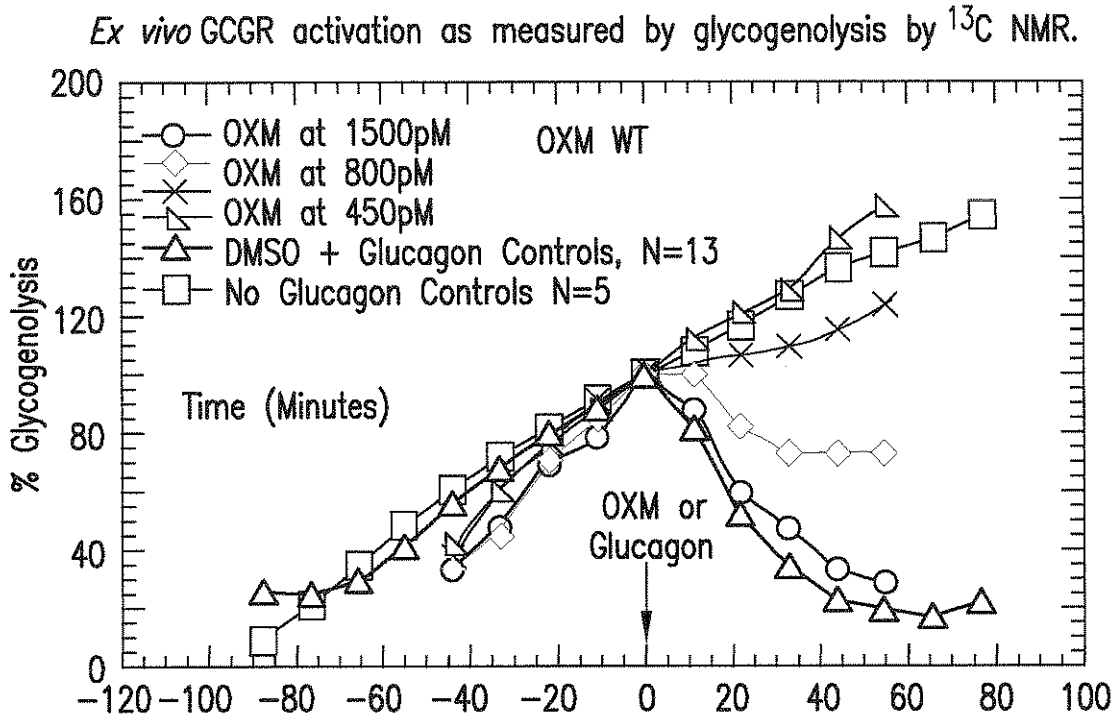

*Ex vivo* GCGR activation as measured by glycogenolysis by $^{13}C$ NMR.
% Glycogenolysis
200
160
120
80
40
0
−120 −100 −80 −60 −40 −20 0 20 40 60 80 100
OXM at 1500pM
OXM at 800pM
OXM at 450pM
DMSO + Glucagon Controls, N=13
No Glucagon Controls N=5
OXM WT
Time (Minutes)
OXM or
Glucagon

FIG.1A

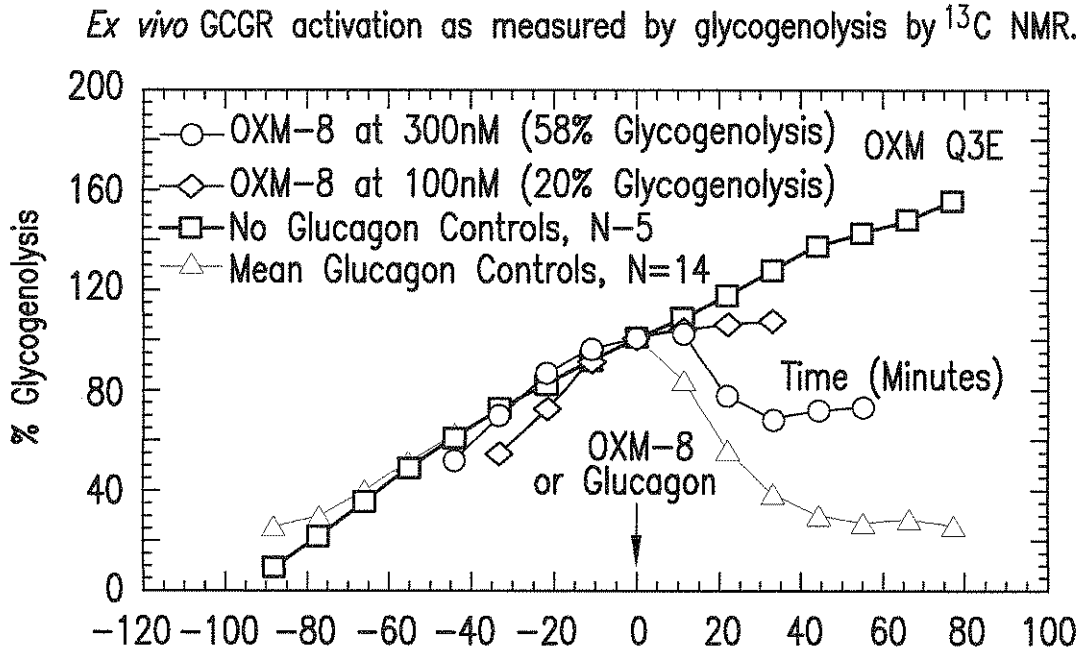

Ex vivo GCGR activation as measured by glycogenolysis by 13C NMR.
% Glycogenolysis
200
160
120
80
40
0
−120 −100 −80 −60 −40 −20 0 20 40 60 80 100
OXM−8 at 300nM (58% Glycogenolysis)
OXM−8 at 100nM (20% Glycogenolysis)
No Glucagon Controls, N−5
Mean Glucagon Controls, N=14
OXM Q3E
Time (Minutes)
OXM−8
or Glucagon

