FIGURE 1

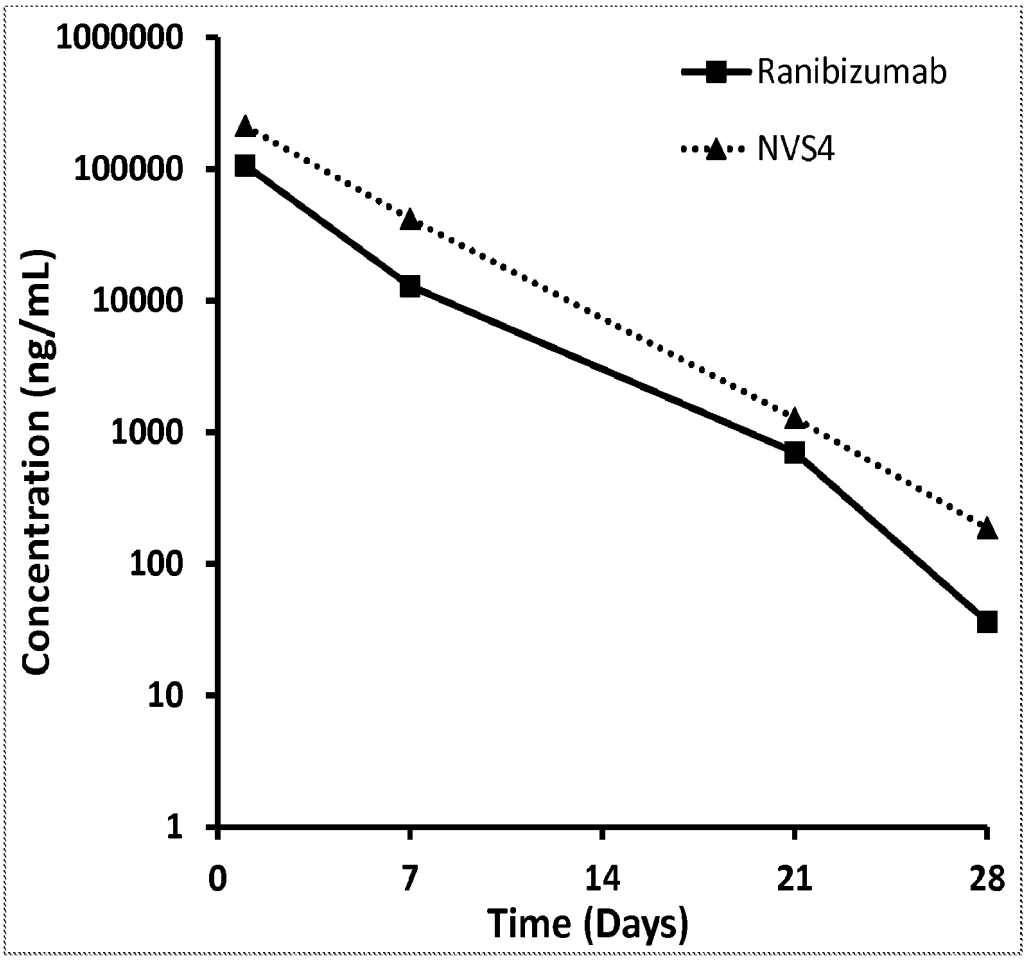

1000000
100000
10000
1000
100
10
1
Concentration (ng/mL)
0
7
14
21
28
Time (Days)
Ranibizumab
NVS4

FIGURE 2

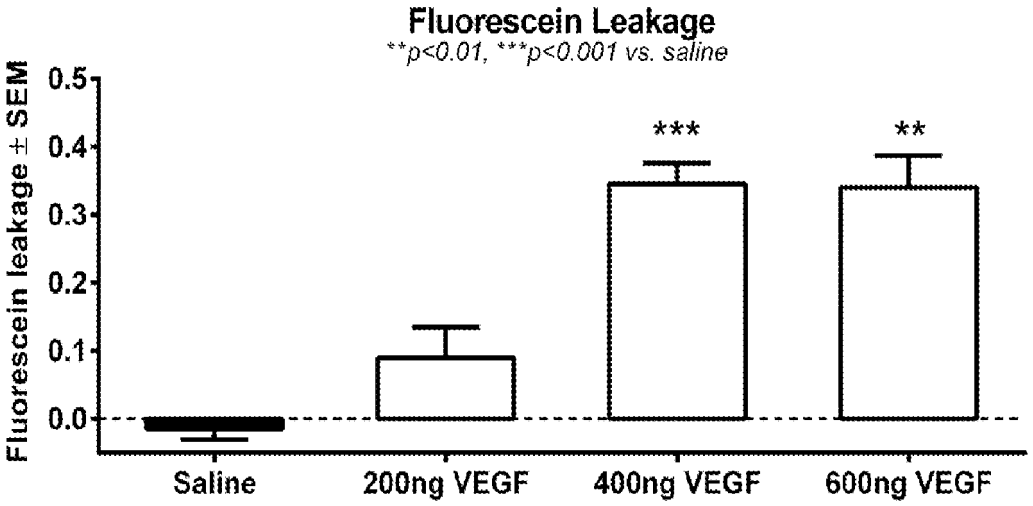

Fluorescein Leakage
**p<0.01, ***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
***
**
Saline
200ng VEGF
400ng VEGF
600ng VEGF

FIGURE 3

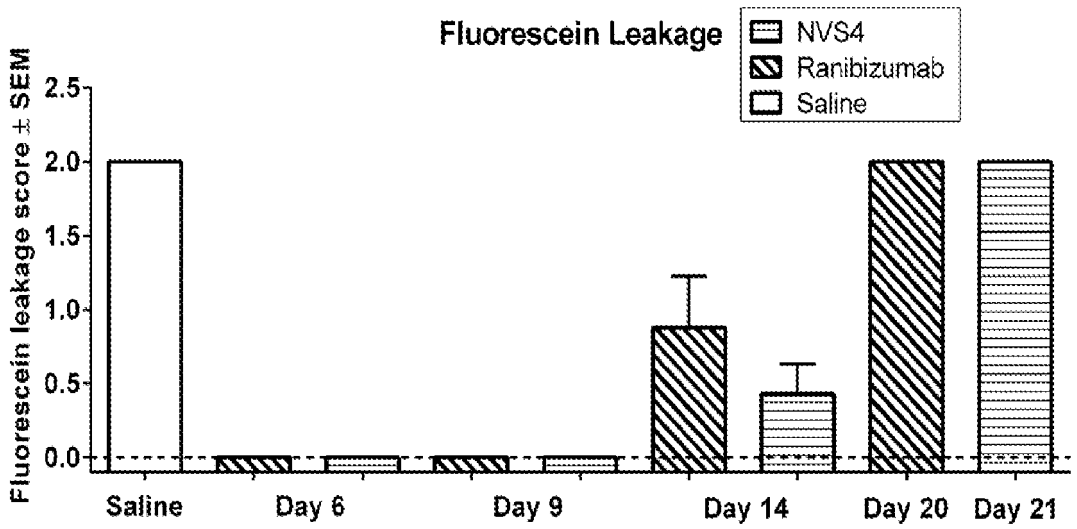

Fluorescein Leakage
NVS4
Ranibizumab
Saline
Fluorescein leakage score ± SEM
2.5
2.0
1.5
1.0
0.5
0.0
Saline
Day 6
Day 9
Day 14
Day 20
Day 21

