FIG. 1

IgG Competition

Anti-FcRn mAbs compete effectively for IgG (Fc) binding to FcRn at pH 6.0

EC50 (nM)	N022	N023	N024	N026	N027
Human FcRn	2.93	2.48	2.48	3.24	3.25
Cynomolgus FcRn	4.80	5.16	3.51	2.68	4.46

FIG. 2 Human IgG Catabolism

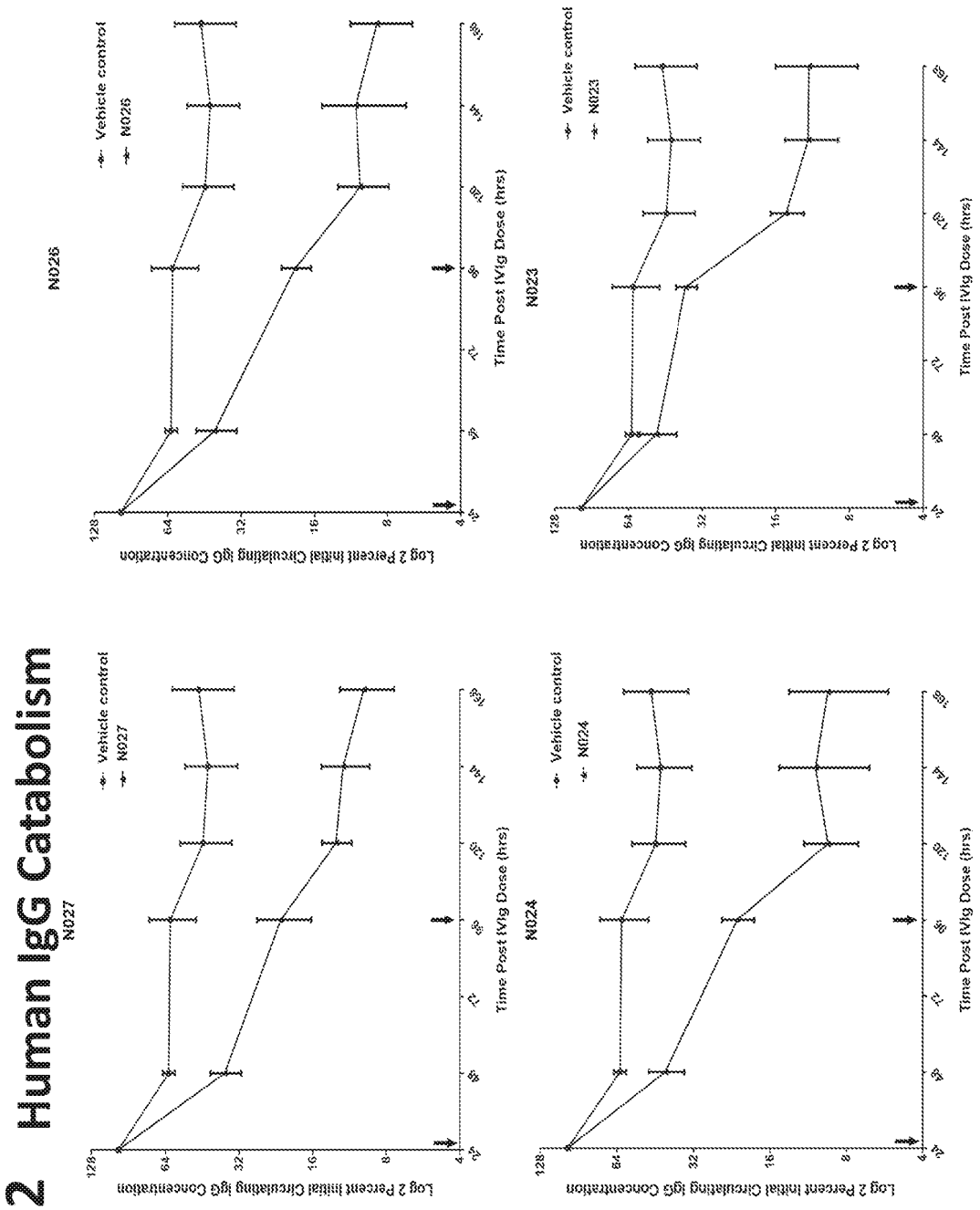
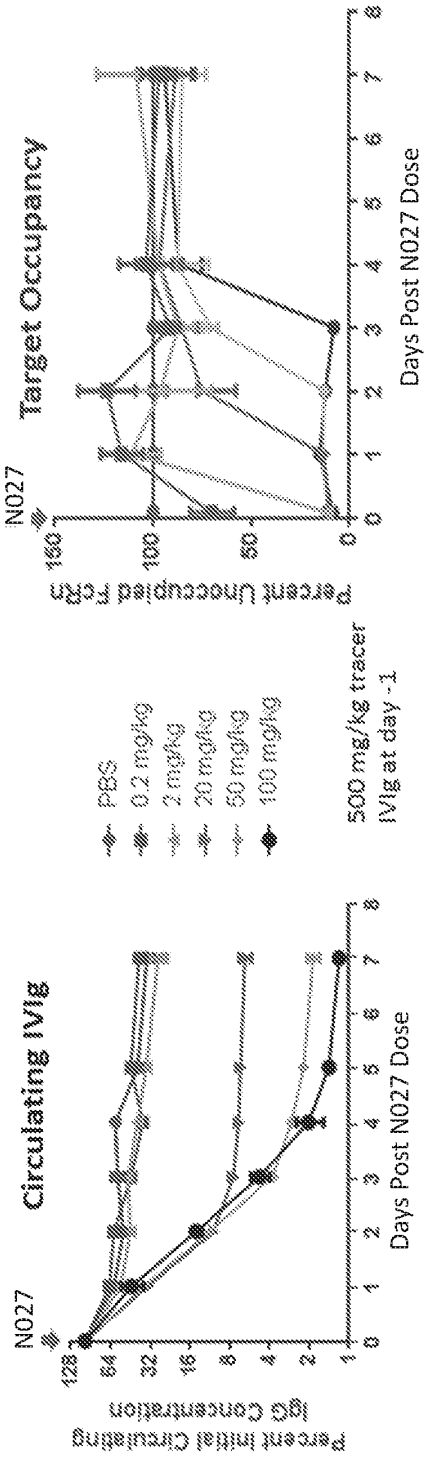


FIG. 3


Target Occupancy
N027
Percent Unoccupied FcRn
160
100
60
0
0 1 2 3 4 5 6 7 8
Days Post N027 Dose
PBS
0.2 mg/kg
2 mg/kg
20 mg/kg
50 mg/kg
100 mg/kg
500 mg/kg tracer
IVIg at day -1
Circulating IVIg
N027
Percent Initial Circulating
IgG Concentration
128
64
32
16
8
4
2
1
0 1 2 3 4 5 6 7 8
Days Post N027 Dose

FIGS. 4A-4C

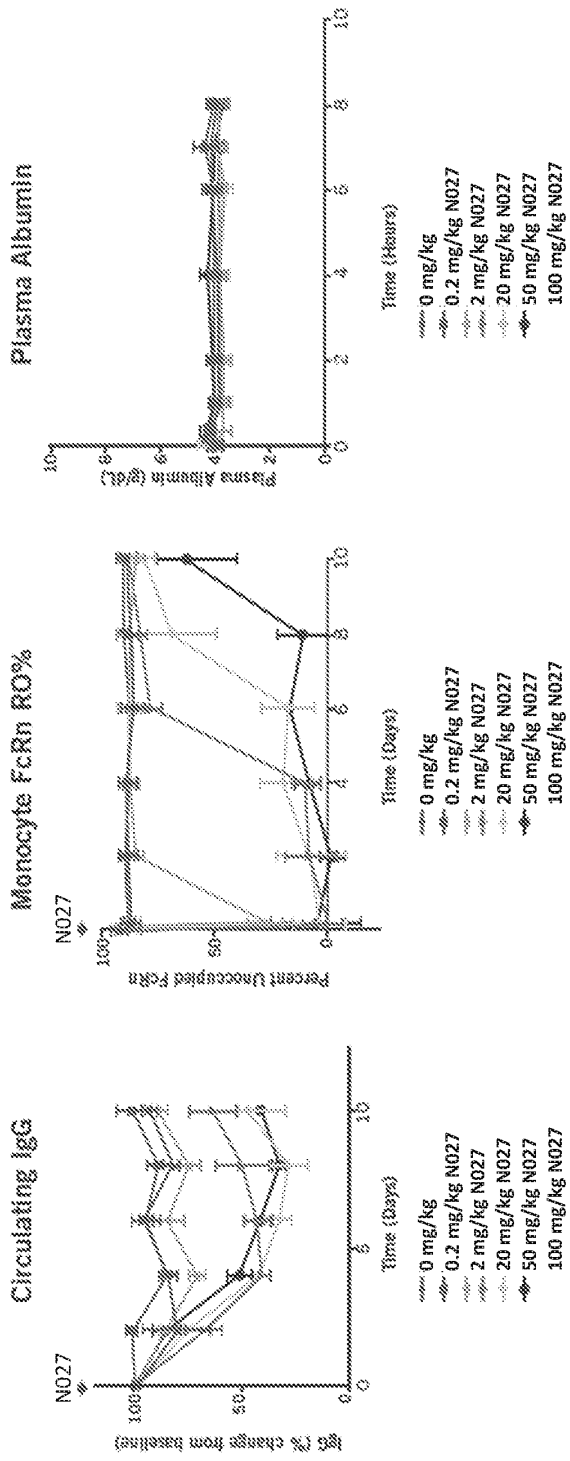

Circulating IgG
N027
IgG (% change from baseline)
100
50
0
0
5
10
Time (Days)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027
Monocyte FcRn RO%
N027
Percent Unoccupied FcRn
100
50
0
0
5
10
Time (Days)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027
Plasma Albumin
Plasma Albumin (g/dL)
10
8
6
4
2
0
0
2
4
6
8
10
Time (Hours)
0 mg/kg
0.2 mg/kg N027
2 mg/kg N027
20 mg/kg N027
50 mg/kg N027
100 mg/kg N027