FIG.1B

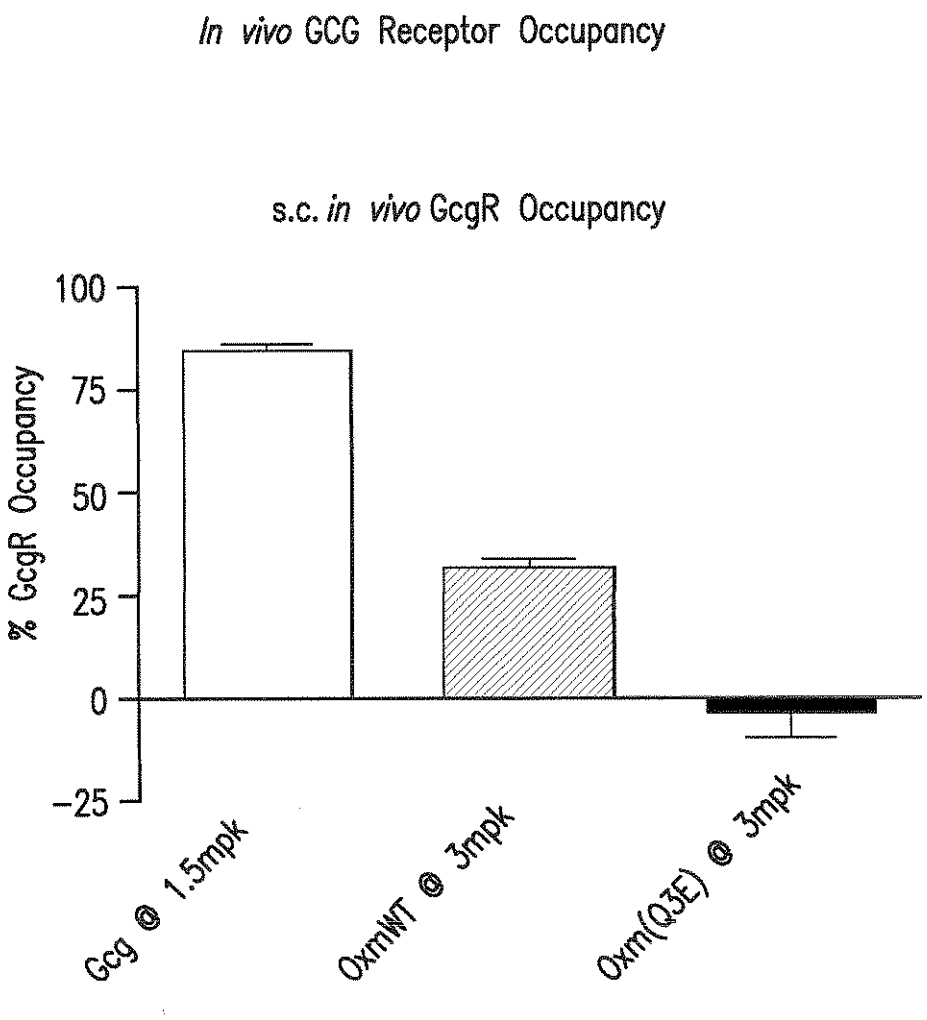

In vivo GCG Receptor Occupancy
s.c. in vivo GcgR Occupancy
% GcgR Occupancy
100
75
50
25
0
-25
Gcg @ 1.5mpk
OxmWT @ 3mpk
Oxm(Q3E) @ 3mpk

FIG.2

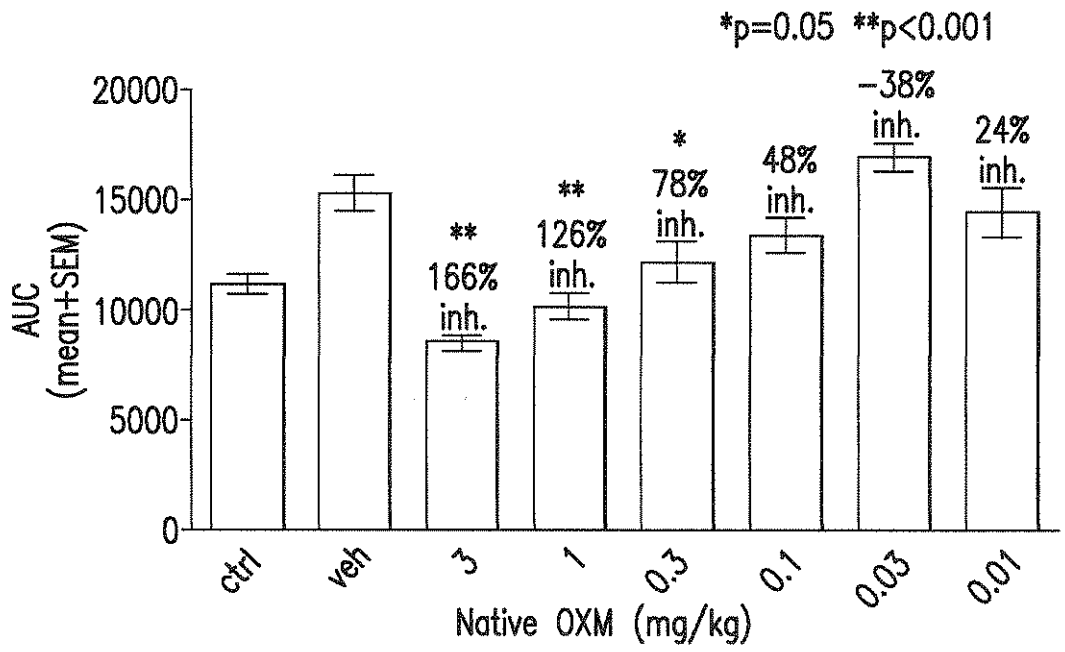

*p=0.05 **p<0.001
AUC (mean+SEM)
20000
15000
10000
5000
0
** 166% inh.
** 126% inh.
* 78% inh.
48% inh.
-38% inh.
24% inh.
ctrl
veh
3
1
0.3
0.1
0.03
0.01
Native OXM (mg/kg)

FIG.3A

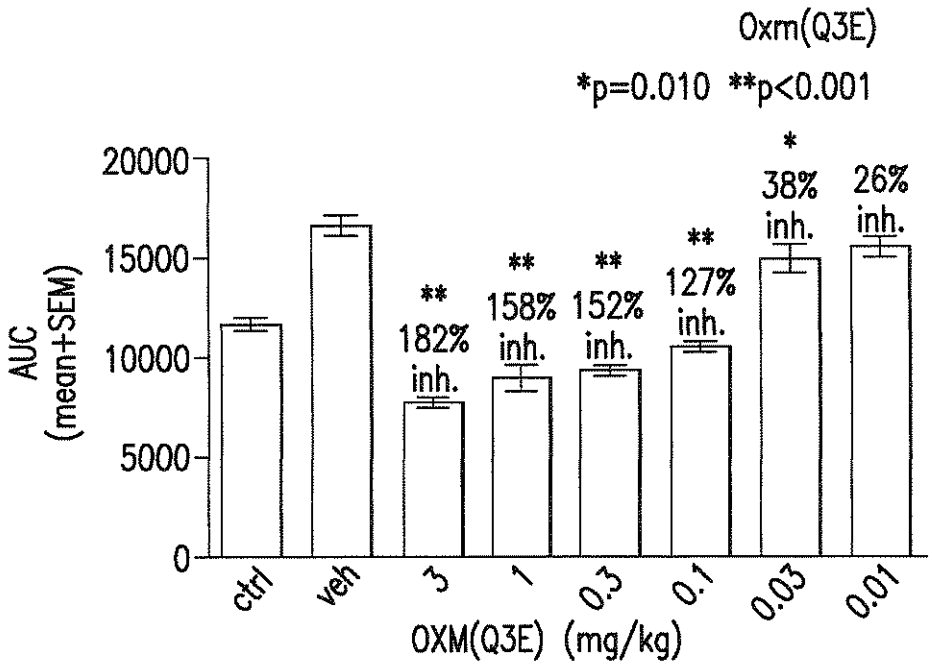

Oxm(Q3E)
*p=0.010 **p<0.001
AUC (mean+SEM)
20000
15000
10000
5000
0
**
182% inh.
**
158% inh.
**
152% inh.
**
127% inh.
*
38% inh.
26% inh.
ctrl
veh
3
1
0.3
0.1
0.03
0.01
OXM(Q3E) (mg/kg)

