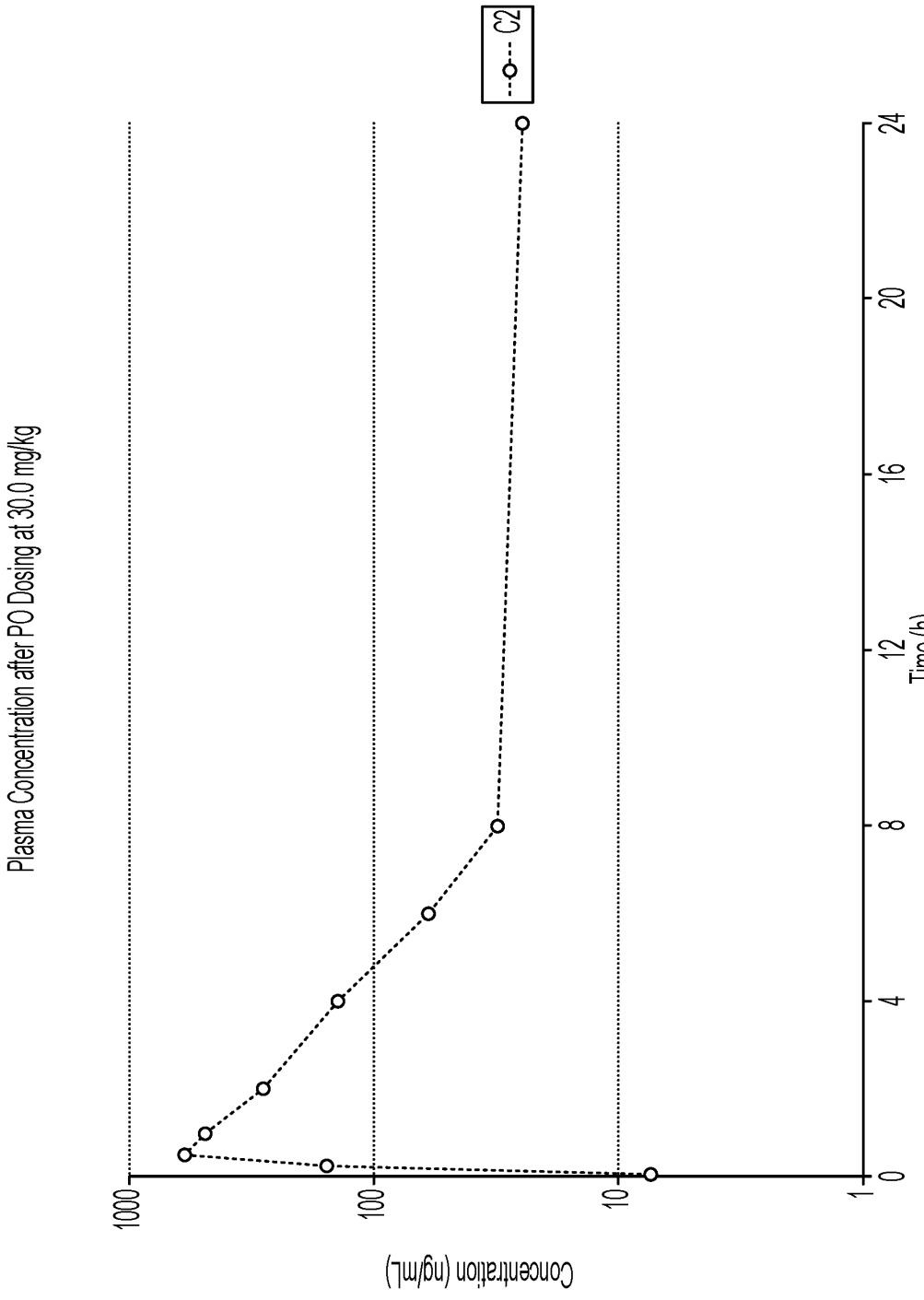

Plasma Concentration after PO Dosing at 30.0 mg/kg
C2
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)

FIG. 1

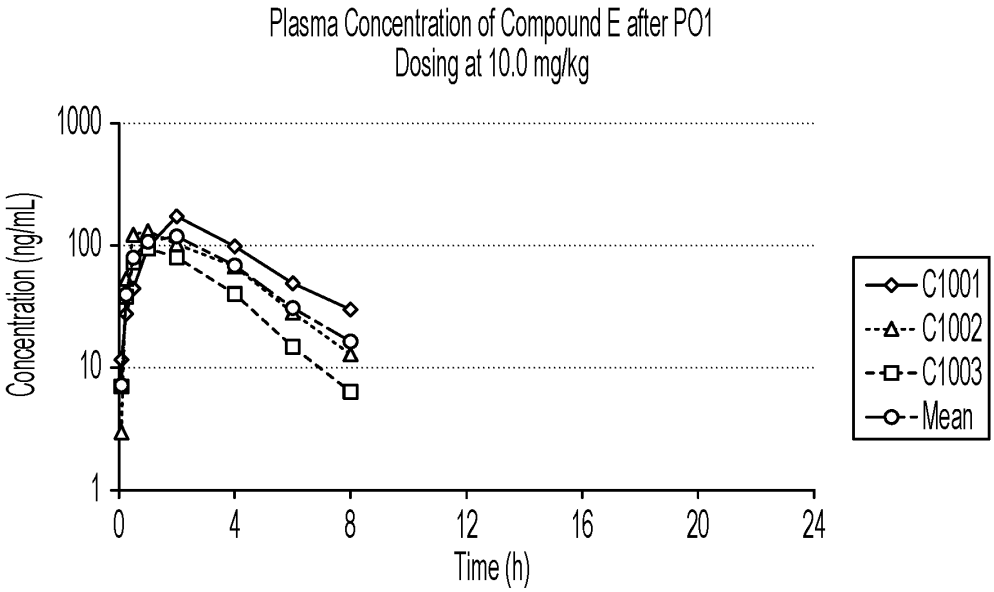

Plasma Concentration of Compound E after PO1
Dosing at 10.0 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
C1001
C1002
C1003
Mean

FIG. 2A

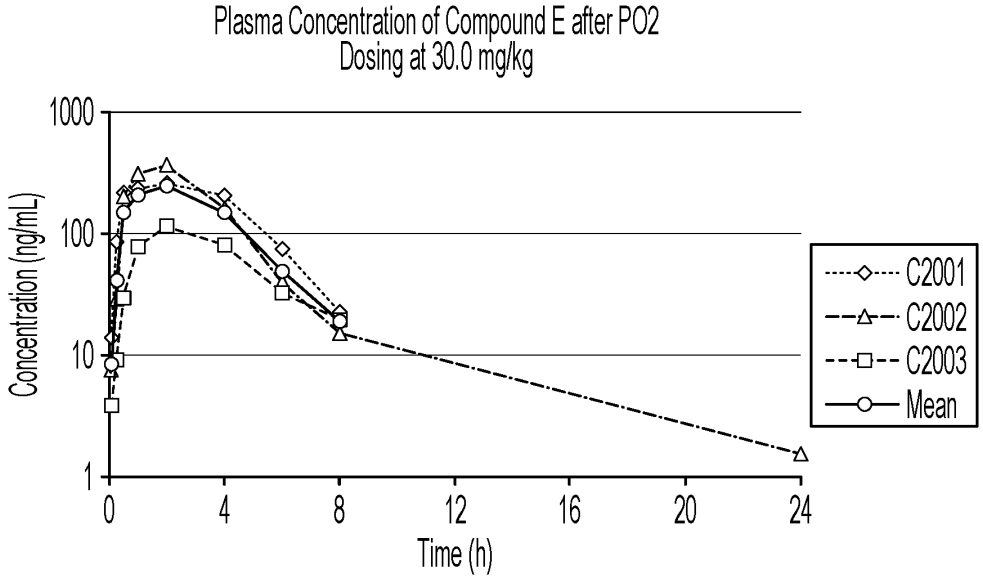

Plasma Concentration of Compound E after PO2
Dosing at 30.0 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
C2001
C2002
C2003
Mean

FIG. 2B

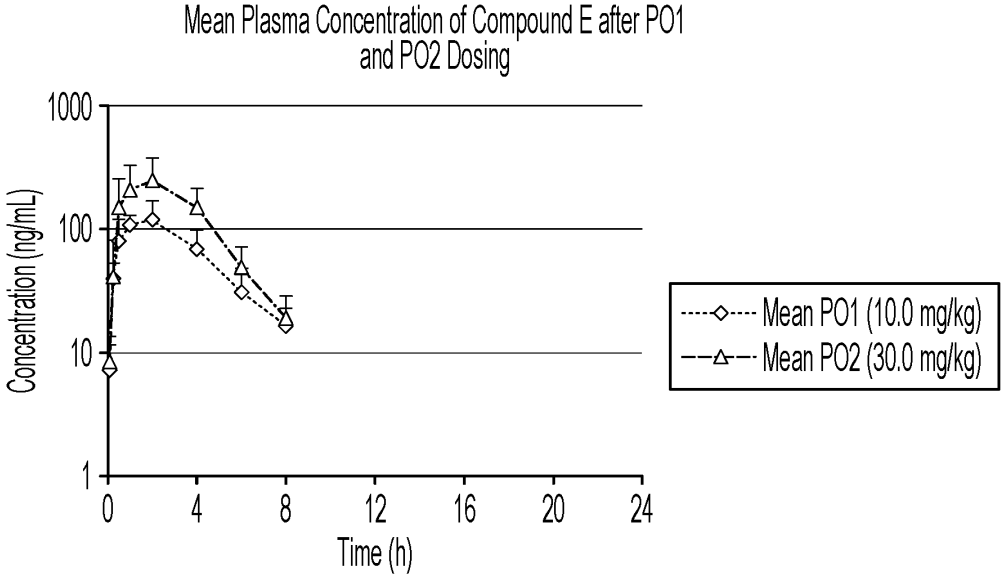

Mean Plasma Concentration of Compound E after PO1 and PO2 Dosing
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean PO1 (10.0 mg/kg)
Mean PO2 (30.0 mg/kg)

FIG. 2C

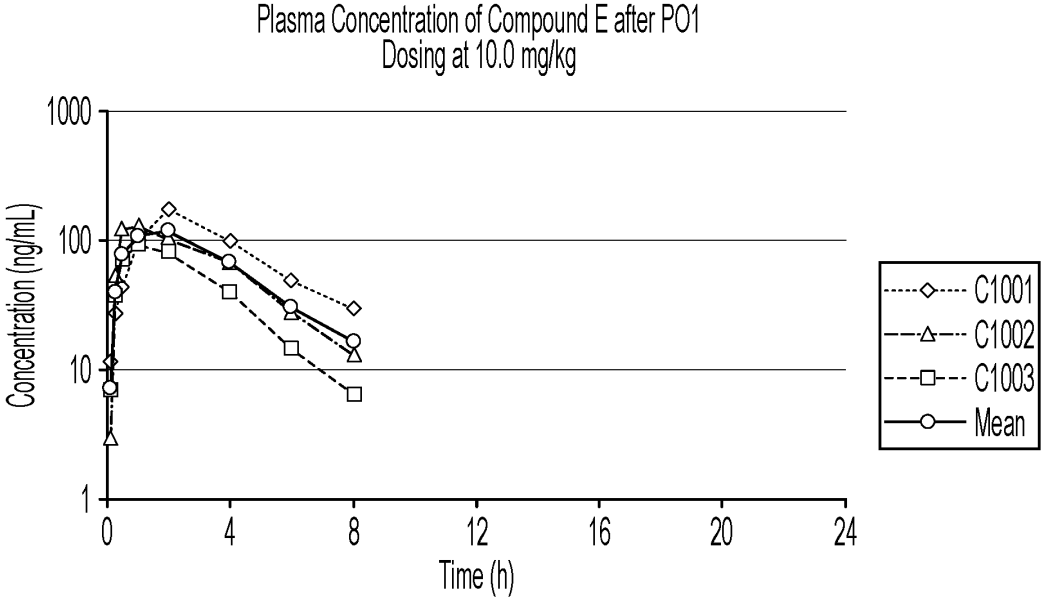

Plasma Concentration of Compound E after PO1 Dosing at 10.0 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
C1001
C1002
C1003
Mean

FIG. 2D

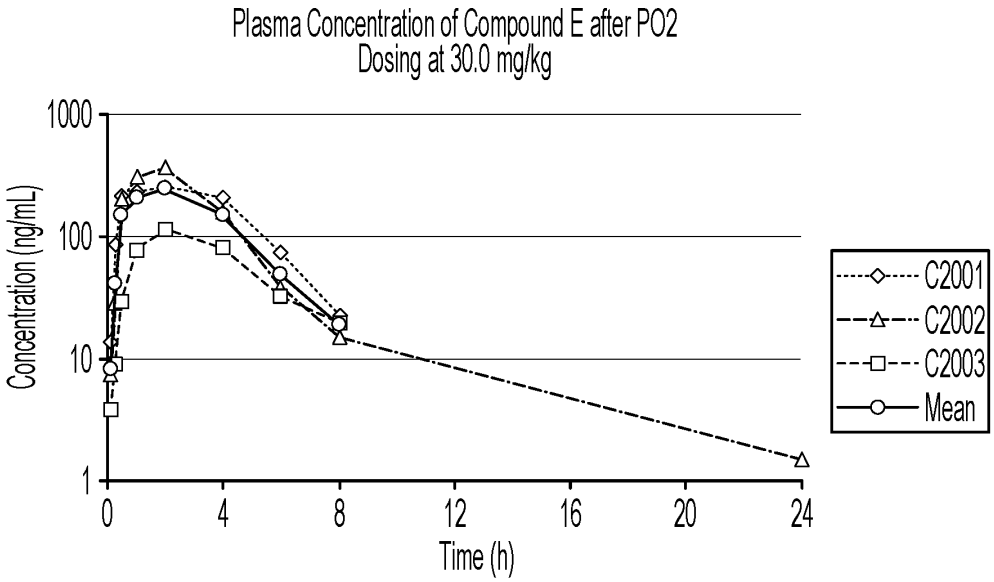

Plasma Concentration of Compound E after PO2
Dosing at 30.0 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
C2001
C2002
C2003
Mean

FIG. 2E

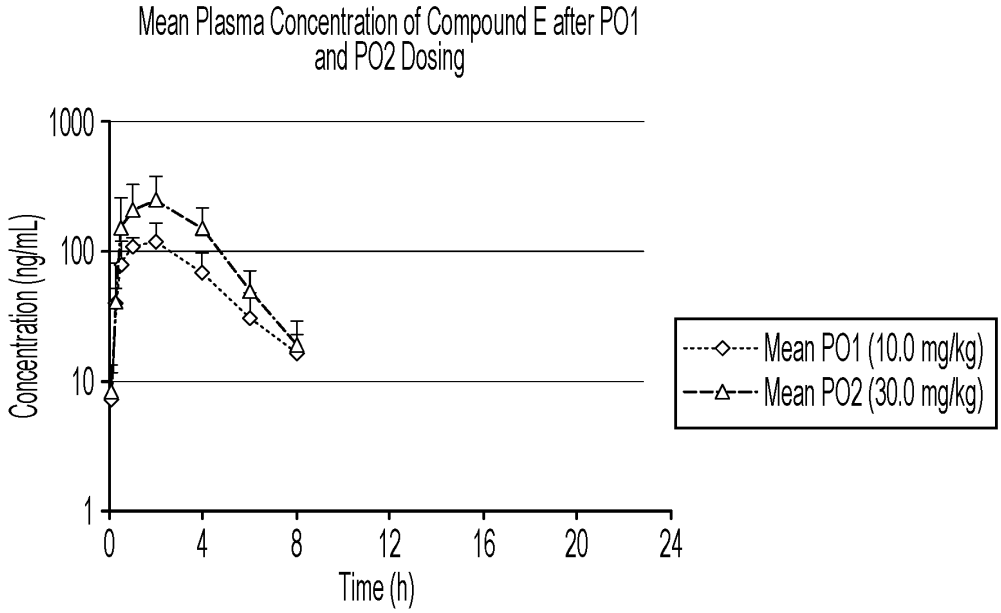

Mean Plasma Concentration of Compound E after PO1
and PO2 Dosing
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean PO1 (10.0 mg/kg)
Mean PO2 (30.0 mg/kg)

FIG. 2F

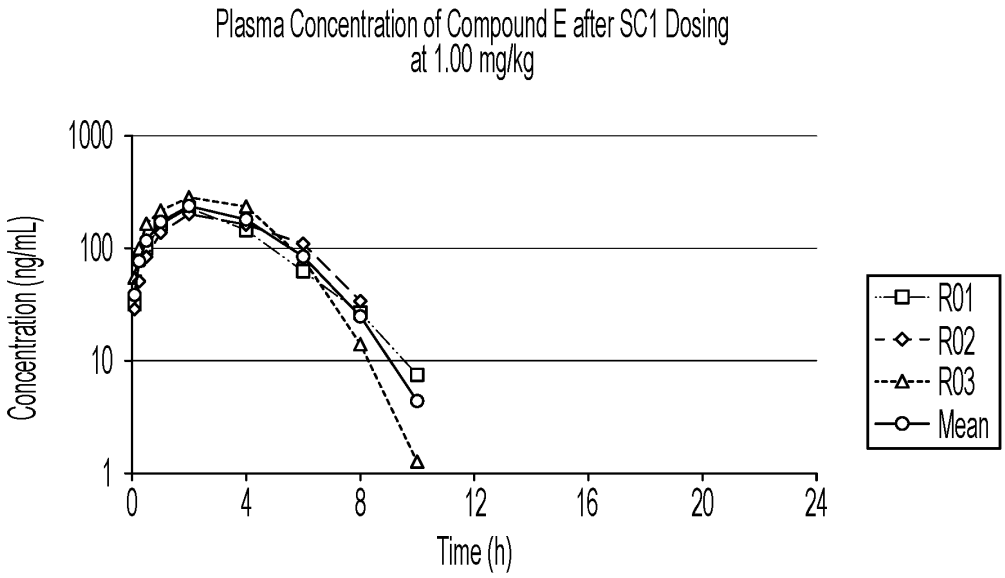

Plasma Concentration of Compound E after SC1 Dosing
at 1.00 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
R01
R02
R03
Mean

FIG. 3A

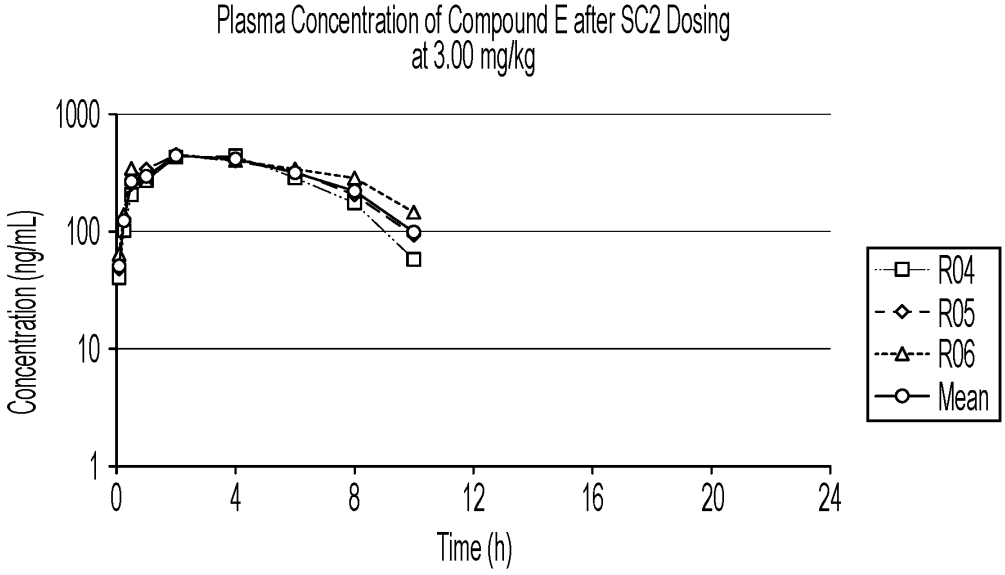

Plasma Concentration of Compound E after SC2 Dosing
at 3.00 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
R04
R05
R06
Mean

FIG. 3B

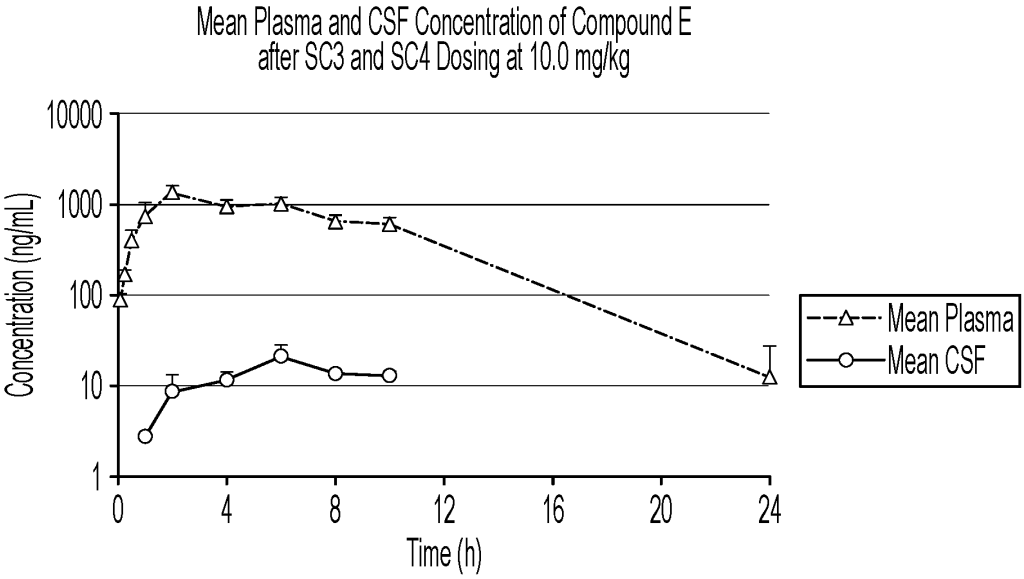

Mean Plasma and CSF Concentration of Compound E
after SC3 and SC4 Dosing at 10.0 mg/kg
Concentration (ng/mL)
10000
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean Plasma
Mean CSF

FIG. 3C

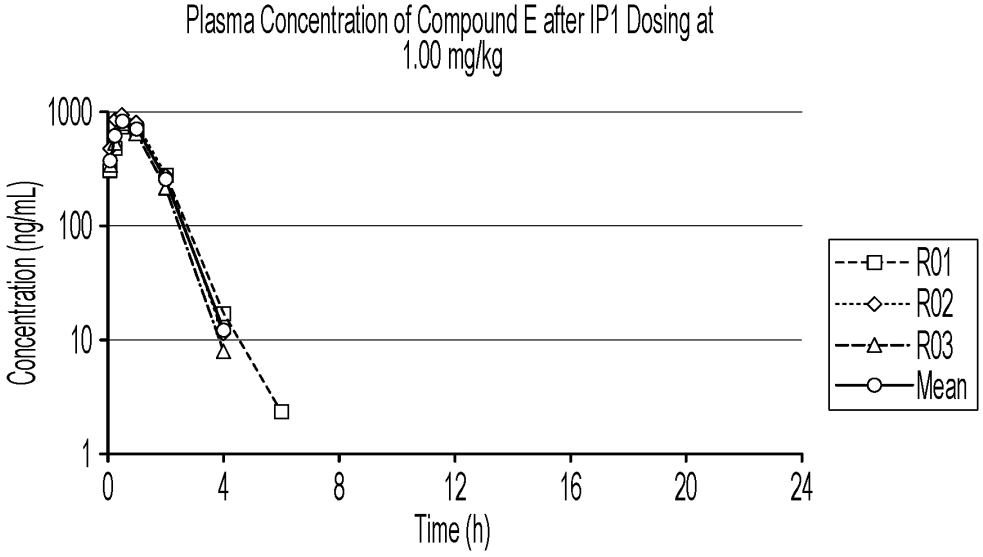

Plasma Concentration of Compound E after IP1 Dosing at
1.00 mg/kg
Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
R01
R02
R03
Mean

FIG. 4A

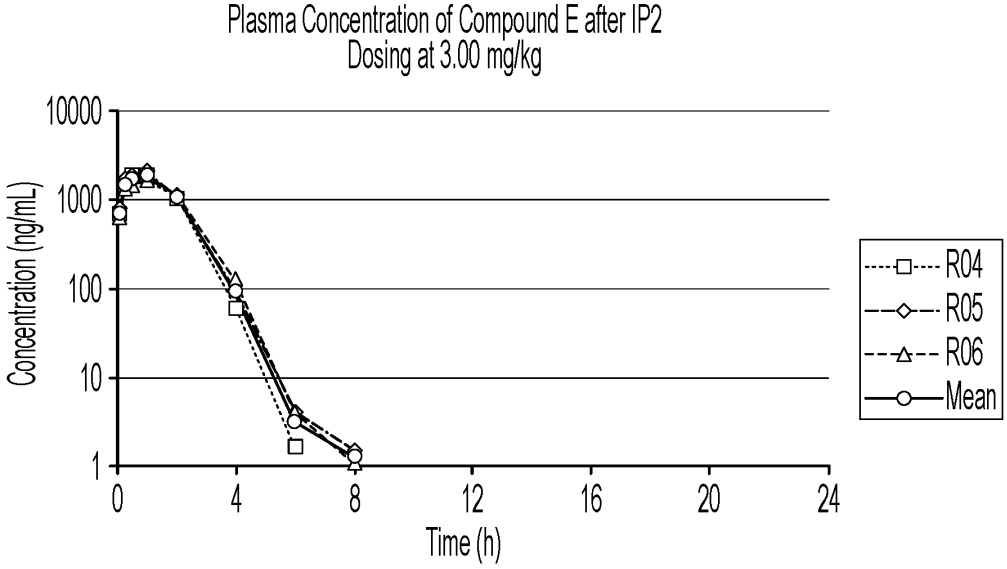

Plasma Concentration of Compound E after IP2
Dosing at 3.00 mg/kg
Concentration (ng/mL)
10000
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
R04
R05
R06
Mean

FIG. 4B

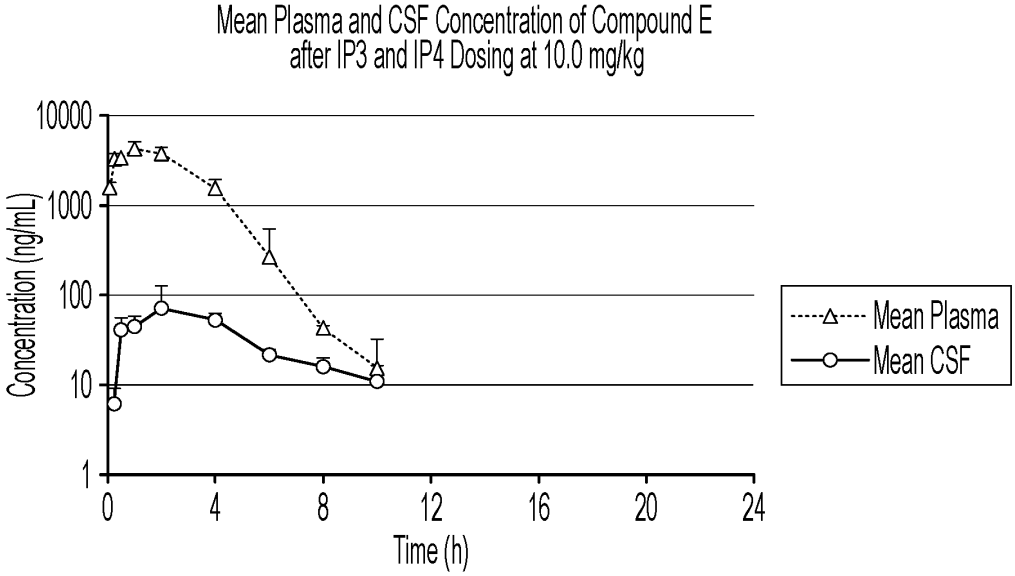

Mean Plasma and CSF Concentration of Compound E
after IP3 and IP4 Dosing at 10.0 mg/kg
Concentration (ng/mL)
10000
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean Plasma
Mean CSF