FIG. 5

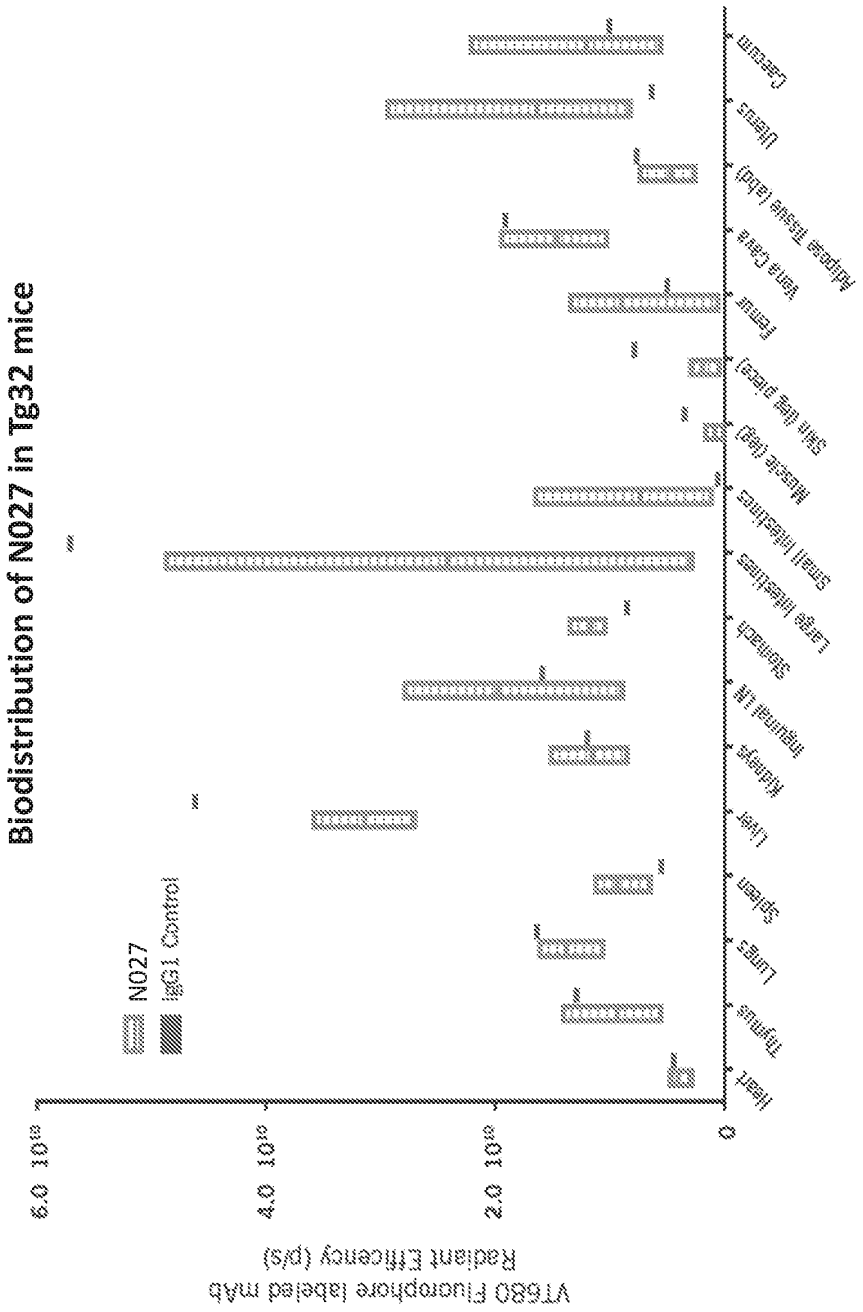

Biodistribution of N027 in Tg32 mice
N027
IgG1 Control
VT680 Fluorophore labeled mAb
Radiant Efficiency (p/s)
6.0 10^8
4.0 10^8
2.0 10^8
0
Heart
Thymus
Lungs
Spleen
Liver
Kidneys
Inguinal LN
Stomach
Large Intestines
Small Intestines
Muscle (leg)
Skin (leg piece)
Femur
Bone Case
Adipose Tissue (abd)
Uterus
Cecum

FIG. 6

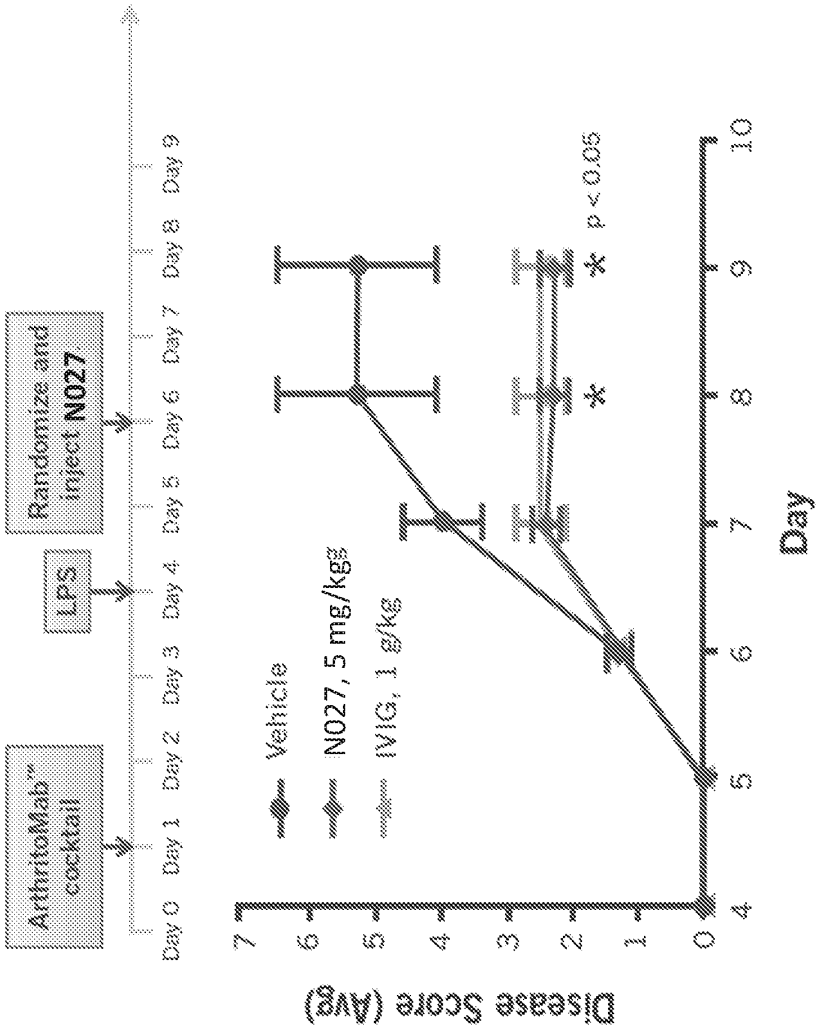
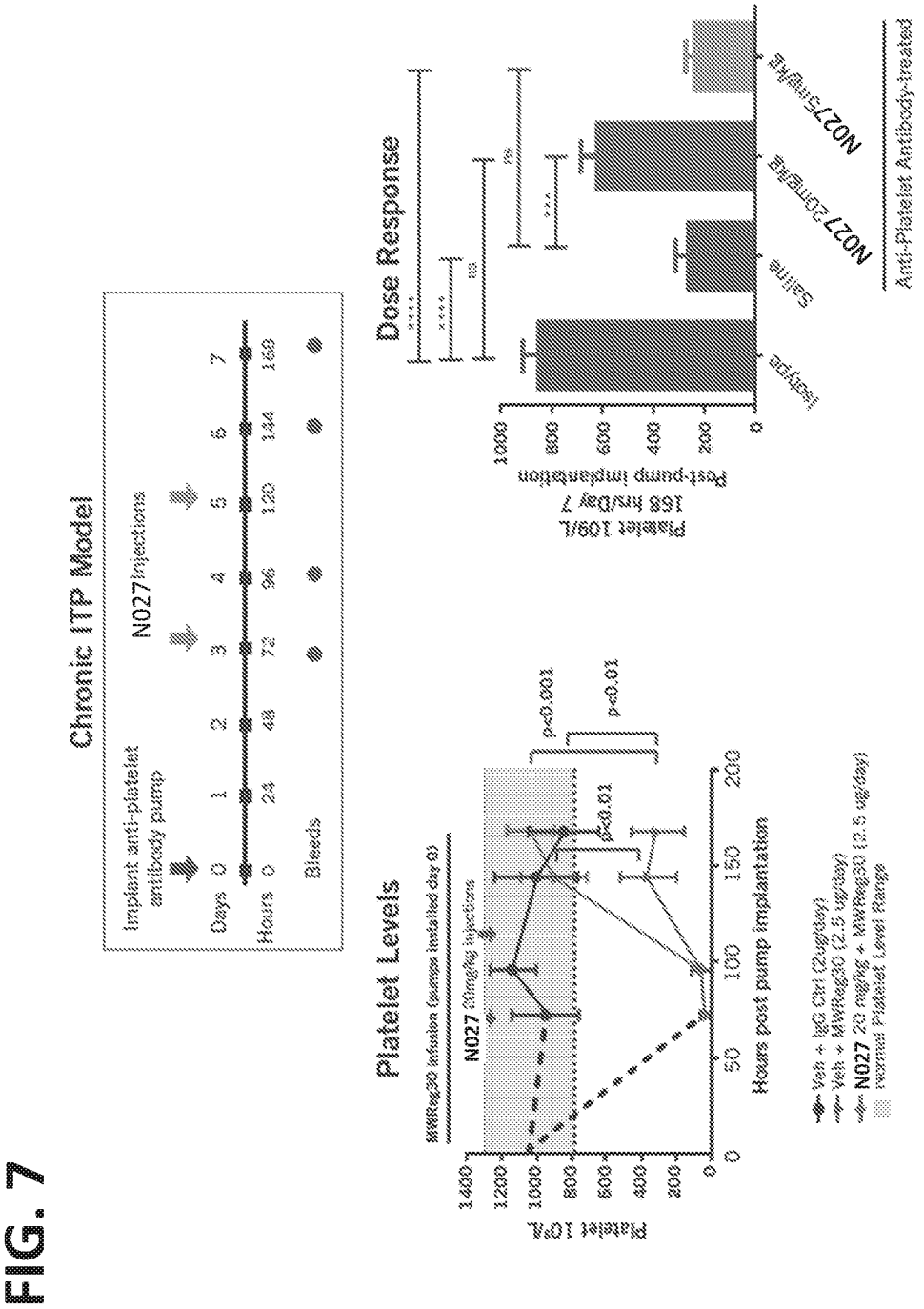
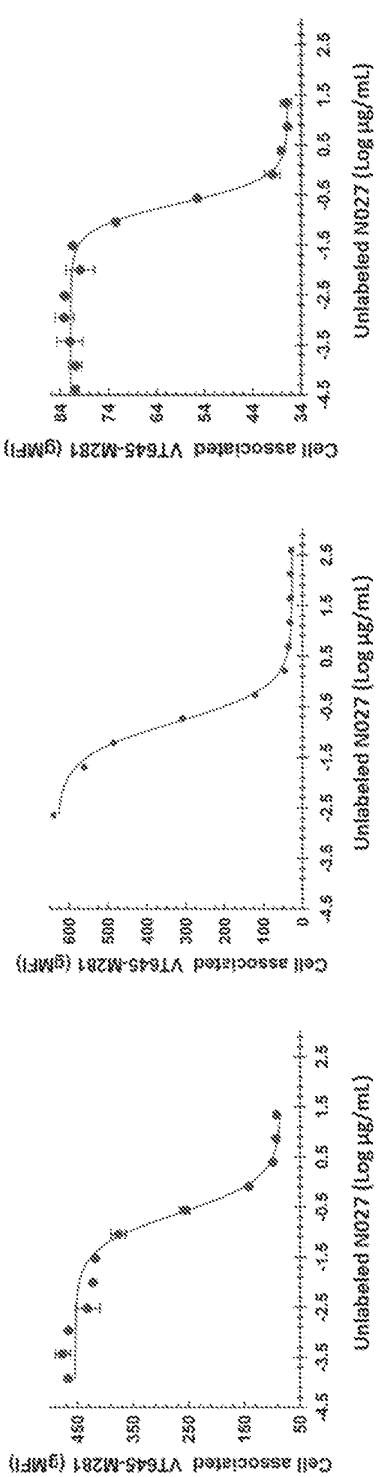