FIG.3B

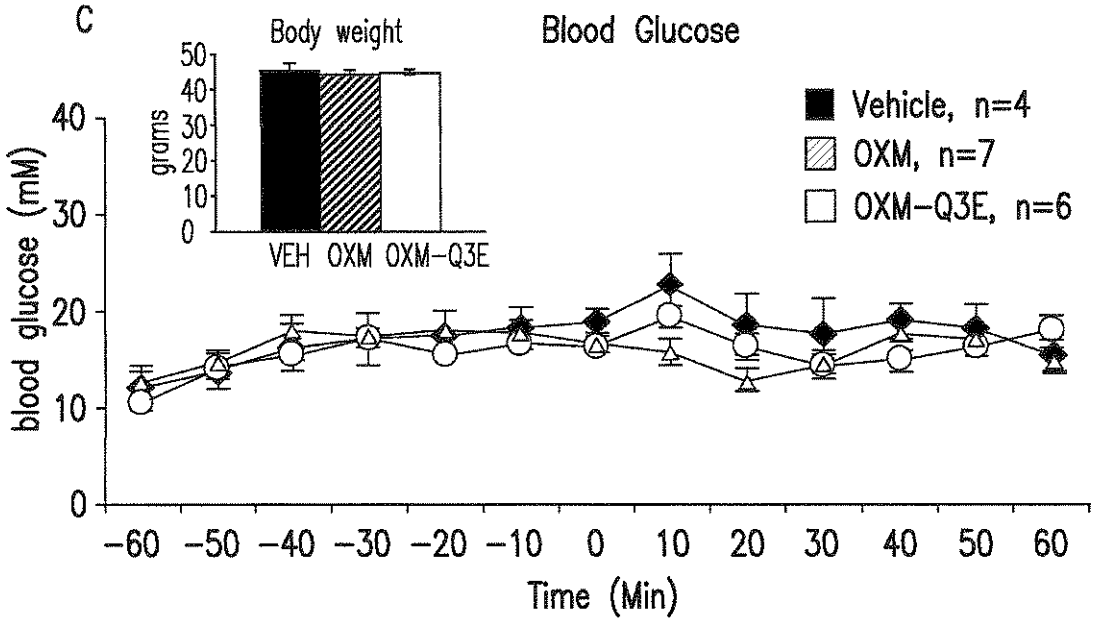

C
Body weight
grams
50
40
30
20
10
0
VEH OXM OXM-Q3E
Blood Glucose
Vehicle, n=4
OXM, n=7
OXM-Q3E, n=6
blood glucose (mM)
40
30
20
10
0
-60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60
Time (Min)

FIG.4A

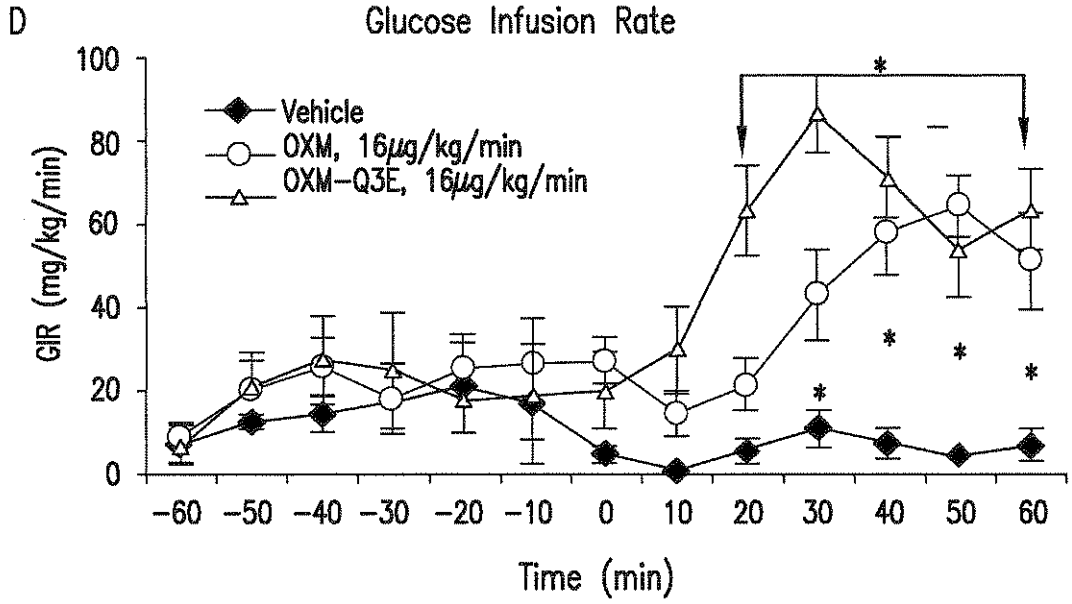

D
Glucose Infusion Rate
GIR (mg/kg/min)
100
80
60
40
20
0
Vehicle
OXM, 16μg/kg/min
OXM-Q3E, 16μg/kg/min
*
*
*
*
*
*
−60 −50 −40 −30 −20 −10 0 10 20 30 40 50 60
Time (min)

FIG.4B

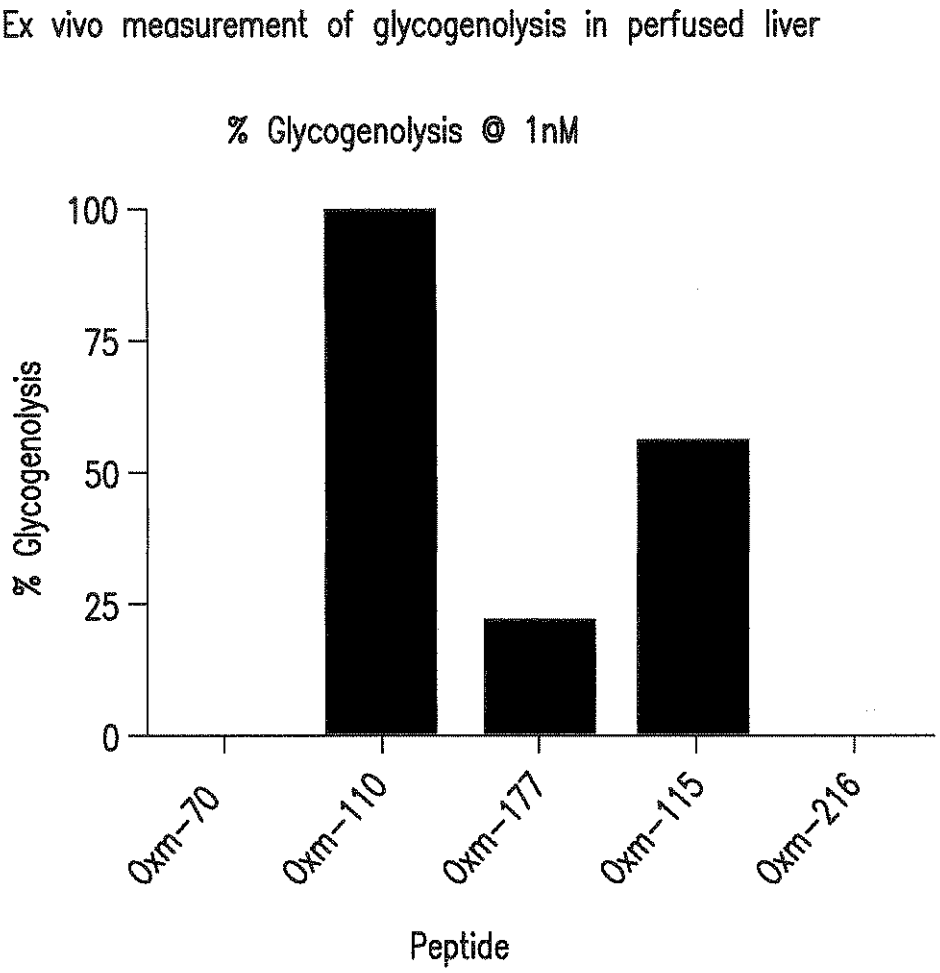

Ex vivo measurement of glycogenolysis in perfused liver
% Glycogenolysis @ 1nM
% Glycogenolysis
100
75
50
25
0
Oxm-70
Oxm-110
Oxm-177
Oxm-115
Oxm-216
Peptide

FIG.5A

GGCR occupancy following s.c. or i.v. administration of the test peptides.