FIG. 4C

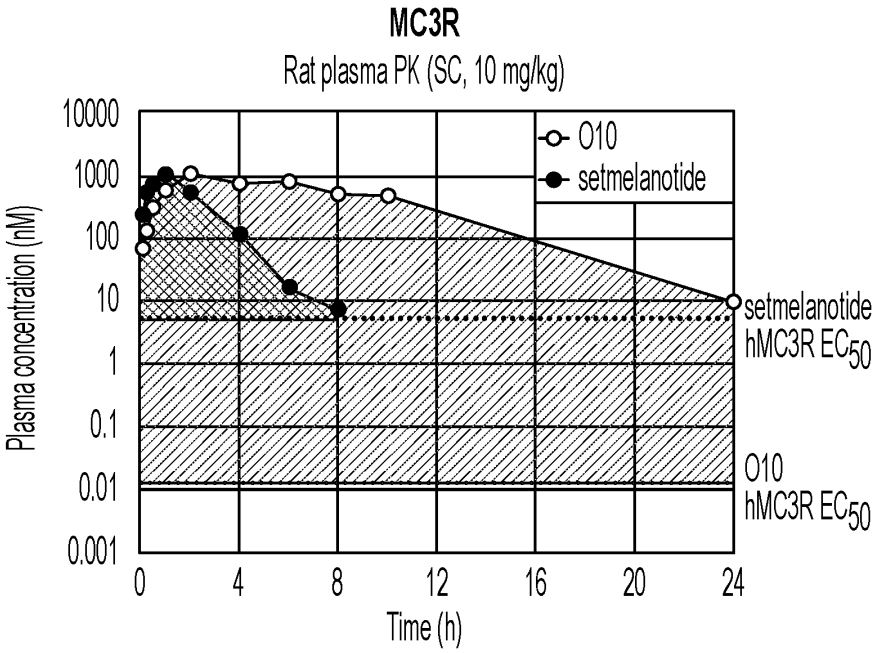

MC3R
Rat plasma PK (SC, 10 mg/kg)
Plasma concentration (nM)
10000
1000
100
10
1
0.1
0.01
0.001
0
4
8
12
16
20
24
Time (h)
O10
setmelanotide
setmelanotide hMC3R EC50
O10 hMC3R EC50

FIG. 4D

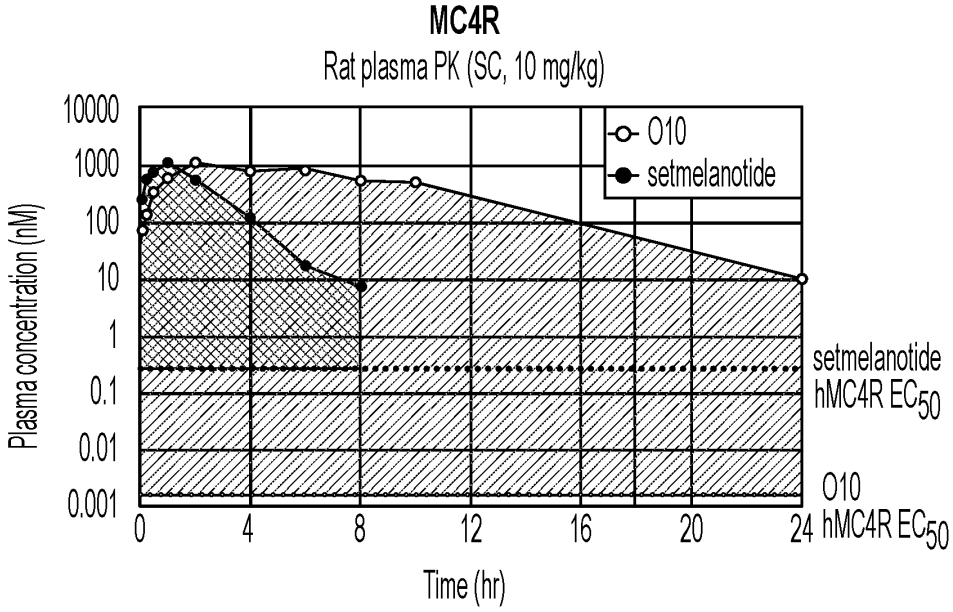

MC4R
Rat plasma PK (SC, 10 mg/kg)
Plasma concentration (nM)
10000
1000
100
10
1
0.1
0.01
0.001
0
4
8
12
16
20
24
Time (hr)
O10
setmelanotide
setmelanotide hMC4R EC50
O10 hMC4R EC50

FIG. 4E

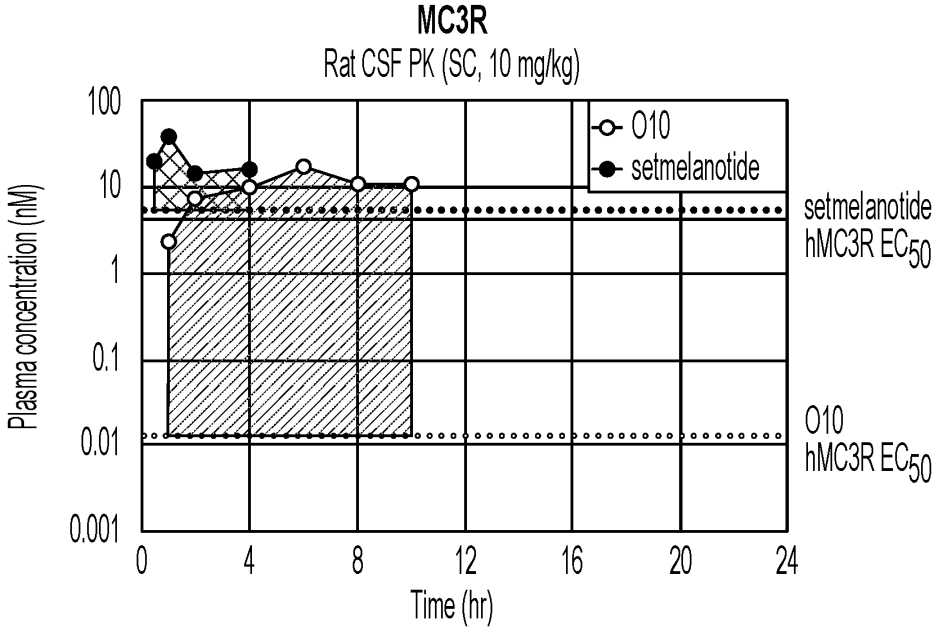

MC3R
Rat CSF PK (SC, 10 mg/kg)
Plasma concentration (nM)
100
10
1
0.1
0.01
0.001
0
4
8
12
16
20
24
Time (hr)
O10
setmelanotide
setmelanotide hMC3R EC50
O10 hMC3R EC50

FIG. 4F

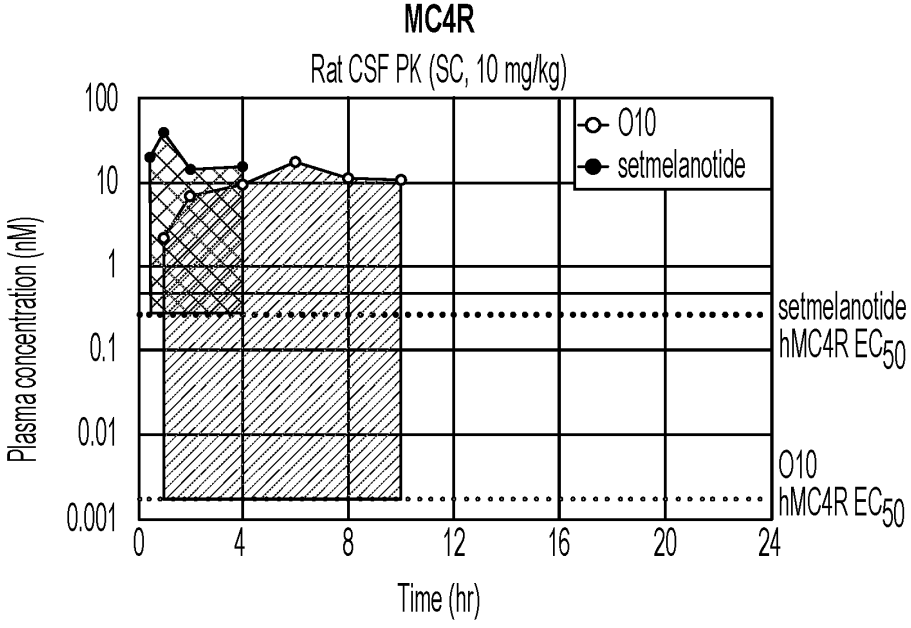

MC4R
Rat CSF PK (SC, 10 mg/kg)
Plasma concentration (nM)
100
10
1
0.1
0.01
0.001
0
4
8
12
16
20
24
Time (hr)
O10
setmelanotide
setmelanotide hMC4R EC50
O10 hMC4R EC50

FIG. 4G

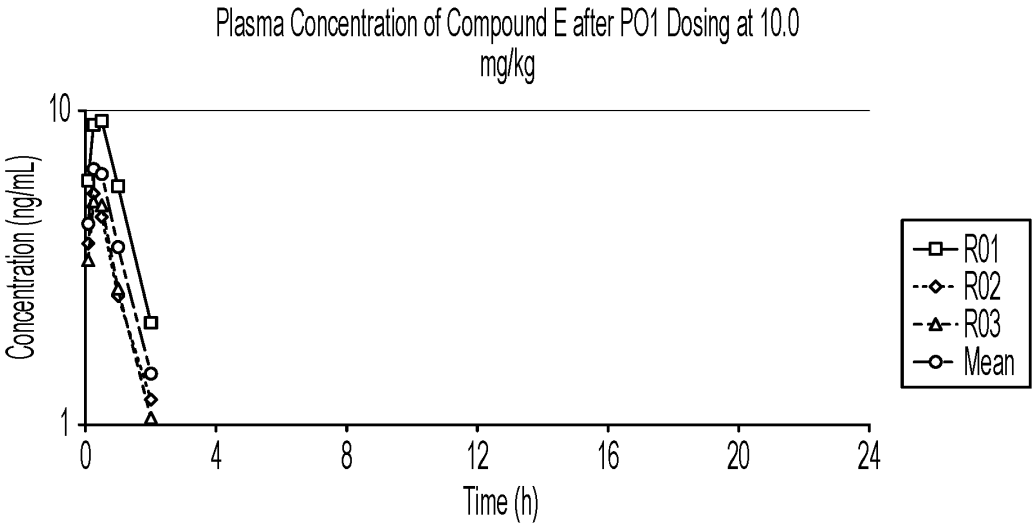

Plasma Concentration of Compound E after PO1 Dosing at 10.0 mg/kg
Concentration (ng/mL)
10
1
0
4
8
12
16
20
24
Time (h)
R01
R02
R03
Mean

FIG. 5A

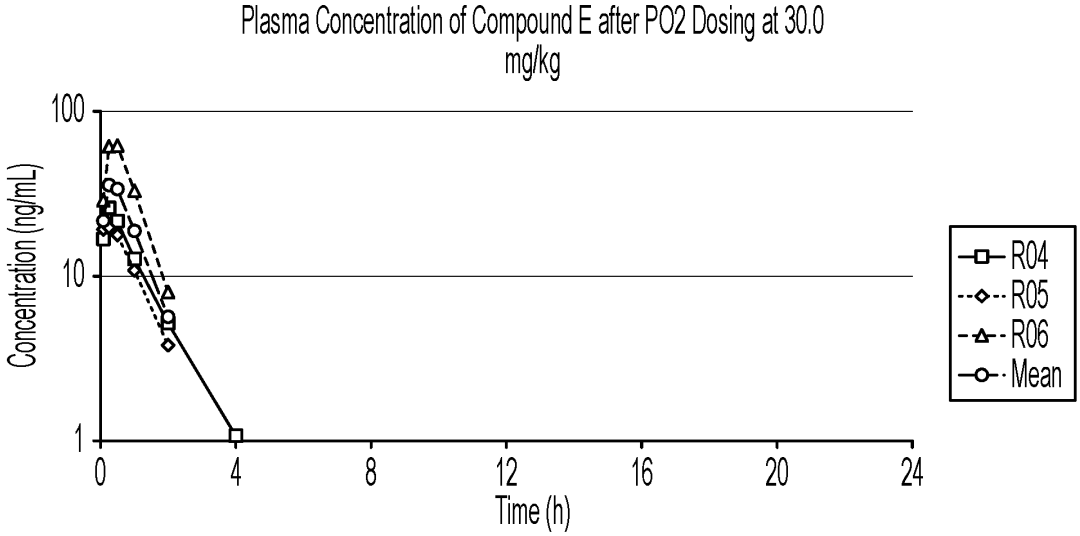

Plasma Concentration of Compound E after PO2 Dosing at 30.0 mg/kg
Concentration (ng/mL)
100
10
1
0
4
8
12
16
20
24
Time (h)
R04
R05
R06
Mean

FIG. 5B

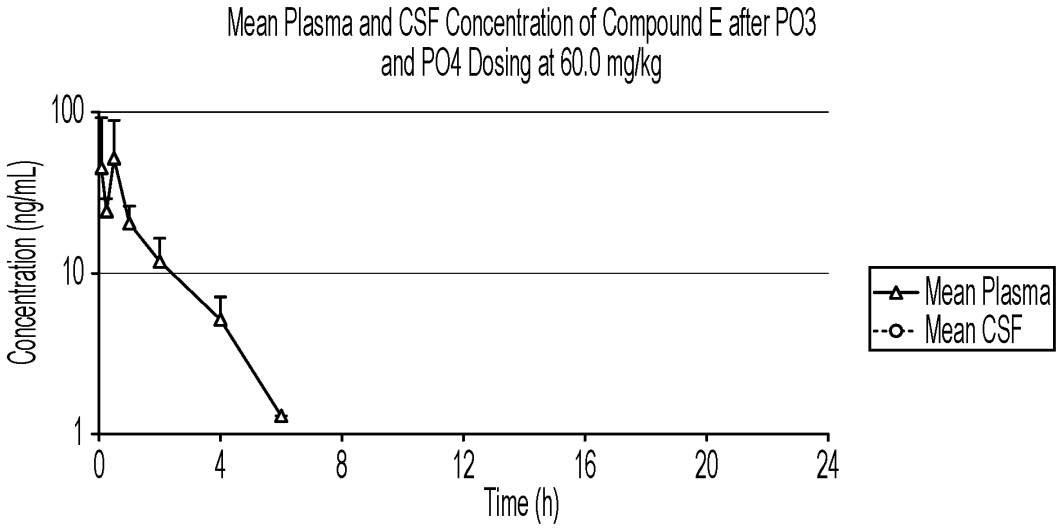

Mean Plasma and CSF Concentration of Compound E after PO3 and PO4 Dosing at 60.0 mg/kg
Concentration (ng/mL)
100
10
1
0
4
8
12
16
20
24
Time (h)
Mean Plasma
Mean CSF

FIG. 5C

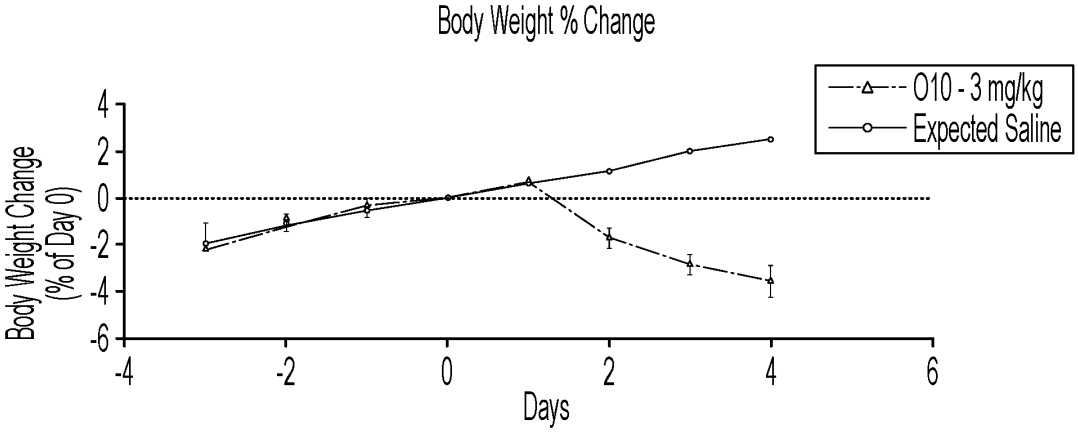

Body Weight % Change
O10 - 3 mg/kg
Expected Saline
Body Weight Change (% of Day 0)
4
2
0
-2
-4
-6
-4
-2
0
2
4
6
Days

FIG. 6A

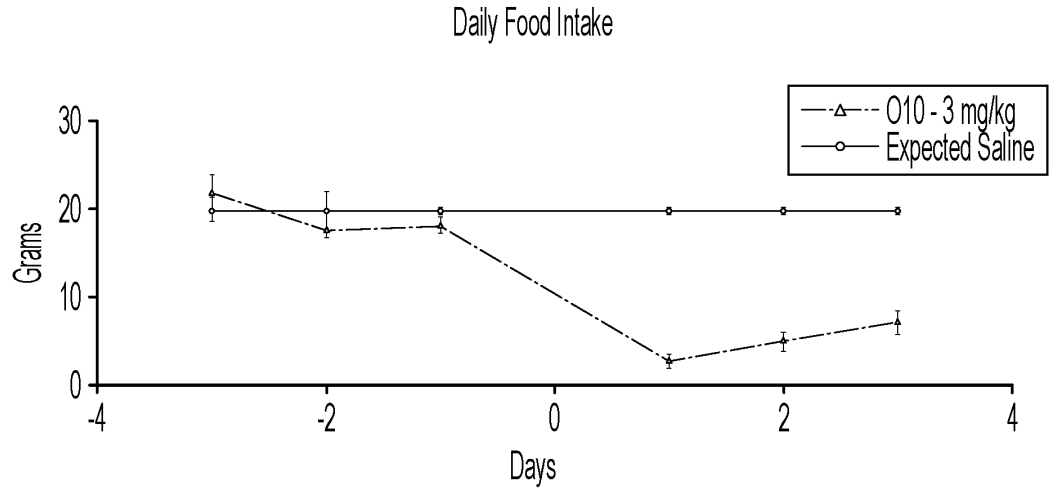

Daily Food Intake
O10 - 3 mg/kg
Expected Saline
Grams
30
20
10
0
-4
-2
0
2
4
Days

FIG. 6B

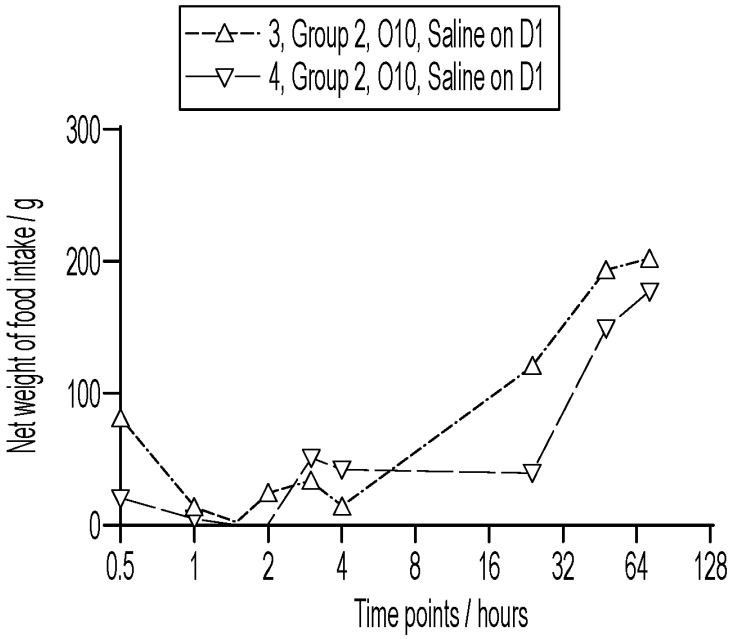

3, Group 2, O10, Saline on D1
4, Group 2, O10, Saline on D1
Net weight of food intake / g
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 7A

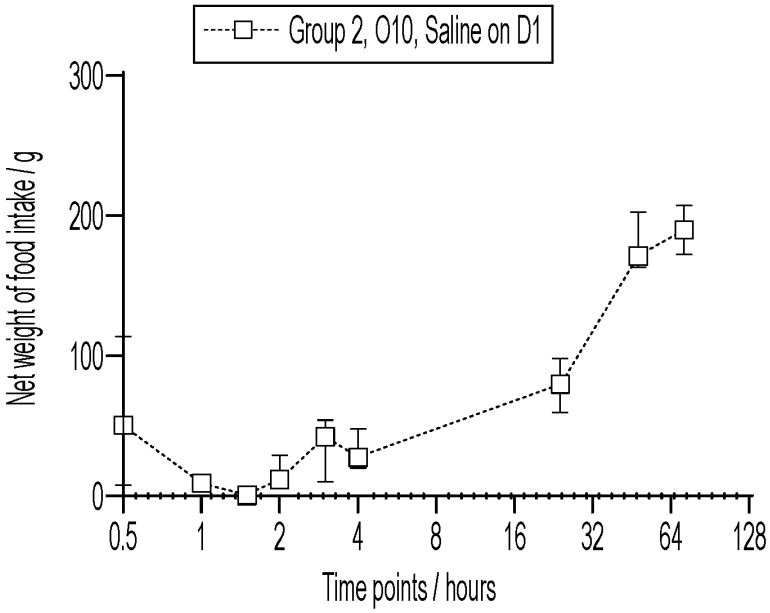

Group 2, O10, Saline on D1
Net weight of food intake / g
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 7B

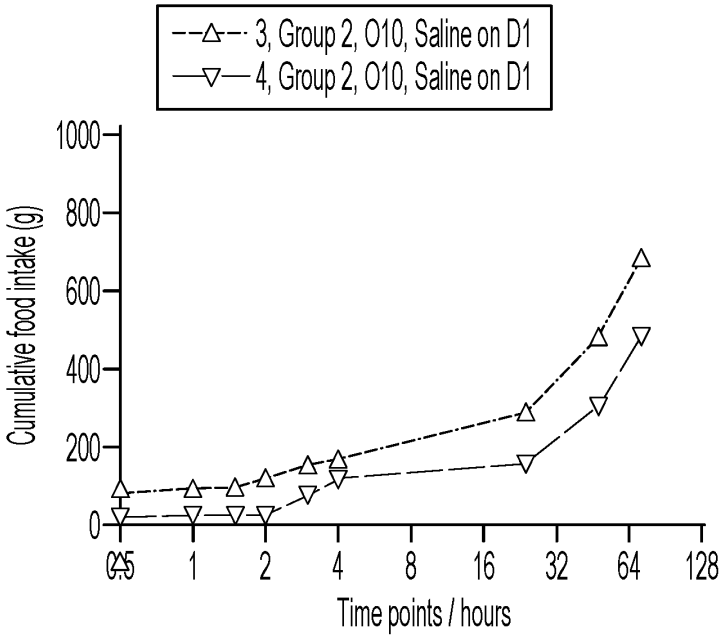

3, Group 2, O10, Saline on D1
4, Group 2, O10, Saline on D1
Cumulative food intake (g)
1000
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 7C

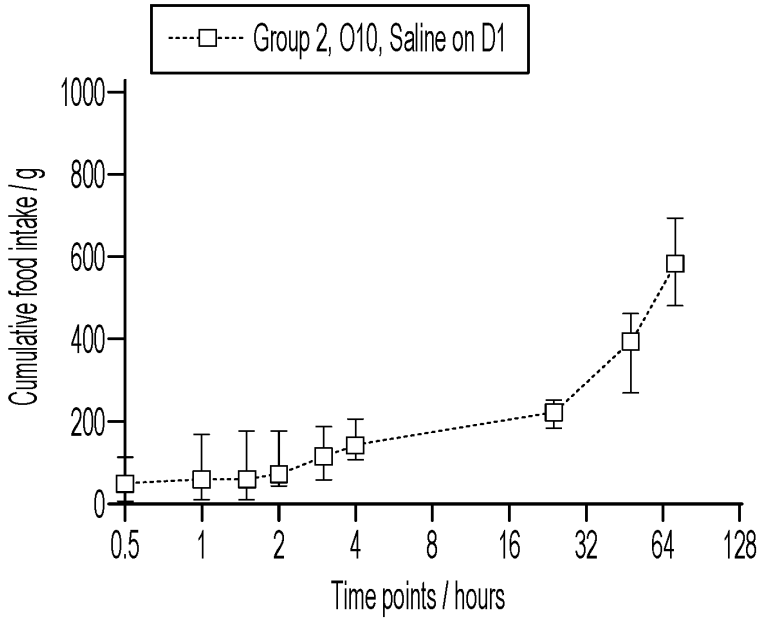

Group 2, O10, Saline on D1
Cumulative food intake / g
1000
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 7D

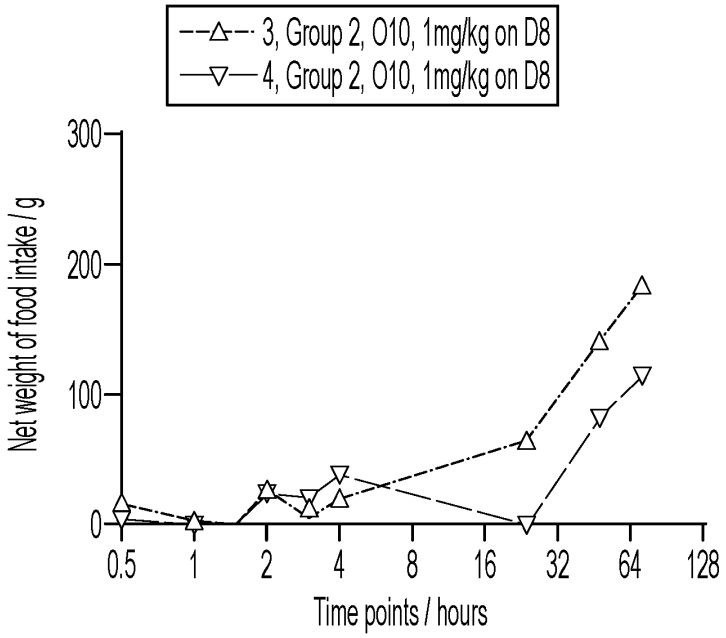

3, Group 2, O10, 1mg/kg on D8
4, Group 2, O10, 1mg/kg on D8
Net weight of food intake / g
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8A

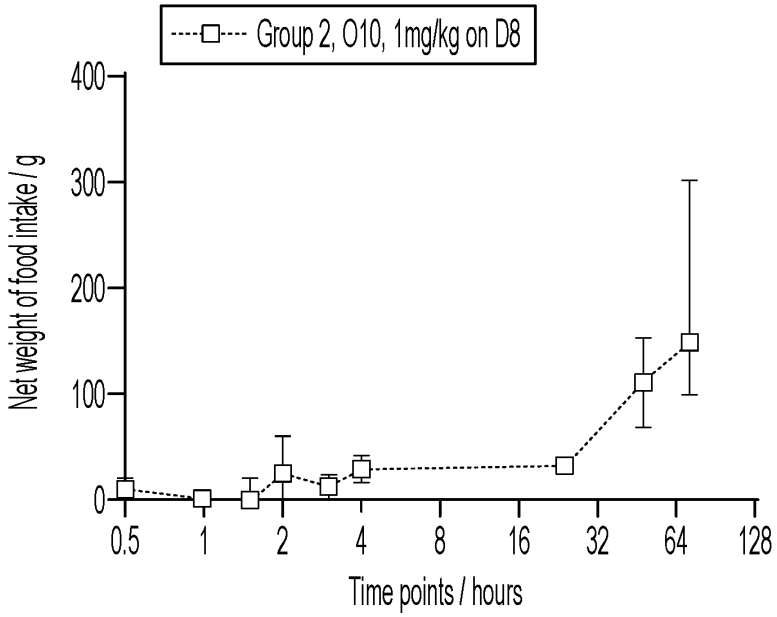

Group 2, O10, 1mg/kg on D8
Net weight of food intake / g
400
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8B