ArthritoMab™ cocktail
LPS
Randomize and inject N027
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Vehicle
N027, 5 mg/kg
IVIG, 1 g/kg
p < 0.05
Disease Score (Avg)
Day

FIG. 7


Chronic ITP Model
Implant anti-platelet antibody pump
N027 Injections
Days 0 1 2 3 4 5 6 7
Hours 0 24 48 72 96 120 144 168
Bleeds
Platelet Levels
MWReg30 infusion (pumps installed day 0)
N027 (3mg/kg injections
p<0.001
p<0.01
p<0.01
Platelet 10^9/L
Hours post pump implantation
Veh + IgG Ctrl (2 ug/day)
Veh + MWReg30 (2.5 ug/day)
N027 20 mg/kg + MWReg30 (2.5 ug/day)
Normal Platelet Level Range
Dose Response
Platelet 10^9/L
168 hrs/Day 7
Post-pump implantation
Isotype
Saline
N027 20mg/kg
N027 5mg/kg
Anti-Platelet Antibody-treated

FIGS. 8A-8C


A. Aortic endothelial cells
B. Venous endothelial cells
C. Placental trophoblasts
Cell associated VT645-M281 (gMFI)
Unlabeled N027 (Log µg/mL)

FIGS. 9A-9C

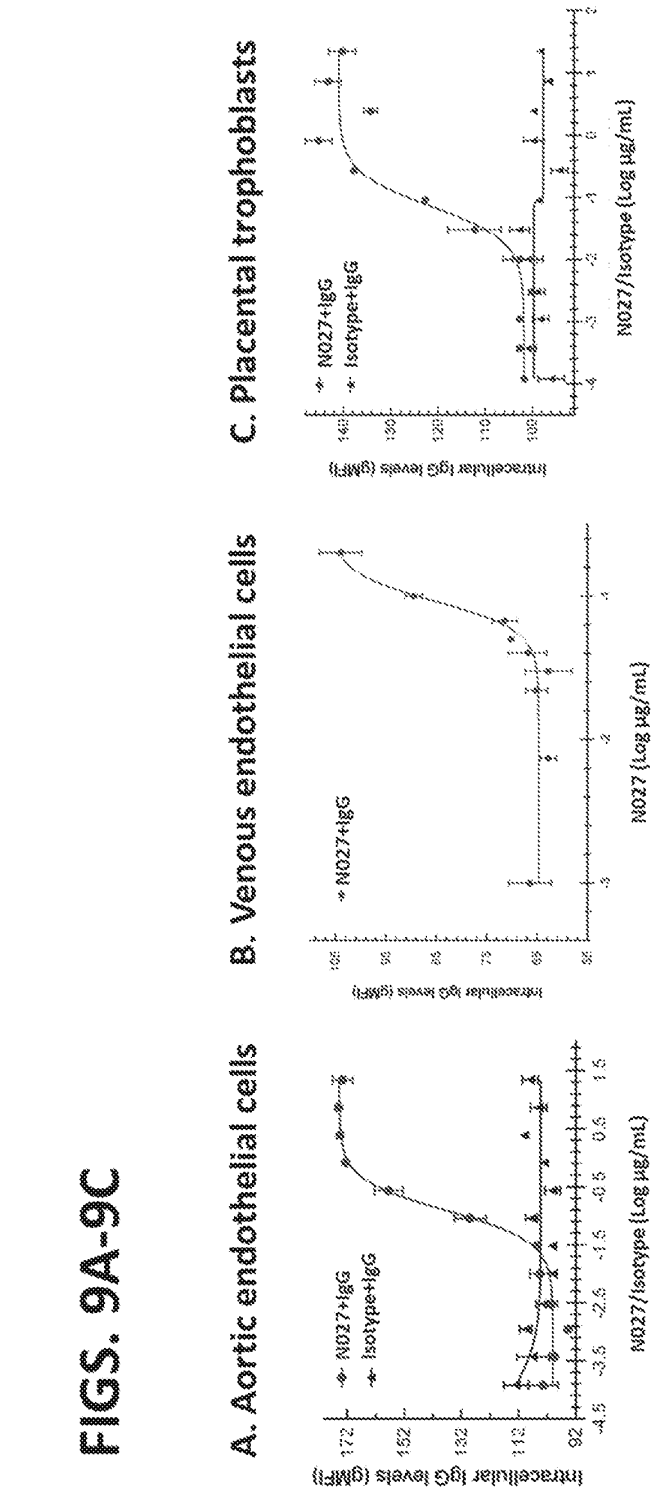
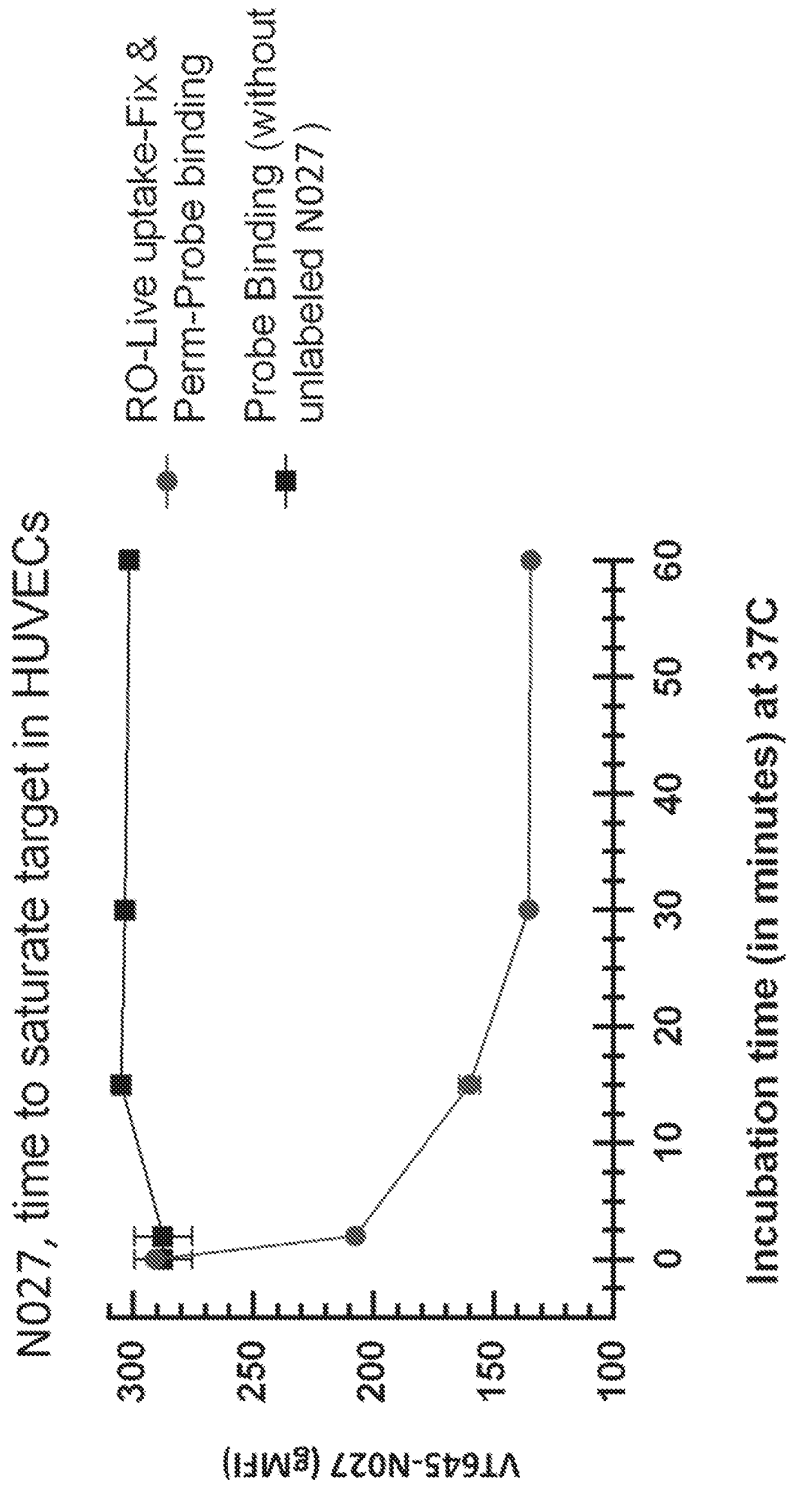
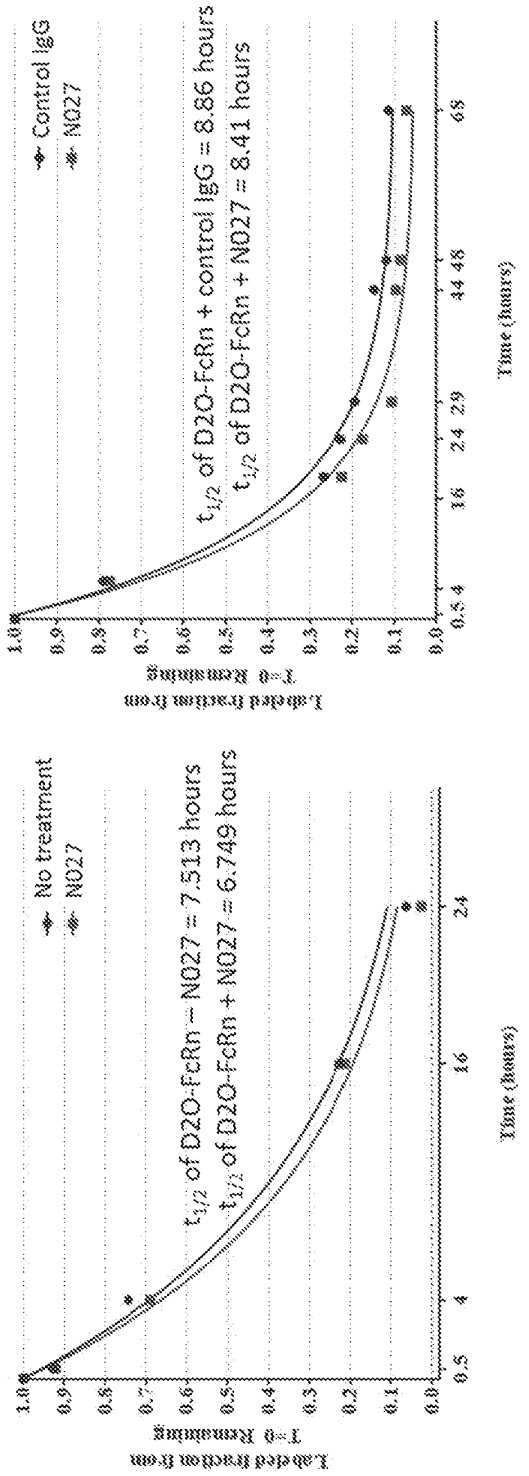