FIGURE 4

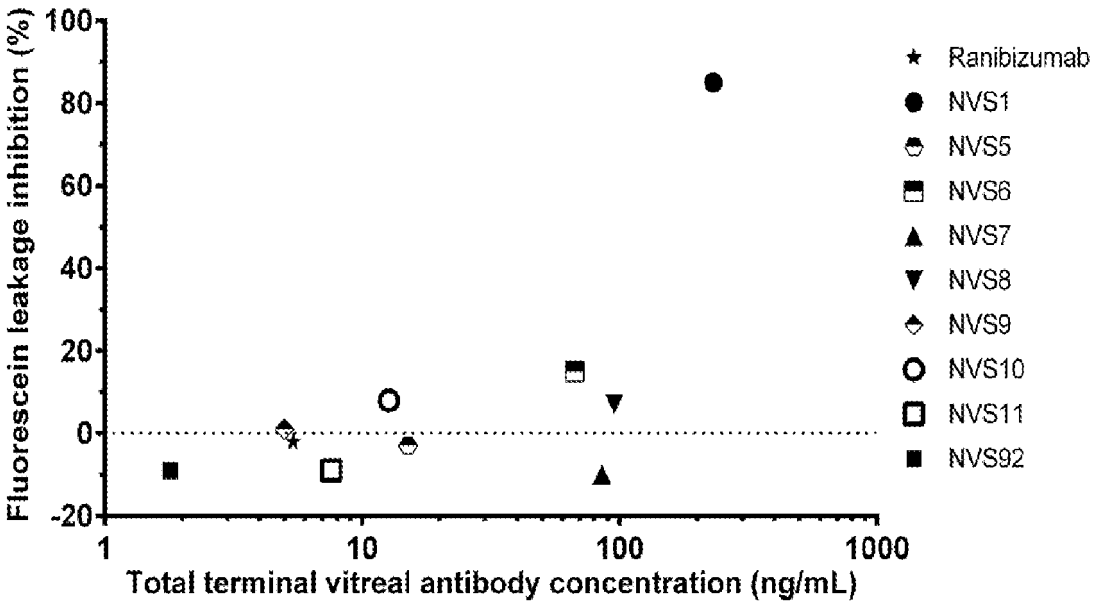

Fluorescein leakage inhibition (%)
100
80
60
40
20
0
-20
1
10
100
1000
Total terminal vitreal antibody concentration (ng/mL)
Ranibizumab
NVS1
NVS5
NVS6
NVS7
NVS8
NVS9
NVS10
NVS11
NVS92

FIGURE 5

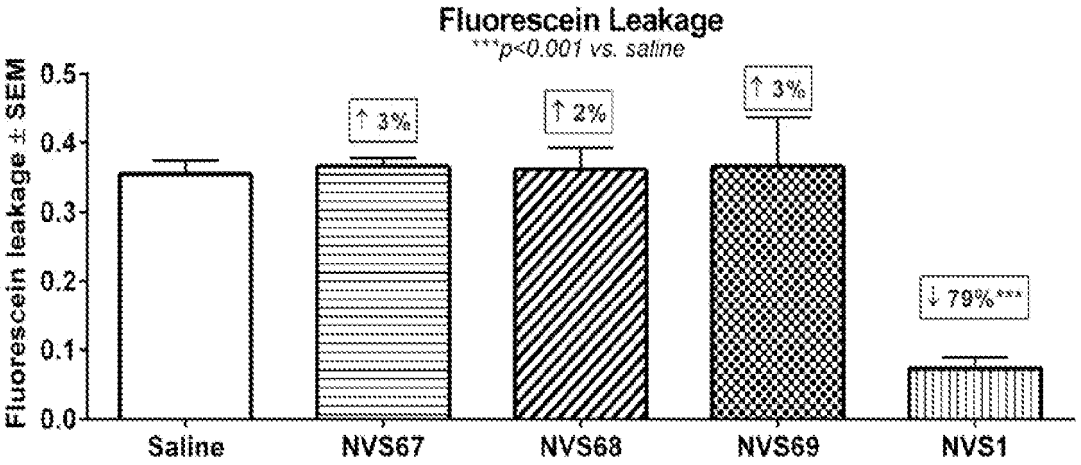

Fluorescein Leakage
***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↑ 3%
↑ 2%
↑ 3%
↓ 79%***
Saline
NVS67
NVS68
NVS69
NVS1

FIGURE 6

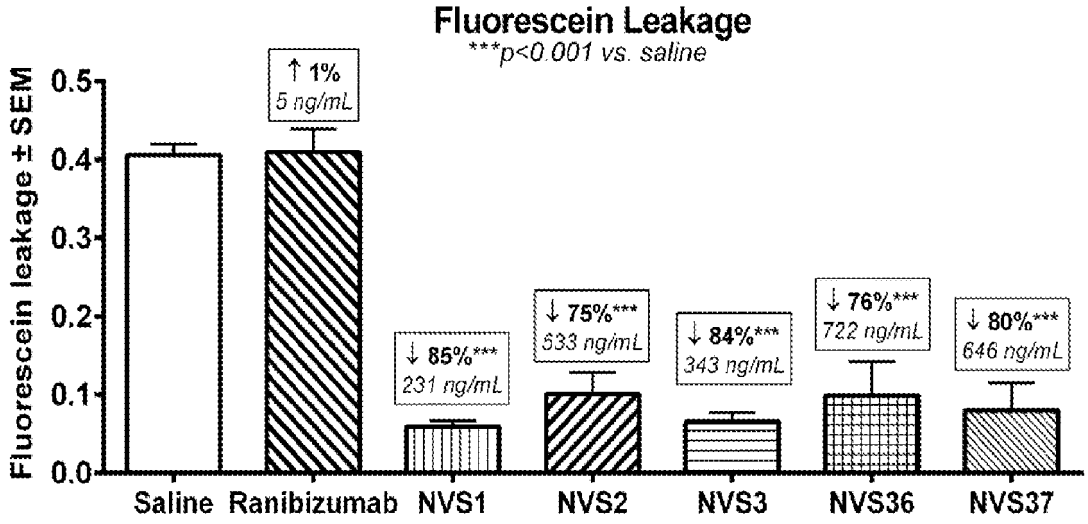

Fluorescein Leakage
***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↑ 1%
5 ng/mL
↓ 85%***
231 ng/mL
↓ 75%***
533 ng/mL
↓ 84%***
343 ng/mL
↓ 76%***
722 ng/mL
↓ 80%***
646 ng/mL
Saline
Ranibizumab
NVS1
NVS2
NVS3
NVS36
NVS37