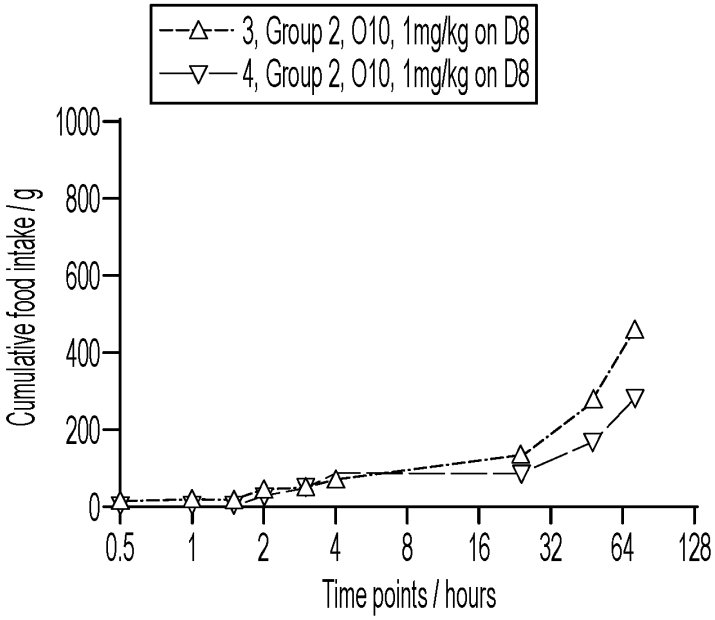

3, Group 2, O10, 1mg/kg on D8
4, Group 2, O10, 1mg/kg on D8
Cumulative food intake / g
1000
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8C

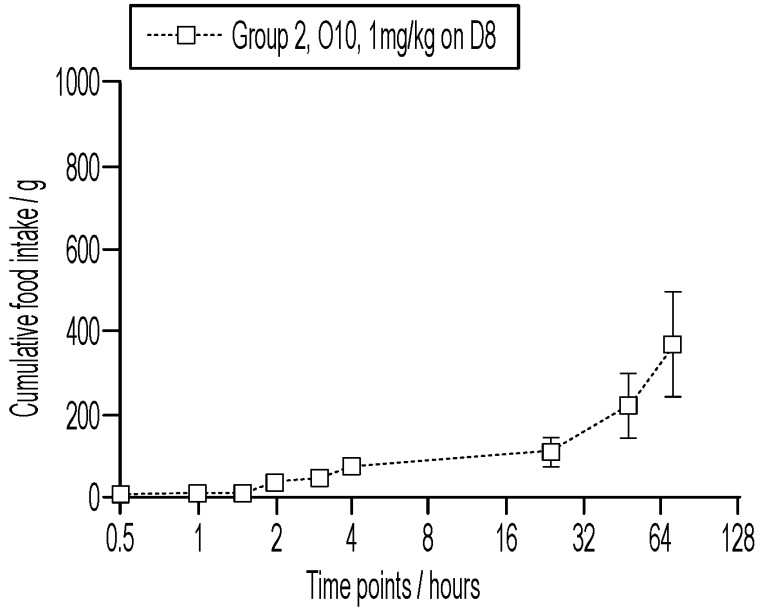

Group 2, O10, 1mg/kg on D8
Cumulative food intake / g
1000
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8D

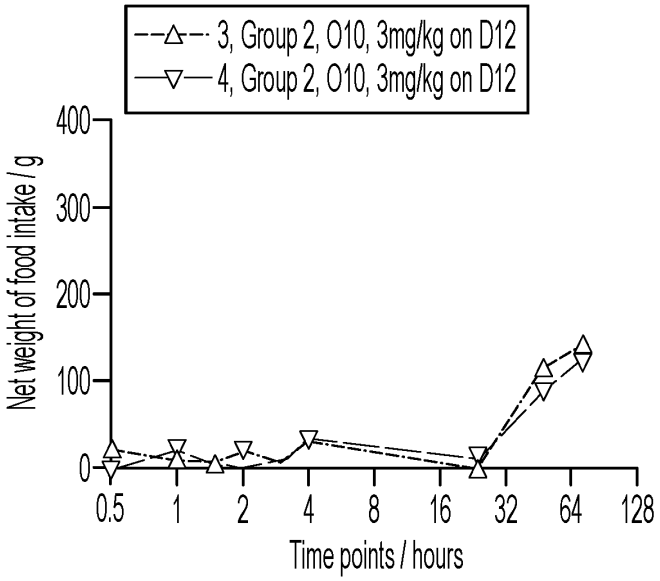

3, Group 2, O10, 3mg/kg on D12
4, Group 2, O10, 3mg/kg on D12
Net weight of food intake / g
400
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8E

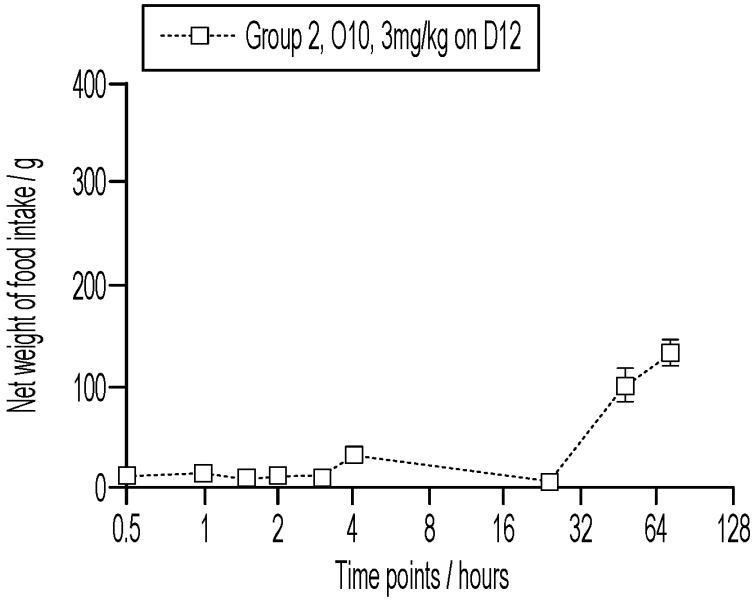

Group 2, O10, 3mg/kg on D12
Net weight of food intake / g
400
300
200
100
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8F

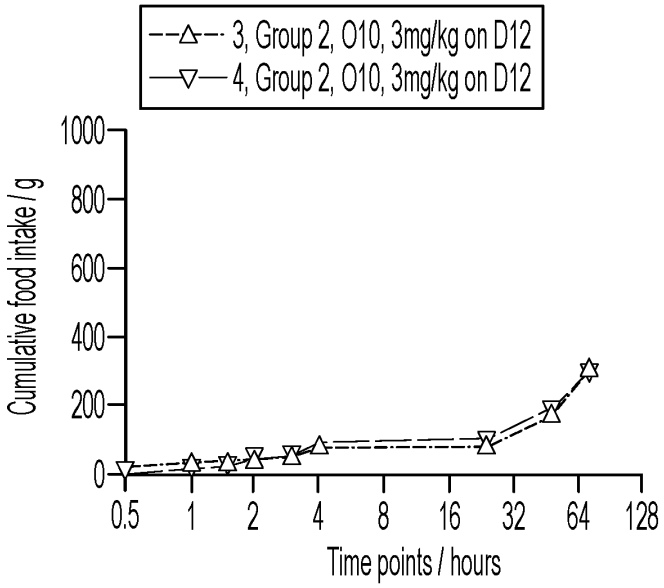

3, Group 2, O10, 3mg/kg on D12
4, Group 2, O10, 3mg/kg on D12
Cumulative food intake / g
1000
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8G

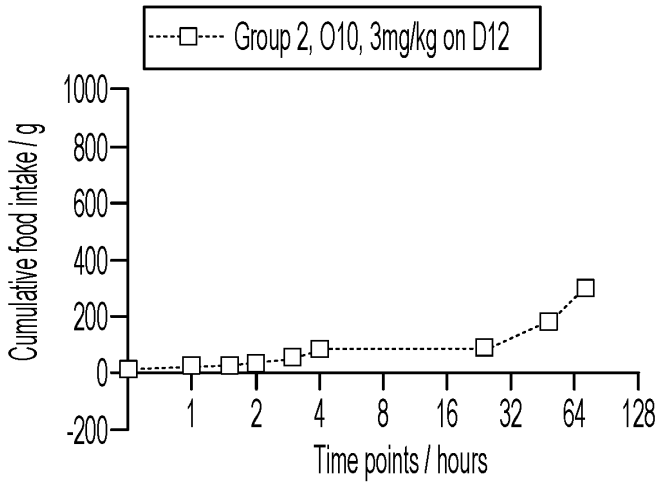

Group 2, O10, 3mg/kg on D12
Cumulative food intake / g
1000
800
600
400
200
0
-200
1
2
4
8
16
32
64
128
Time points / hours

FIG. 8H

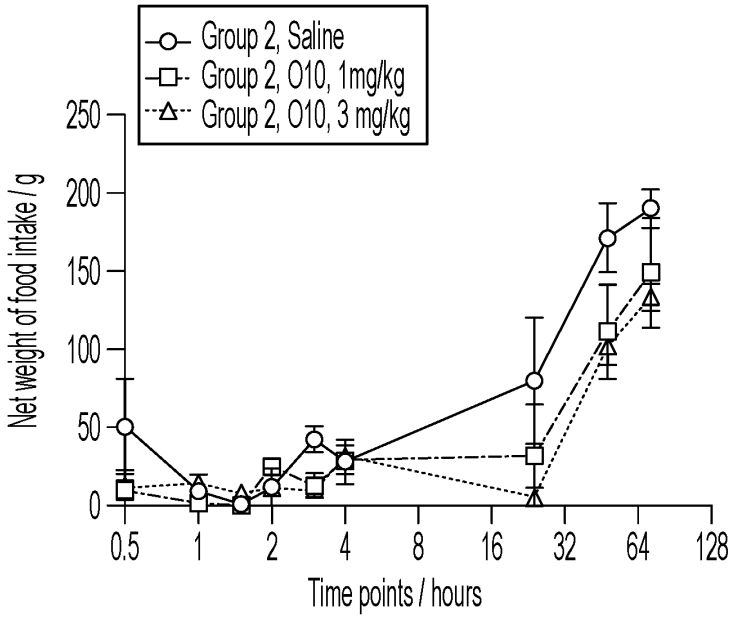

Group 2, Saline
Group 2, O10, 1mg/kg
Group 2, O10, 3 mg/kg
Net weight of food intake / g
250
200
150
100
50
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 9A

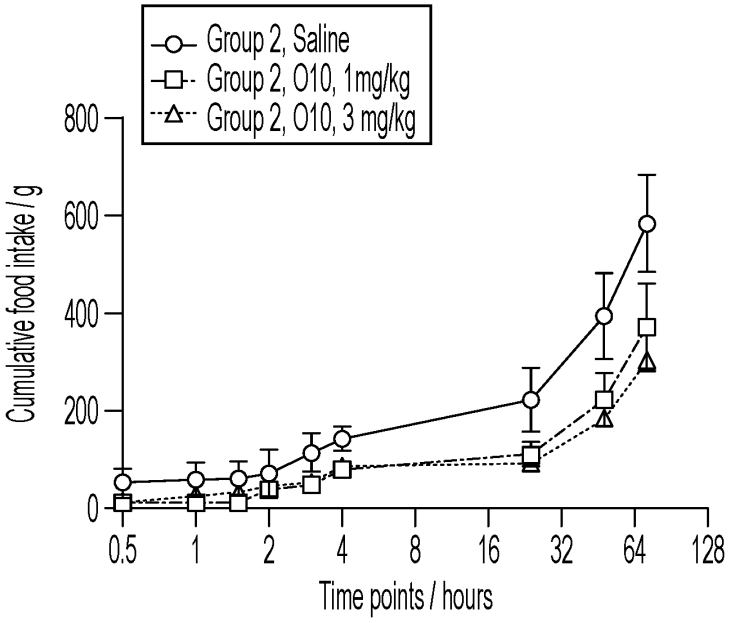

Group 2, Saline
Group 2, O10, 1mg/kg
Group 2, O10, 3 mg/kg
Cumulative food intake / g
800
600
400
200
0
0.5
1
2
4
8
16
32
64
128
Time points / hours

FIG. 9B

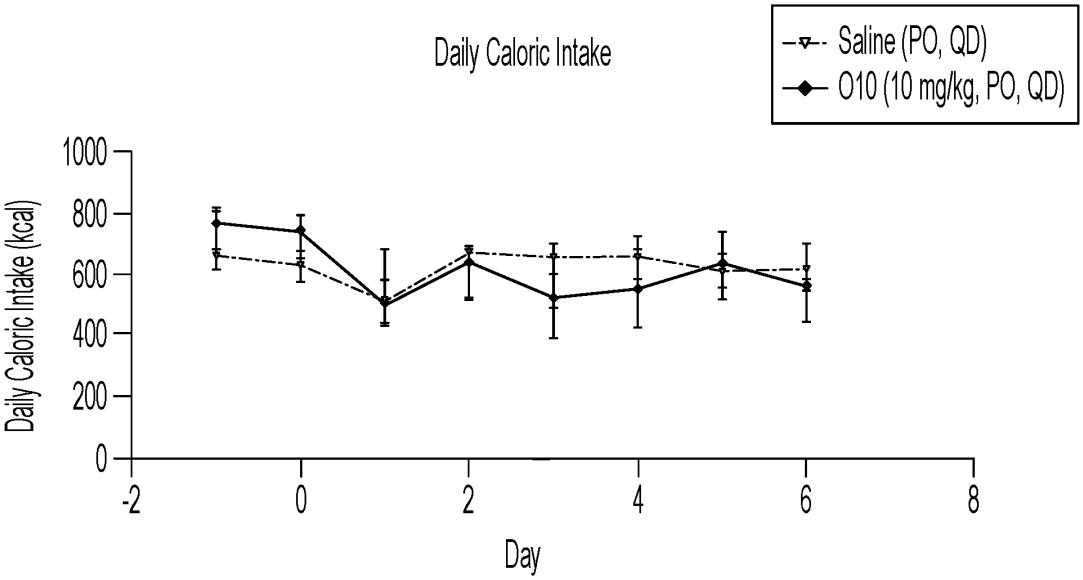


FIG. 10A

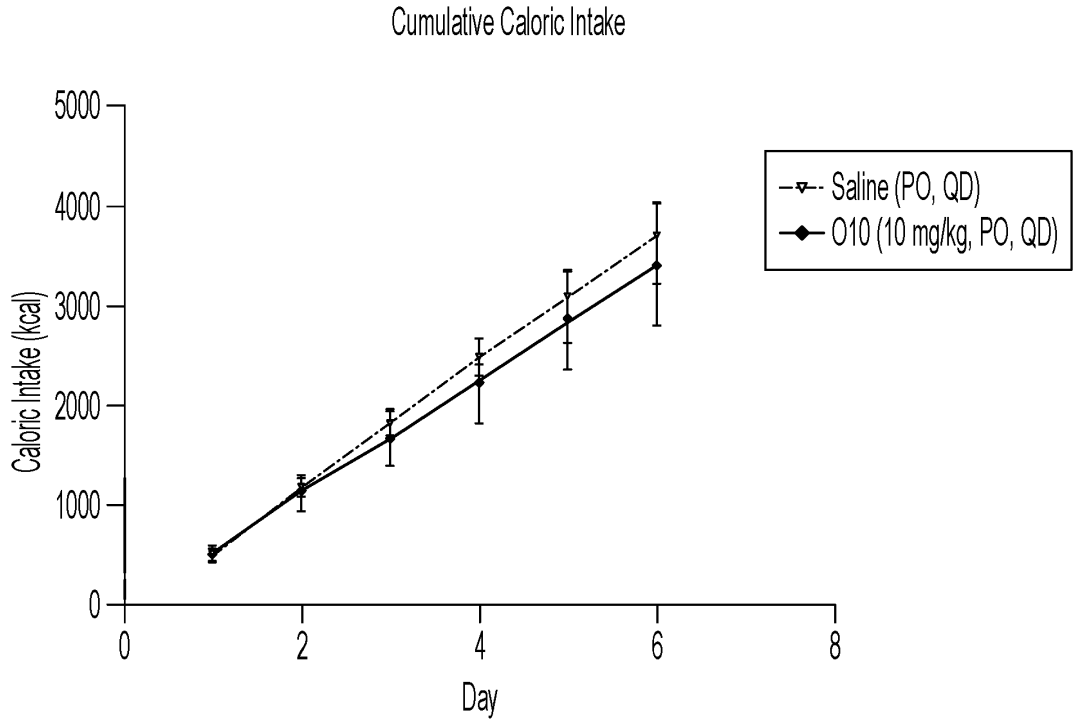


FIG. 10B

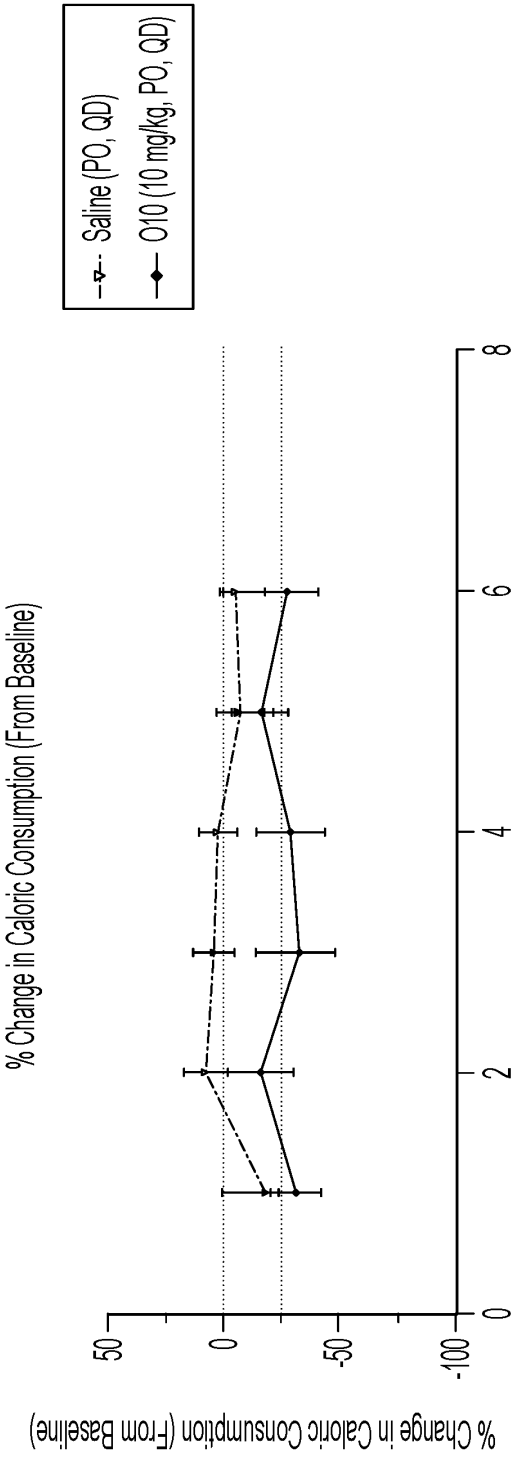

Saline (PO, QD)
O10 (10 mg/kg, PO, QD)
% Change in Caloric Consumption (From Baseline)
50
0
-50
-100
0
2
4
6
8
Day
% Change in Caloric Consumption (From Baseline)

FIG. 10C

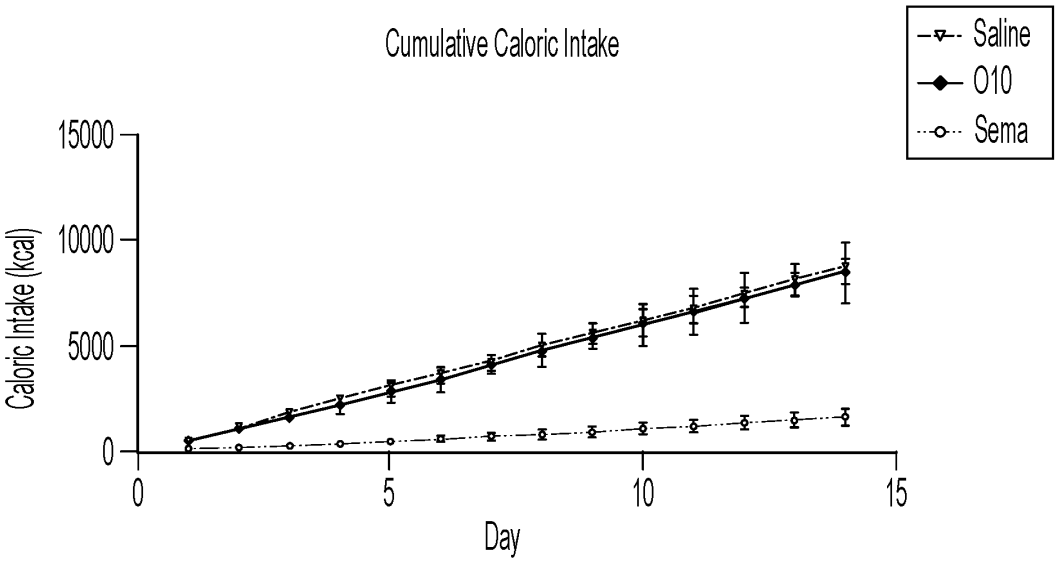


FIG. 11A

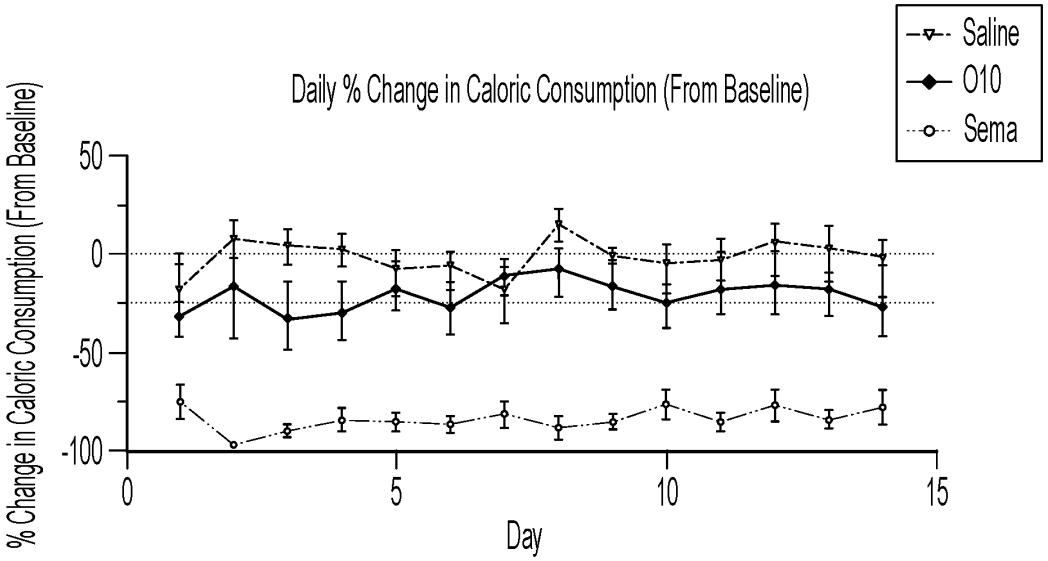


FIG. 11B

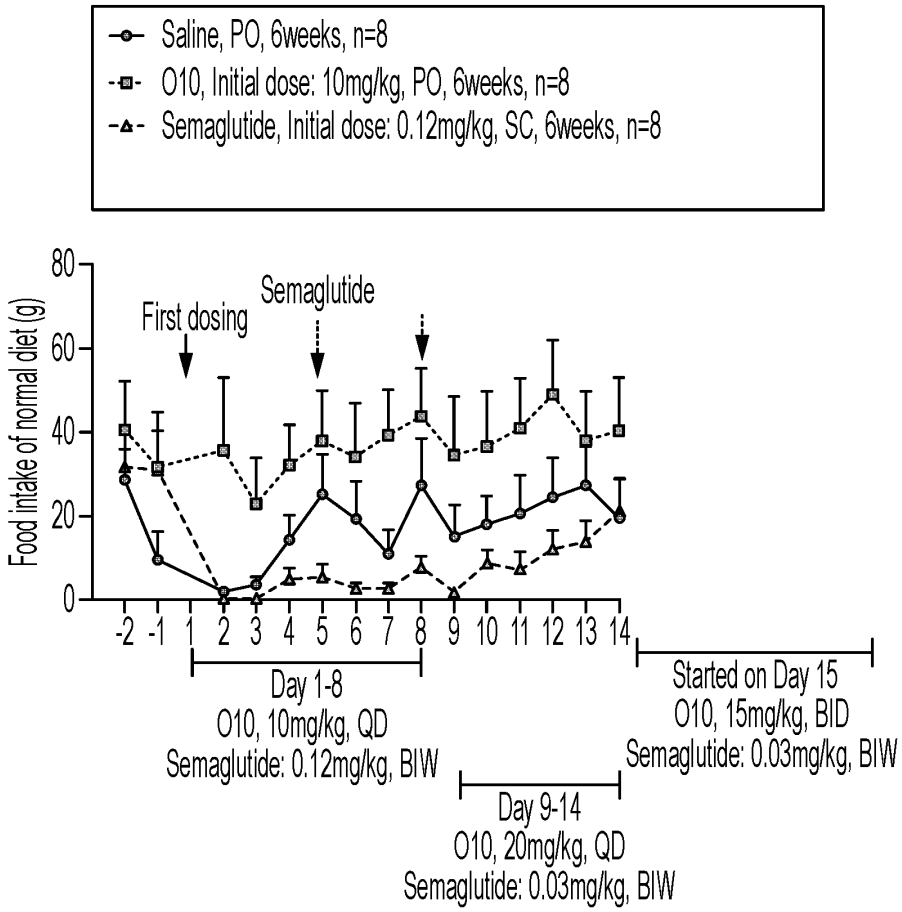

Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Food intake of normal diet (g)
0
20
40
60
80
First dosing
Semaglutide
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: 0.03mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW

FIG. 11C

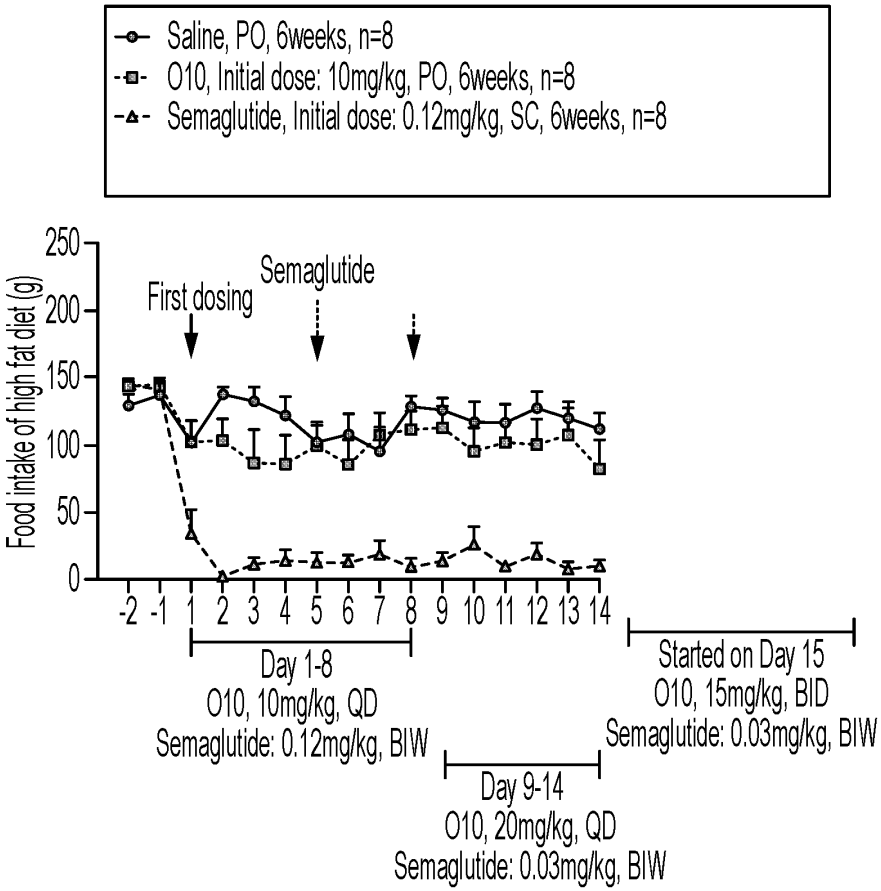

Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Food intake of high fat diet (g)
250
200
150
100
50
0
First dosing
Semaglutide
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: 0.03mg/kg, BIW