A. Aortic endothelial cells
B. Venous endothelial cells
C. Placental trophoblasts
M027+IgG
Isotype+IgG
Intracellular IgG levels (gMFI)
M027/Isotype (Log µg/mL)
M027 (Log µg/mL)

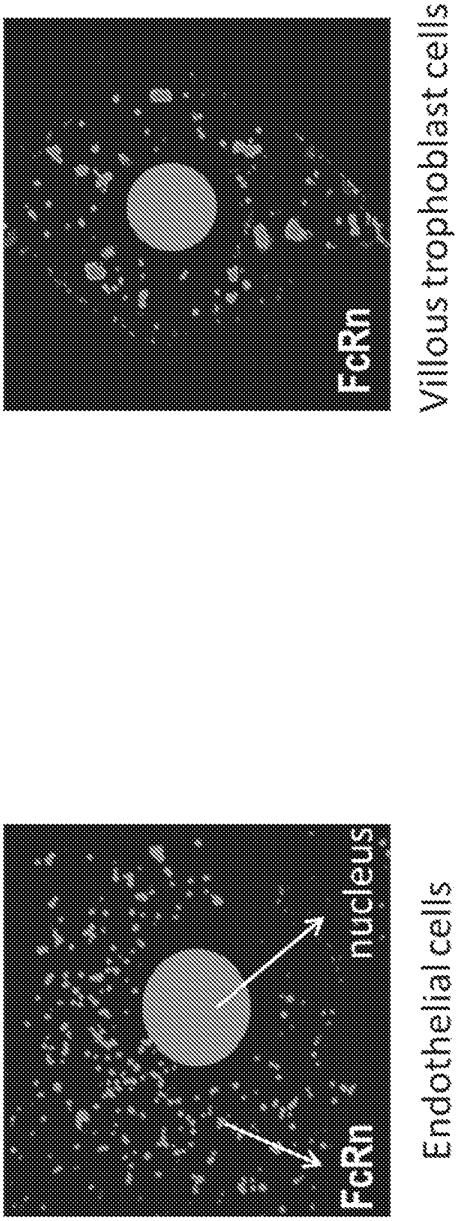
FIG. 10


N027, time to saturate target in HUVECs
RO-Live uptake-Fix & Perm-Probe binding
Probe Binding (without unlabeled N027)
VT645-N027 (gMFI)
300
250
200
150
100
0
10
20
30
40
50
60
Incubation time (in minutes) at 37C

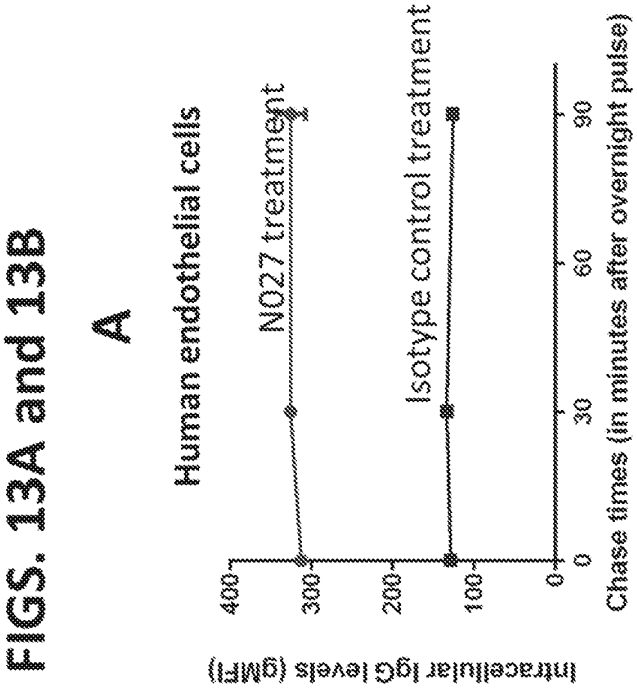
FIGS. 11A and 11B



FIGS. 12A and 12B



FIGS. 13A and 13B



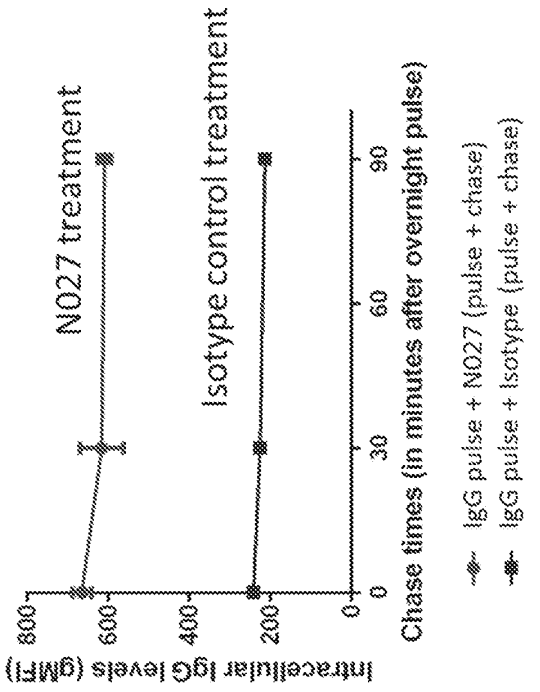


FIG. 13C

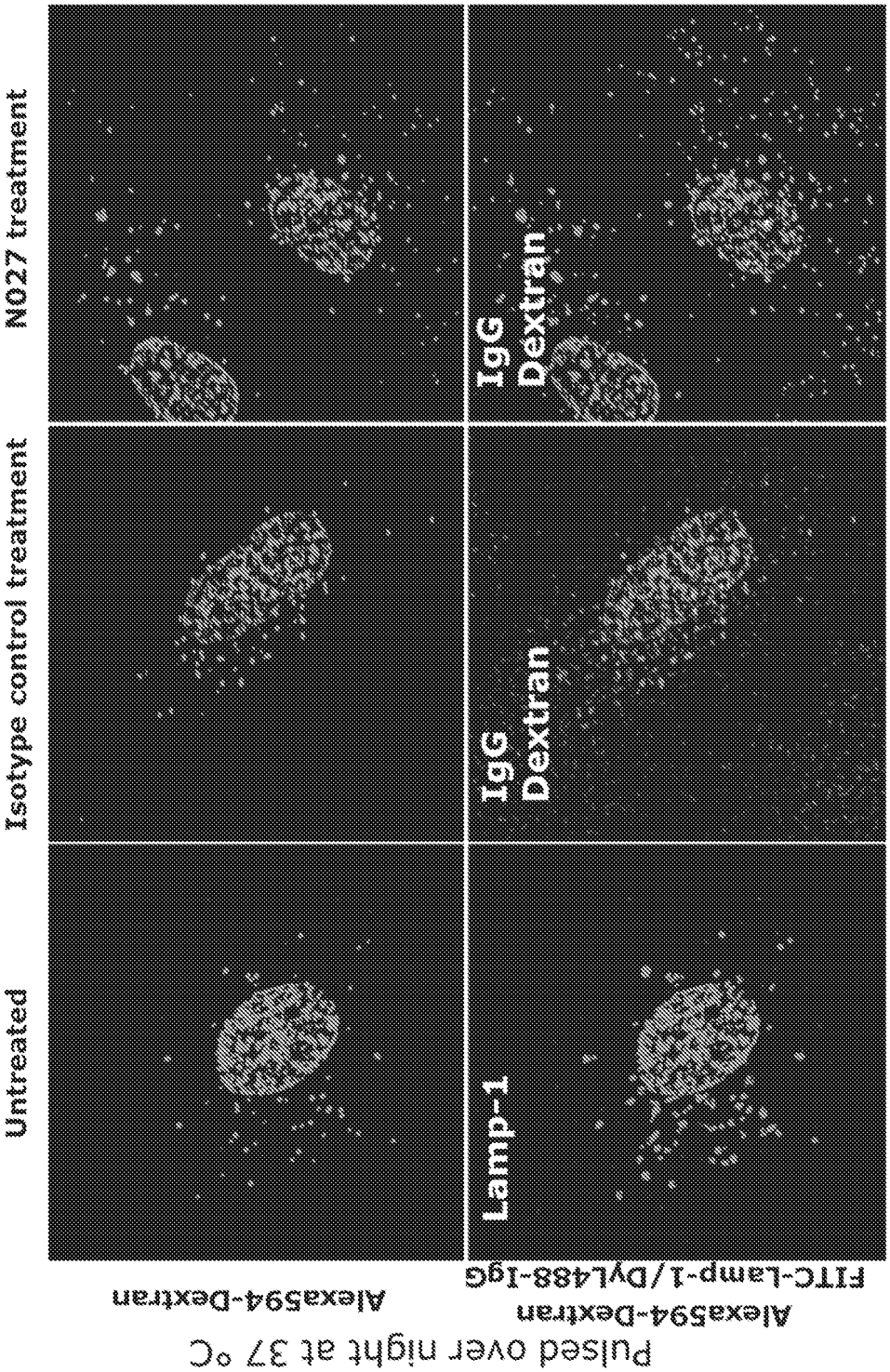

Untreated
Isotype control treatment
N027 treatment
Lamp-1
IgG
Dextran
IgG
Dextran
Alexa594-Dextran
FITC-Lamp-1/DyL488-IgG
Alexa594-Dextran
Pulsed over night at 37 °C