FIGURE 7

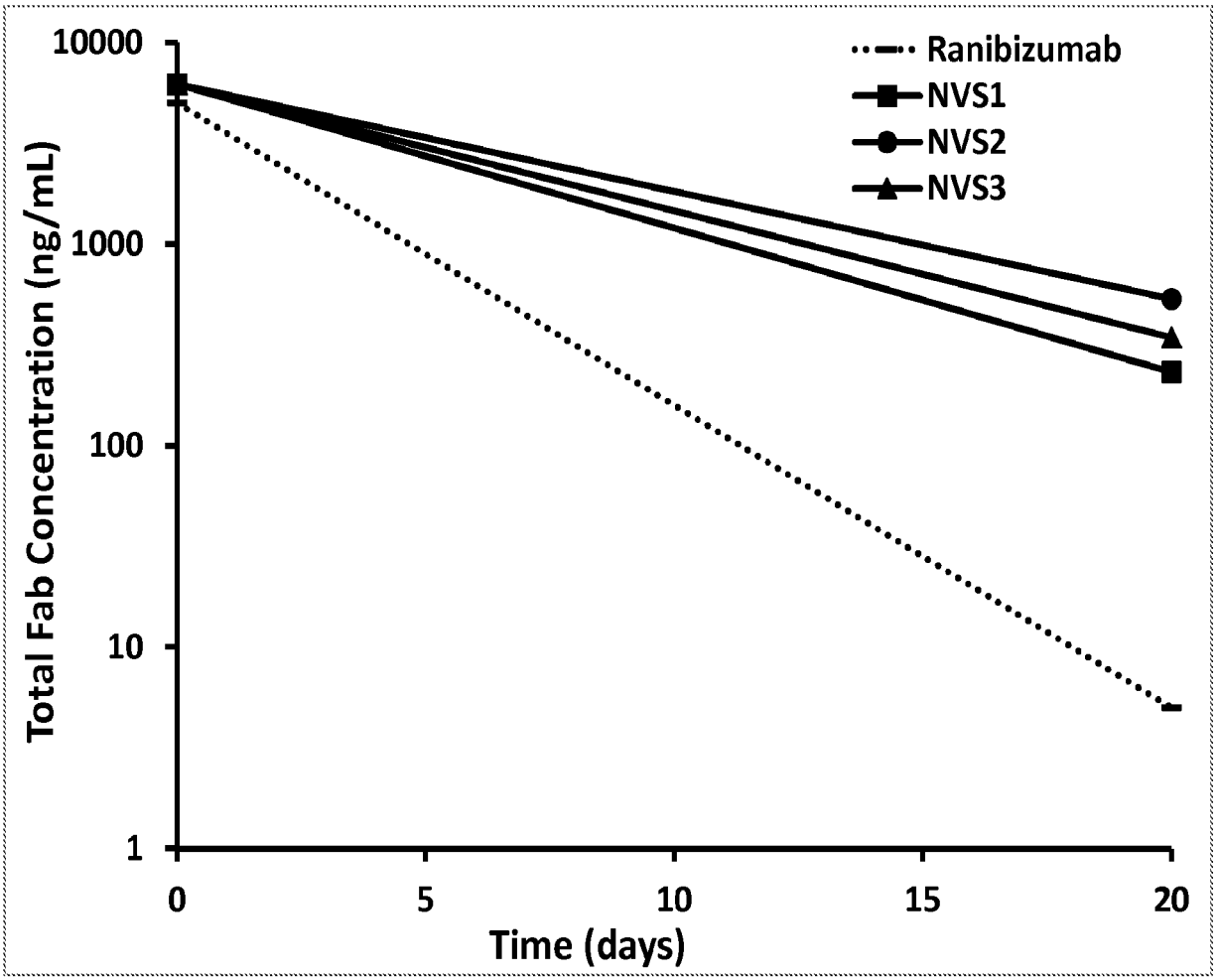

10000
1000
100
10
1
Total Fab Concentration (ng/mL)
0
5
10
15
20
Time (days)
Ranibizumab
NVS1
NVS2
NVS3

FIGURE 8

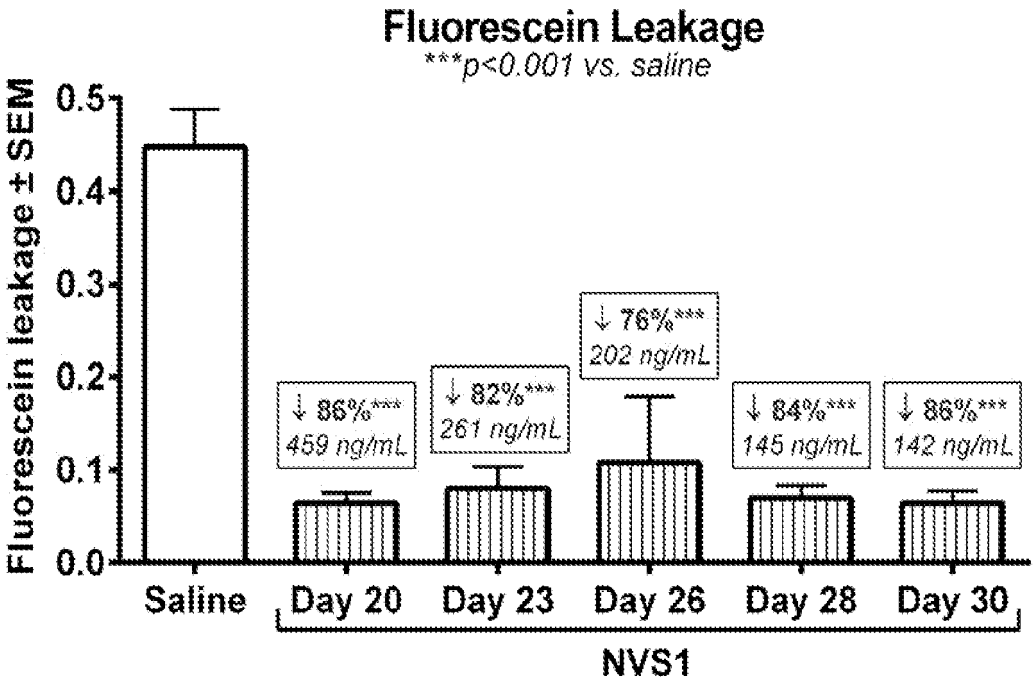

Fluorescein Leakage
***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↓ 86%***
459 ng/mL
↓ 82%***
261 ng/mL
↓ 76%***
202 ng/mL
↓ 84%***
145 ng/mL
↓ 86%***
142 ng/mL
Saline
Day 20
Day 23
Day 26
Day 28
Day 30
NVS1

FIGURE 9

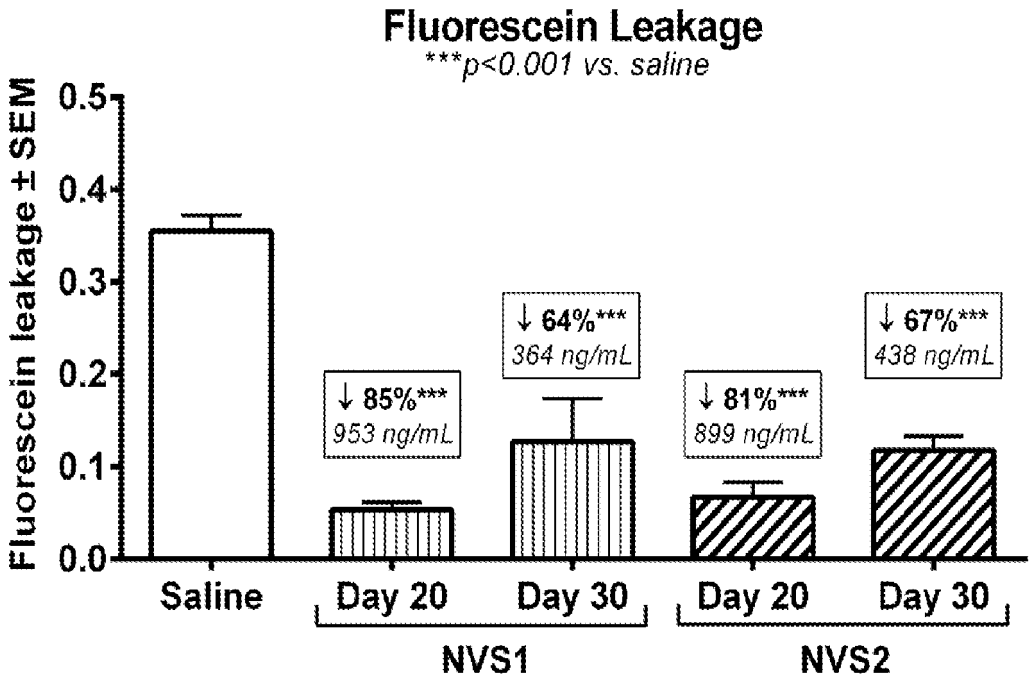

Fluorescein Leakage
***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↓ 85%***
953 ng/mL
↓ 64%***
364 ng/mL
↓ 81%***
899 ng/mL
↓ 67%***
438 ng/mL
Saline
Day 20
Day 30
Day 20
Day 30
NVS1
NVS2

