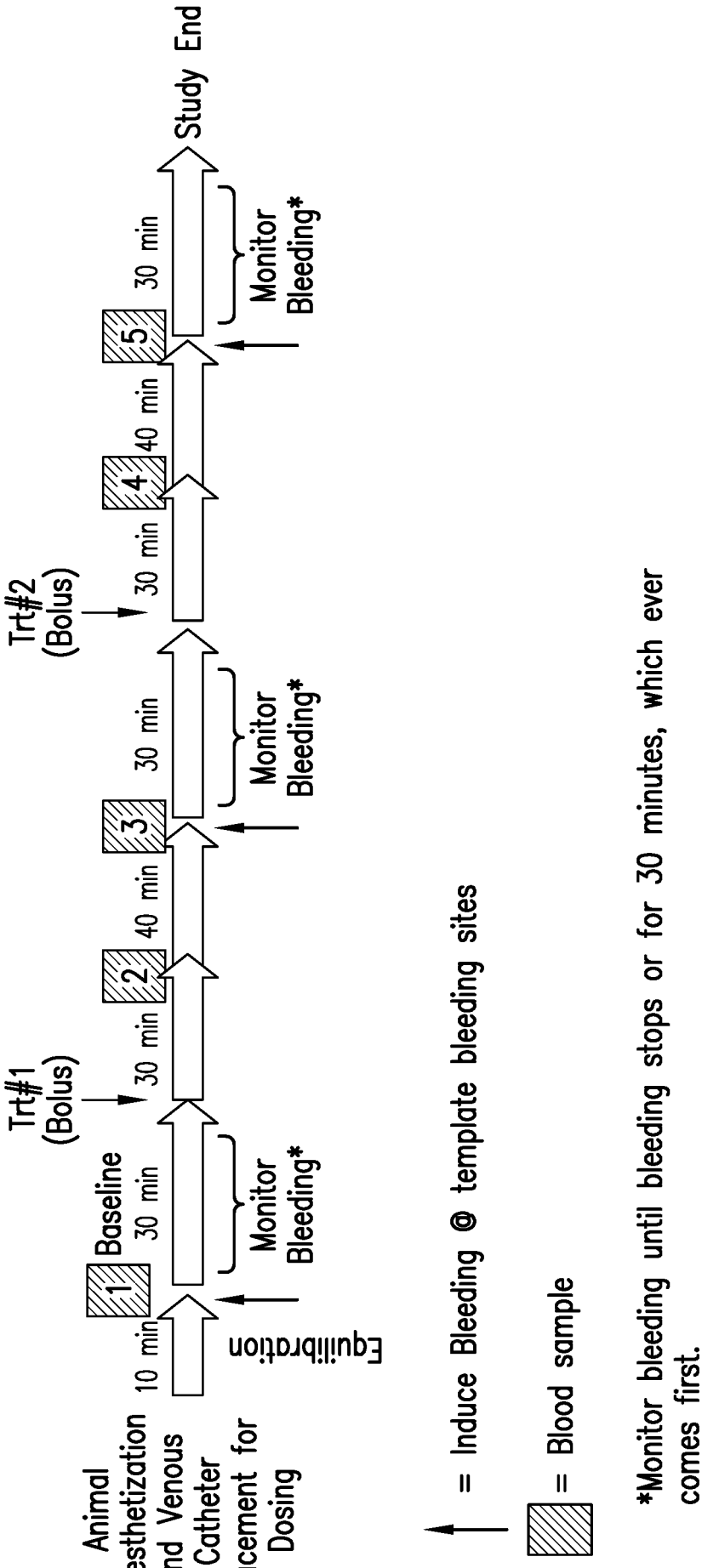
Animal Anesthetization and Venous Catheter Placement for Dosing
10 min
Equilibration
1
Baseline
30 min
Monitor Bleeding*
Trt#1 (Bolus)
30 min
2
40 min
3
30 min
Monitor Bleeding*
Trt#2 (Bolus)
30 min
4
40 min
5
30 min
Monitor Bleeding*
Study End
= Induce Bleeding @ template bleeding sites
= Blood sample
*Monitor bleeding until bleeding stops or for 30 minutes, which ever comes first.