FIG. 13D

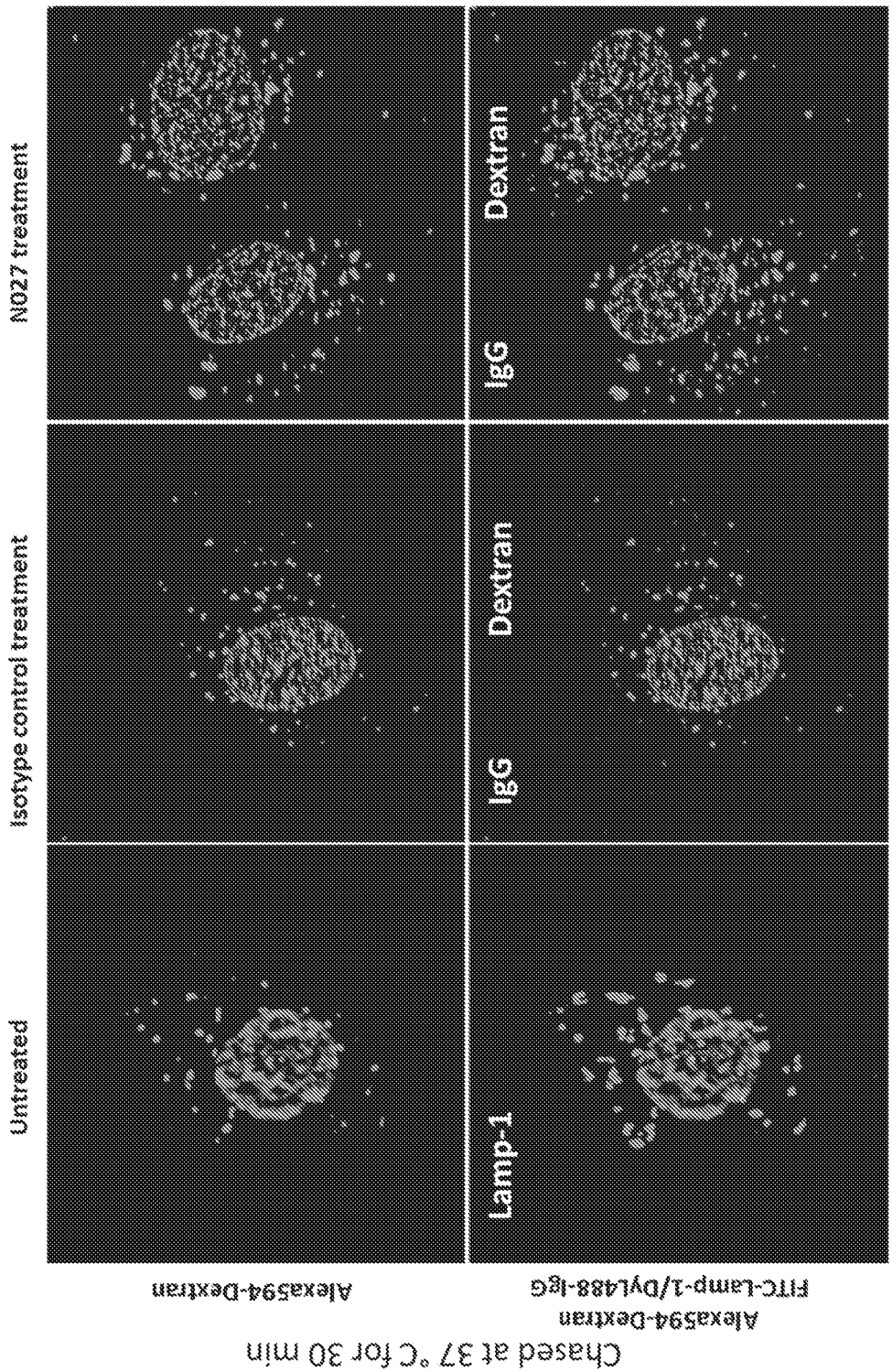

Untreated
Isotype control treatment
N027 treatment
Lamp-1
IgG
Dextran
IgG
Dextran
Alexa594-Dextran
FITC-Lamp-1/DyL488-IgG
Alexa594-Dextran
Chased at 37 °C for 30 min

FIG. 14

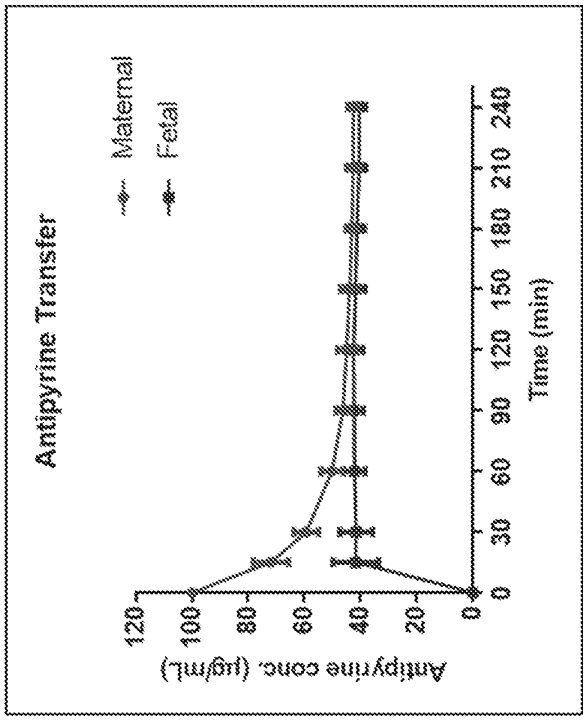

Antipyrine Transfer
Maternal
Fetal
Antipyrine conc. (µg/mL)
120
100
80
60
40
20
0
0
30
60
90
120
150
180
210
240
Time (min)

FIG. 15

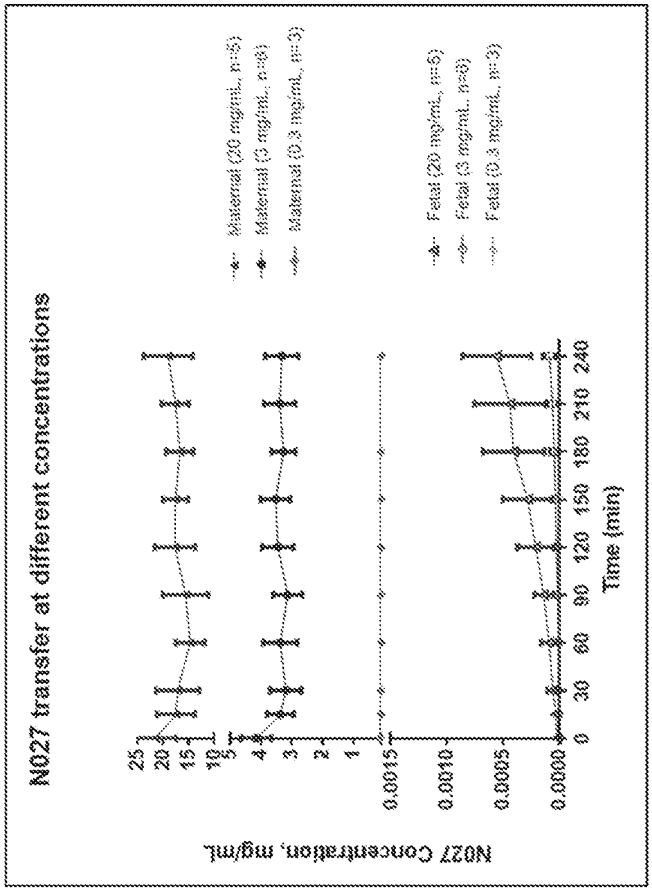

N027 transfer at different concentrations
N027 Concentration, mg/mL
Time (min)
Maternal (20 mg/mL, n=6)
Maternal (3 mg/mL, n=6)
Maternal (0.3 mg/mL, n=3)
Fetal (20 mg/mL, n=6)
Fetal (3 mg/mL, n=6)
Fetal (0.3 mg/mL, n=3)
25
20
15
10
5
4
3
2
1
0.0015
0.0010
0.0005
0.0000
0
30
60
90
120
150
180
210
240

FIG. 16

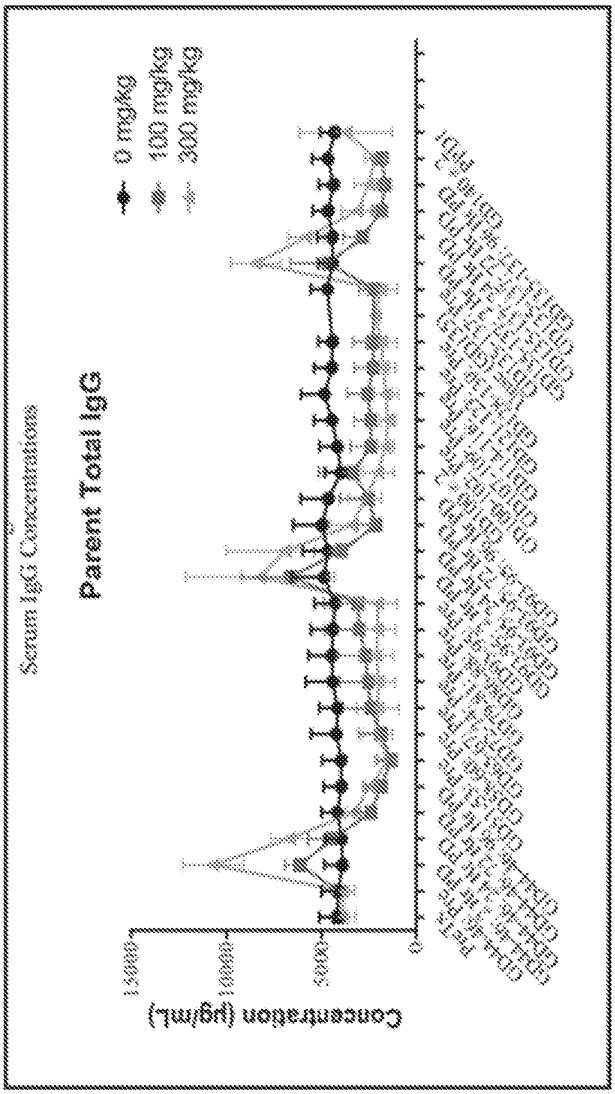
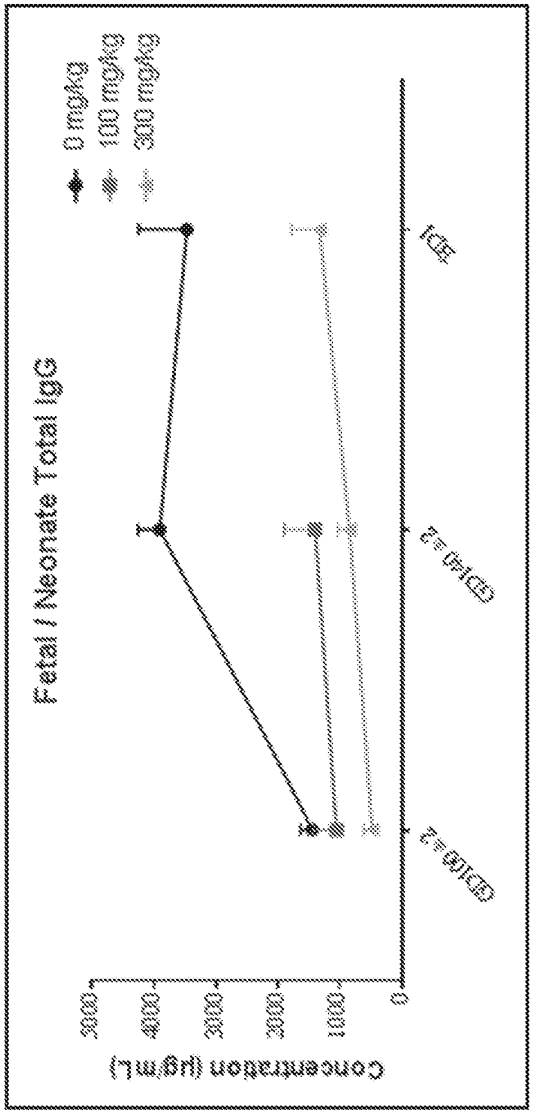
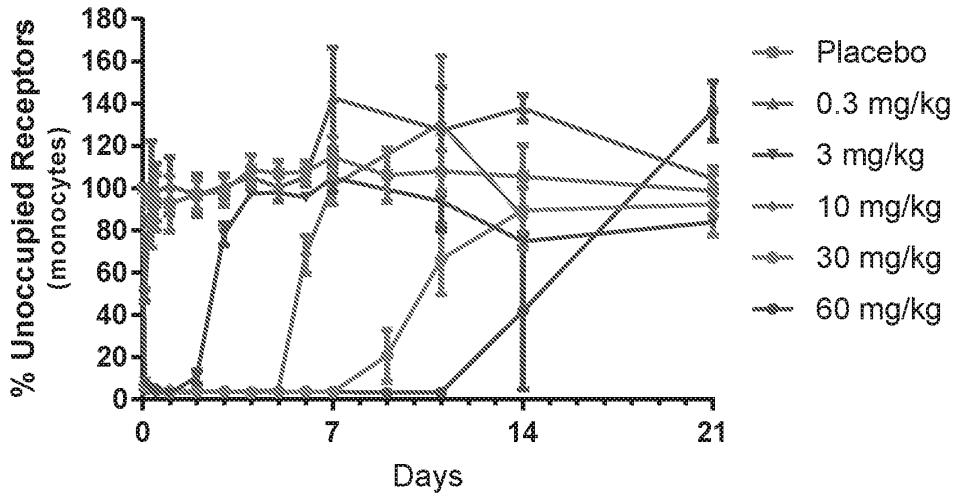