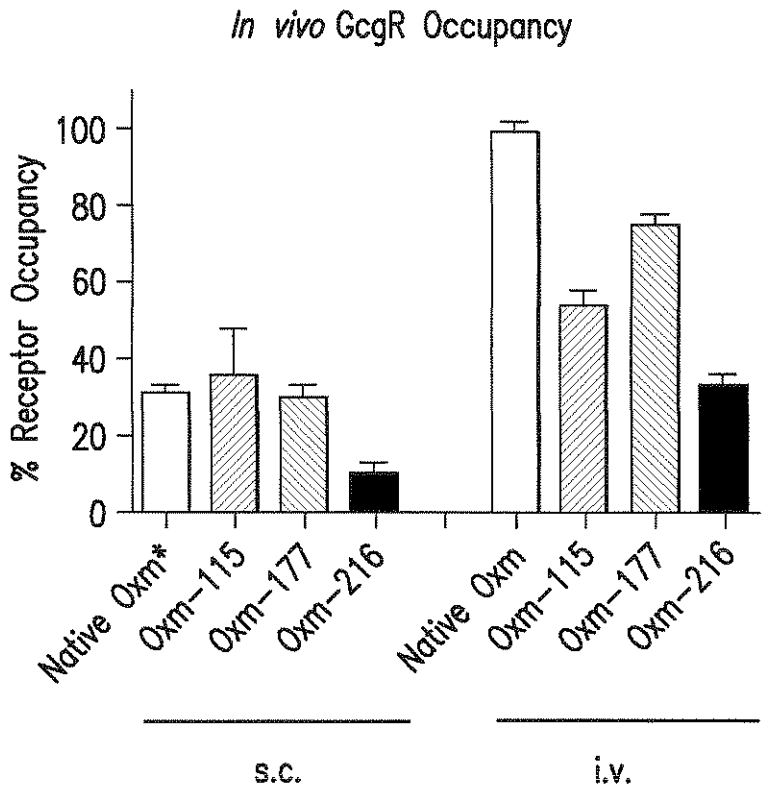



FIG.5B

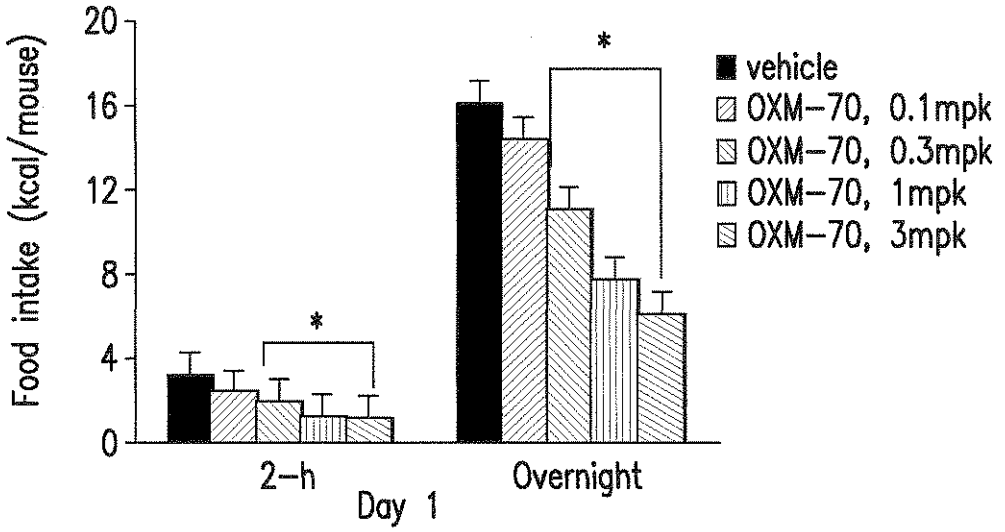

Food intake (kcal/mouse)
20
16
12
8
4
0
*
*
2-h
Overnight
Day 1
vehicle
OXM-70, 0.1mpk
OXM-70, 0.3mpk
OXM-70, 1mpk
OXM-70, 3mpk

FIG.6A

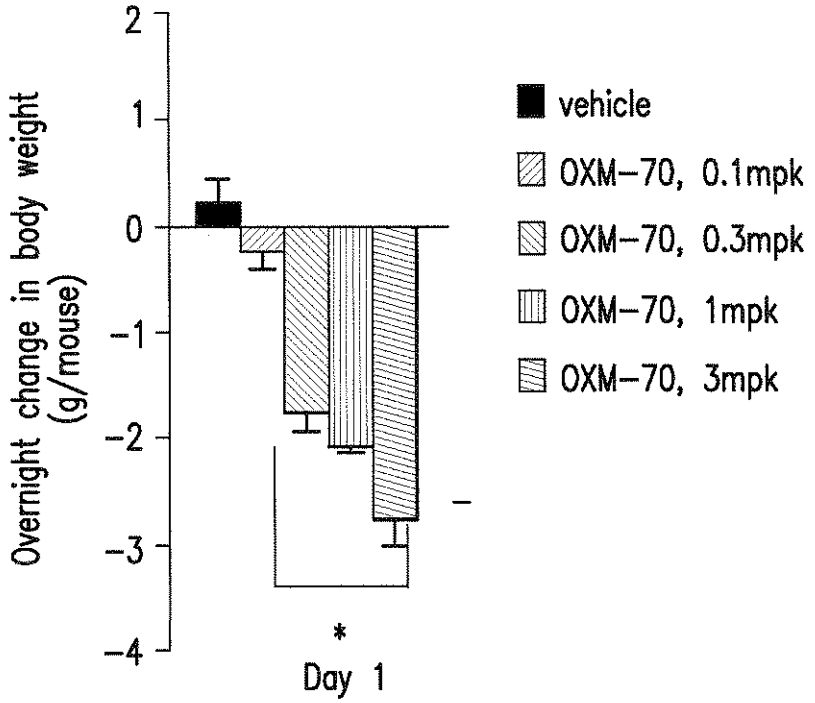

Overnight change in body weight (g/mouse)
2
1
0
-1
-2
-3
-4
*
Day 1
vehicle
OXM-70, 0.1mpk
OXM-70, 0.3mpk
OXM-70, 1mpk
OXM-70, 3mpk