FIG. 15

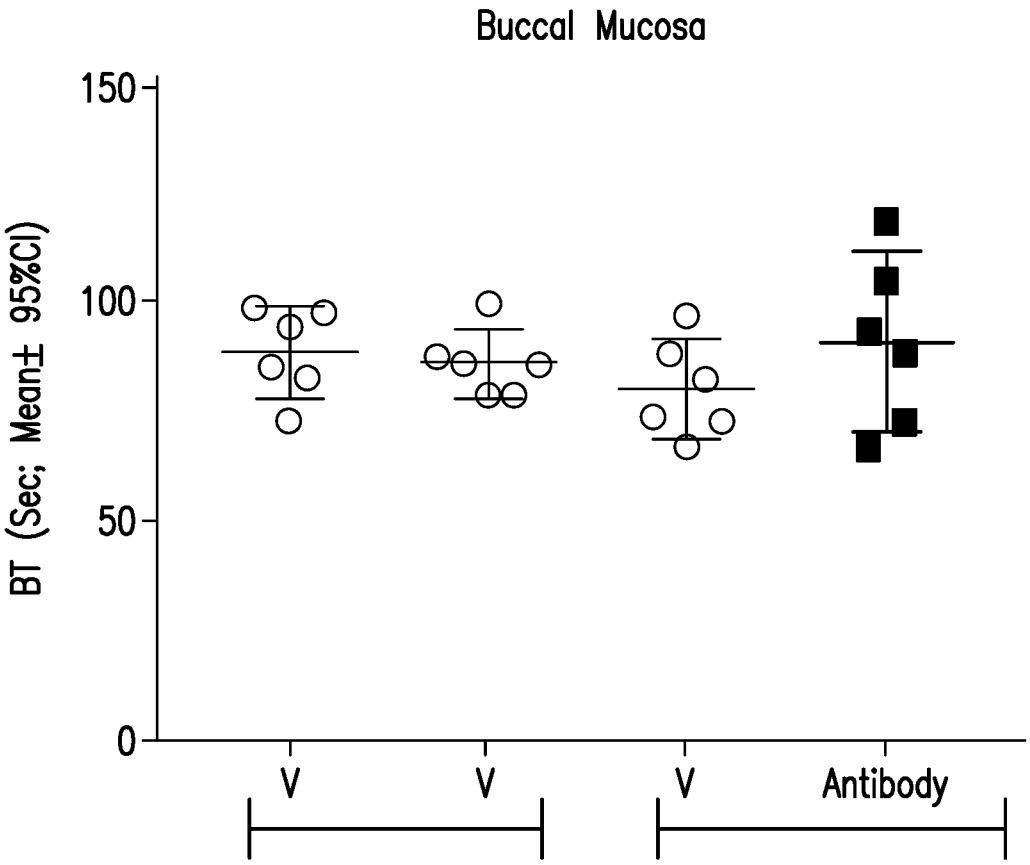

FIG.16A

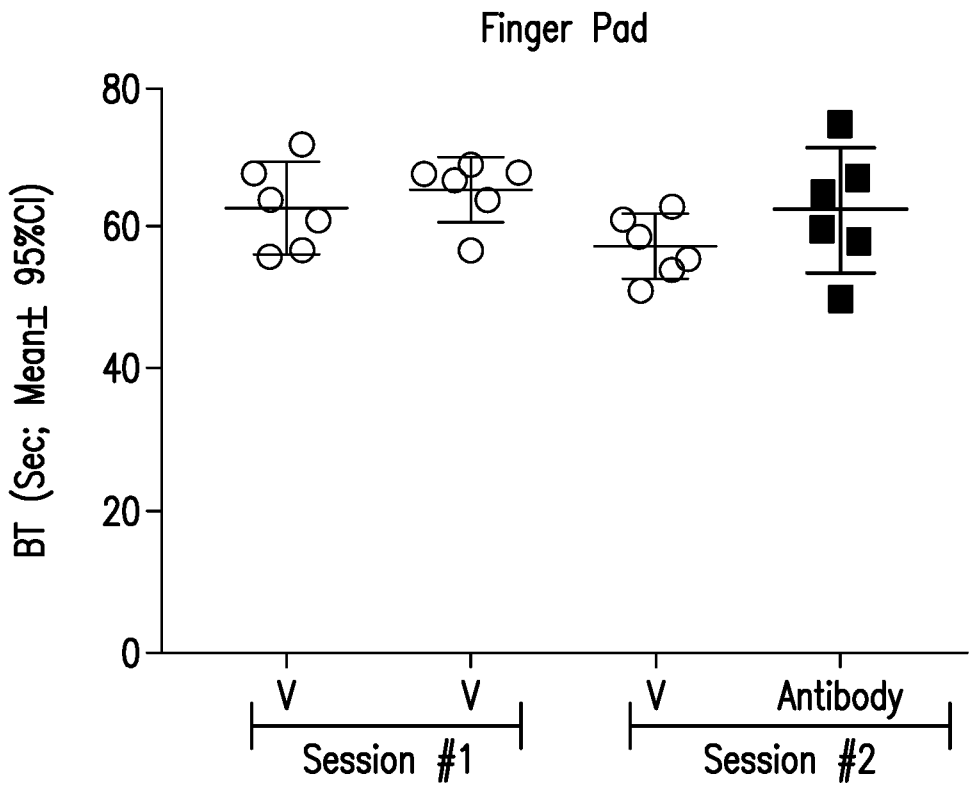
Finger Pad
BT (Sec; Mean± 95%CI)
80
60
40
20
0
V
V
V
Antibody