FIGURE 10

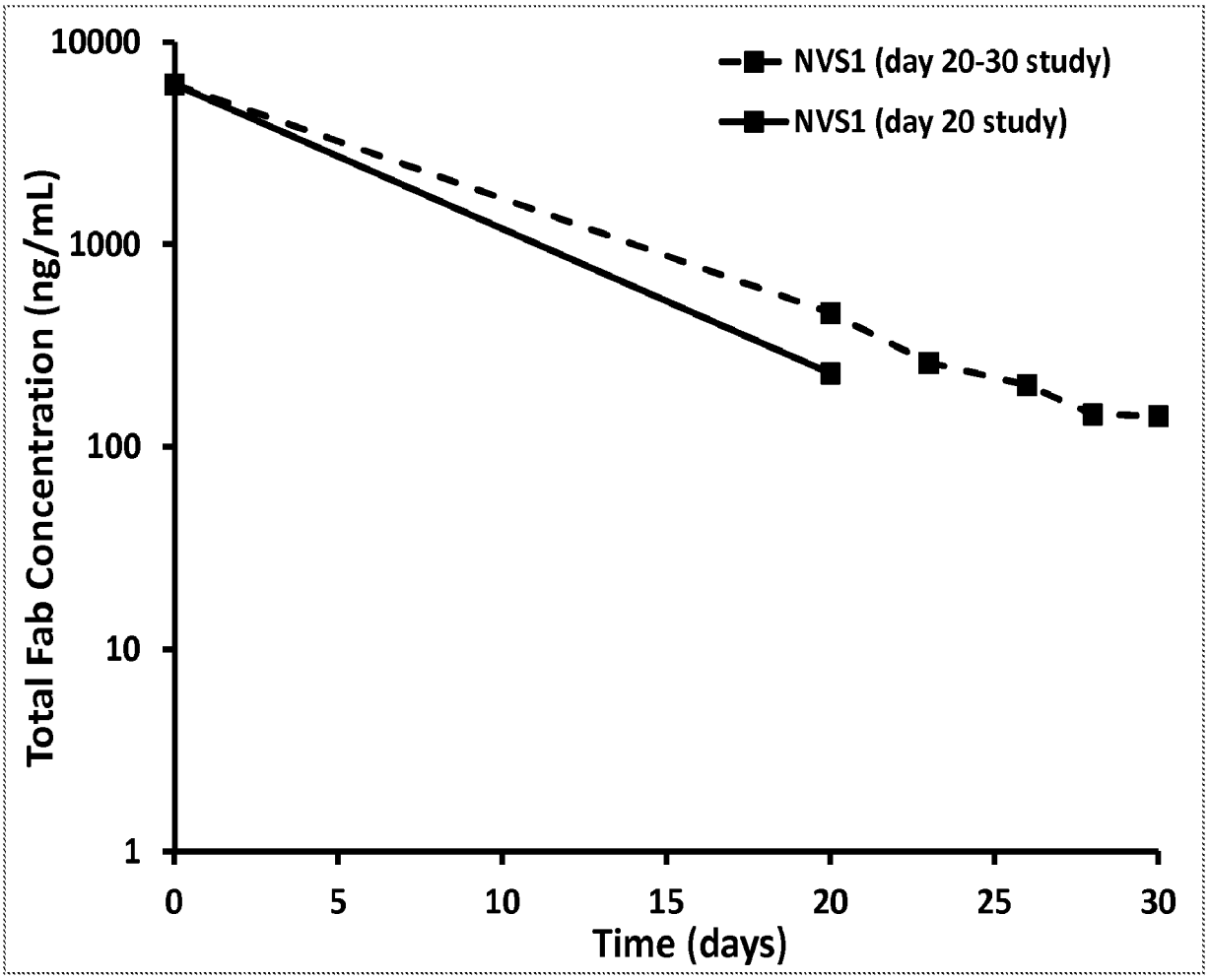
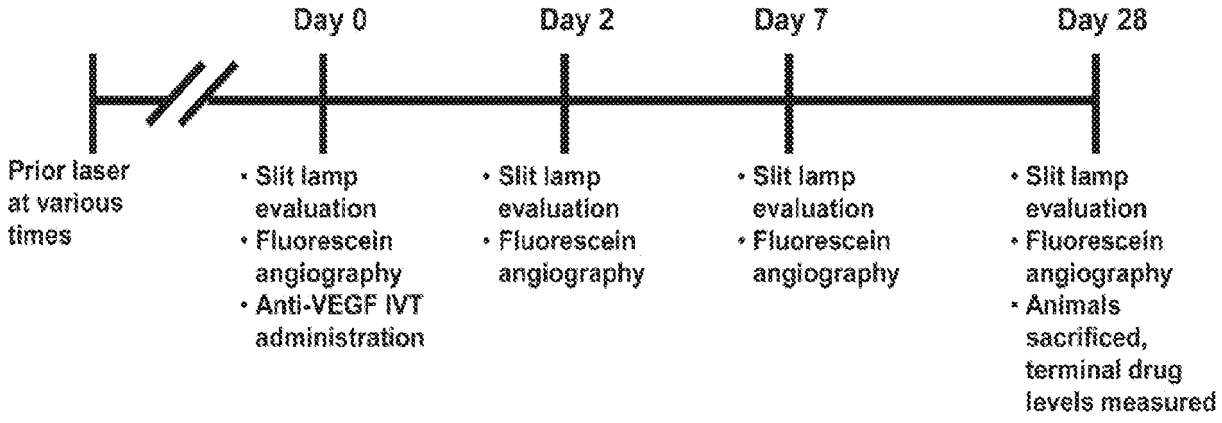

10000
1000
100
10
1
Total Fab Concentration (ng/mL)
0
5
10
15
20
25
30
Time (days)
NVS1 (day 20-30 study)
NVS1 (day 20 study)

FIGURE 11


Day 0
Day 2
Day 7
Day 28
Prior laser at various times
• Slit lamp evaluation
• Fluorescein angiography
• Anti-VEGF IVT administration
• Slit lamp evaluation
• Fluorescein angiography
• Slit lamp evaluation
• Fluorescein angiography
• Slit lamp evaluation
• Fluorescein angiography
• Animals sacrificed, terminal drug levels measured