FIG. 11D

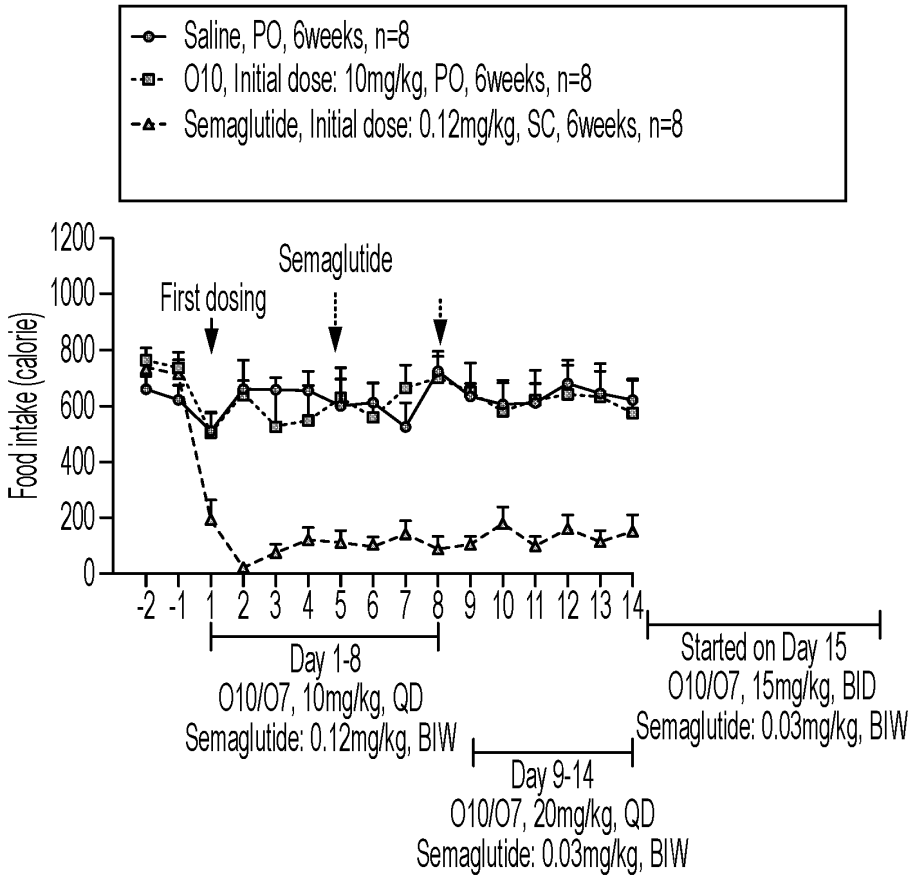

Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Food intake (calorie)
1200
1000
800
600
400
200
0
First dosing
Semaglutide
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Day 1-8
O10/O7, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10/O7, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10/O7, 15mg/kg, BID
Semaglutide: 0.03mg/kg, BIW

FIG. 11E

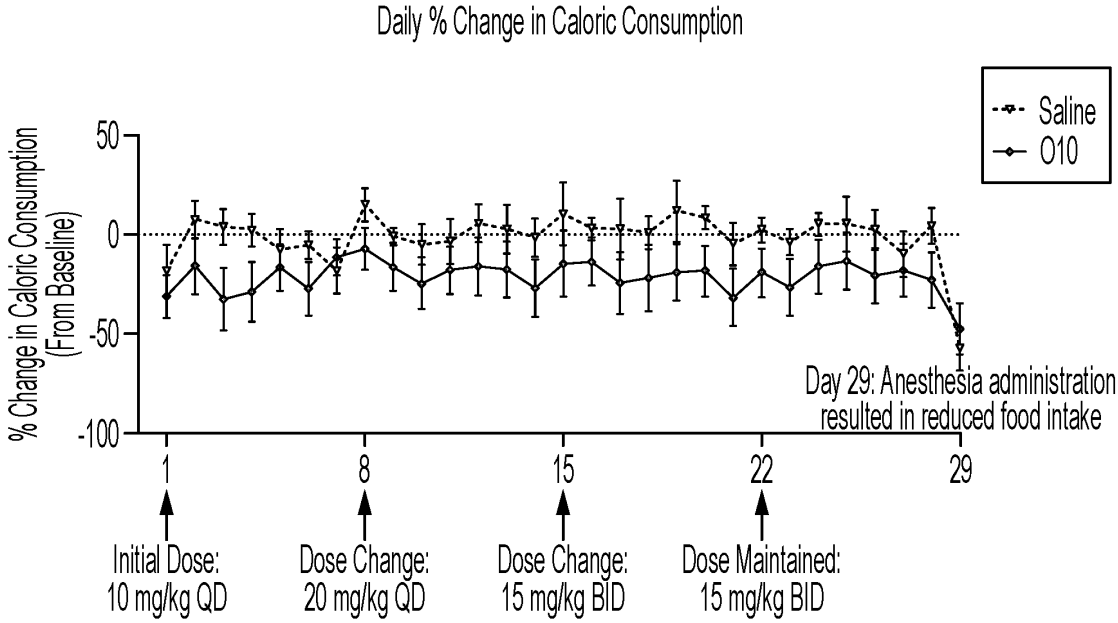

Daily % Change in Caloric Consumption
% Change in Caloric Consumption (From Baseline)
50
0
-50
-100
1
8
15
22
29
Saline
O10
Day 29: Anesthesia administration resulted in reduced food intake
Initial Dose: 10 mg/kg QD
Dose Change: 20 mg/kg QD
Dose Change: 15 mg/kg BID
Dose Maintained: 15 mg/kg BID

FIG. 11F

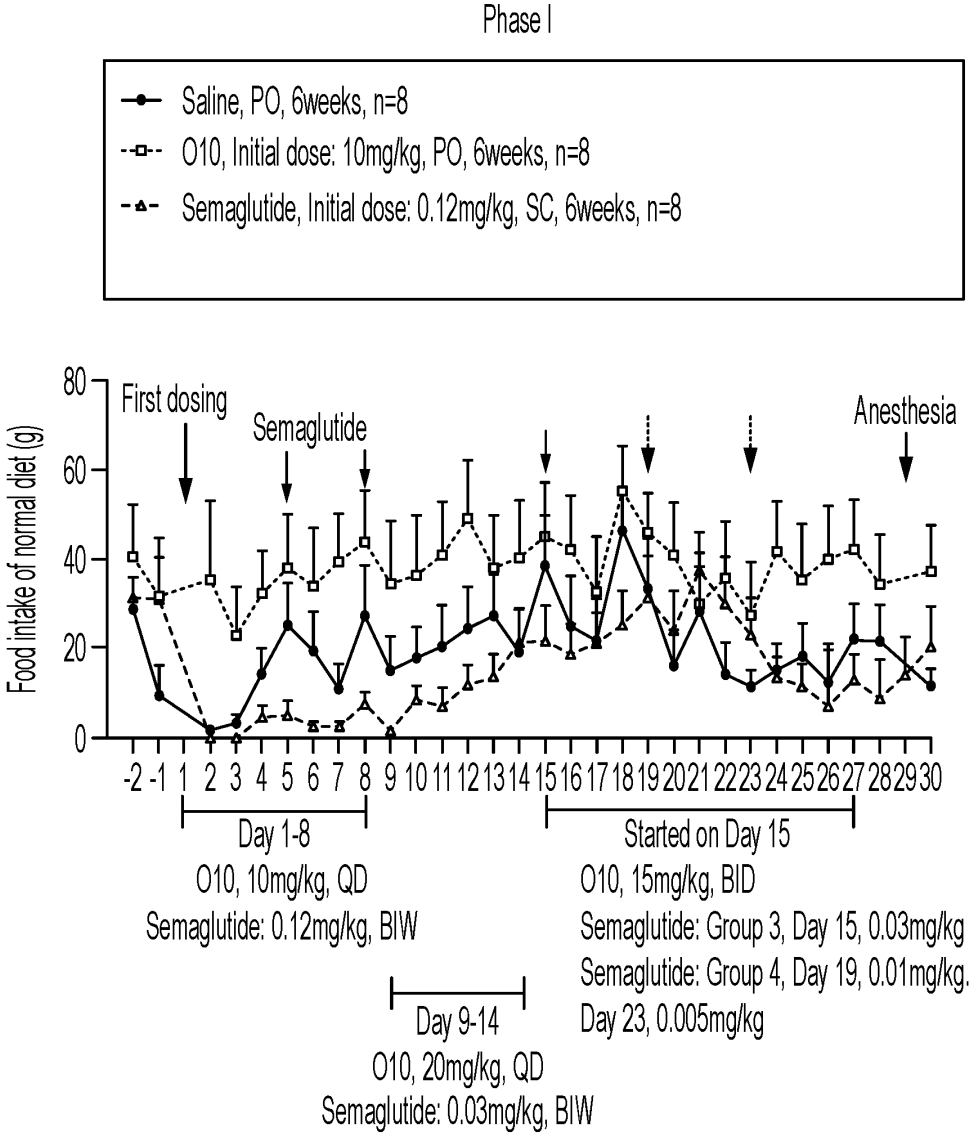

Phase I
Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Food intake of normal diet (g)
0
20
40
60
80
First dosing
Semaglutide
Anesthesia
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: Group 3, Day 15, 0.03mg/kg
Semaglutide: Group 4, Day 19, 0.01mg/kg.
Day 23, 0.005mg/kg

FIG. 11G

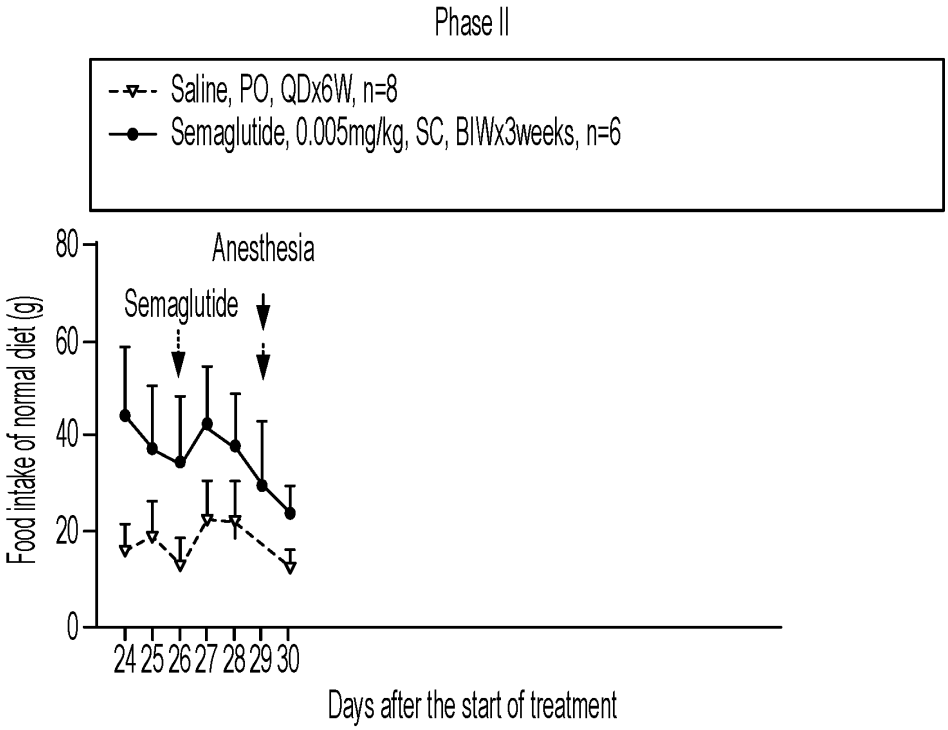

Phase II
Saline, PO, QDx6W, n=8
Semaglutide, 0.005mg/kg, SC, BIWx3weeks, n=6
Anesthesia
Semaglutide
Food intake of normal diet (g)
80
60
40
20
0
24 25 26 27 28 29 30
Days after the start of treatment

FIG. 11H

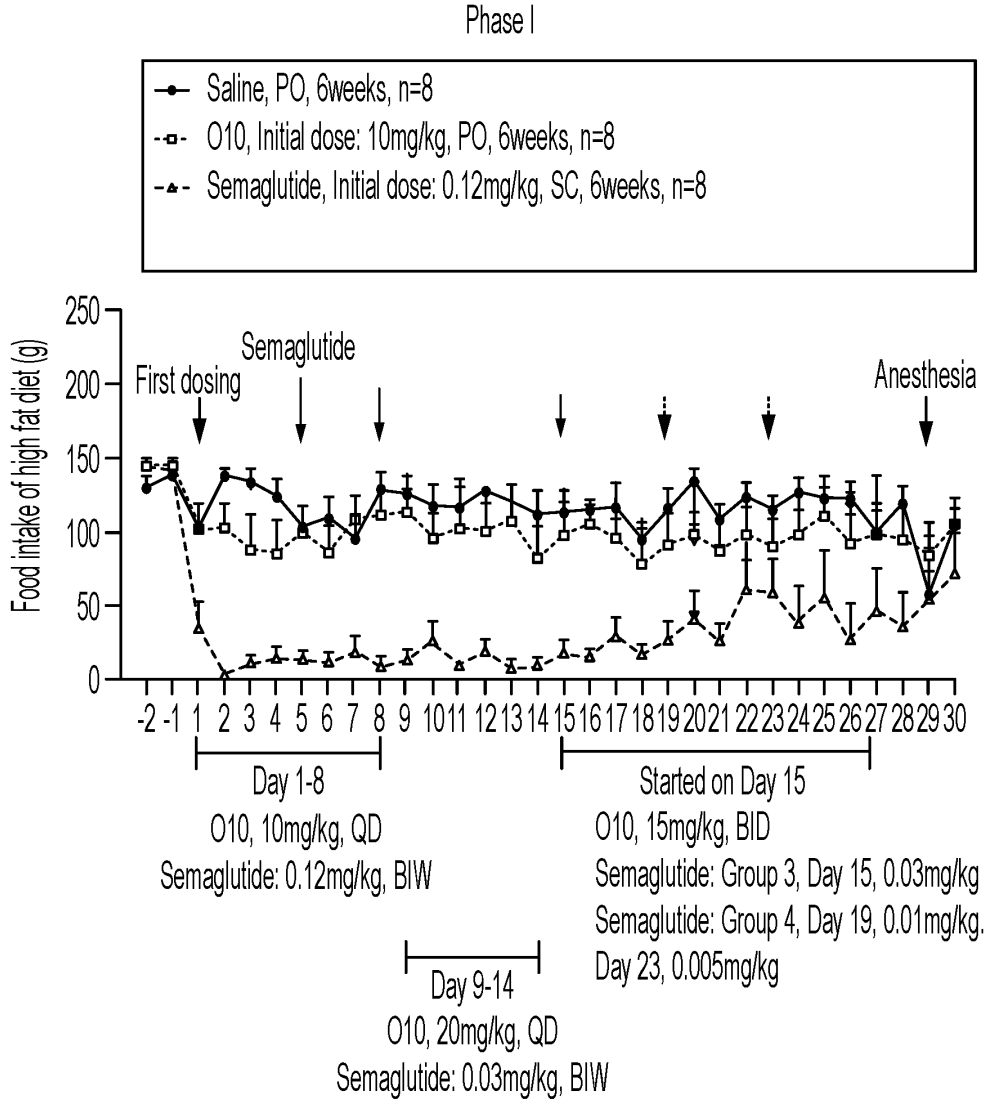

Phase I
Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Food intake of high fat diet (g)
250
200
150
100
50
0
First dosing
Semaglutide
Anesthesia
-2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: Group 3, Day 15, 0.03mg/kg
Semaglutide: Group 4, Day 19, 0.01mg/kg.
Day 23, 0.005mg/kg
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW

FIG. 11I

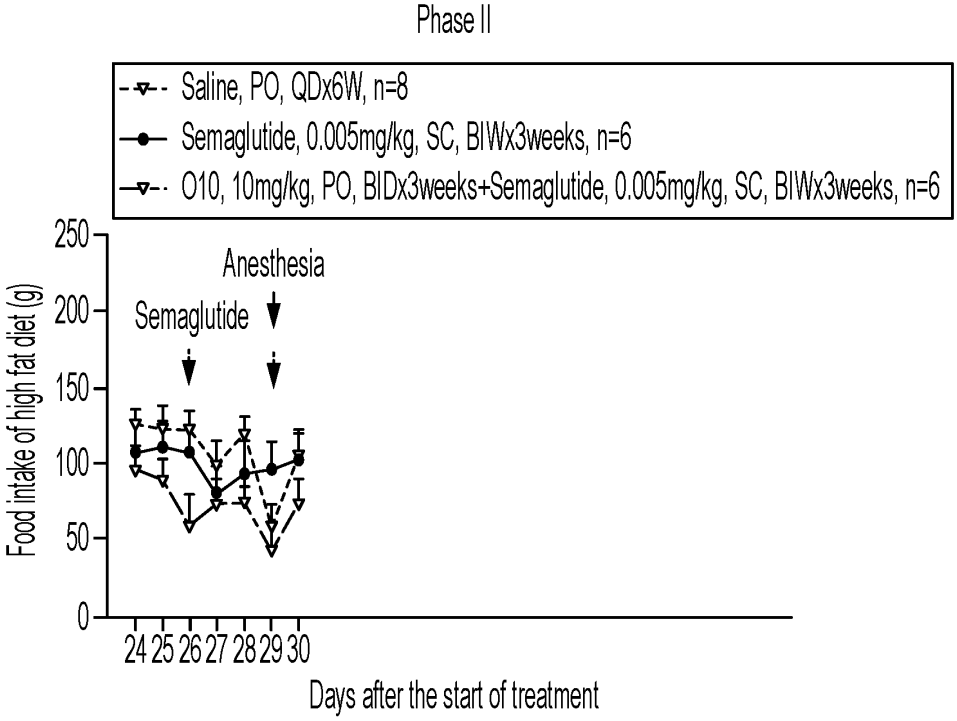

Phase II
Saline, PO, QDx6W, n=8
Semaglutide, 0.005mg/kg, SC, BIWx3weeks, n=6
O10, 10mg/kg, PO, BIDx3weeks+Semaglutide, 0.005mg/kg, SC, BIWx3weeks, n=6
Anesthesia
Semaglutide
Food intake of high fat diet (g)
250
200
150
100
50
0
24 25 26 27 28 29 30
Days after the start of treatment

FIG. 11J

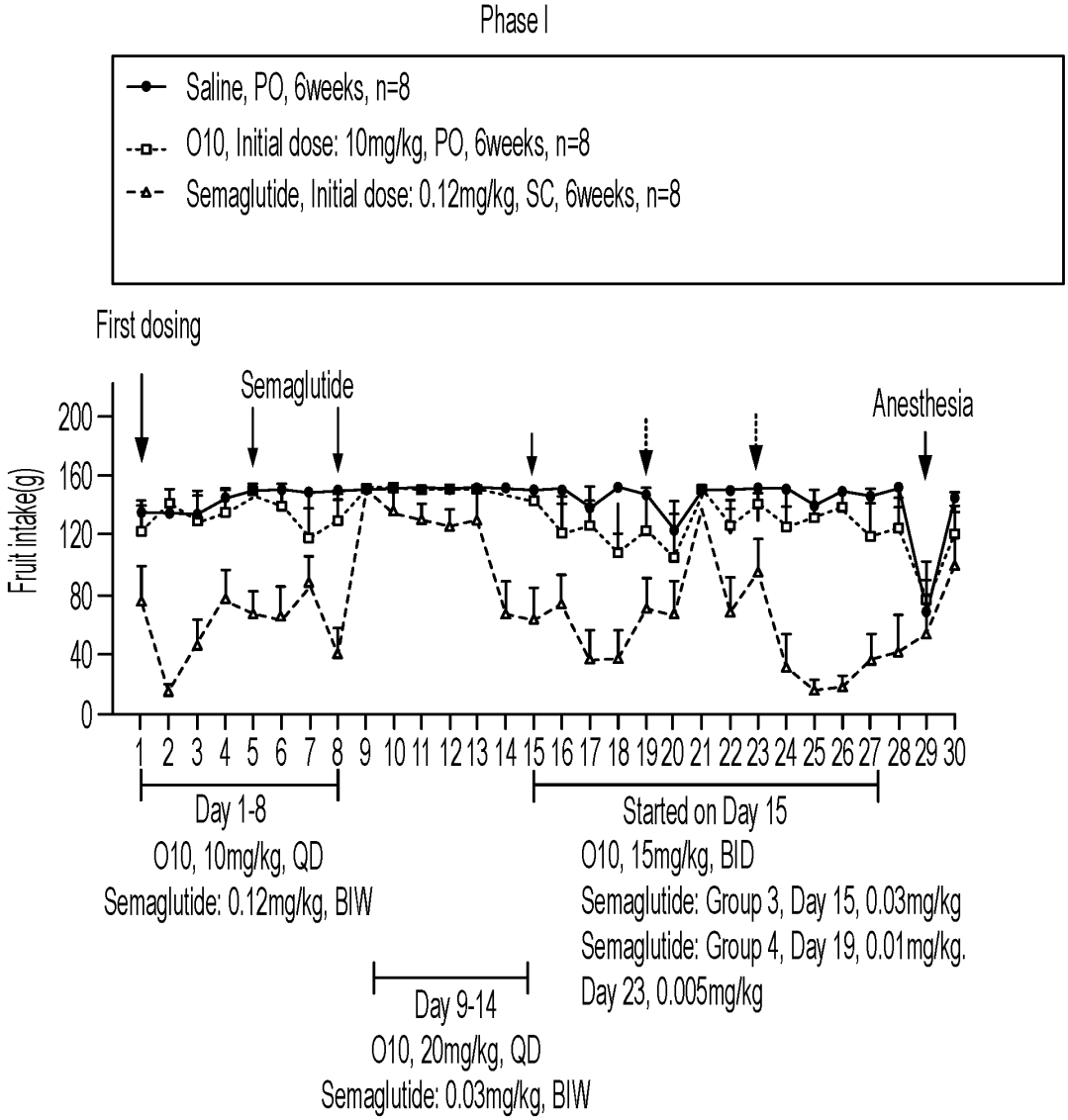

Phase I
Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
First dosing
Semaglutide
Anesthesia
Fruit intake(g)
200
160
120
80
40
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: Group 3, Day 15, 0.03mg/kg
Semaglutide: Group 4, Day 19, 0.01mg/kg.
Day 23, 0.005mg/kg

FIG. 11K

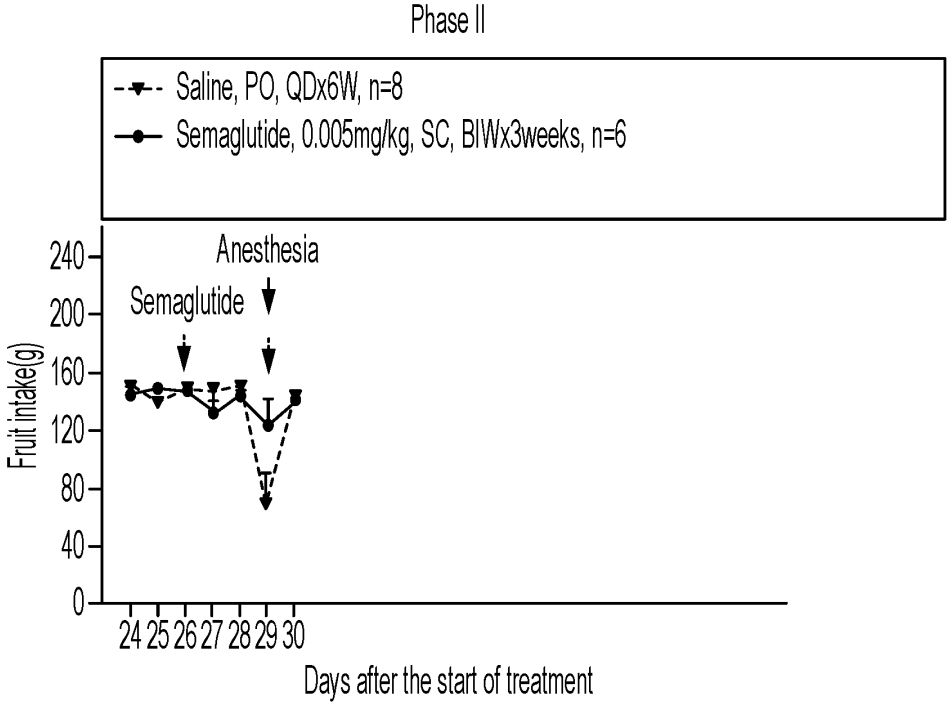

Phase II
Saline, PO, QDx6W, n=8
Semaglutide, 0.005mg/kg, SC, BIWx3weeks, n=6
Anesthesia
Semaglutide
Fruit intake(g)
240
200
160
120
80
40
0
24 25 26 27 28 29 30
Days after the start of treatment