Session #1
Session #2

FIG.16B

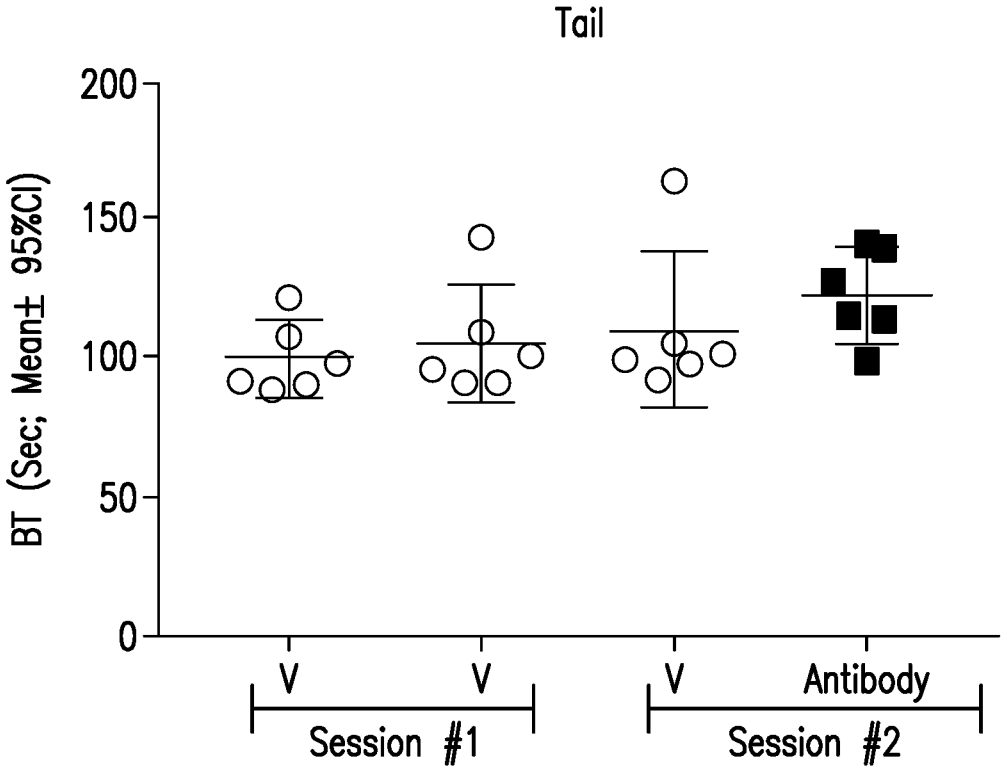
Tail
BT (Sec; Mean± 95%CI)
200
150
100
50
0
V
V
V
Antibody
Session #1
Session #2