FIG.6B

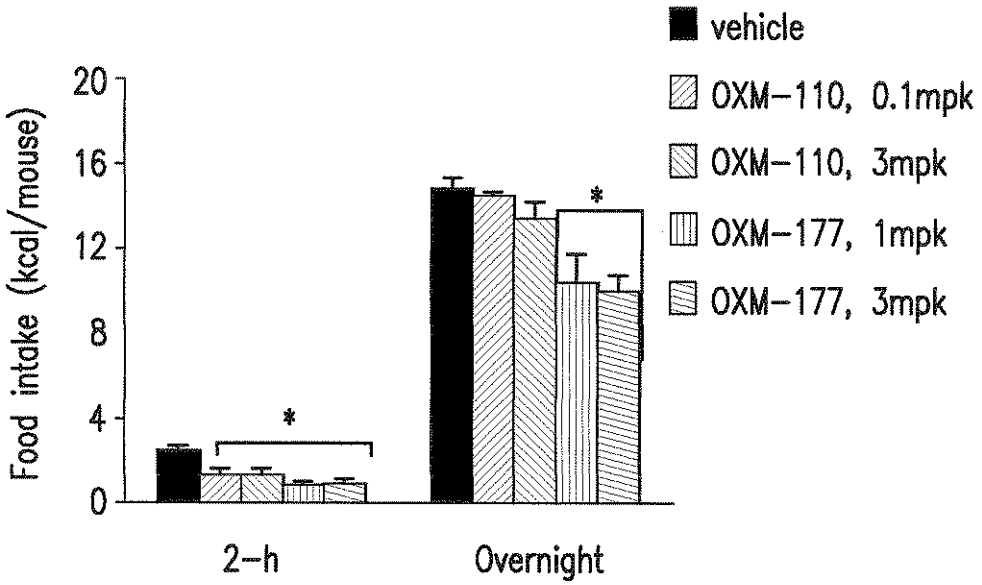

vehicle
OXM-110, 0.1mpk
OXM-110, 3mpk
OXM-177, 1mpk
OXM-177, 3mpk
Food intake (kcal/mouse)
20
16
12
8
4
0
*
*
2-h
Overnight

FIG.7A

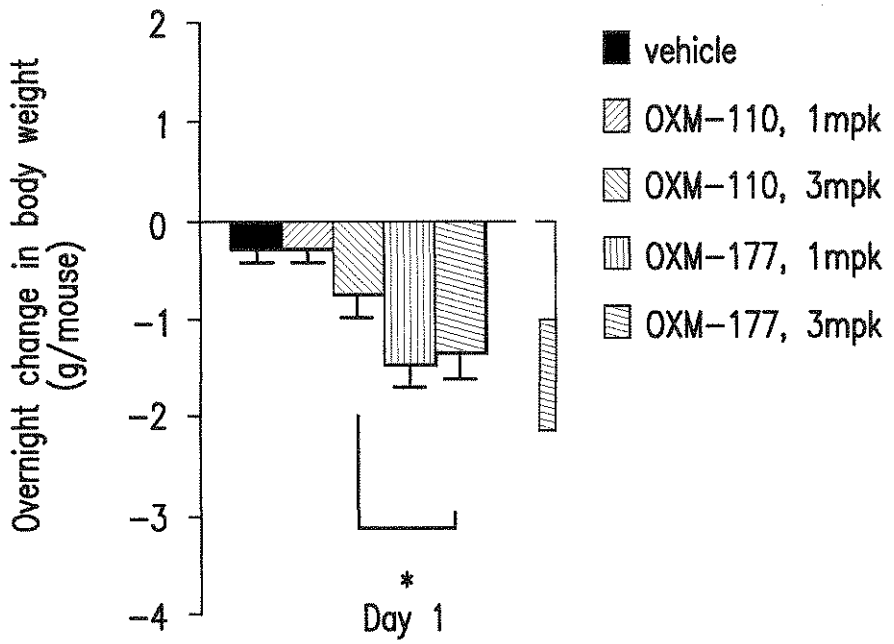

Overnight change in body weight (g/mouse)
2
1
0
−1
−2
−3
−4
*
Day 1
vehicle
OXM−110, 1mpk
OXM−110, 3mpk
OXM−177, 1mpk
OXM−177, 3mpk

FIG.7B

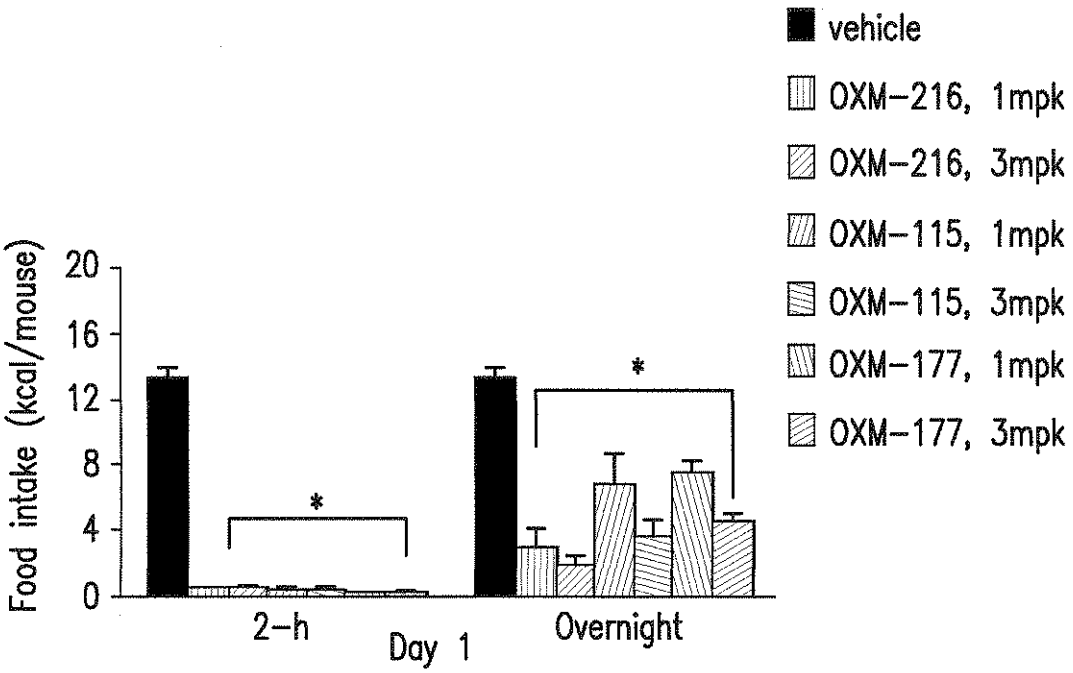

vehicle
OXM-216, 1mpk
OXM-216, 3mpk
OXM-115, 1mpk
OXM-115, 3mpk
OXM-177, 1mpk
OXM-177, 3mpk
Food intake (kcal/mouse)
20
16
12
8
4
0
*
*
2-h
Overnight
Day 1