FIG. 11L

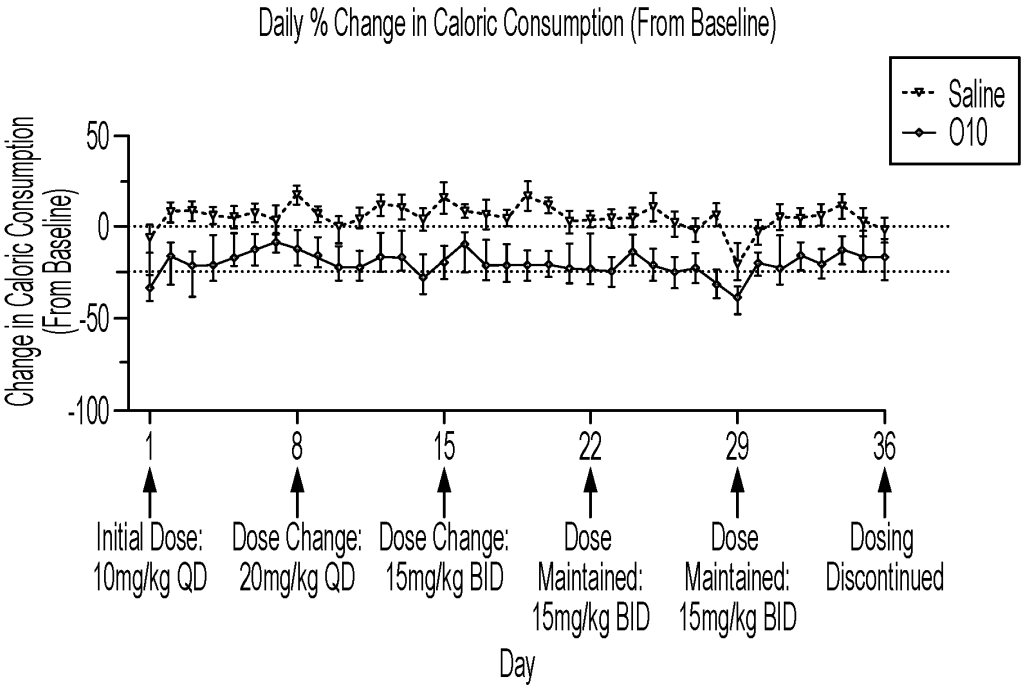


FIG. 11M

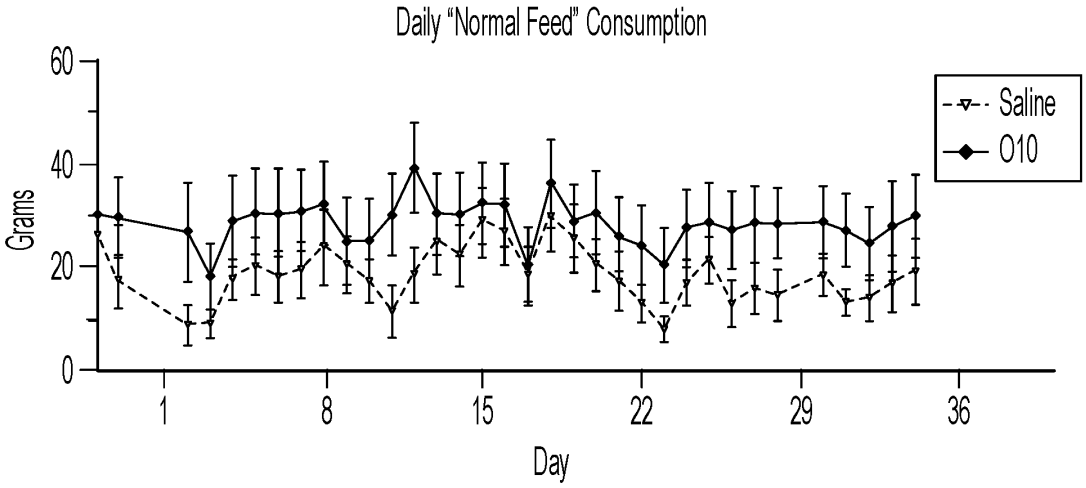


FIG. 11N

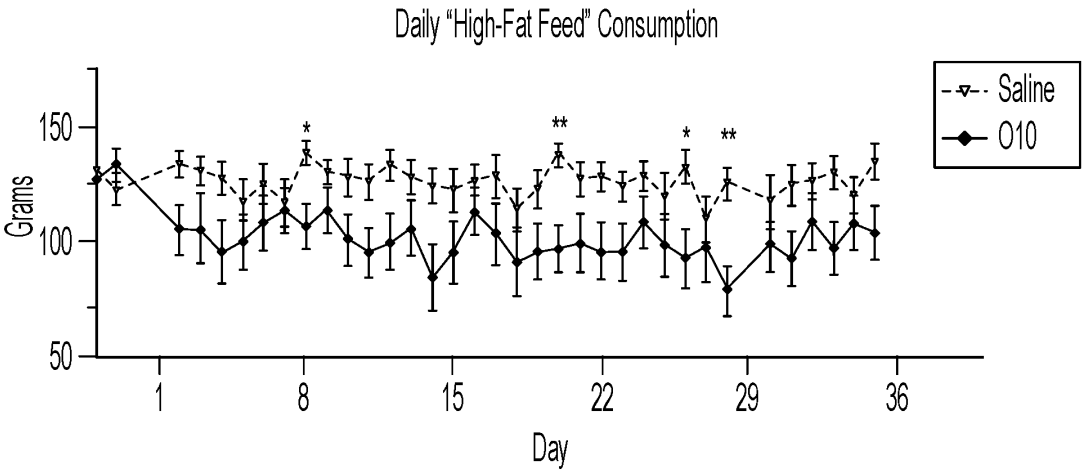


FIG. 11O

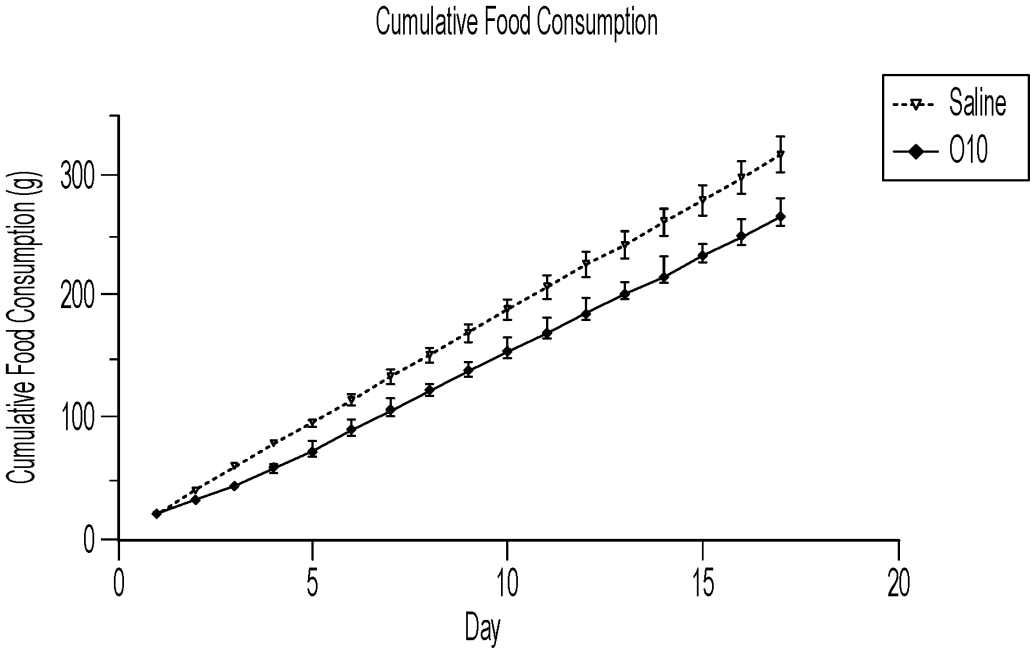


FIG. 11P

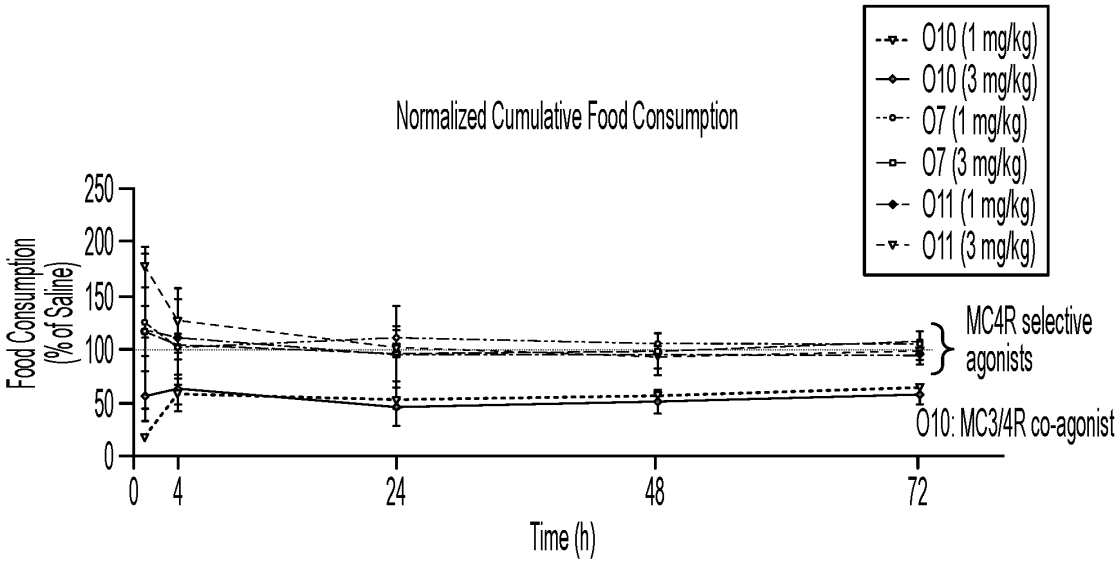


FIG. 11Q

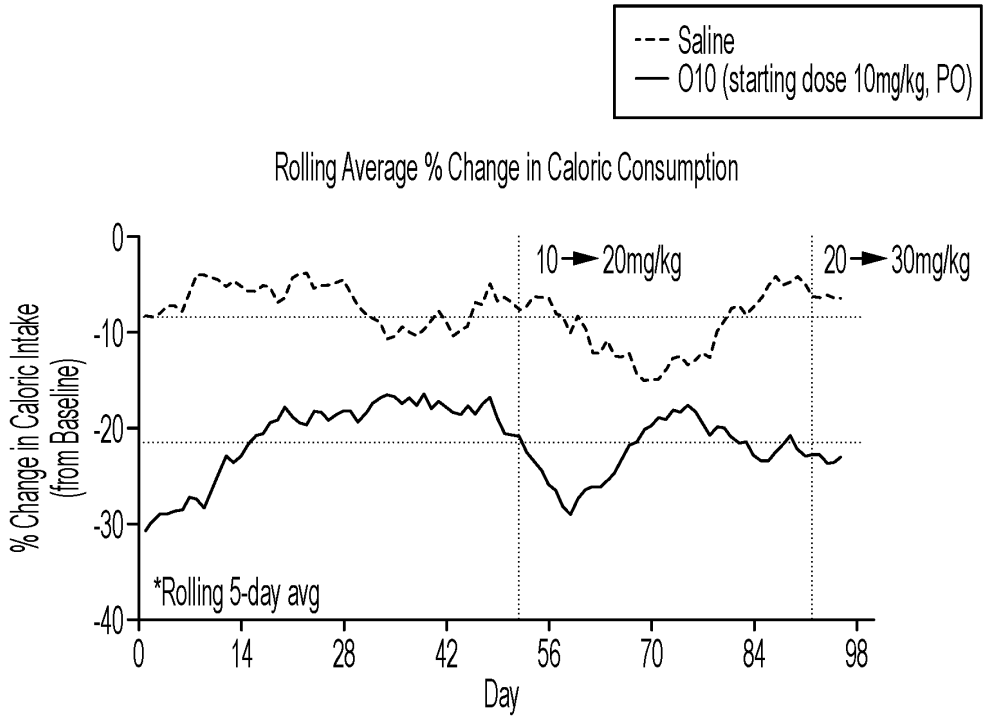


FIG. 11R

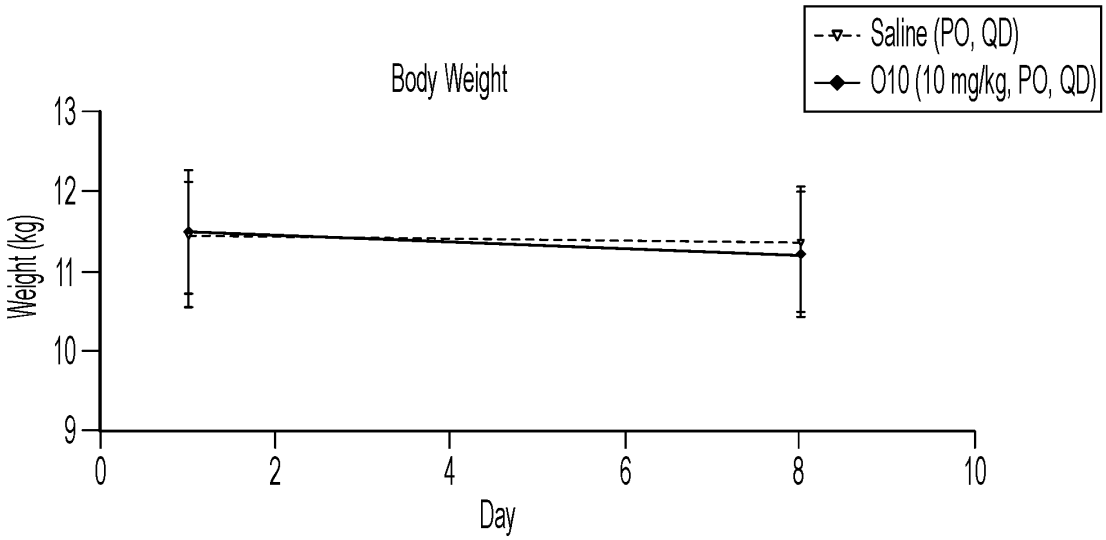


FIG. 12A

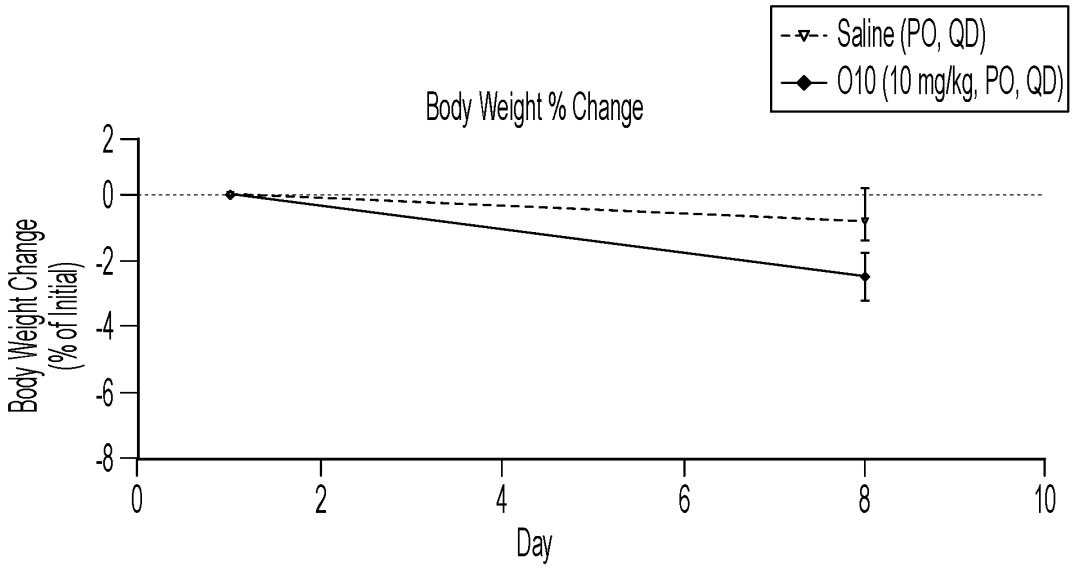


FIG. 12B

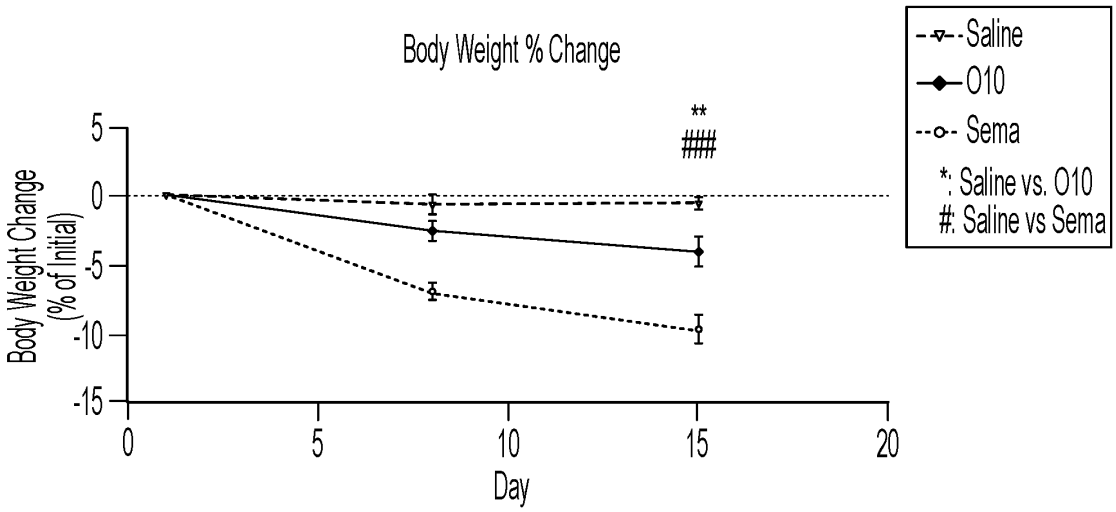


FIG. 12C

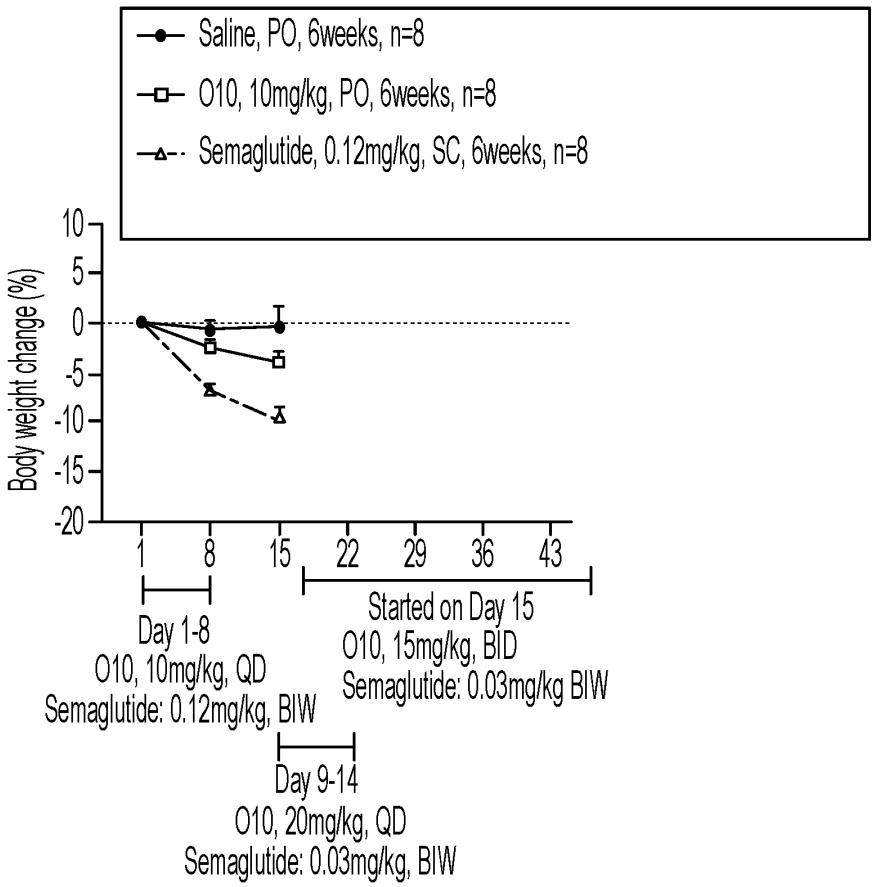


FIG. 12D

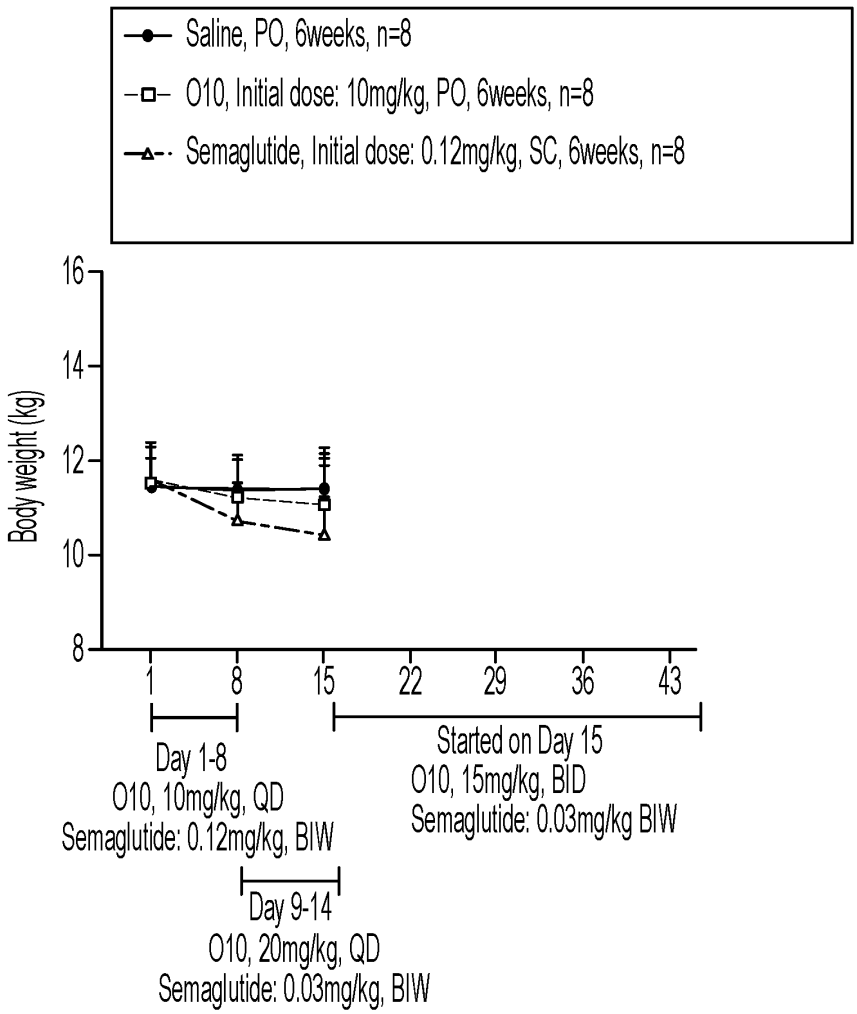

Saline, PO, 6weeks, n=8
O10, Initial dose: 10mg/kg, PO, 6weeks, n=8
Semaglutide, Initial dose: 0.12mg/kg, SC, 6weeks, n=8
Body weight (kg)
16
14
12
10
8
1
8
15
22
29
36
43
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: 0.03mg/kg BIW

FIG. 12E

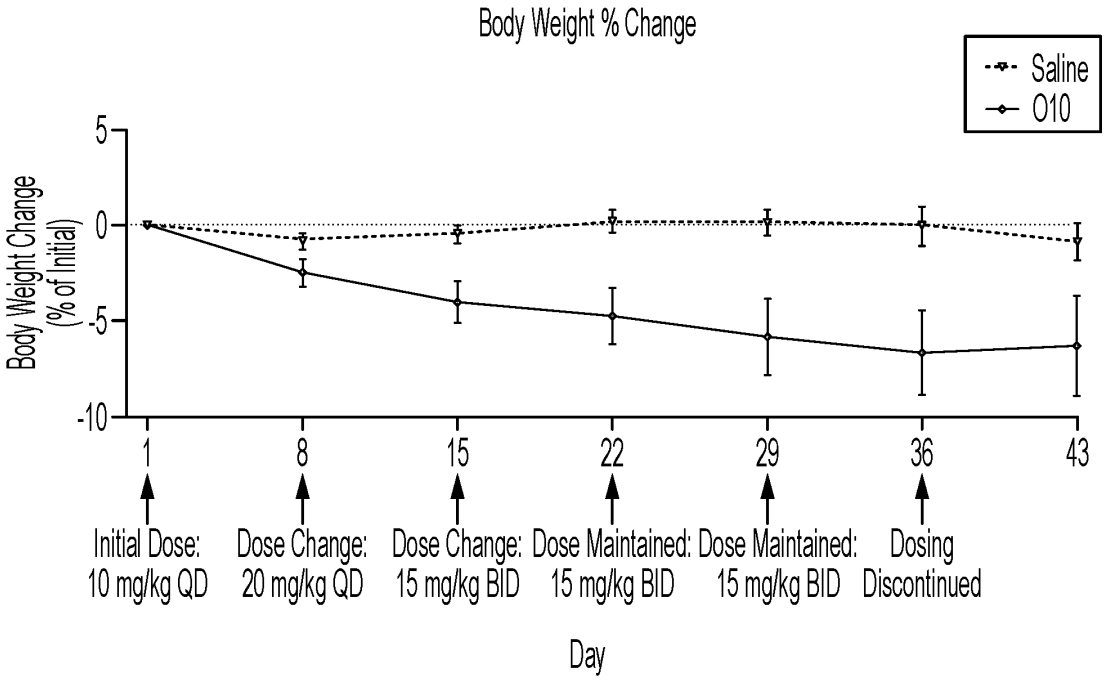

Body Weight % Change
Saline
O10
Body Weight Change (% of Initial)
5
0
-5
-10
1
8
15
22
29
36
43
Initial Dose: 10 mg/kg QD
Dose Change: 20 mg/kg QD
Dose Change: 15 mg/kg BID
Dose Maintained: 15 mg/kg BID
Dose Maintained: 15 mg/kg BID
Dosing Discontinued
Day

FIG. 12F

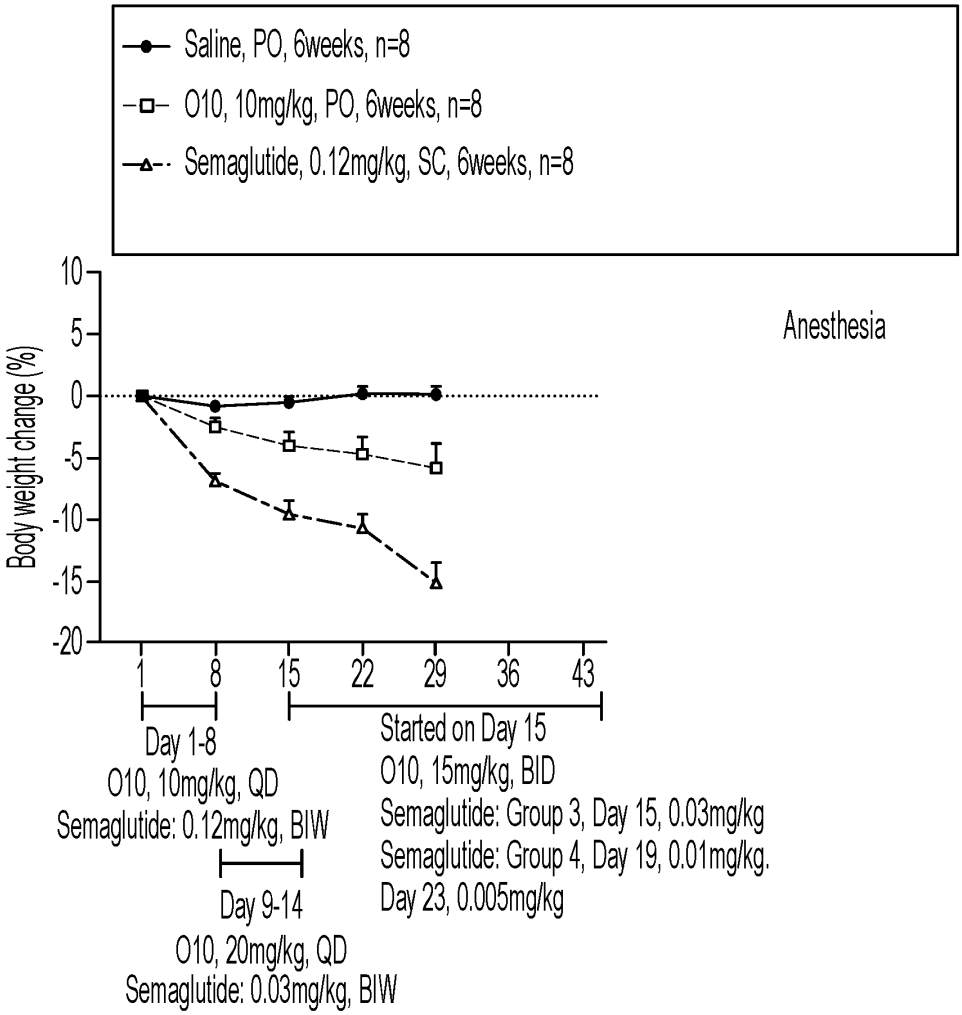

Saline, PO, 6weeks, n=8
O10, 10mg/kg, PO, 6weeks, n=8
Semaglutide, 0.12mg/kg, SC, 6weeks, n=8
Body weight change (%)
10
5
0
-5
-10
-15
-20
1
8
15
22
29
36
43
Anesthesia
Day 1-8
O10, 10mg/kg, QD
Semaglutide: 0.12mg/kg, BIW
Day 9-14
O10, 20mg/kg, QD
Semaglutide: 0.03mg/kg, BIW
Started on Day 15
O10, 15mg/kg, BID
Semaglutide: Group 3, Day 15, 0.03mg/kg
Semaglutide: Group 4, Day 19, 0.01mg/kg.
Day 23, 0.005mg/kg