FIG.16C

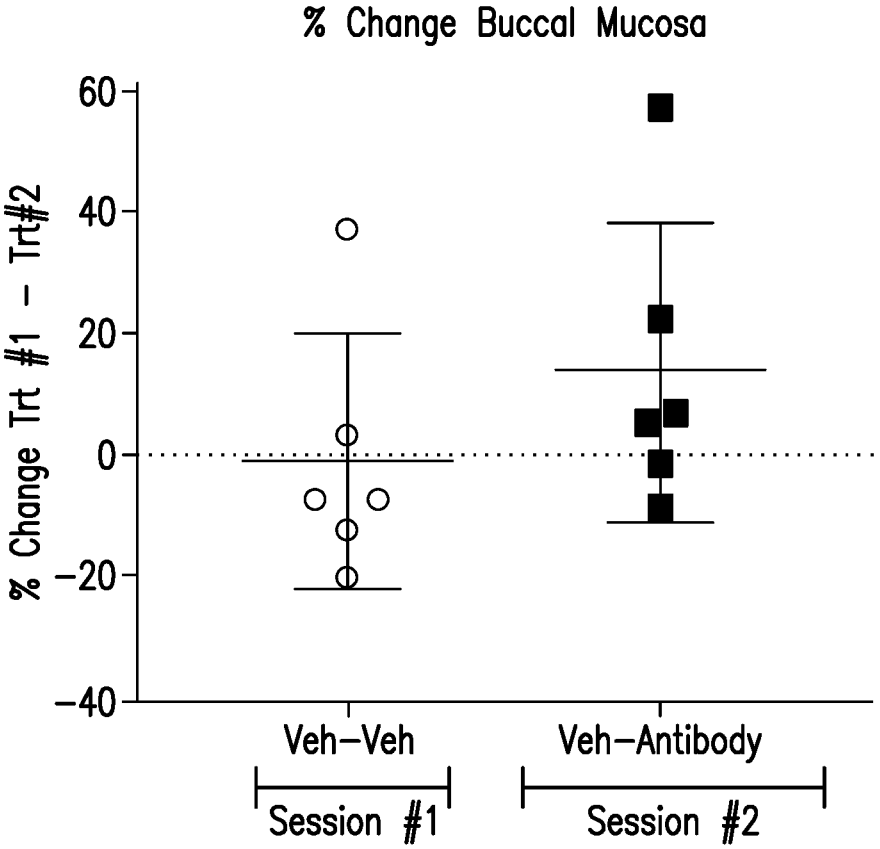
% Change Buccal Mucosa
% Change Trt #1 - Trt#2
60
40
20
0
−20
−40
Veh−Veh
Veh−Antibody
Session #1
Session #2