FIG.8A

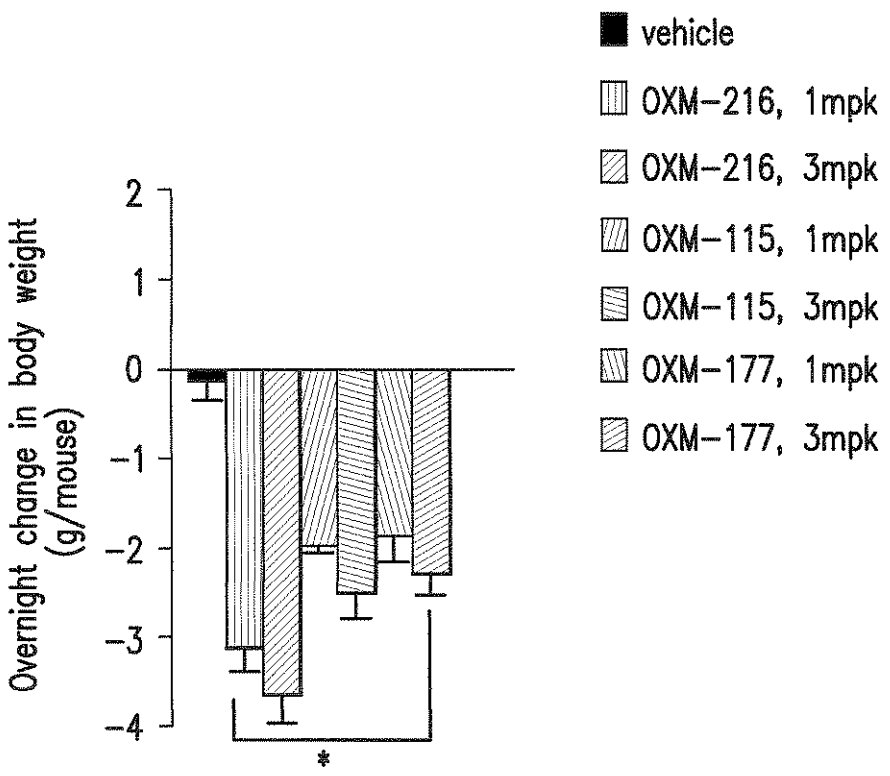

vehicle
OXM-216, 1mpk
OXM-216, 3mpk
OXM-115, 1mpk
OXM-115, 3mpk
OXM-177, 1mpk
OXM-177, 3mpk
Overnight change in body weight (g/mouse)
2
1
0
-1
-2
-3
-4
*

FIG.8B

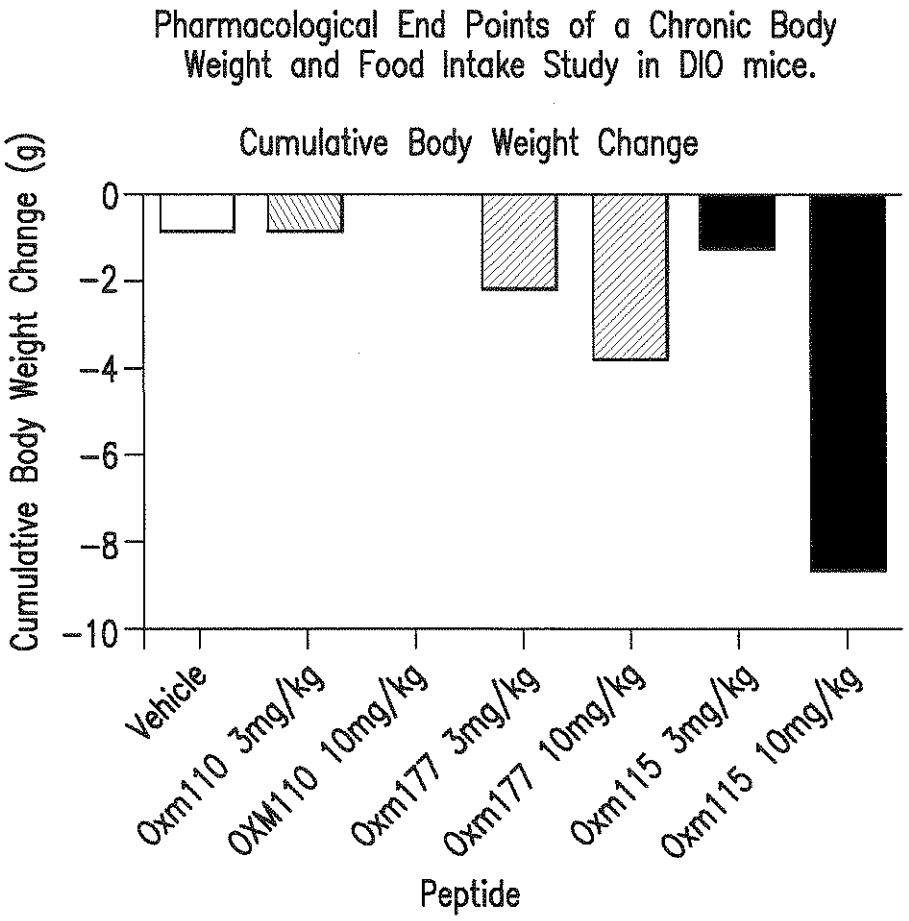

Pharmacological End Points of a Chronic Body Weight and Food Intake Study in DIO mice.
Cumulative Body Weight Change
Cumulative Body Weight Change (g)
0
-2
-4
-6
-8
-10
Vehicle
Oxm110 3mg/kg
OXM110 10mg/kg
Oxm177 3mg/kg
Oxm177 10mg/kg
Oxm115 3mg/kg
Oxm115 10mg/kg
Peptide

FIG.9A

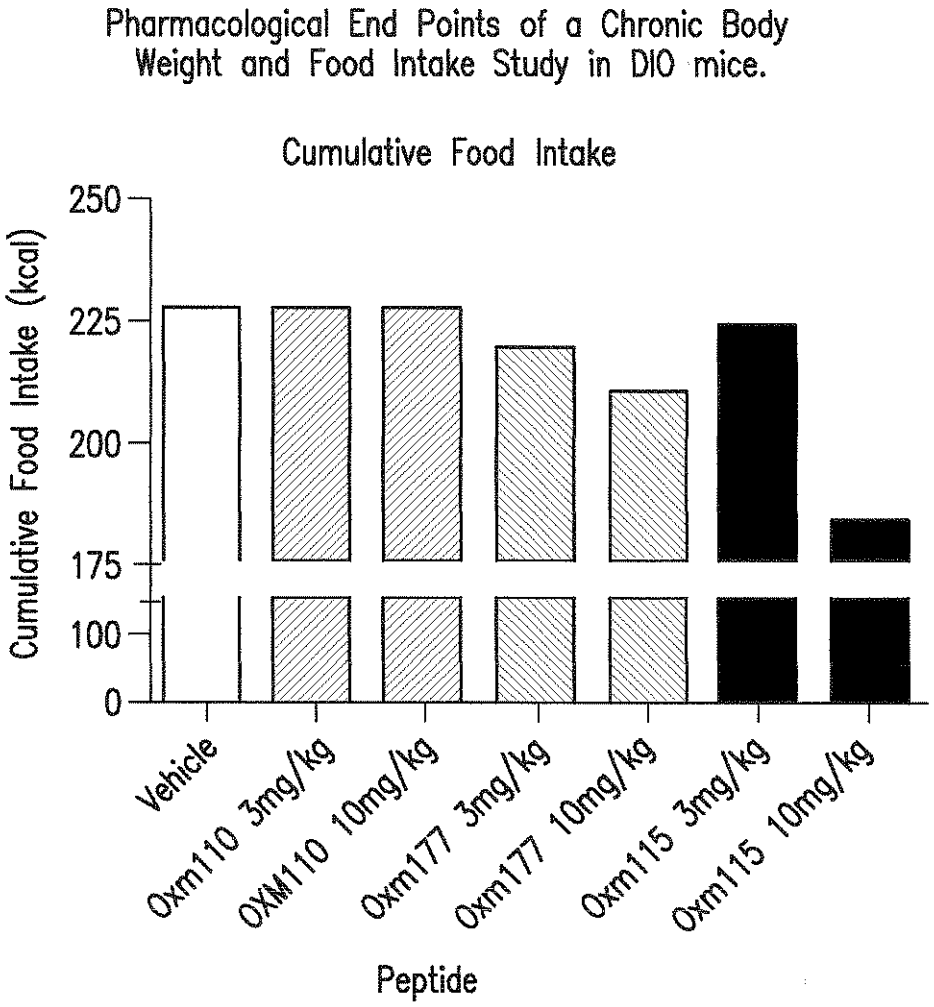

Pharmacological End Points of a Chronic Body Weight and Food Intake Study in DIO mice.
Cumulative Food Intake
Cumulative Food Intake (kcal)
250
225
200
175
100
0
Vehicle
Oxm110 3mg/kg
OXM110 10mg/kg
Oxm177 3mg/kg
Oxm177 10mg/kg
Oxm115 3mg/kg
Oxm115 10mg/kg
Peptide

FIG.9B

Pharmacological End Points of a Chronic Body Weight and Food Intake Study in DIO mice.