FIG. 12G

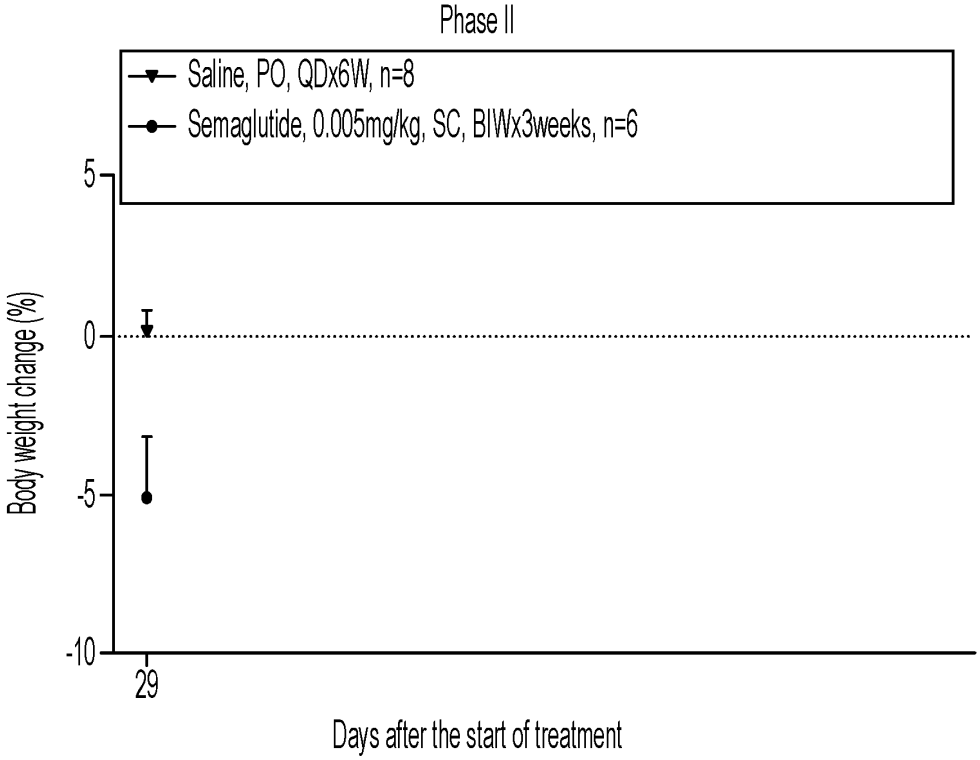

Phase II
Saline, PO, QDx6W, n=8
Semaglutide, 0.005mg/kg, SC, BIWx3weeks, n=6
5
0
-5
-10
Body weight change (%)
29
Days after the start of treatment

FIG. 12H

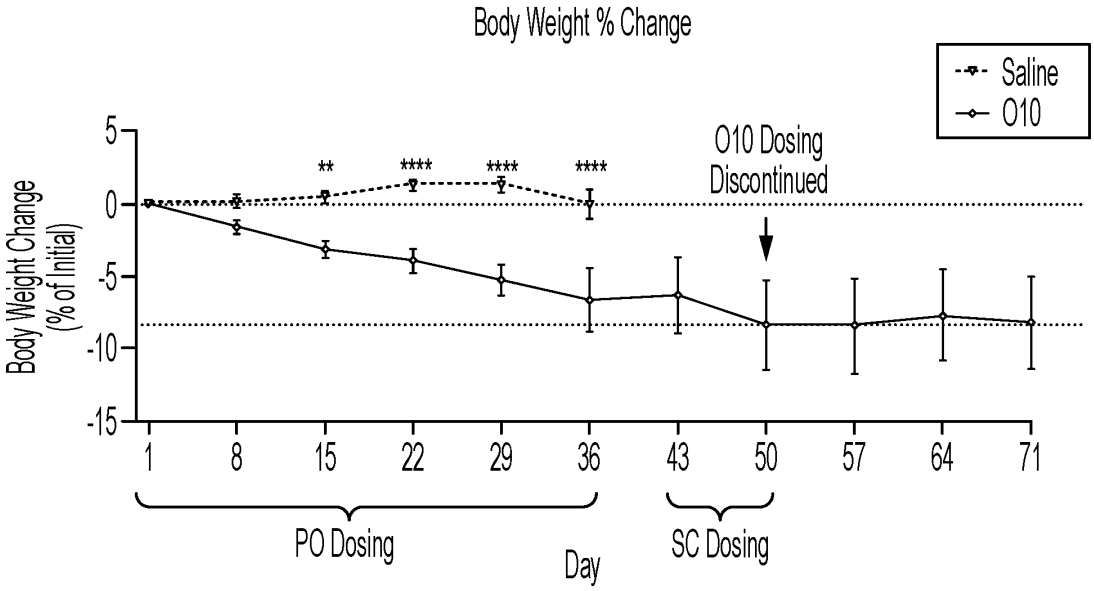


FIG. 12I

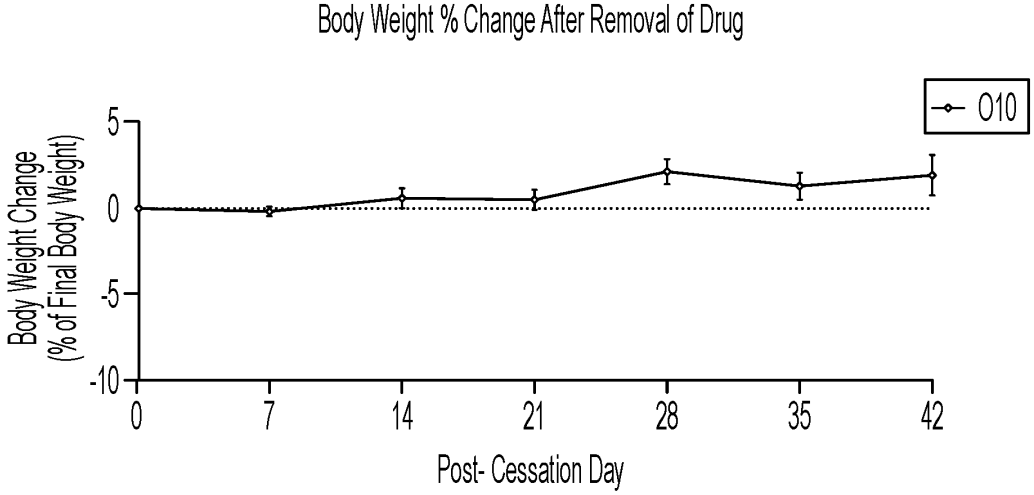


FIG. 12J

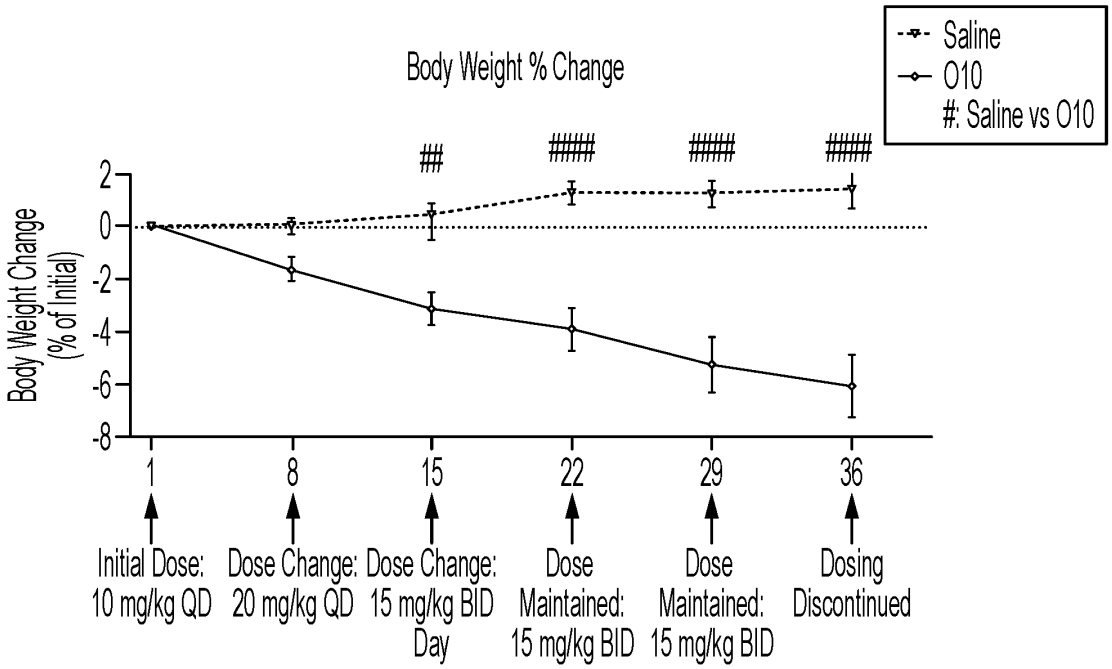

Body Weight % Change
Saline
O10
#: Saline vs O10
Body Weight Change (% of Initial)
2
0
-2
-4
-6
-8
##
####
####
####
1
8
15
22
29
36
Initial Dose: 10 mg/kg QD
Dose Change: 20 mg/kg QD
Dose Change: 15 mg/kg BID Day
Dose Maintained: 15 mg/kg BID
Dose Maintained: 15 mg/kg BID
Dosing Discontinued