FIG.16D

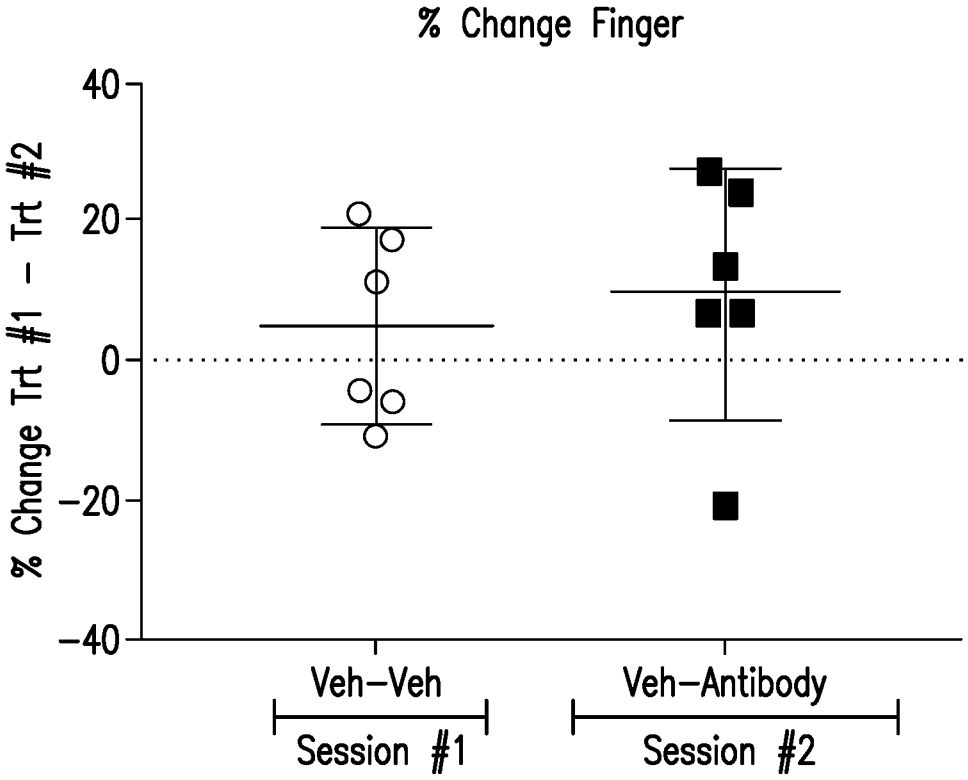
% Change Finger
% Change Trt #1 – Trt #2
40
20
0
−20
−40
Veh–Veh
Session #1
Veh–Antibody
Session #2

FIG.16E

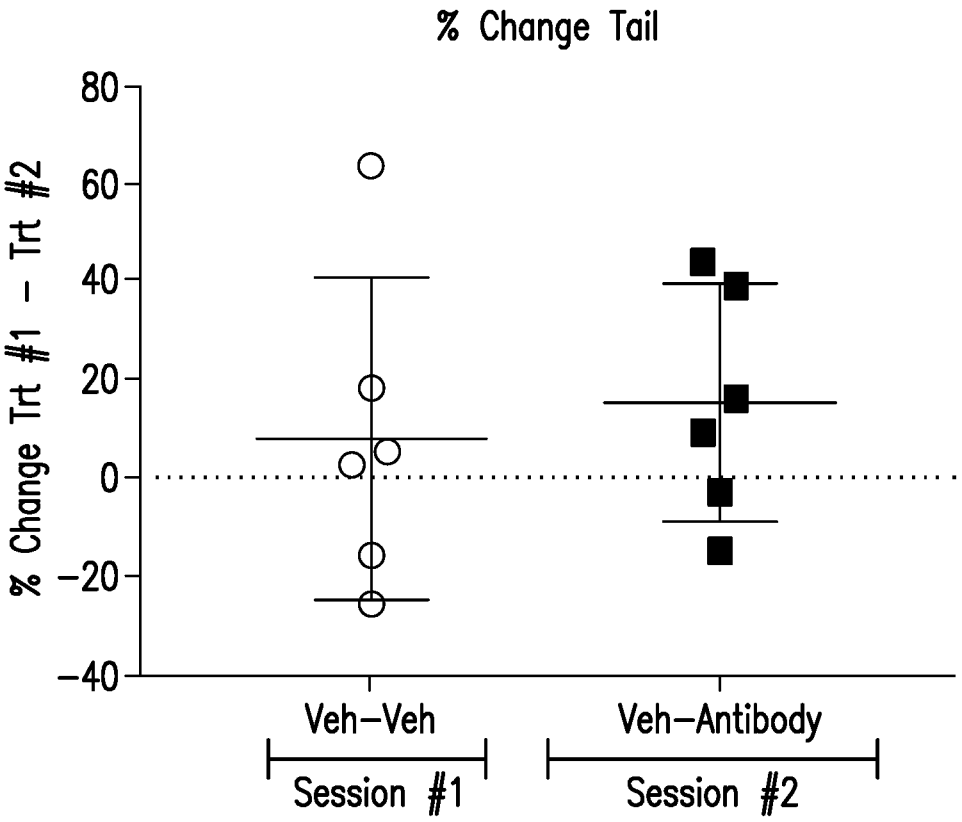
% Change Tail
% Change Trt #1 - Trt #2
80
60
40
20
0
−20
−40
Veh−Veh
Veh−Antibody
Session #1
Session #2