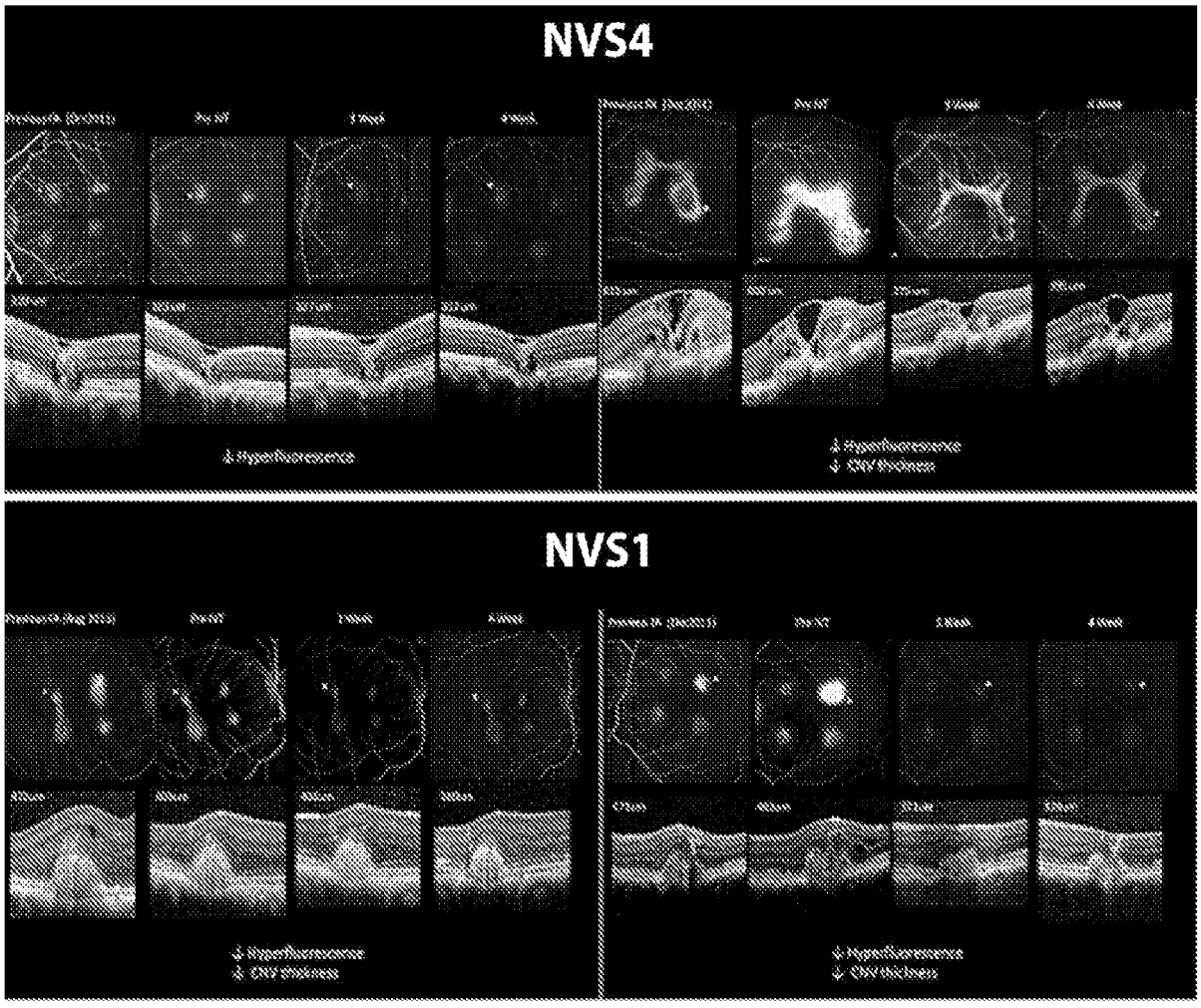

NVS4
NVS1

FIGURE 12

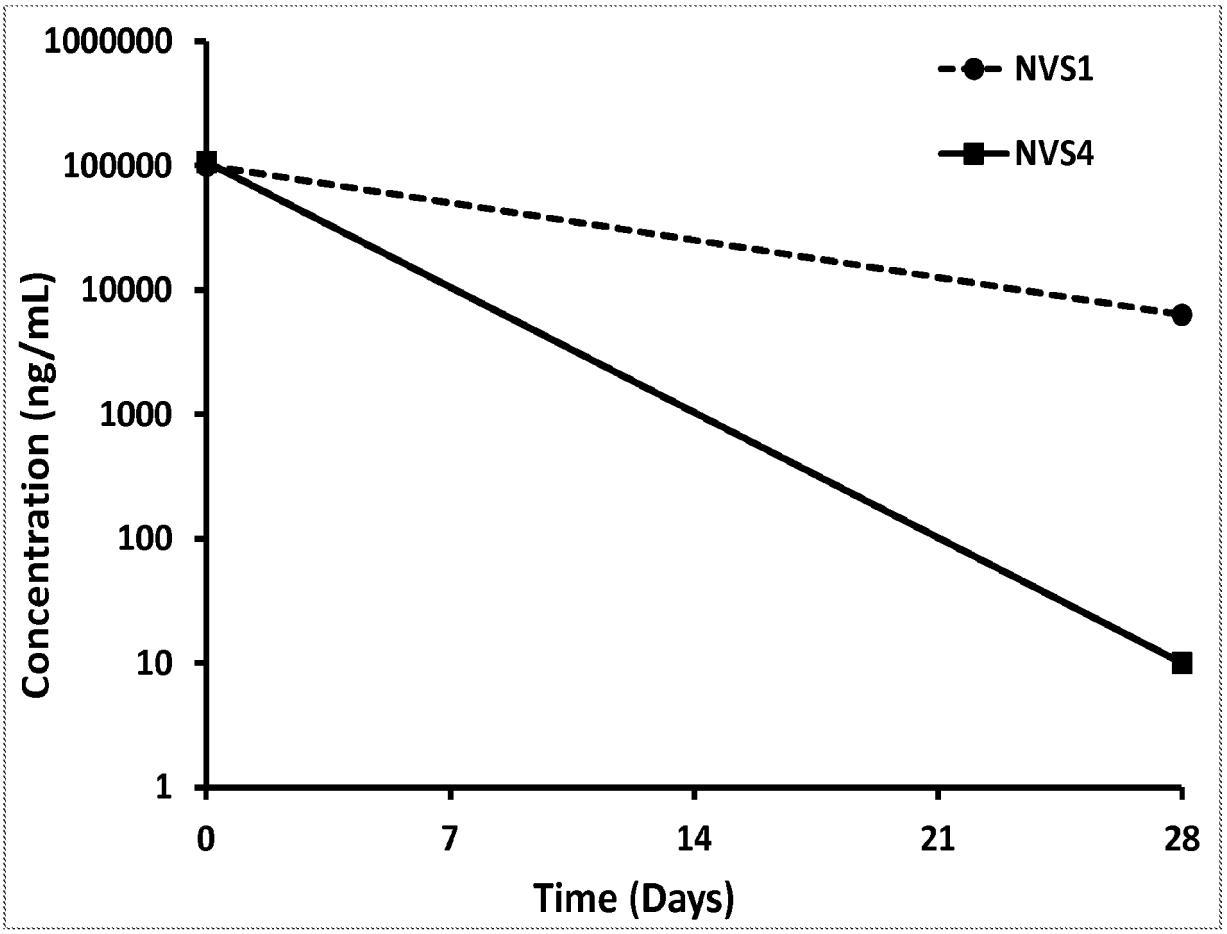

1000000
100000
10000
1000
100
10
1
Concentration (ng/mL)
0
7
14
21
28
Time (Days)
NVS1
NVS4