FIG. 12K

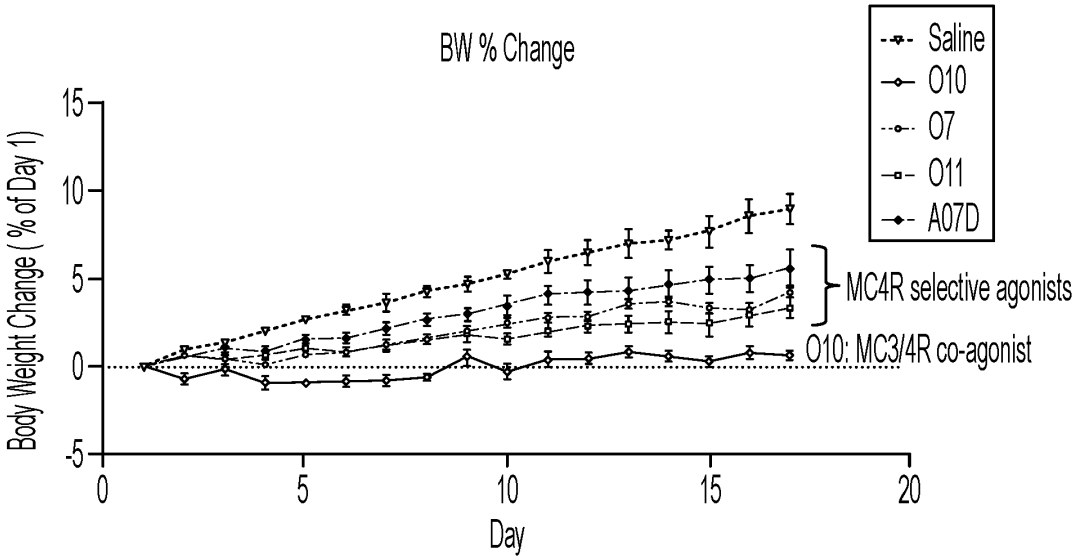


FIG. 12L

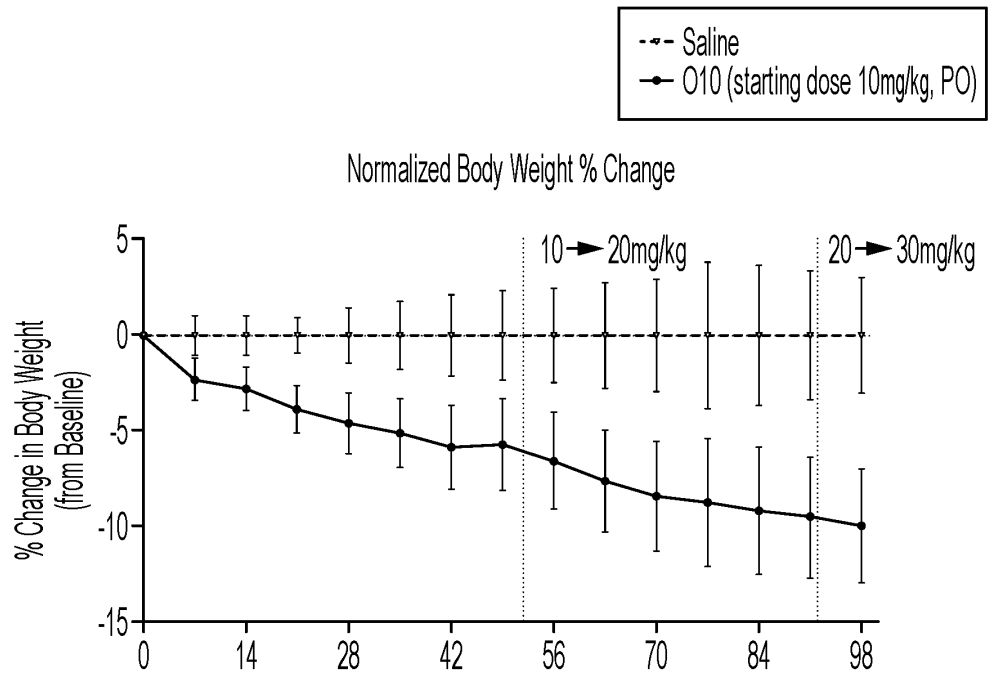


FIG. 12M

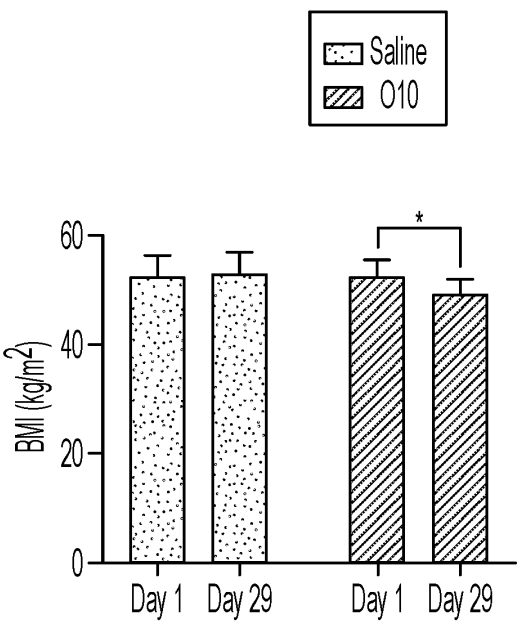


FIG. 13A

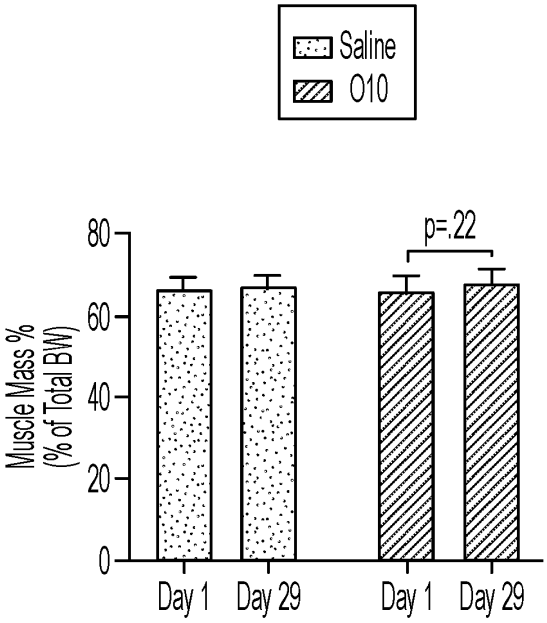


FIG. 13B

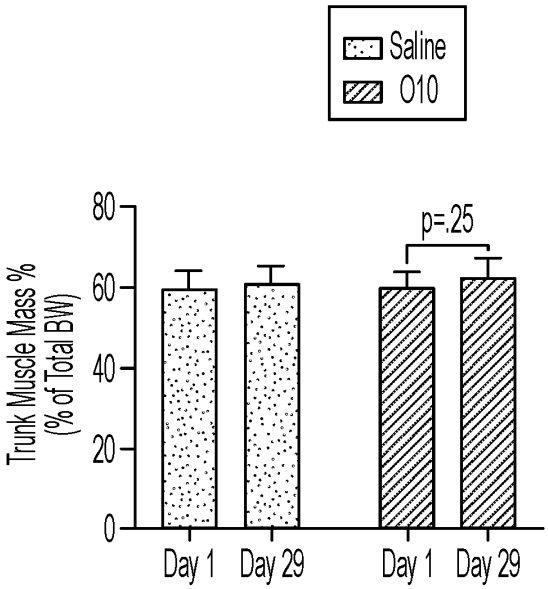


FIG. 13C

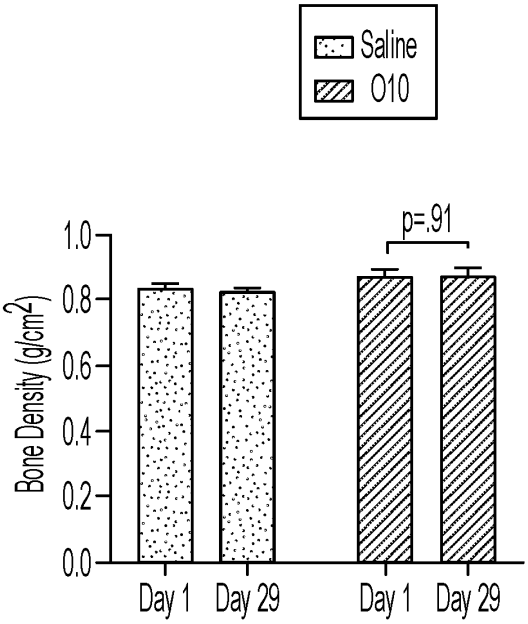


FIG. 13D

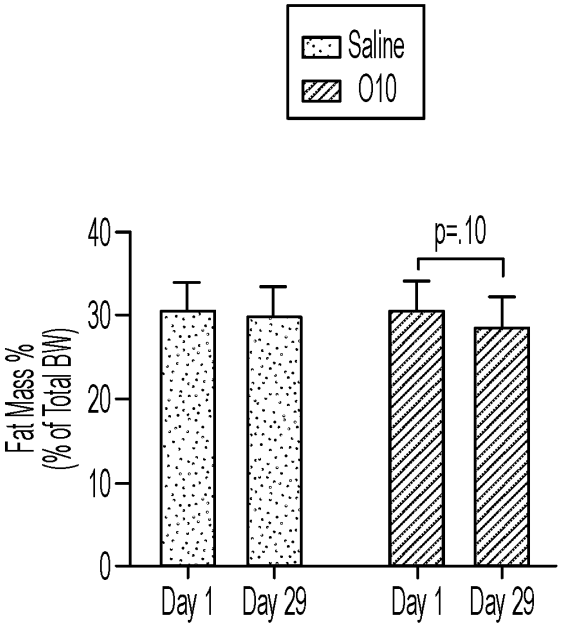


FIG. 13E

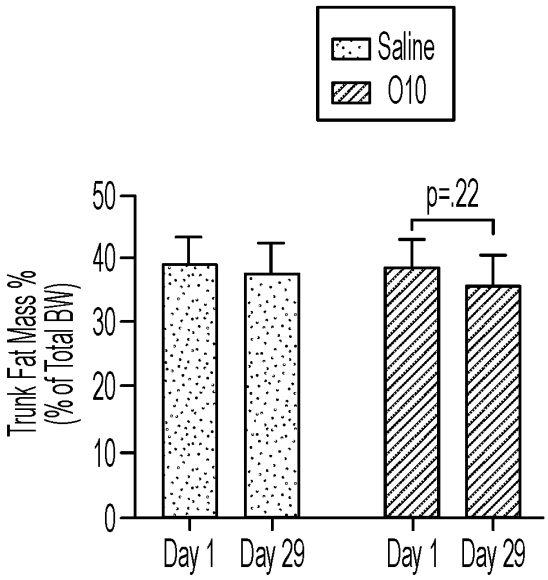


FIG. 13F

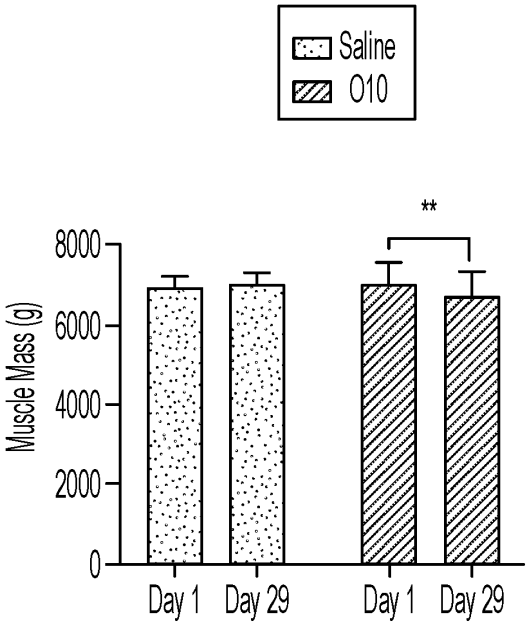


FIG. 13G

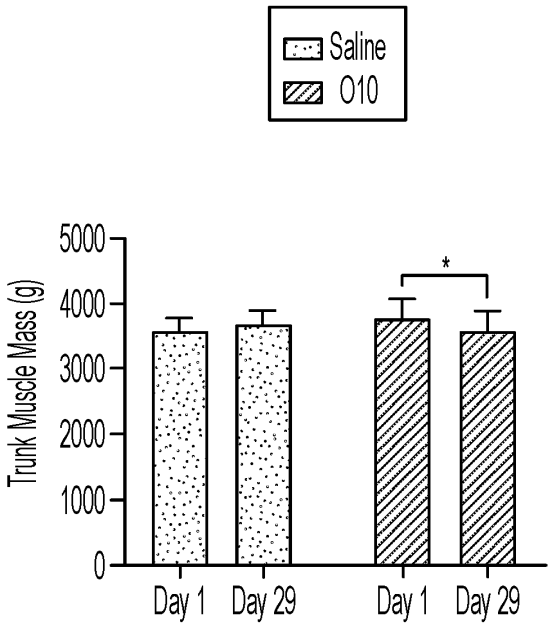


FIG. 13H

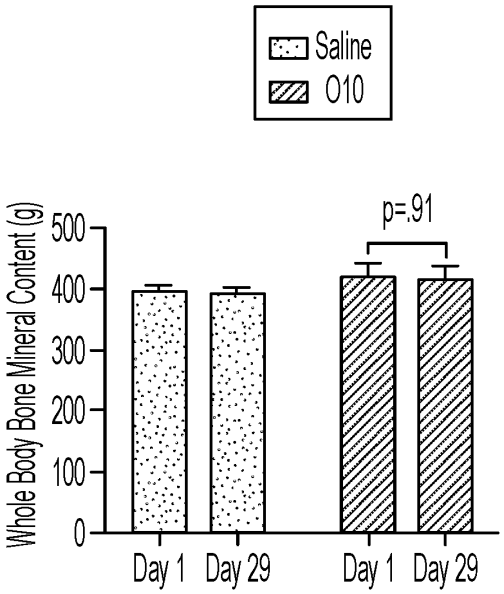


FIG. 13I

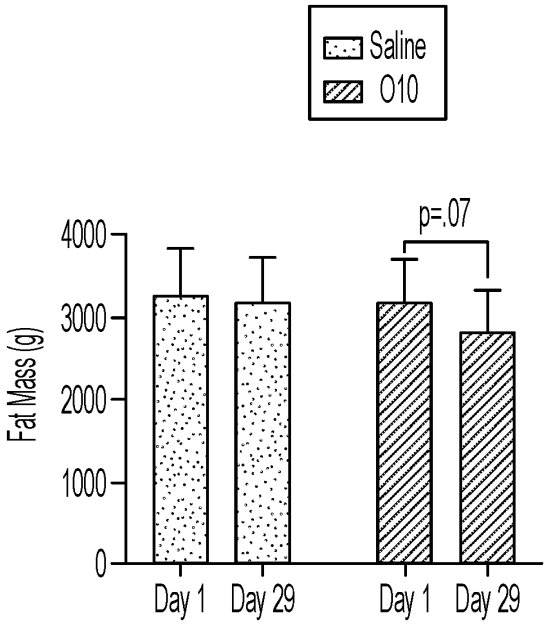


FIG. 13J

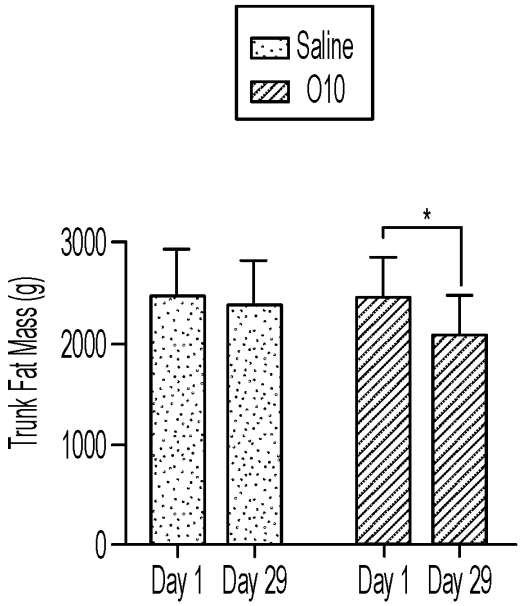


FIG. 13K

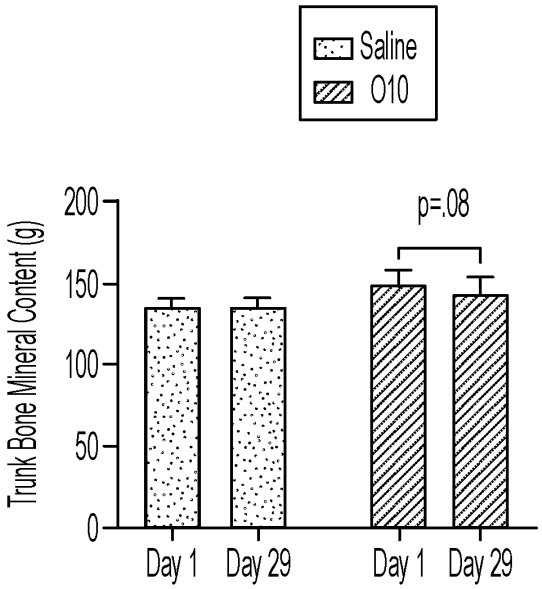


FIG. 13L

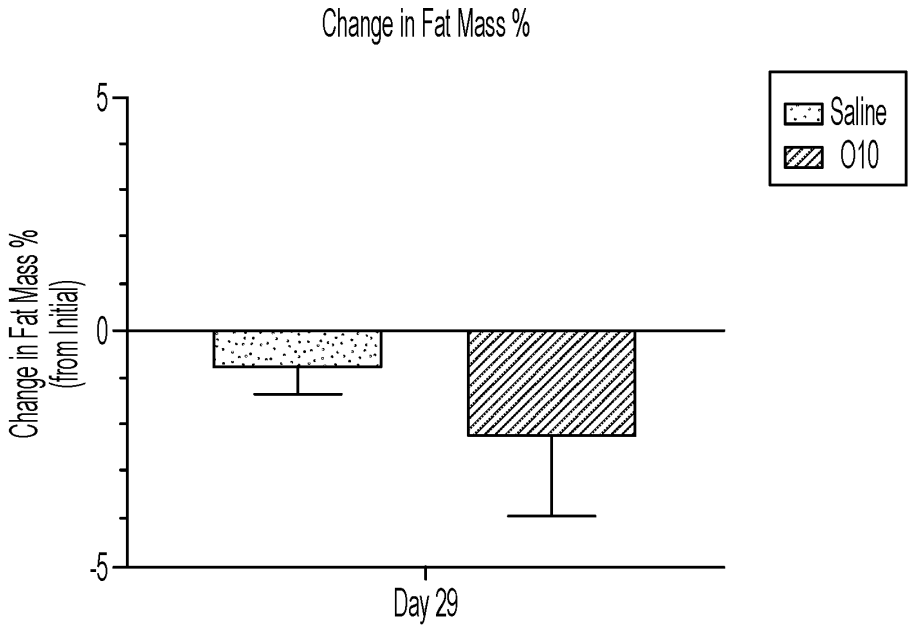


FIG. 13M

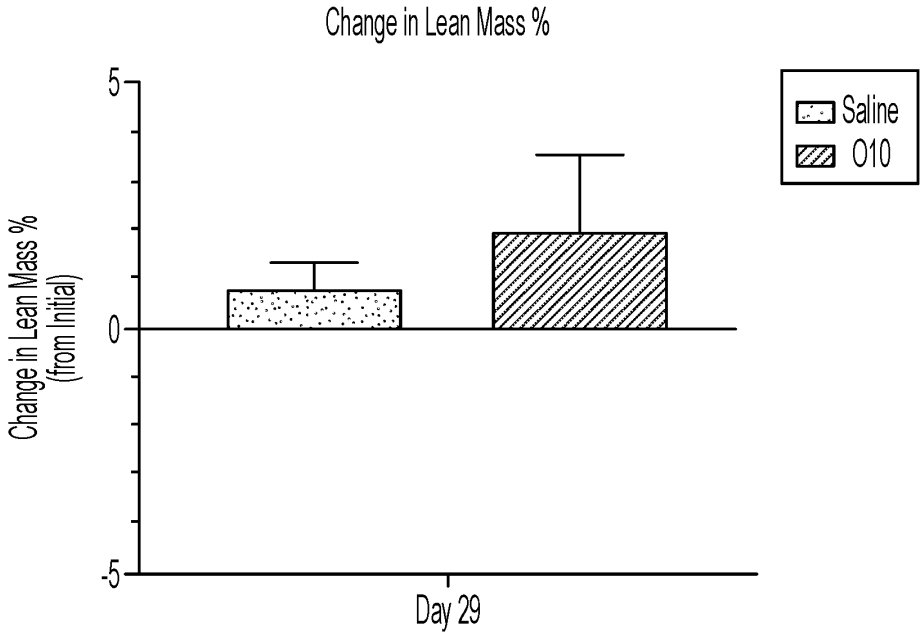


FIG. 13N

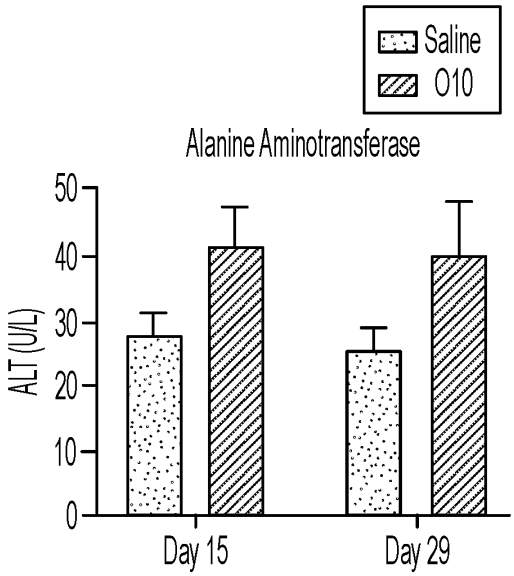


FIG. 14A

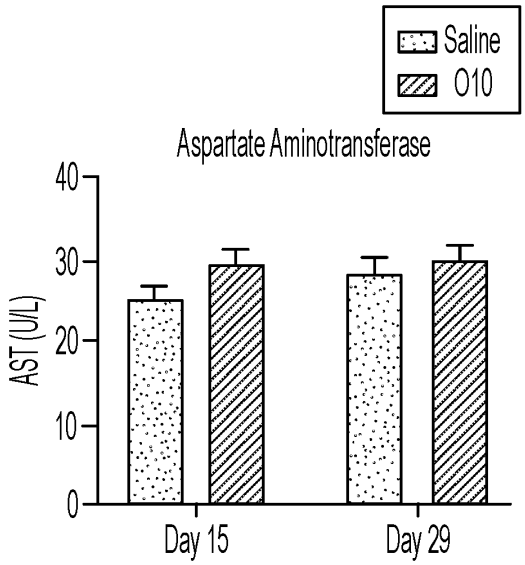


FIG. 14B

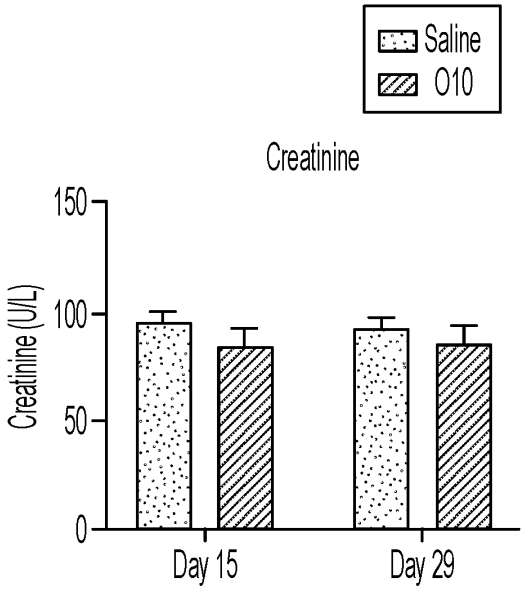


FIG. 14C

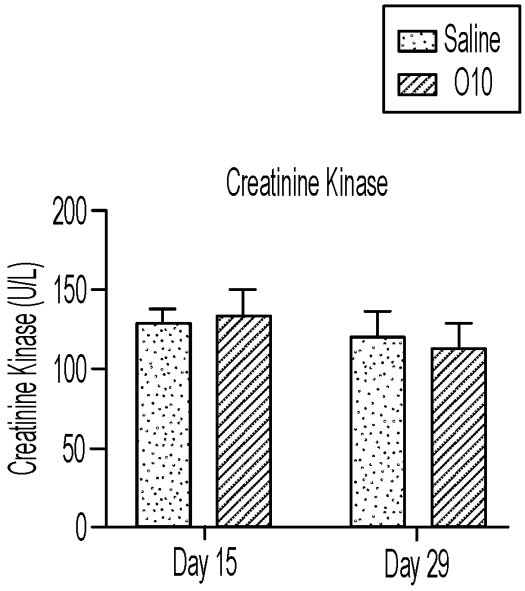


FIG. 14D

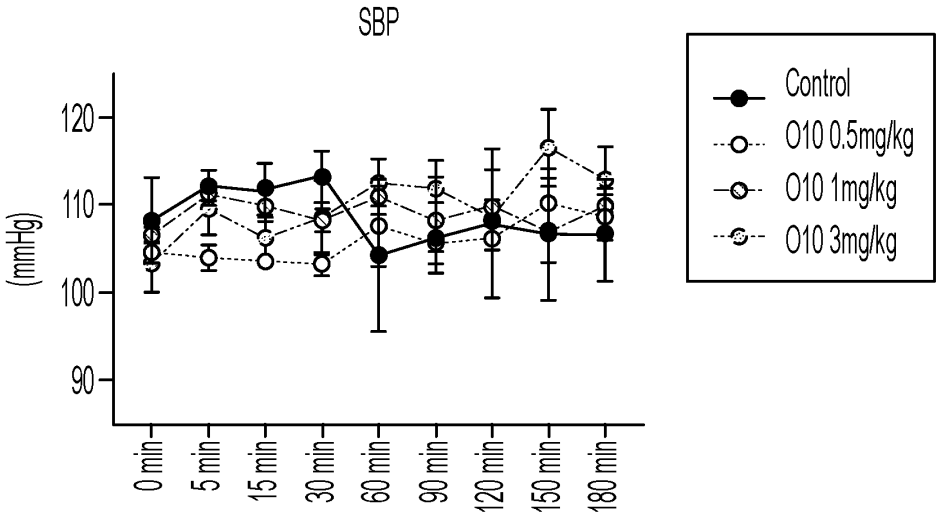


FIG. 15A

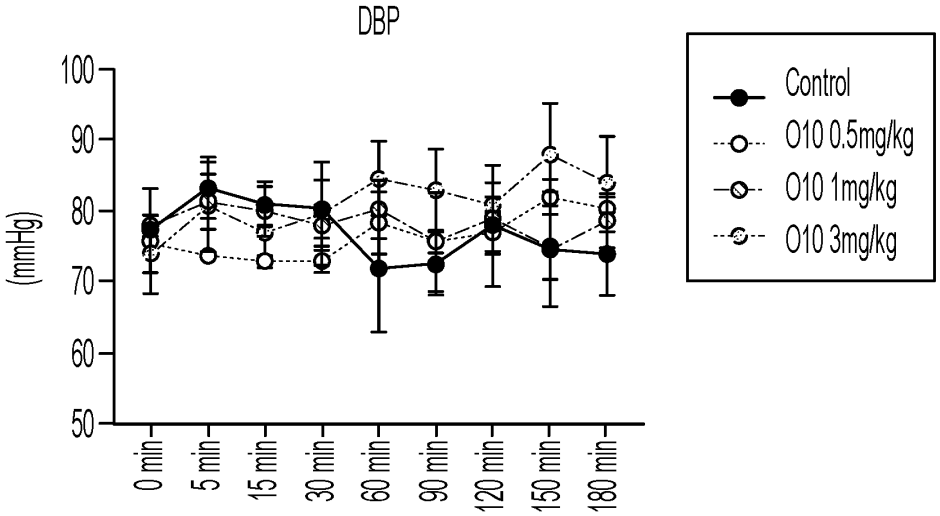


FIG. 15B

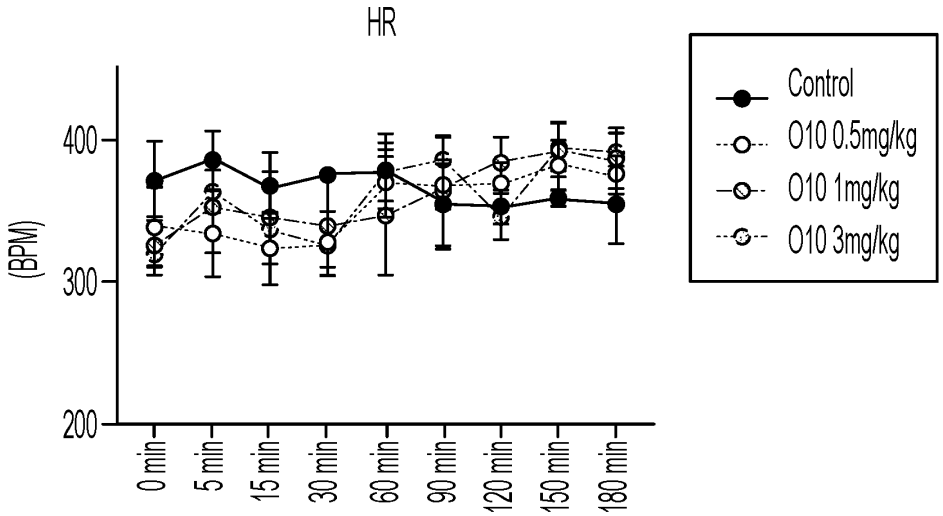

HR
(BPM)
400
300
200
0 min
5 min
15 min
30 min
60 min
90 min
120 min
150 min
180 min
Control
O10 0.5mg/kg
O10 1mg/kg
O10 3mg/kg

FIG. 15C

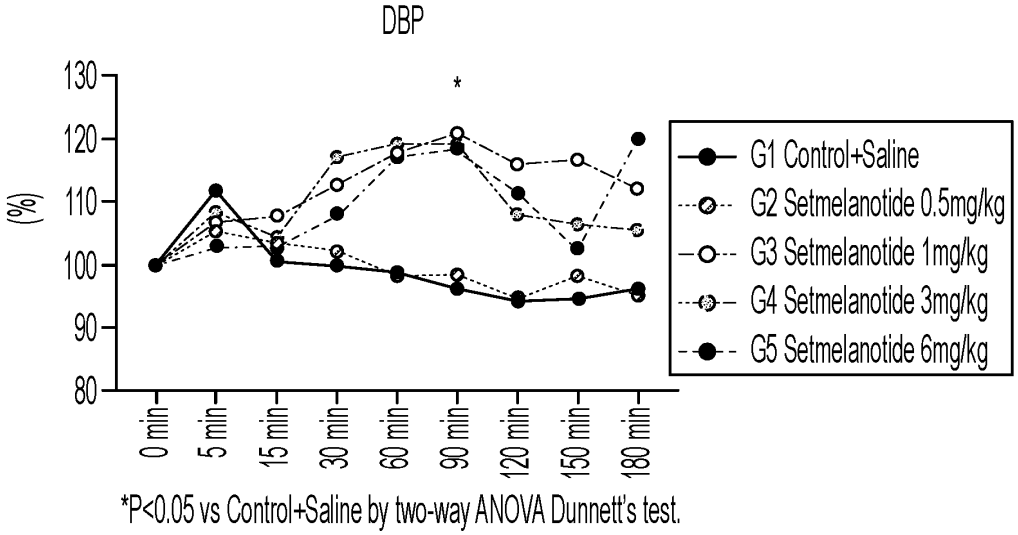


FIG. 16A

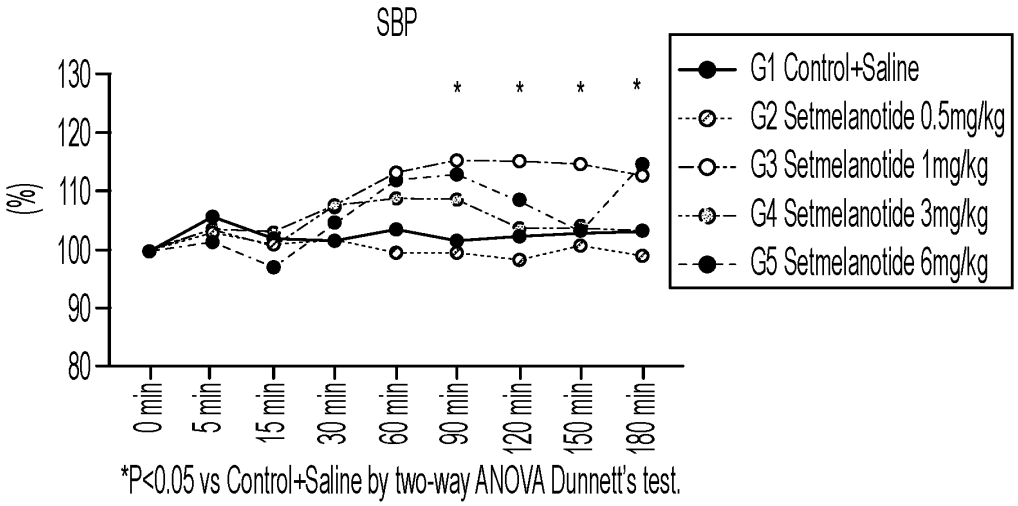


FIG. 16B

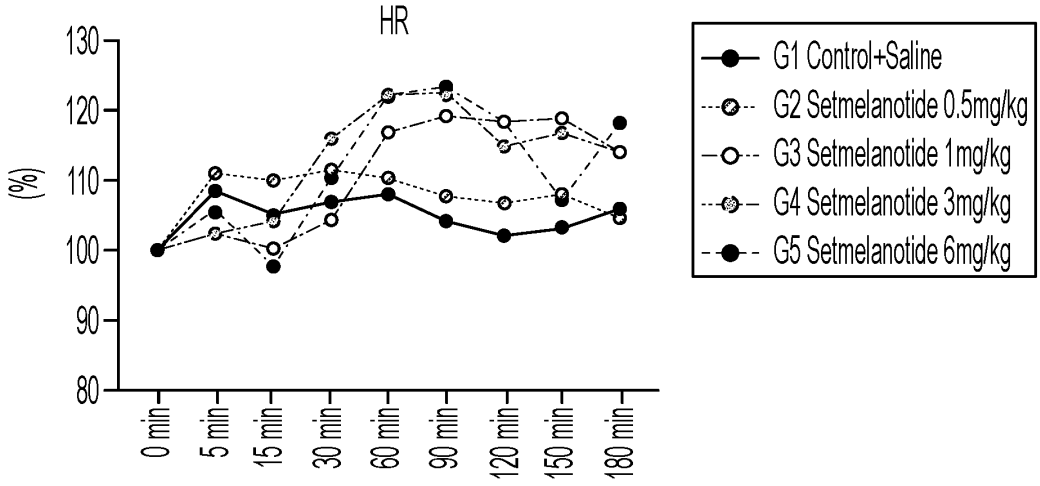


FIG. 16C

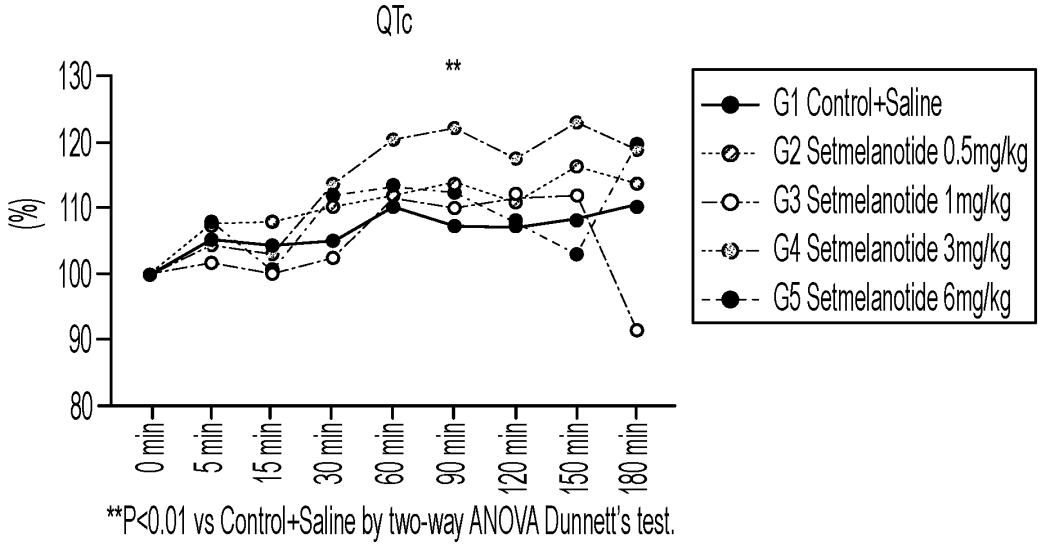


FIG. 16D

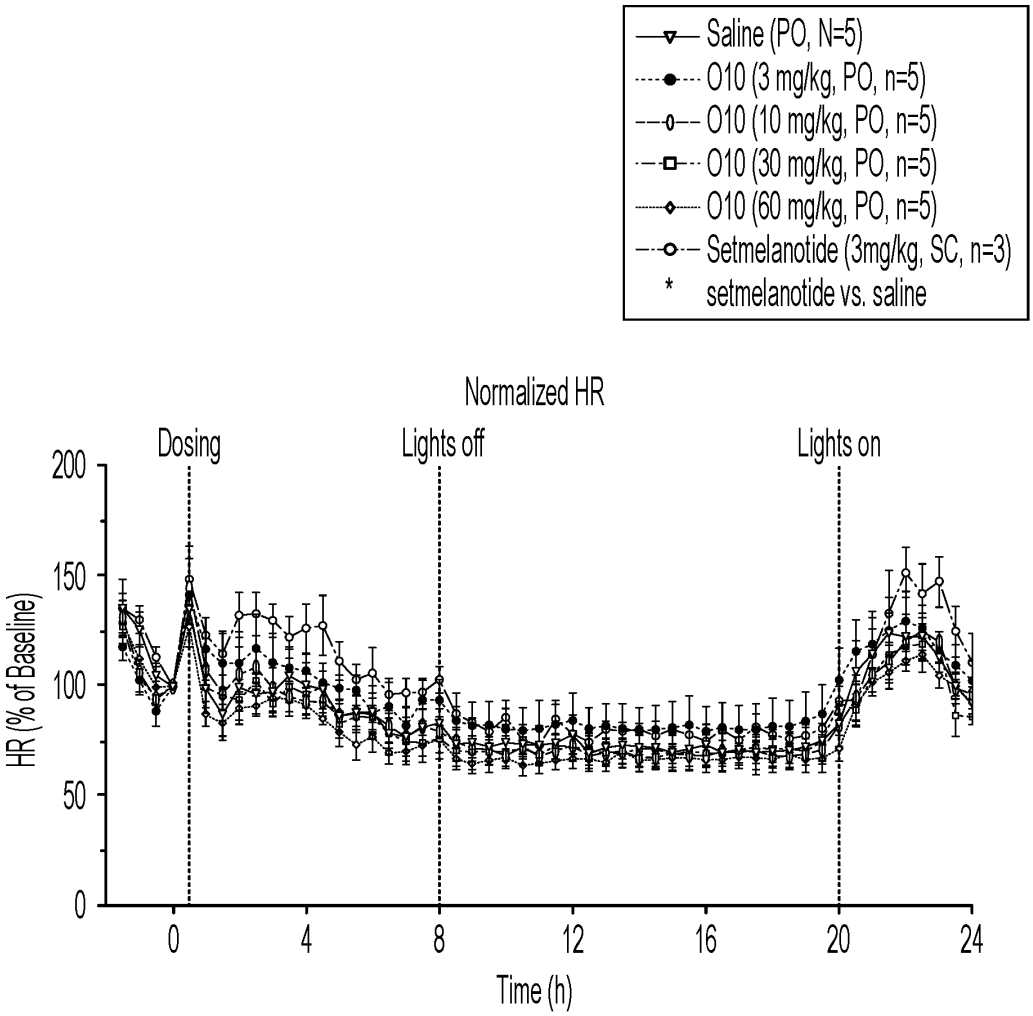

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized HR
Dosing
Lights off
Lights on
HR (% of Baseline)
200
150
100
50
0
0
4
8
12
16
20
24
Time (h)

FIG. 17A

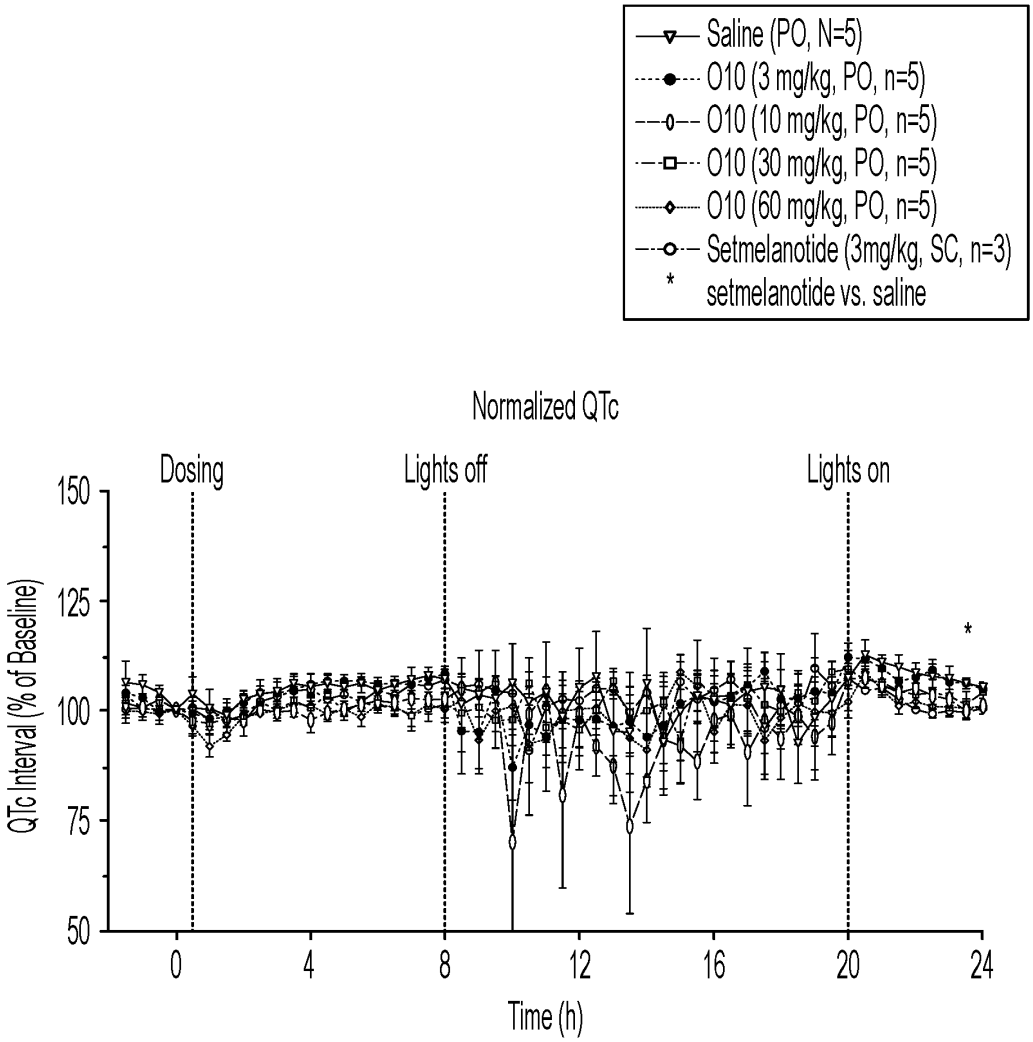

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized QTc
Dosing
Lights off
Lights on
QTc Interval (% of Baseline)
150
125
100
75
50
0
4
8
12
16
20
24
Time (h)
*

FIG. 17B

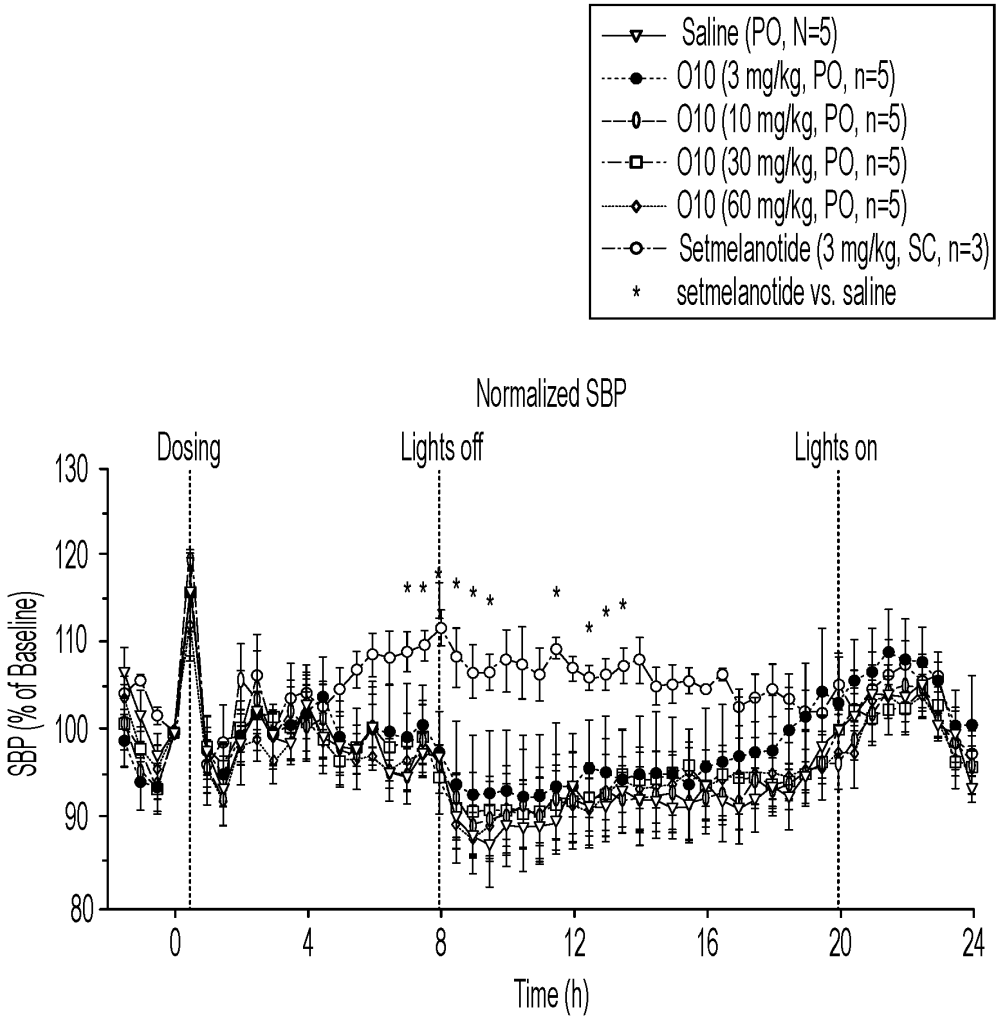

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
setmelanotide vs. saline
Normalized SBP
Dosing
Lights off
Lights on
SBP (% of Baseline)
130
120
110
100
90
80
0
4
8
12
16
20
24
Time (h)