FIG.16F

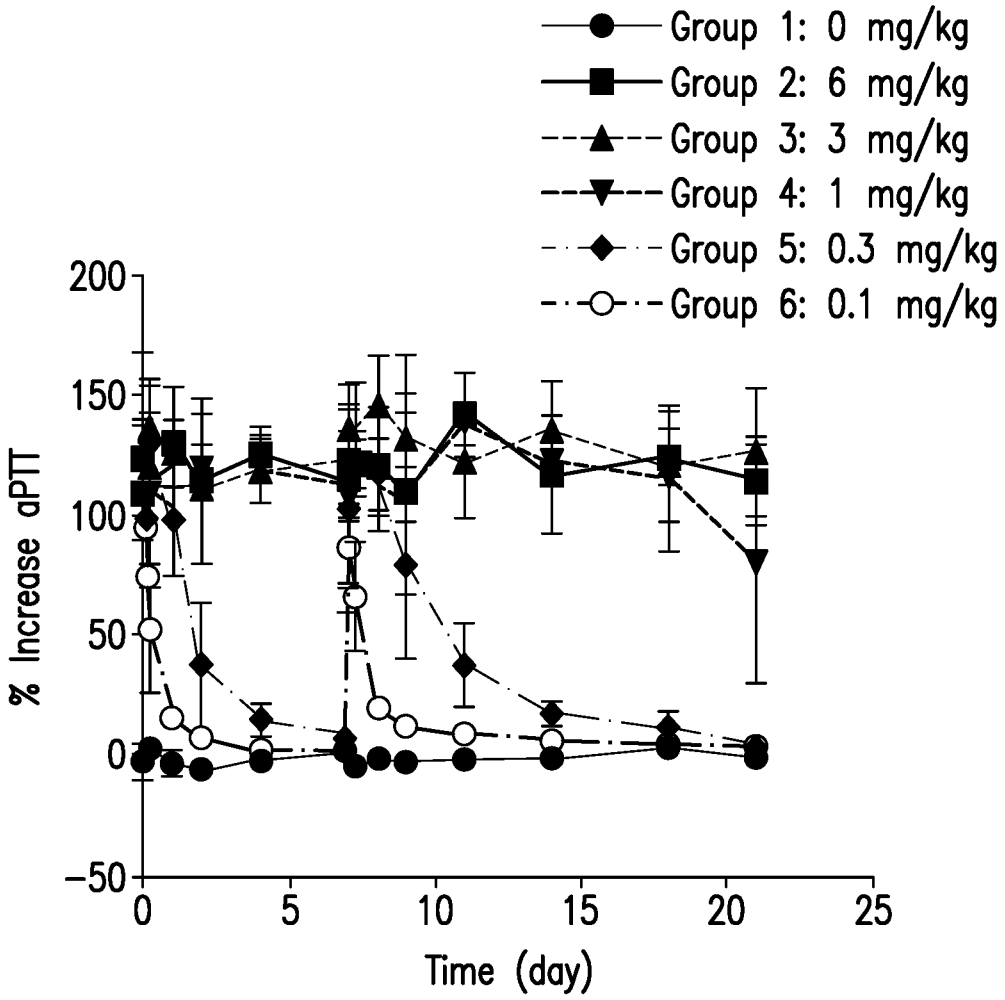
Group 1: 0 mg/kg
Group 2: 6 mg/kg
Group 3: 3 mg/kg
Group 4: 1 mg/kg
Group 5: 0.3 mg/kg
Group 6: 0.1 mg/kg
% Increase aPTT
200
150
100
50
0
−50
0
5
10
15
20
25
Time (day)