FIGURE 13

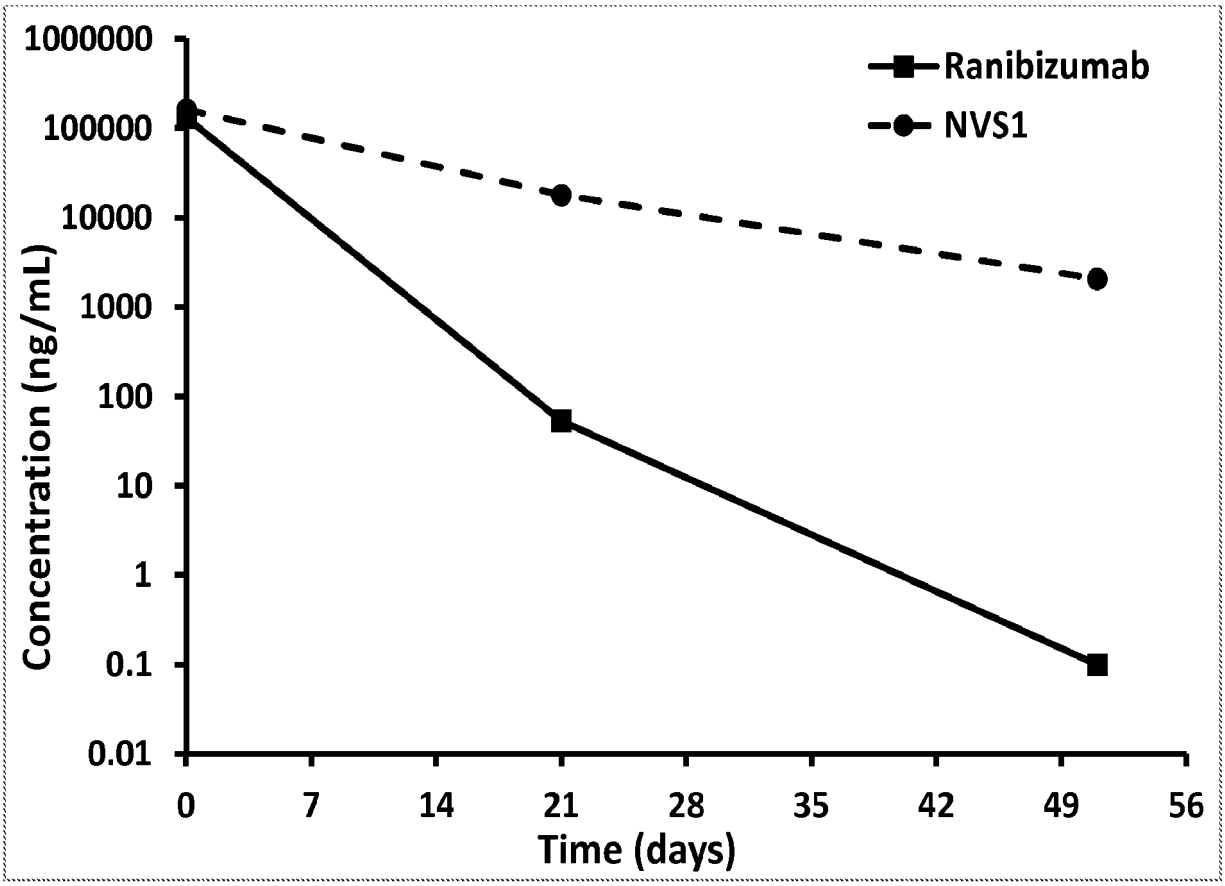

1000000
100000
10000
1000
100
10
1
0.1
0.01
Concentration (ng/mL)
0
7
14
21
28
35
42
49
56
Time (days)
Ranibizumab
NVS1

FIGURE 14

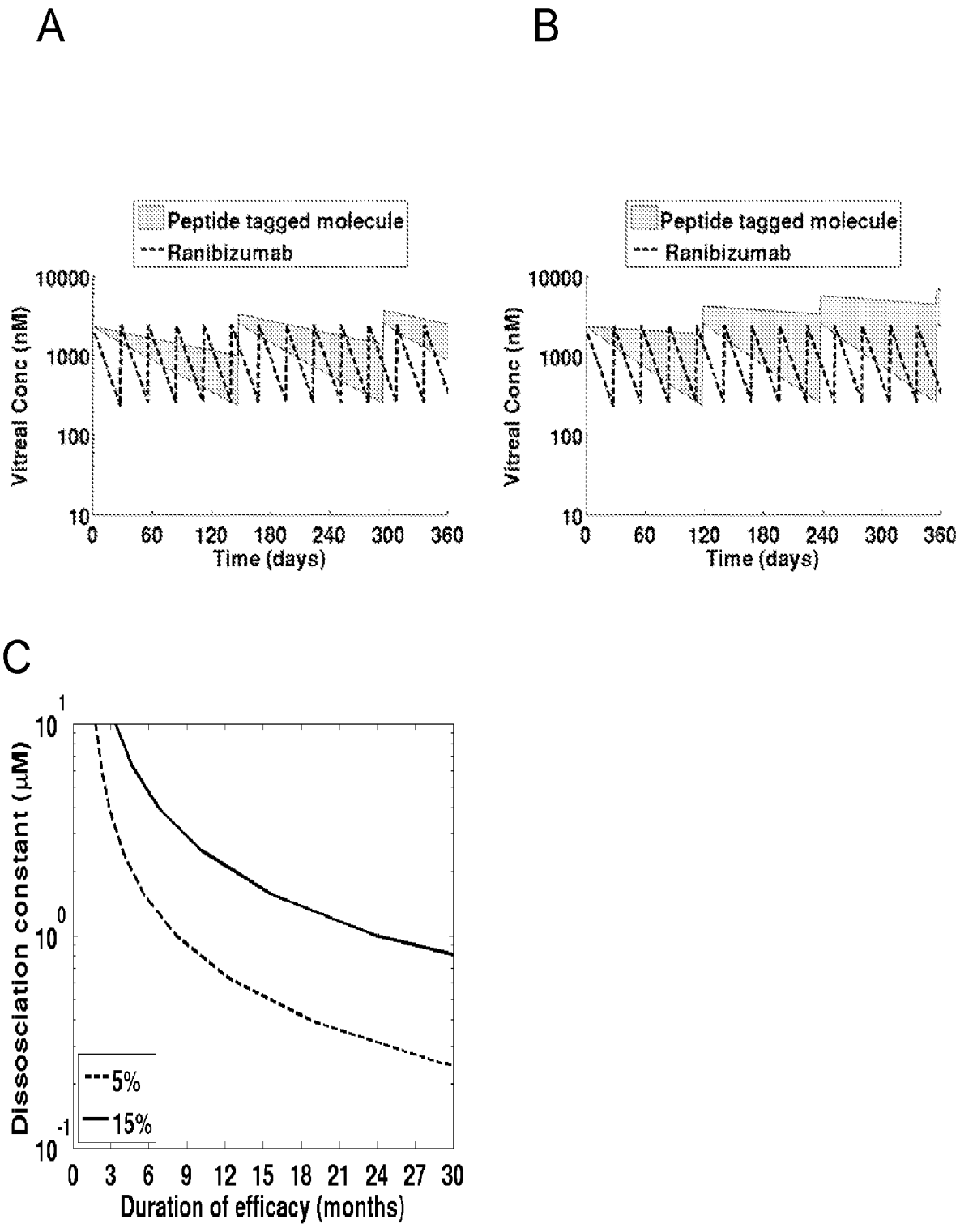

A
B
Peptide tagged molecule
Ranibizumab
Vitreal Conc (nM)
10000
1000
100
10
0
60
120
180
240
300
360
Time (days)
C
Dissociation constant (μM)
10^1
10^0
10^-1
5%
15%
0
3
6
9
12
15
18
21
24
27
30
Duration of efficacy (months)