Serum IgG Concentrations
Parent Total IgG
0 mg/kg
100 mg/kg
300 mg/kg
Concentration (µg/mL)
150000
100000
50000
0

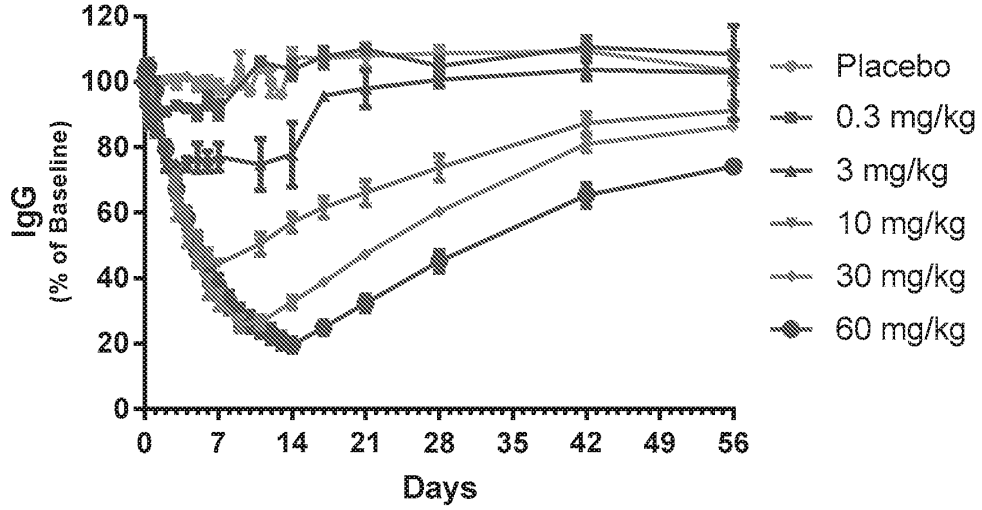
FIG. 17


Fetal / Neonate Total IgG
0 mg/kg
100 mg/kg
300 mg/kg
Concentration (µg/mL)
4000
3000
2000
1000
0
GD106 = 2
GD140 = 2
EOS



Abbreviations: FcRn = neonatal Fc receptor; SD = standard deviation.

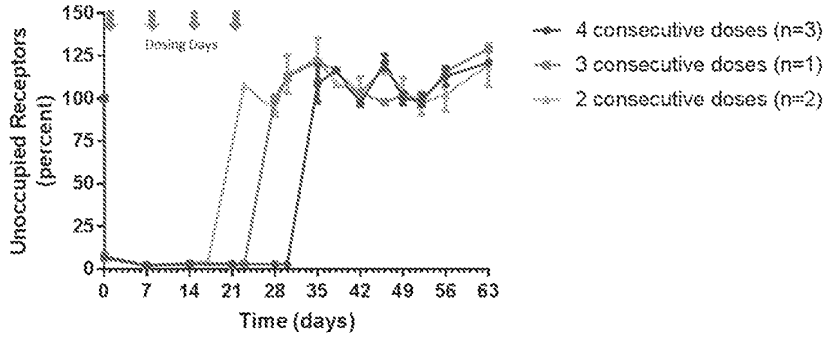
FIG. 18



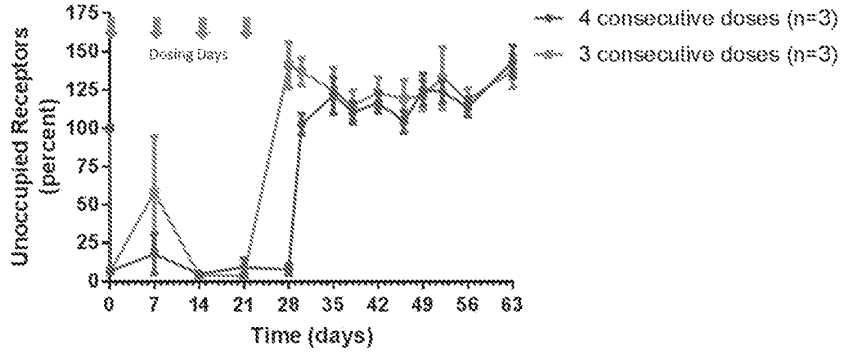
Abbreviations: IgG = immunoglobulin G; SD = standard deviation.

FIG. 19

A) 30 mg/kg



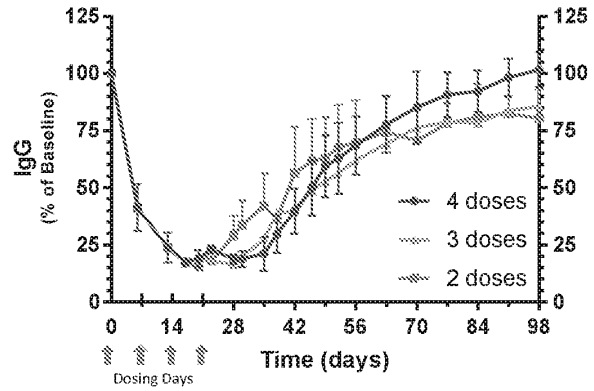
B) 15 mg/kg



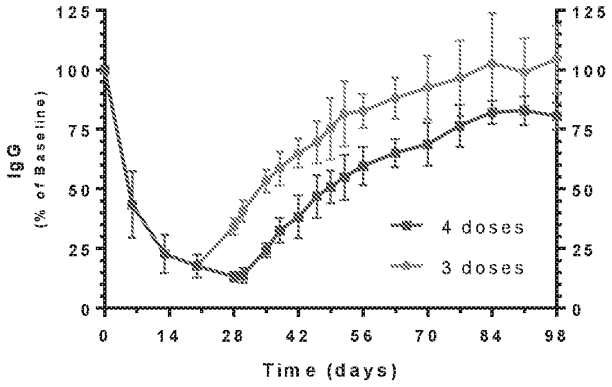
Abbreviations: FcRn = neonatal Fc receptor; MAD = multiple ascending dose; SD = standard deviation.

FIG. 20

A) 30 mg/kg



B) 15 mg/kg



Abbreviations: IgG = immunoglobulin G; MAD = multiple ascending dose; SD = standard deviation

FIG. 21

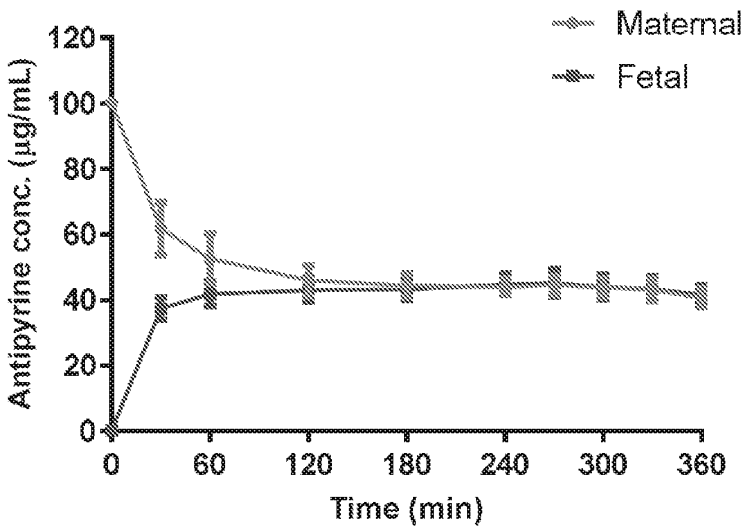

Maternal
Fetal
Antipyrine conc. (µg/mL)
120
100
80
60
40
20
0
0
60
120
180
240
300
360
Time (min)