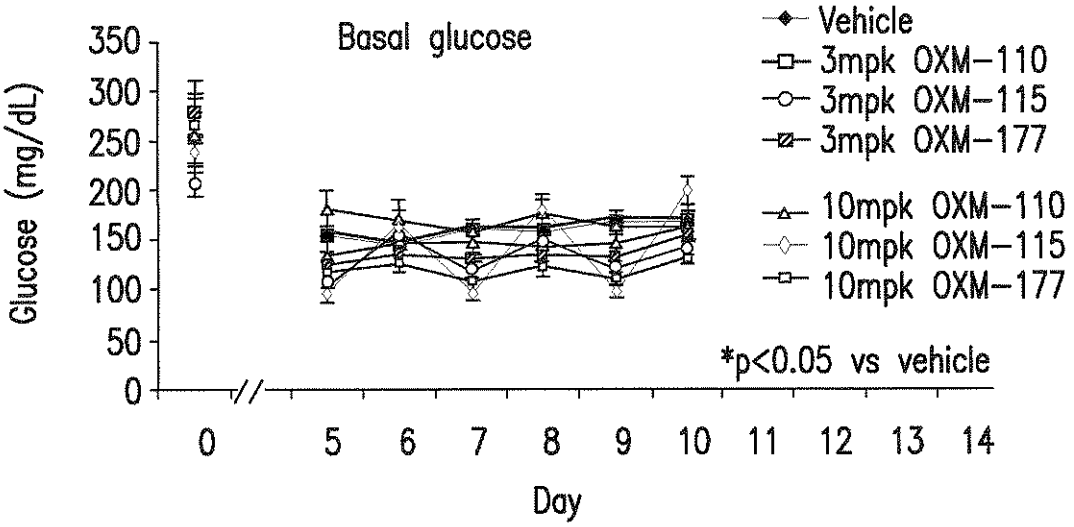



FIG.9C

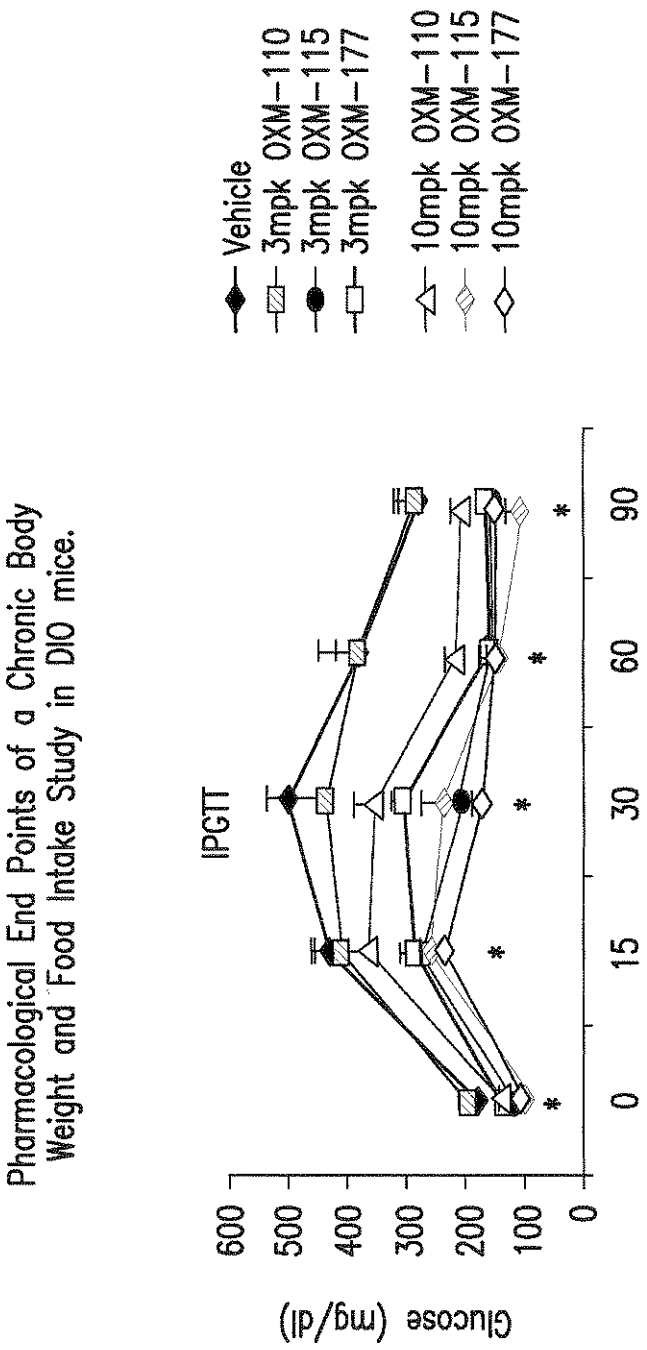

Pharmacological End Points of a Chronic Body Weight and Food Intake Study in DIO mice.
IPGTT
Vehicle
3mpk OXM-110
3mpk OXM-115
3mpk OXM-177
10mpk OXM-110
10mpk OXM-115
10mpk OXM-177
Glucose (mg/dl)
600
500
400
300
200
100
0
0
15
30
60
90
Time (min)
*
*
*
*