FIG.17A

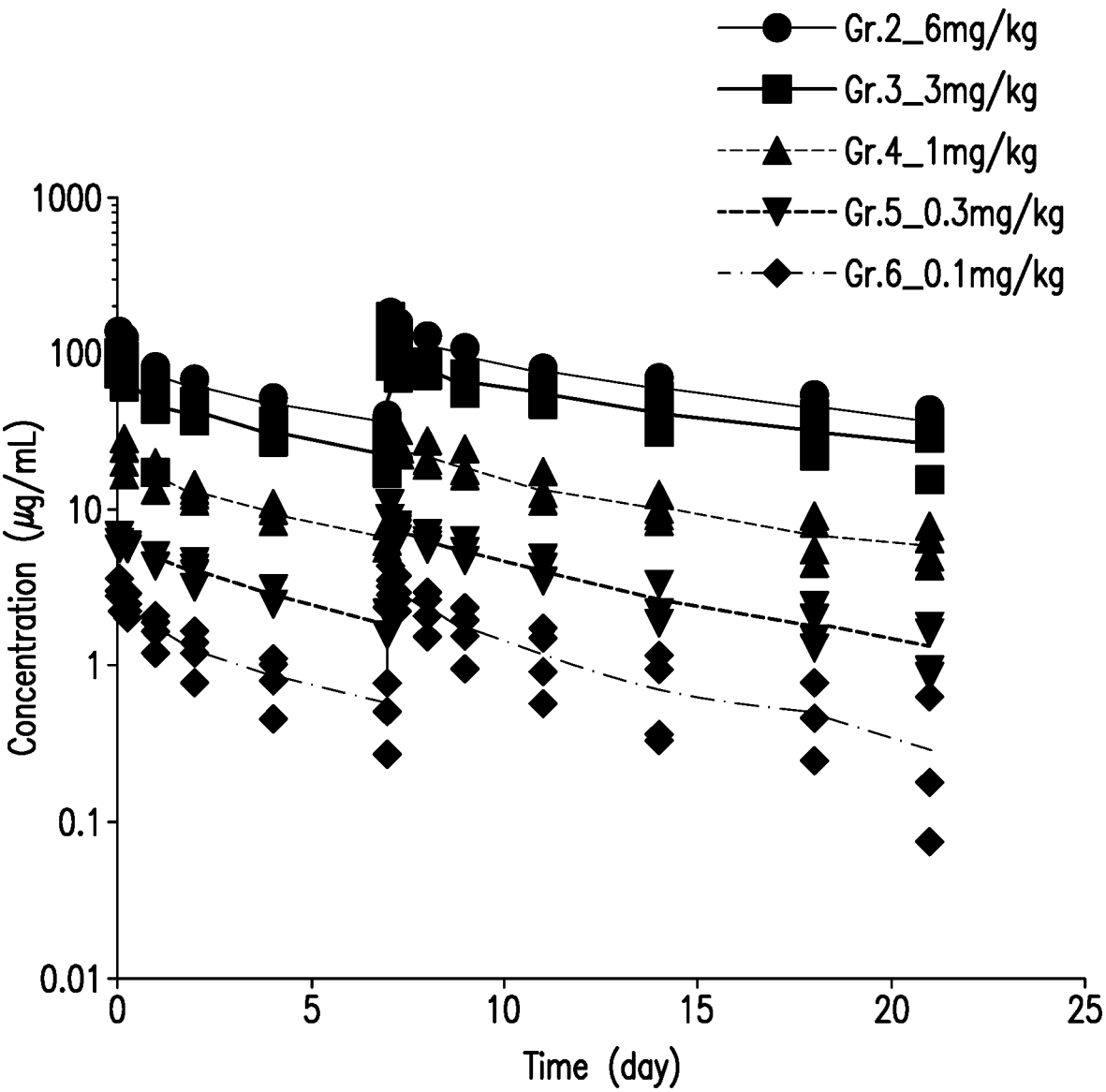
Gr.2_6mg/kg
Gr.3_3mg/kg
Gr.4_1mg/kg
Gr.5_0.3mg/kg
Gr.6_0.1mg/kg
1000
100
10
1
0.1
0.01
Concentration (μg/mL)
0
5
10
15
20
25
Time (day)

FIG.17B