FIG. 22

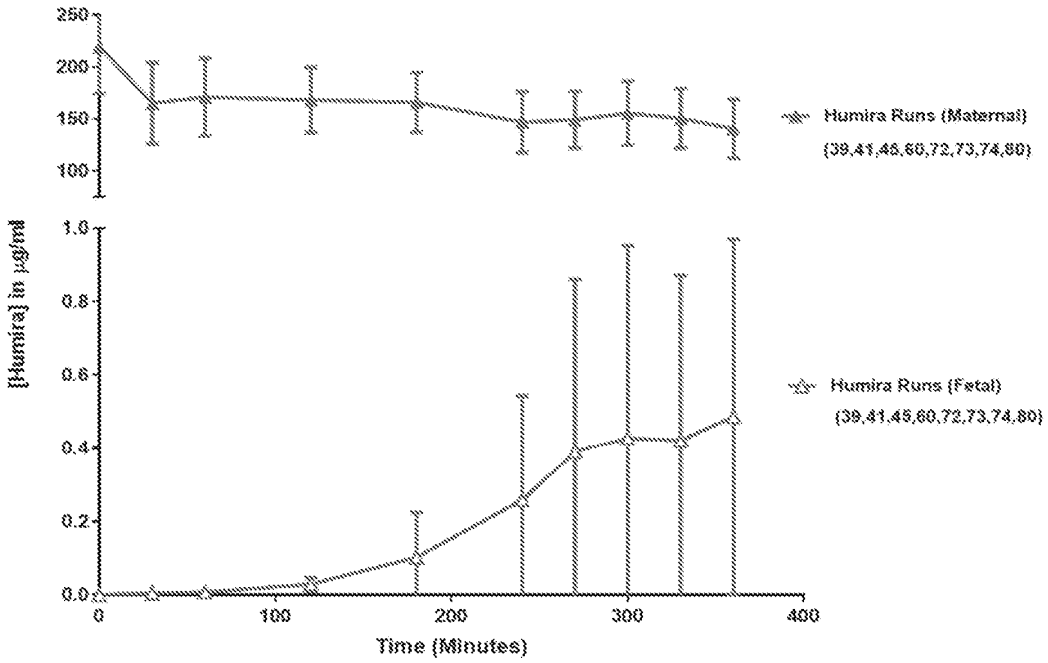

250
200
150
100
Humira Runs (Maternal)
(39,41,45,60,72,73,74,80)
[Humira] in µg/ml
1.0
0.8
0.6
0.4
0.2
0.0
Humira Runs (Fetal)
(39,41,45,60,72,73,74,80)
0
100
200
300
400
Time (Minutes)

FIG. 23

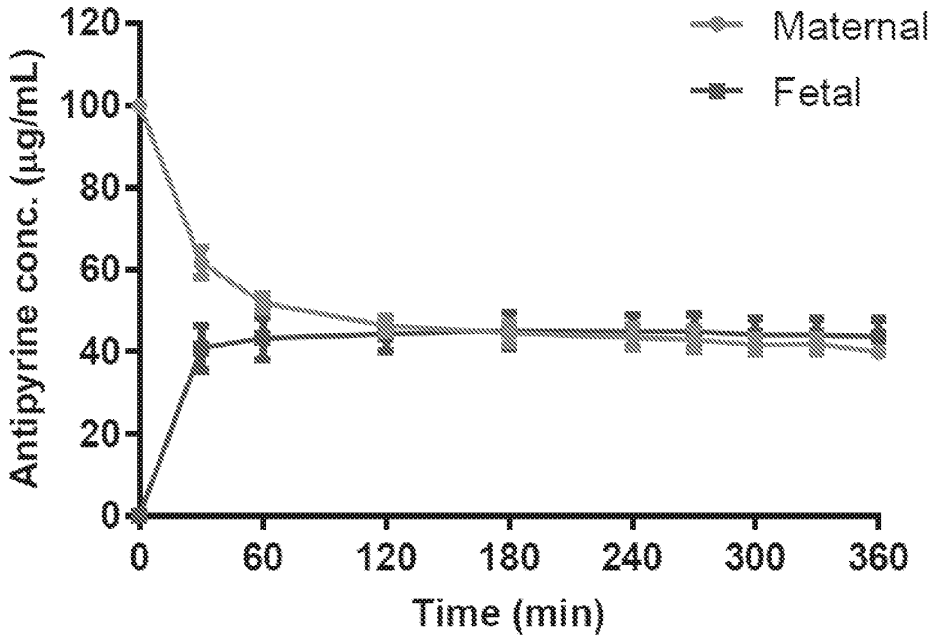

Maternal
Fetal
Antipyrine conc. (µg/mL)
120
100
80
60
40
20
0
0
60
120
180
240
300
360
Time (min)

FIG. 24

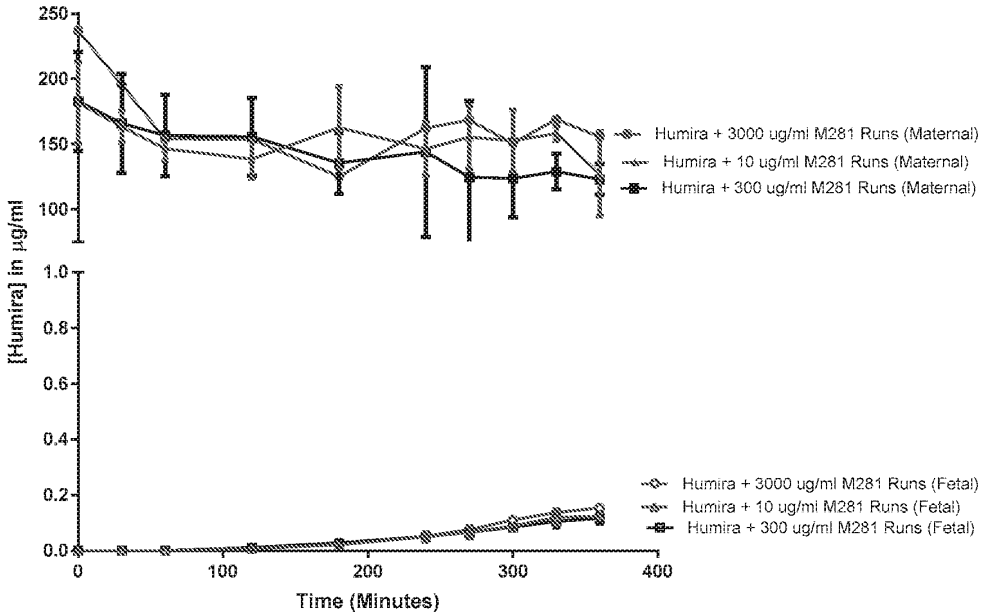

250
200
150
100
[Humira] in µg/ml
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Time (Minutes)
Humira + 3000 ug/ml M281 Runs (Maternal)
Humira + 10 ug/ml M281 Runs (Maternal)
Humira + 300 ug/ml M281 Runs (Maternal)
Humira + 3000 ug/ml M281 Runs (Fetal)
Humira + 10 ug/ml M281 Runs (Fetal)
Humira + 300 ug/ml M281 Runs (Fetal)

FIG. 25

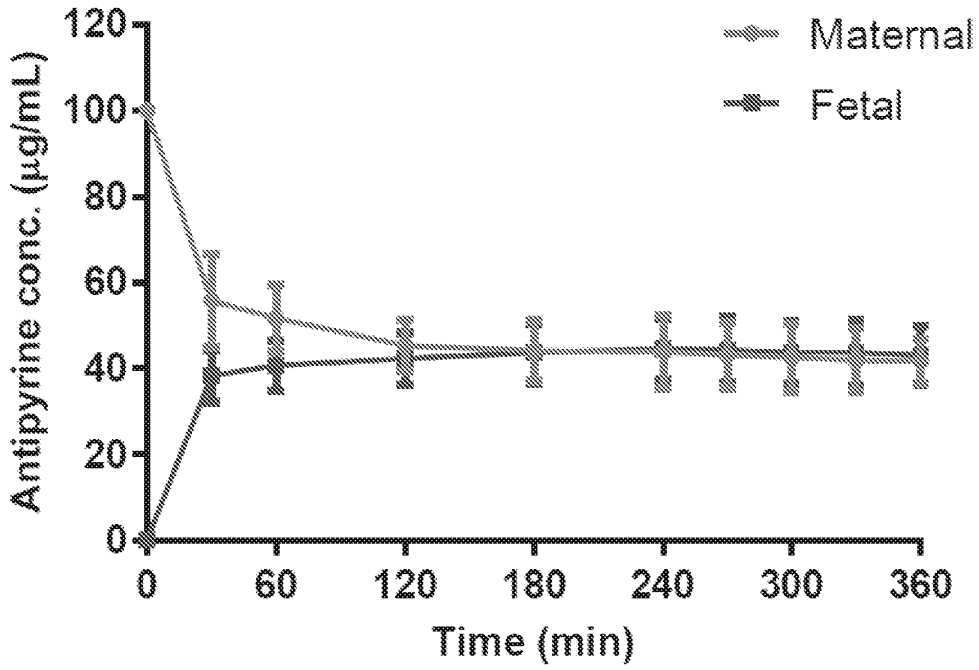

Maternal
Fetal
Antipyrine conc. (µg/mL)
120
100
80
60
40
20
0
0
60
120
180
240
300
360
Time (min)

FIG. 26

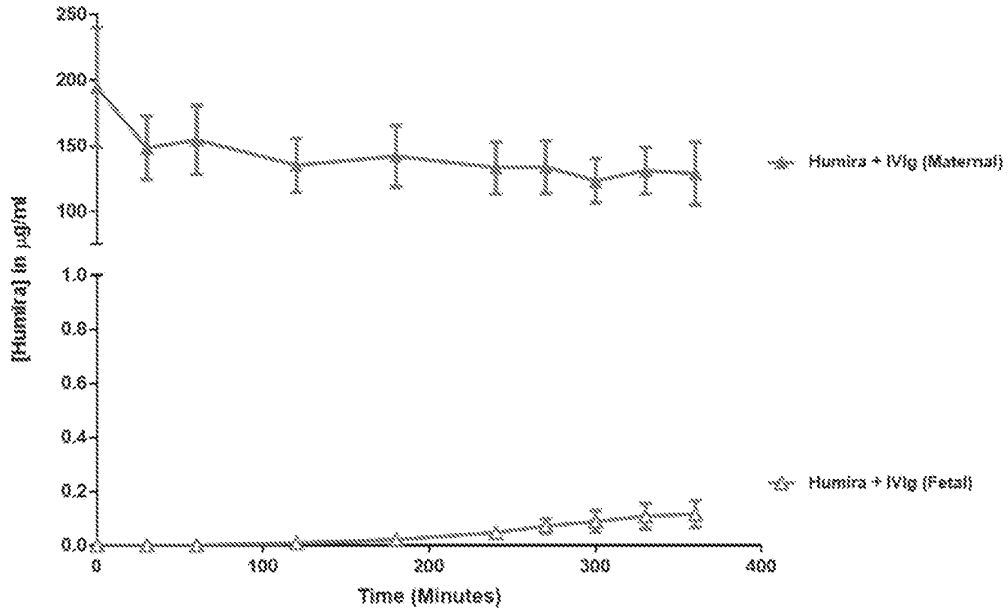

250
200
150
100
1.0
0.8
0.6
0.4
0.2
0.0
[Humira] in µg/ml
0
100
200
300
400
Time (Minutes)
Humira + IVig (Maternal)
Humira + IVig (Fetal)