FIGURE 14

D

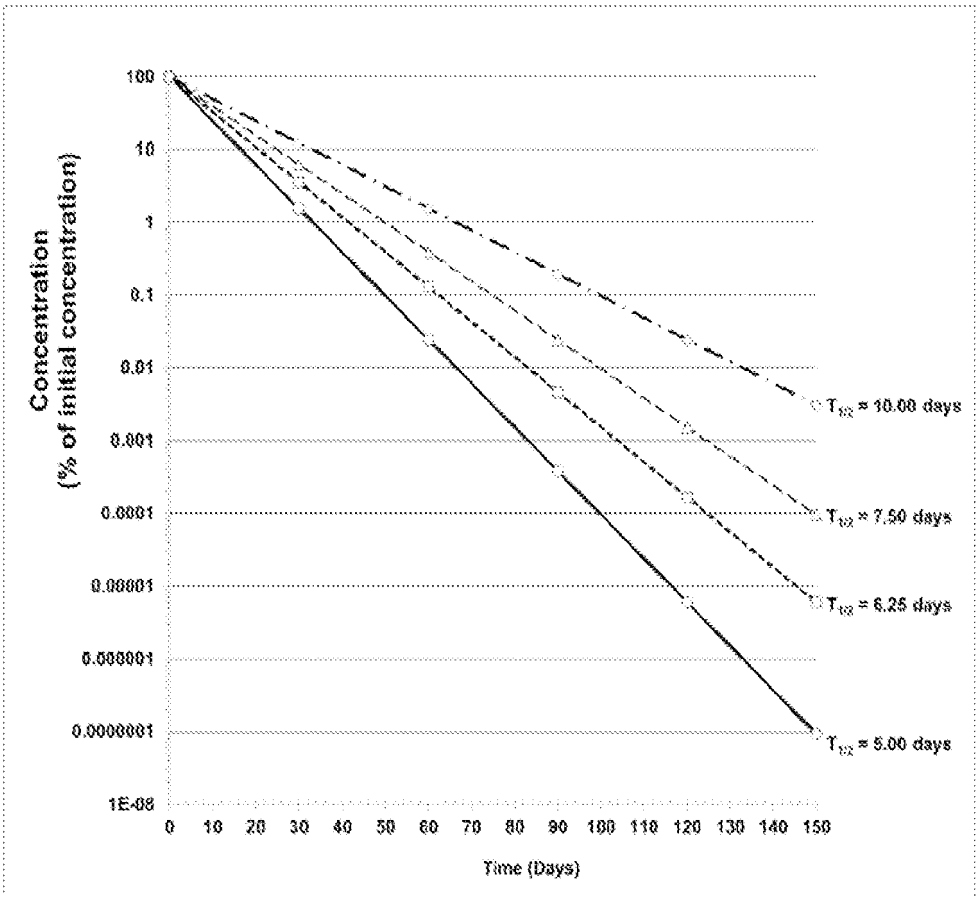

Concentration
(% of initial concentration)
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
1E-08
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Time (Days)
T1/2 = 10.00 days
T1/2 = 7.50 days
T1/2 = 6.25 days
T1/2 = 5.00 days

FIGURE 14

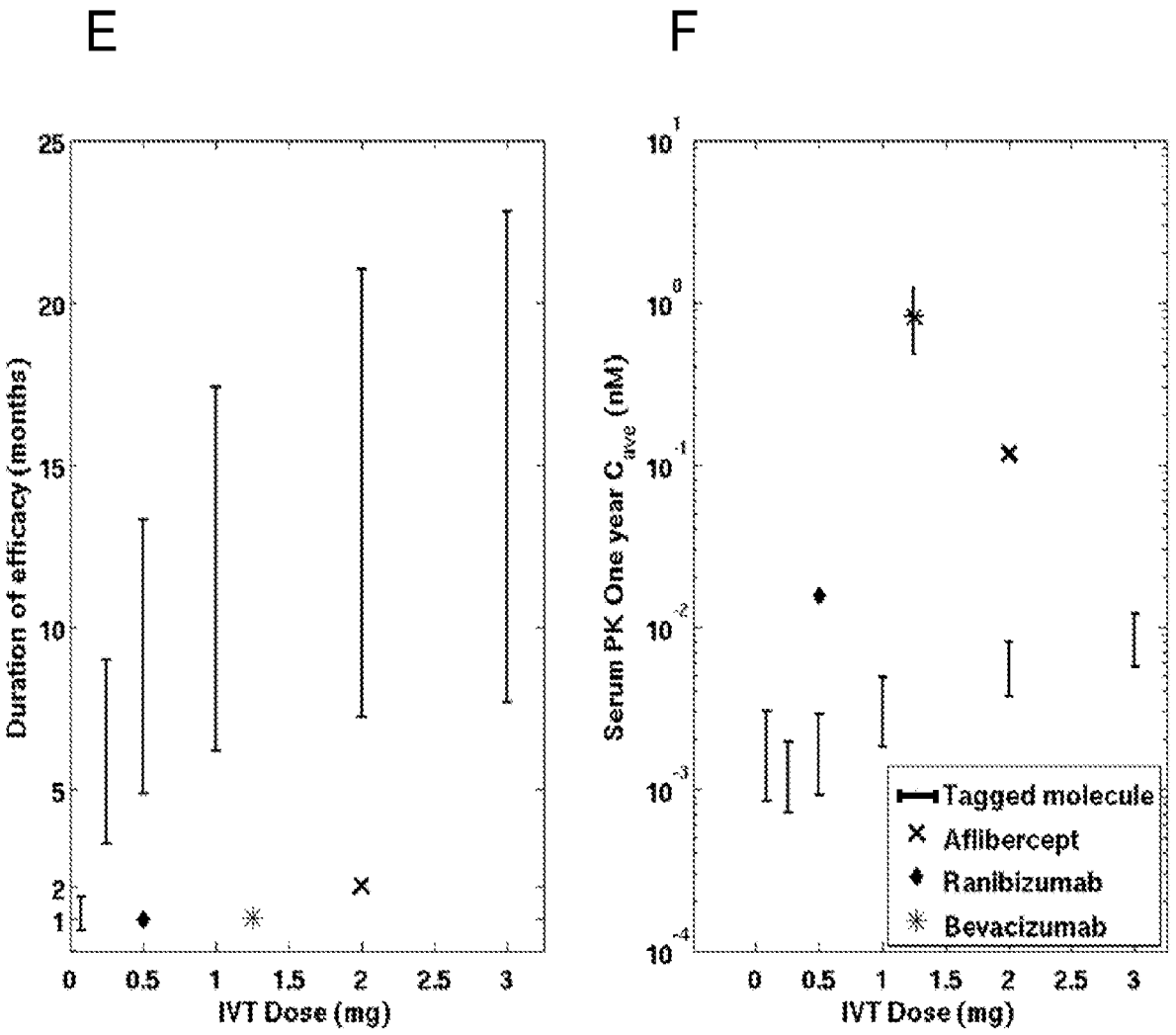

E
F
Duration of efficacy (months)
IVT Dose (mg)
Serum PK One year C_{ave} (nM)
IVT Dose (mg)
Tagged molecule
Aflibercept
Ranibizumab
Bevacizumab

FIGURE 15

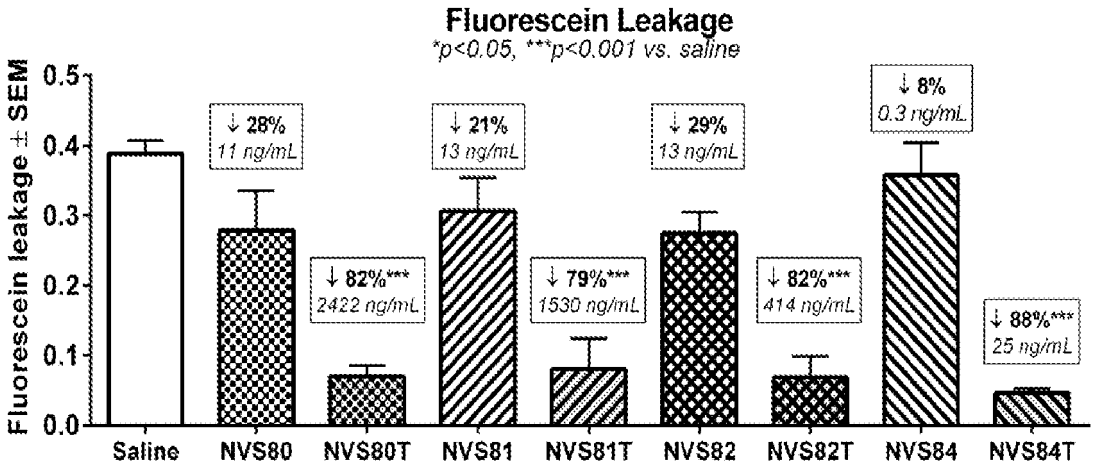

Fluorescein Leakage
*p<0.05, ***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↓ 28%
11 ng/mL
↓ 82%***
2422 ng/mL
↓ 21%
13 ng/mL
↓ 79%***
1530 ng/mL
↓ 29%
13 ng/mL
↓ 82%***
414 ng/mL
↓ 8%
0.3 ng/mL
↓ 88%***
25 ng/mL
Saline
NVS80
NVS80T
NVS81
NVS81T
NVS82
NVS82T
NVS84
NVS84T