FIG. 17C

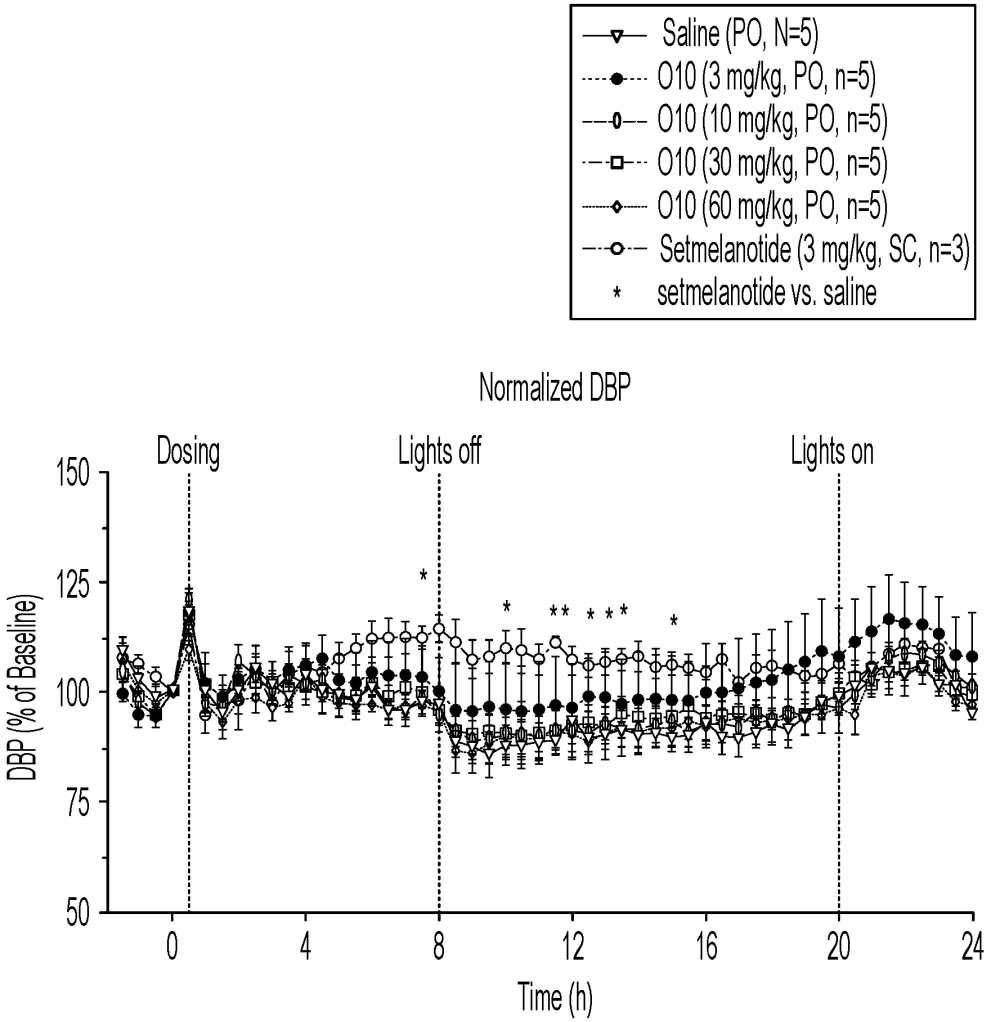

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized DBP
Dosing
Lights off
Lights on
DBP (% of Baseline)
150
125
100
75
50
0
4
8
12
16
20
24
Time (h)

FIG. 17D

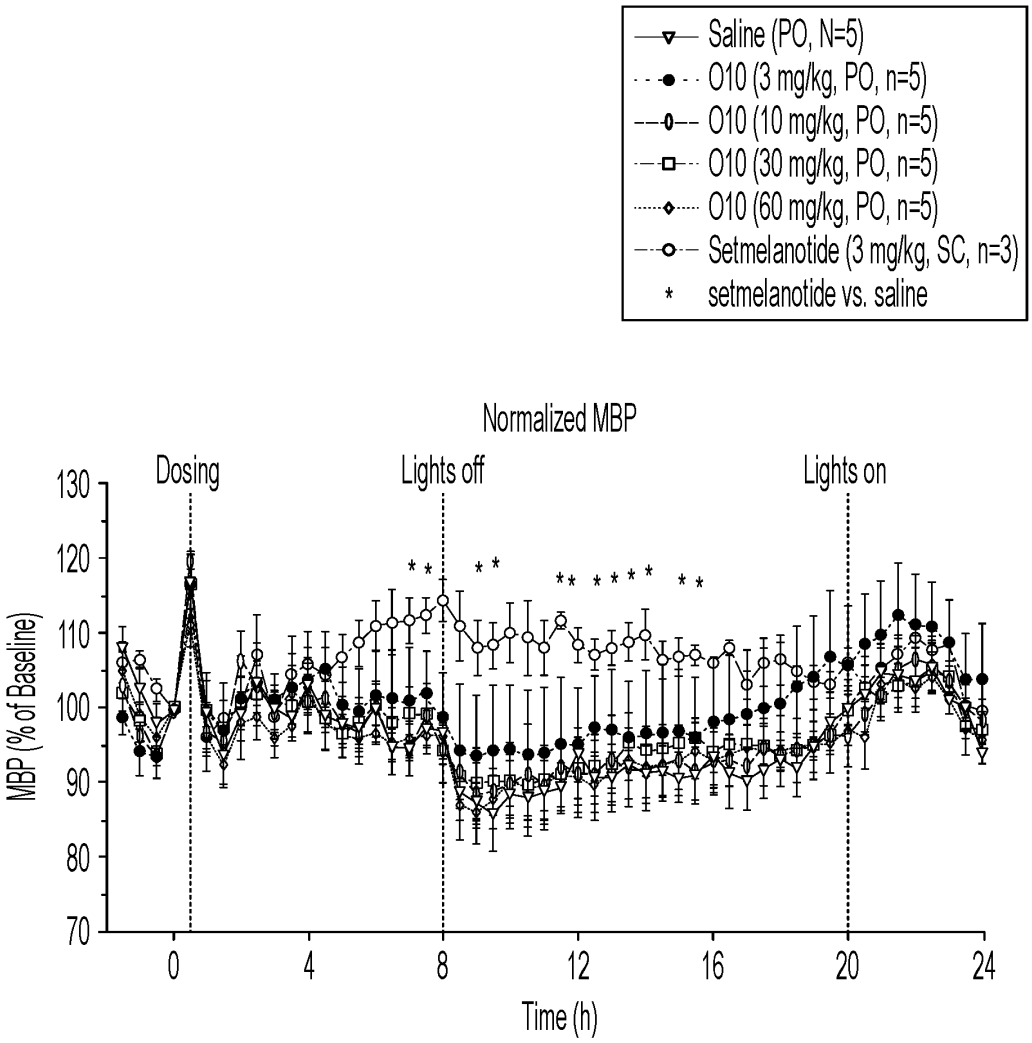

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
setmelanotide vs. saline
Normalized MBP
Dosing
Lights off
Lights on
MBP (% of Baseline)
130
120
110
100
90
80
70
0
4
8
12
16
20
24
Time (h)

FIG. 17E

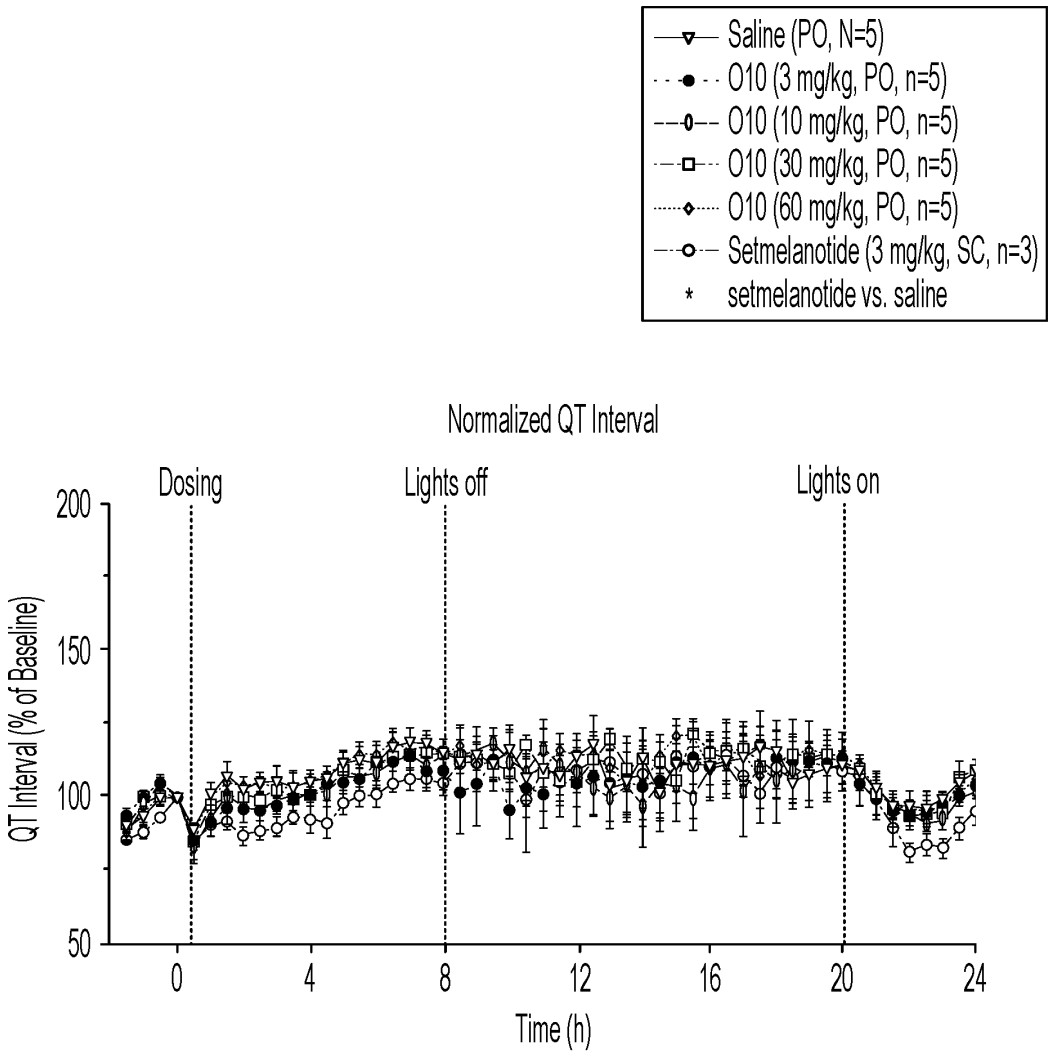

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized QT Interval
Dosing
Lights off
Lights on
QT Interval (% of Baseline)
200
150
100
50
0
4
8
12
16
20
24
Time (h)

FIG. 17F

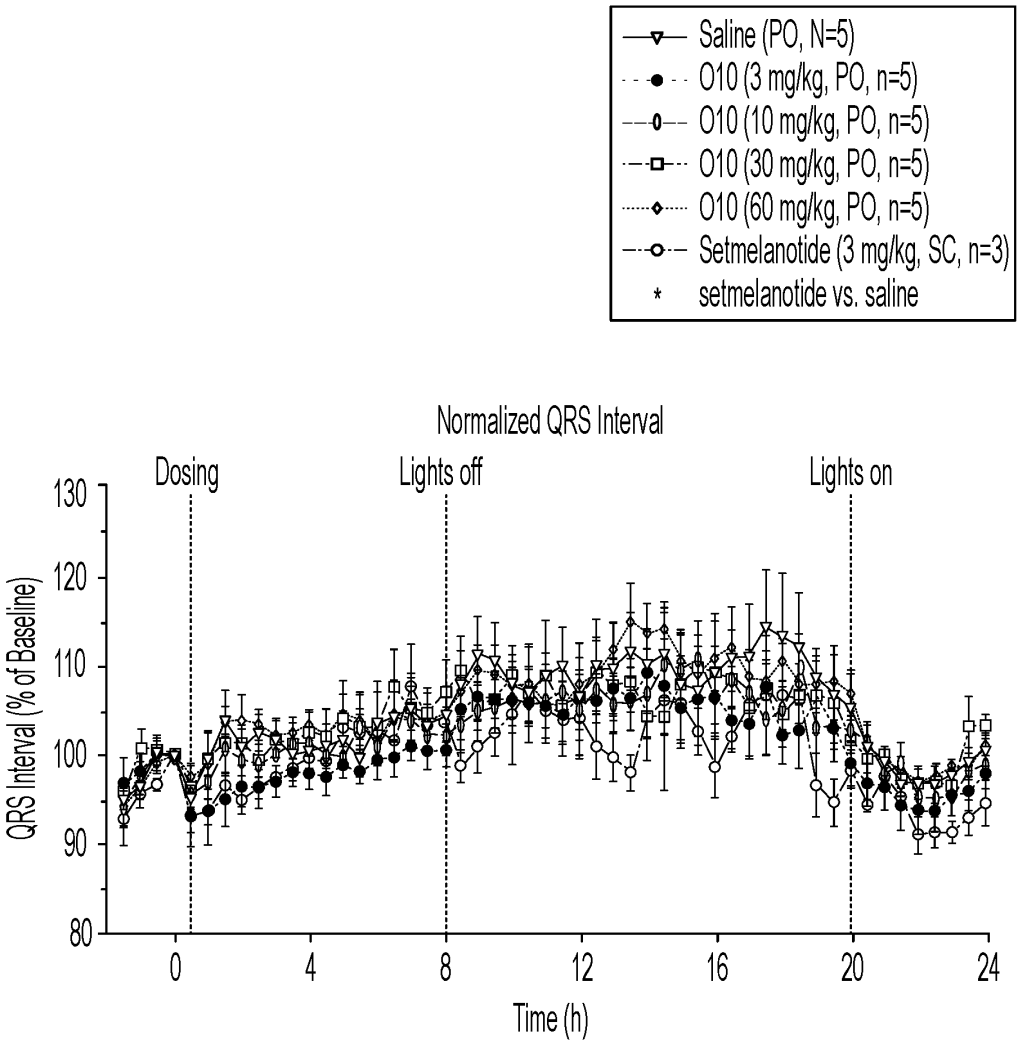

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized QRS Interval
Dosing
Lights off
Lights on
QRS Interval (% of Baseline)
130
120
110
100
90
80
0
4
8
12
16
20
24
Time (h)

FIG. 17G

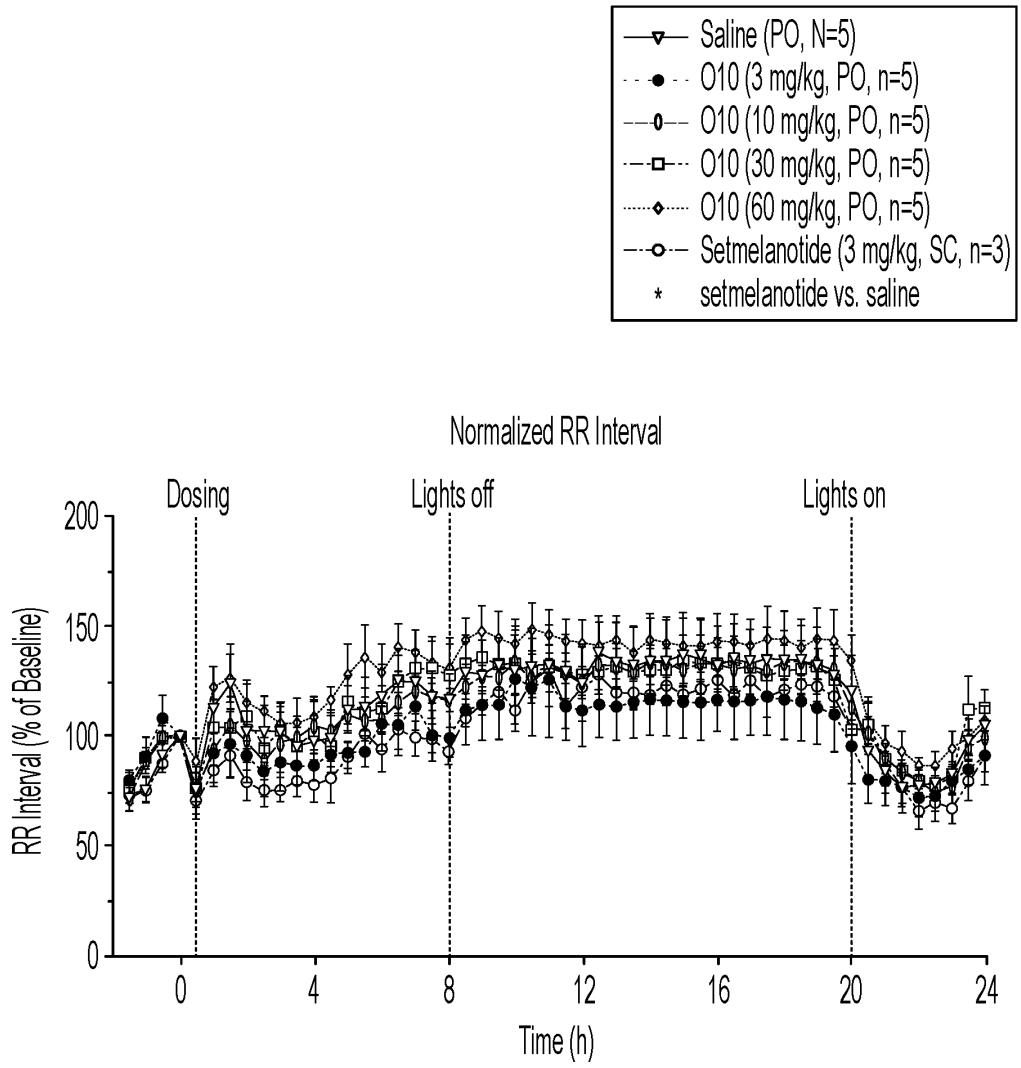

Saline (PO, N=5)
O10 (3 mg/kg, PO, n=5)
O10 (10 mg/kg, PO, n=5)
O10 (30 mg/kg, PO, n=5)
O10 (60 mg/kg, PO, n=5)
Setmelanotide (3 mg/kg, SC, n=3)
* setmelanotide vs. saline
Normalized RR Interval
Dosing
Lights off
Lights on
RR Interval (% of Baseline)
200
150
100
50
0
0
4
8
12
16
20
24
Time (h)

FIG. 17H

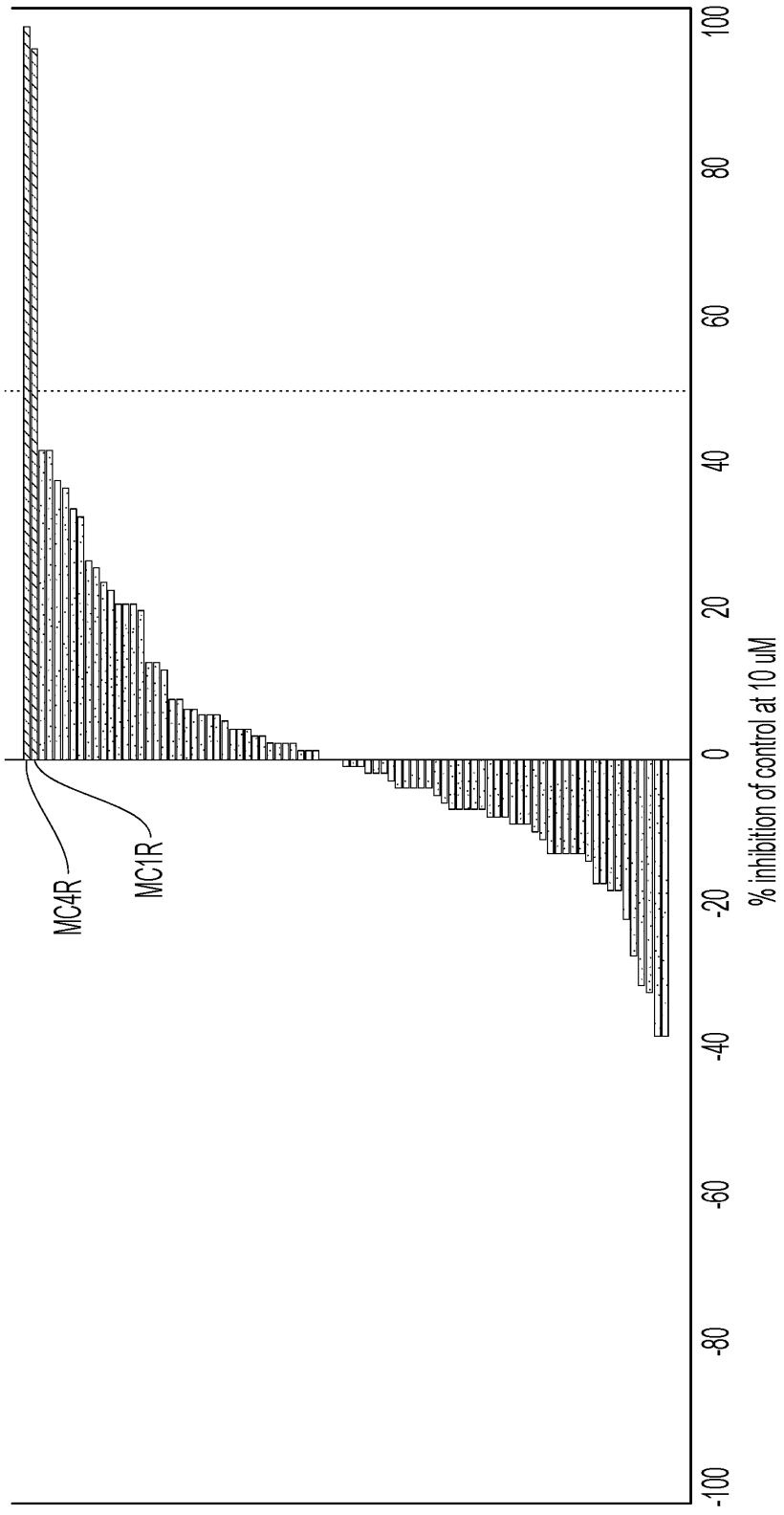

100
80
60
40
20
0
-20
-40
-60
-80
-100
% inhibition of control at 10 uM
MC4R
MC1R

FIG. 18

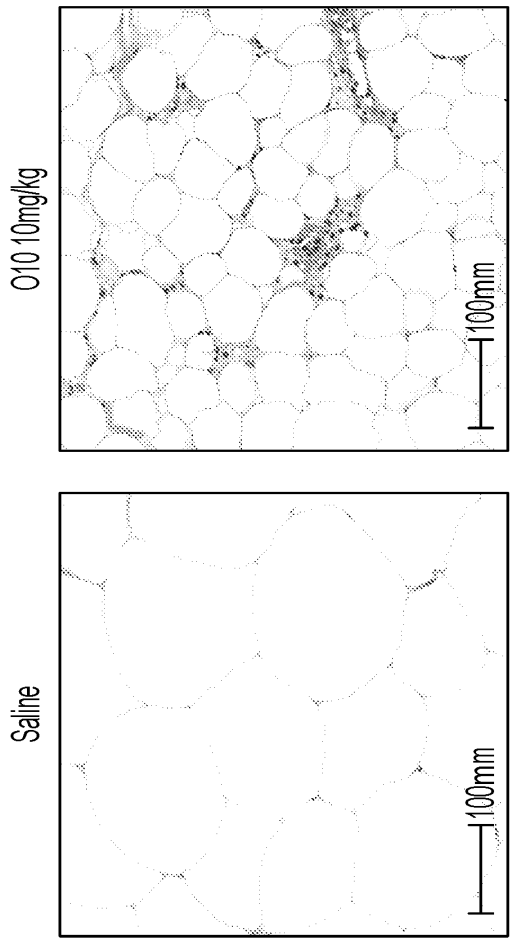


FIG. 19

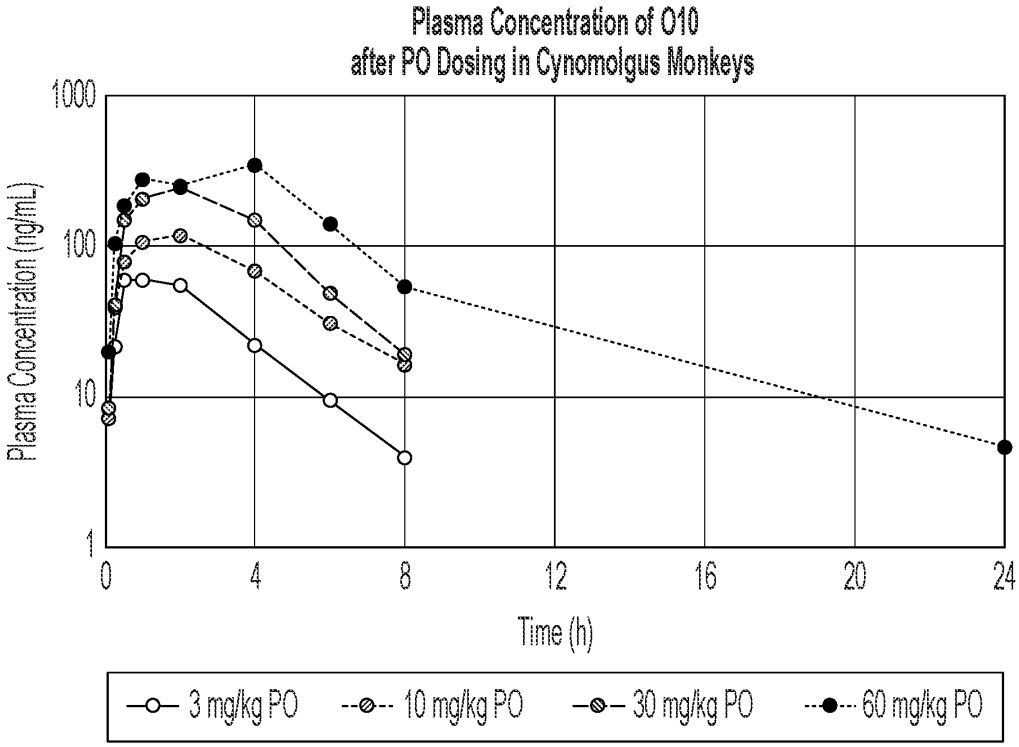

Plasma Concentration of O10
after PO Dosing in Cynomolgus Monkeys
Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (h)
3 mg/kg PO
10 mg/kg PO
30 mg/kg PO
60 mg/kg PO

FIG. 20