FIG. 27

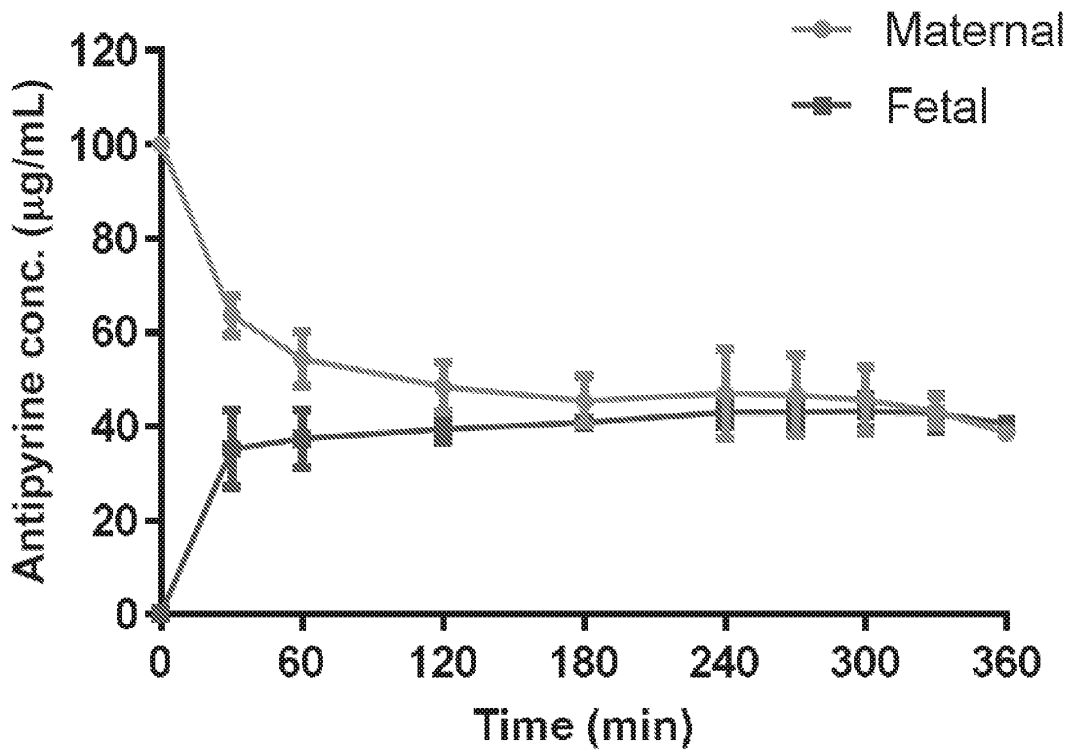

Maternal
Fetal
Antipyrine conc. (µg/mL)
120
100
80
60
40
20
0
0
60
120
180
240
300
360
Time (min)

FIG. 28

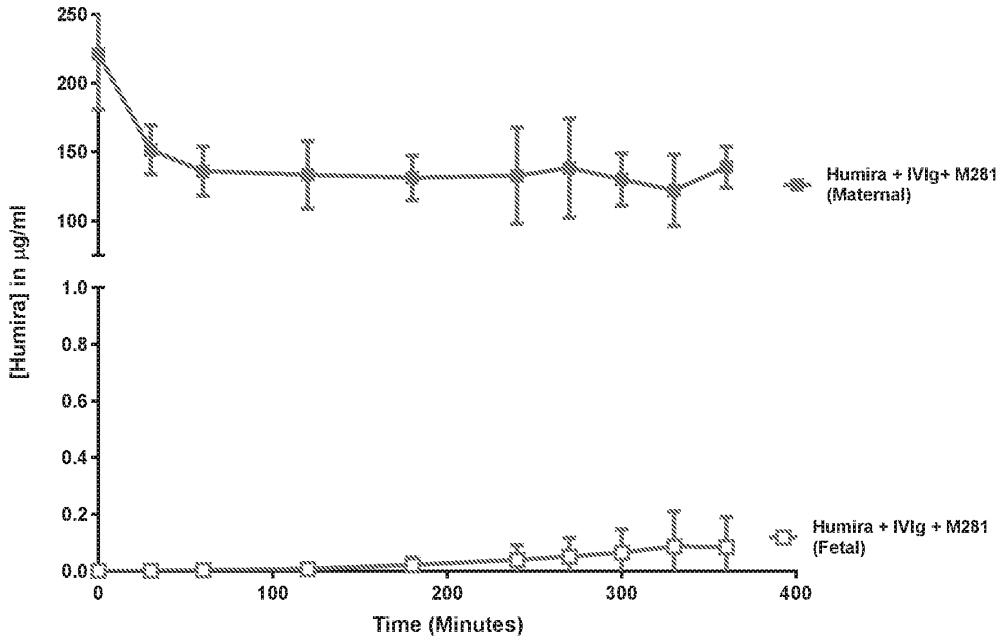

250
200
150
100
1.0
0.8
0.6
0.4
0.2
0.0
[Humira] in µg/ml
0
100
200
300
400
Time (Minutes)
Humira + IVIg+ M281
(Maternal)
Humira + IVIg + M281
(Fetal)

FIG. 29

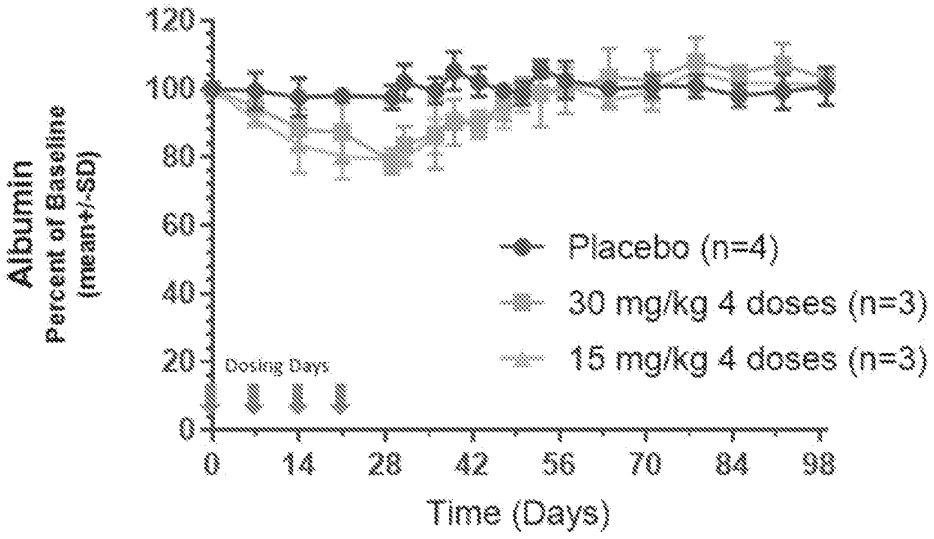

Albumin
Percent of Baseline
(mean+/-SD)
120
100
80
60
40
20
0
Dosing Days
0
14
28
42
56
70
84
98
Time (Days)
Placebo (n=4)
30 mg/kg 4 doses (n=3)
15 mg/kg 4 doses (n=3)

FIG. 30

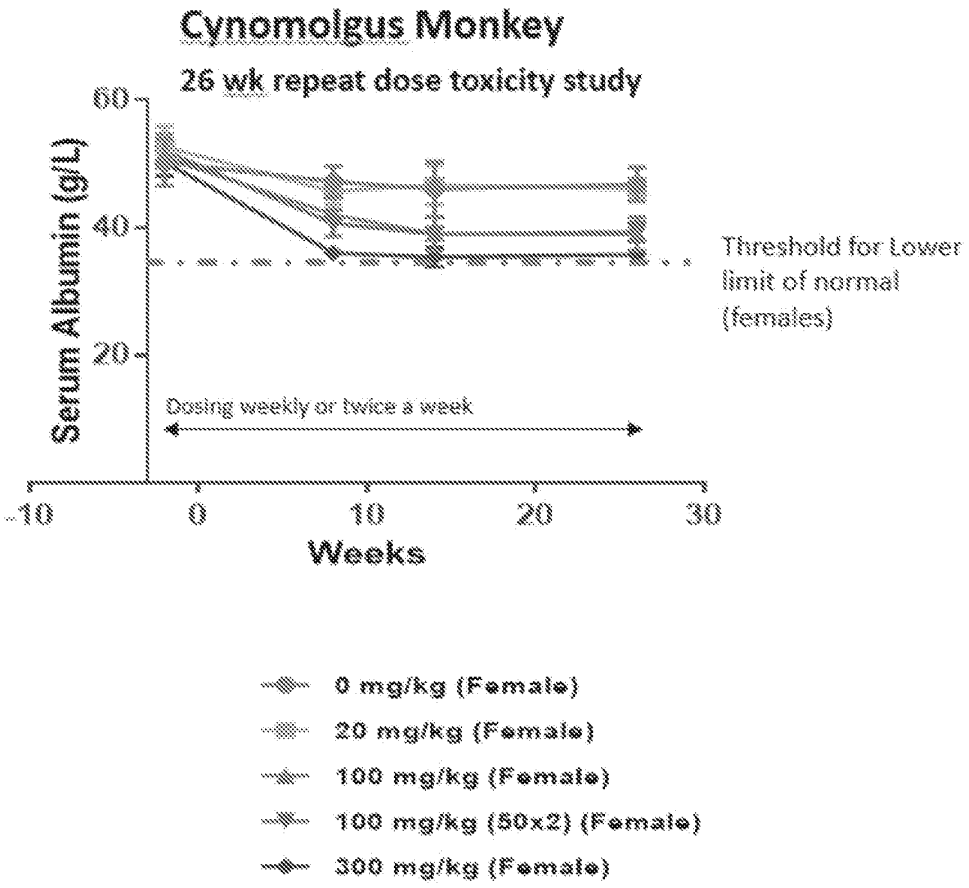

Cynomolgus Monkey
26 wk repeat dose toxicity study
Serum Albumin (g/L)
60
40
20
Threshold for Lower limit of normal (females)
Dosing weekly or twice a week
-10
0
10
20
30
Weeks
0 mg/kg (Female)
20 mg/kg (Female)
100 mg/kg (Female)
100 mg/kg (50x2) (Female)
300 mg/kg (Female)

FIG. 31

M281 Dose	Gestation Day					
	EFD				ePPND	
	38	66	100/115	142	44-46	135-137
0 mg/kg	3.9 ± 0.3	3.1 ± 0.4	2.8 ± 0.3	2.5 ± 0.4	3.5 ± 0.3	2.7 ± 0.3
100 mg/kg	3.7 ± 0.1	2.4 ± 0.2	2.5 ± 0.2	2.3 ± 0.3	3.4 ± 0.3	2.3 ± 0.2
300 mg/kg	3.5 ± 0.3	2.0 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	3.4 ± 0.3	2.0 ± 0.2

FIG. 32