FIGURE 16

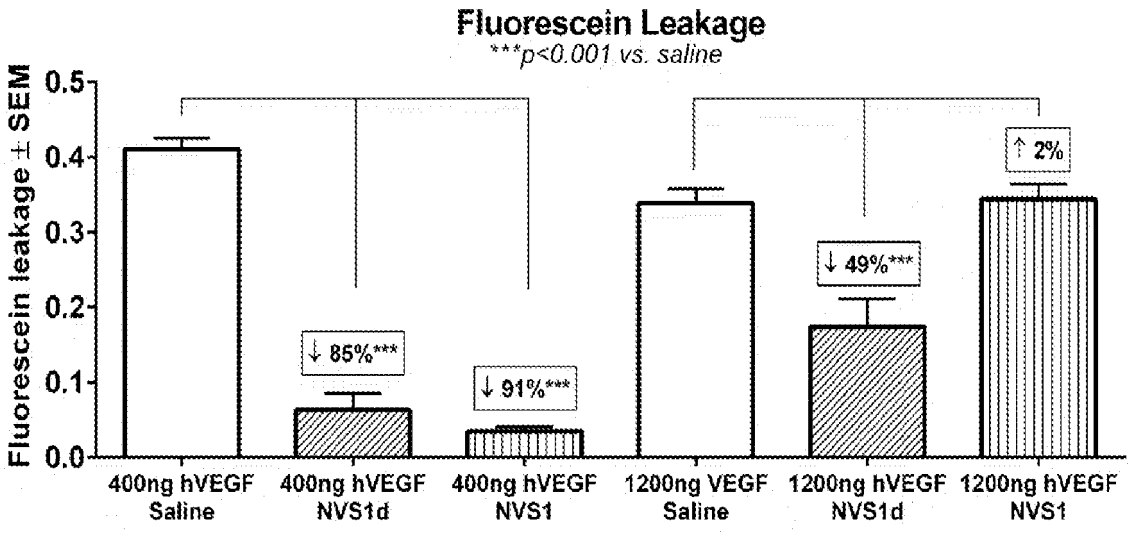
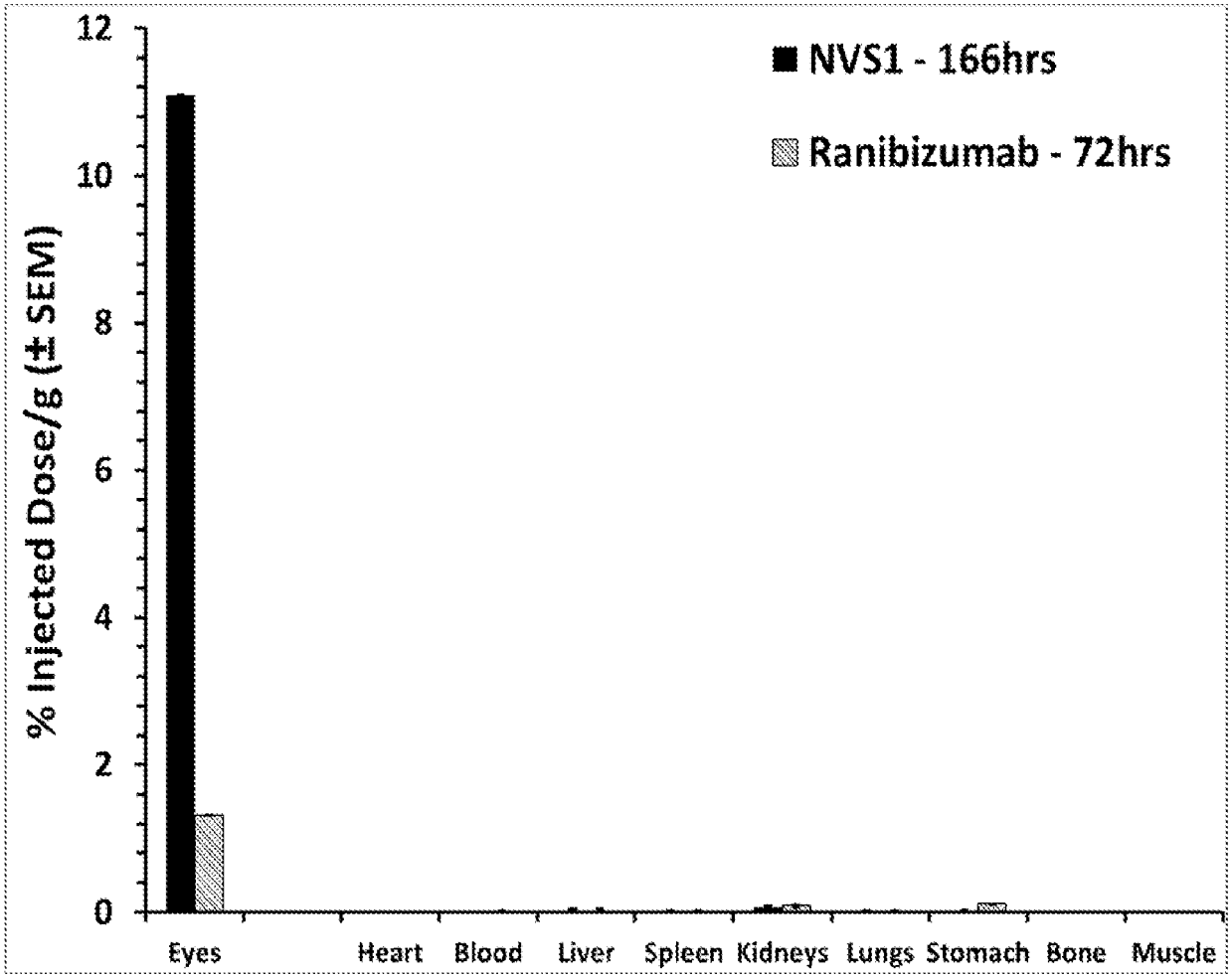

Fluorescein Leakage
***p<0.001 vs. saline
Fluorescein leakage ± SEM
0.5
0.4
0.3
0.2
0.1
0.0
↓ 85%***
↓ 91%***
↓ 49%***
↑ 2%
400ng hVEGF Saline
400ng hVEGF NVS1d
400ng hVEGF NVS1
1200ng VEGF Saline
1200ng hVEGF NVS1d
1200ng hVEGF NVS1

FIGURE 17


NVS1 - 166hrs
Ranibizumab - 72hrs
% Injected Dose/g (± SEM)
12
10
8
6
4
2
0
Eyes
Heart
Blood
Liver
Spleen
Kidneys
Lungs
Stomach
Bone
Muscle