FIG.9D

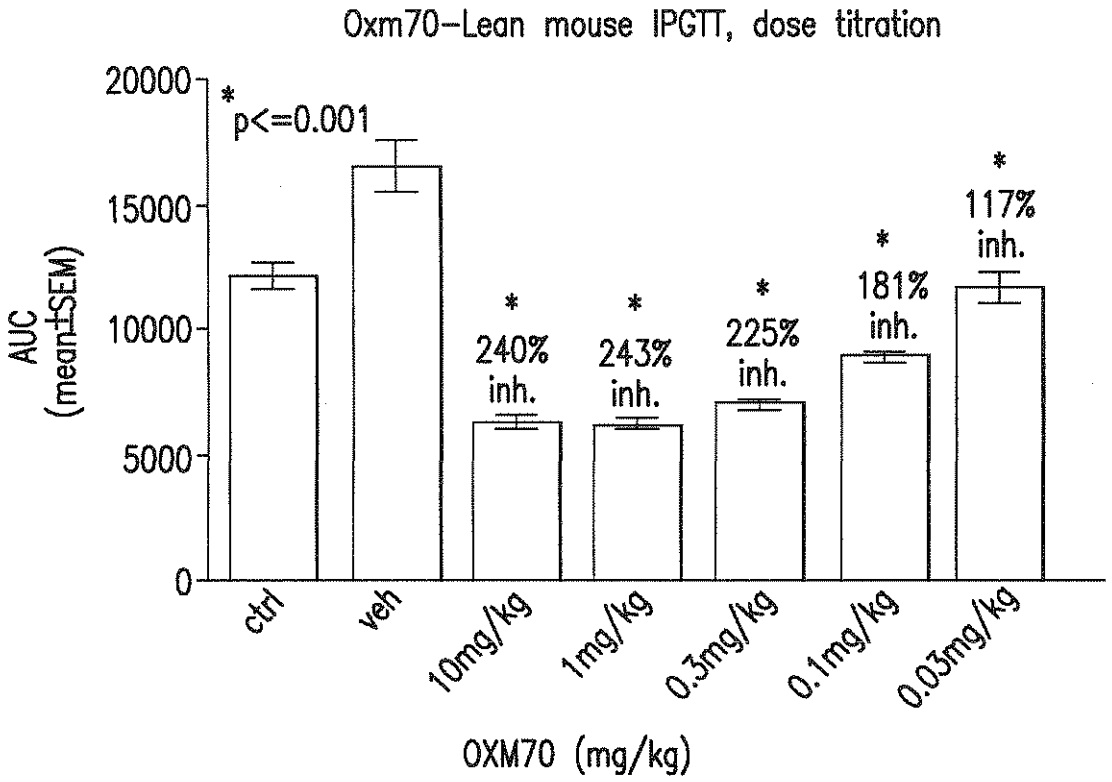

Oxm70-Lean mouse IPGTT, dose titration
AUC (mean±SEM)
20000
15000
10000
5000
0
* p<=0.001
* 240% inh.
* 243% inh.
* 225% inh.
* 181% inh.
* 117% inh.
ctrl
veh
10mg/kg
1mg/kg
0.3mg/kg
0.1mg/kg
0.03mg/kg
OXM70 (mg/kg)

FIG.10

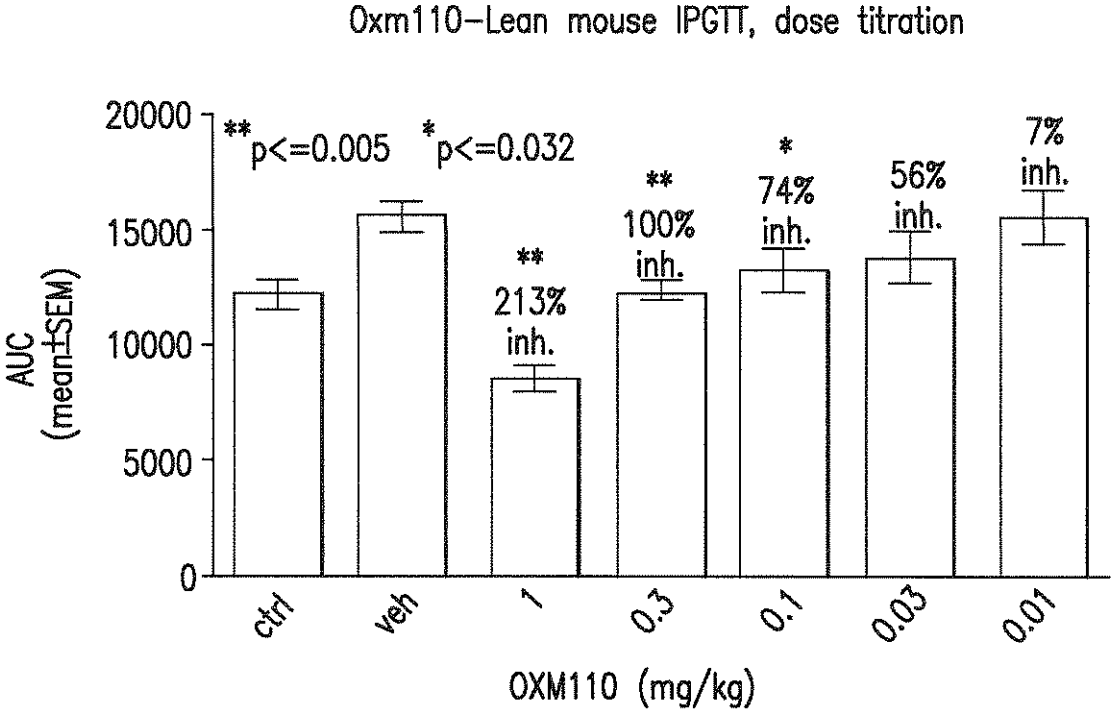

Oxm110-Lean mouse IPGTT, dose titration
AUC (mean±SEM)
20000
15000
10000
5000
0
**p<=0.005
*p<=0.032
**
213%
inh.
**
100%
inh.
*
74%
inh.
56%
inh.
7%
inh.
ctrl
veh
1
0.3
0.1
0.03
0.01
OXM110 (mg/kg)

FIG. 11

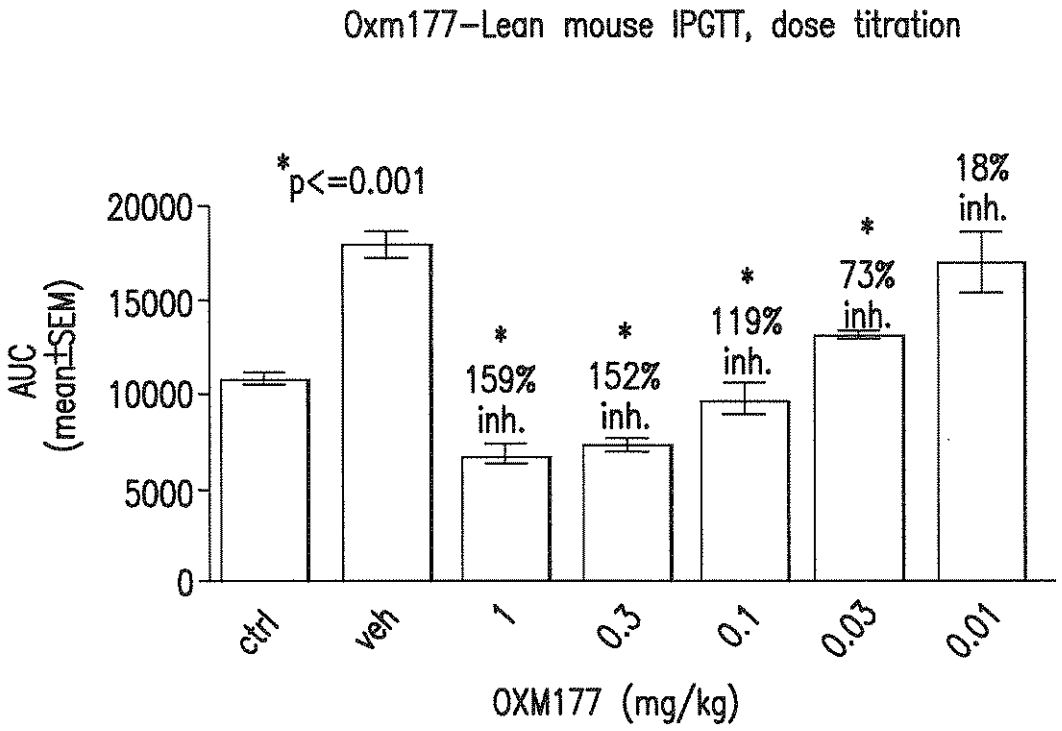

Oxm177-Lean mouse IPGTT, dose titration
*p<=0.001
18% inh.
*
73% inh.
*
119% inh.
*
159% inh.
*
152% inh.
AUC (mean±SEM)
20000
15000
10000
5000
0
ctrl
veh
1
0.3
0.1
0.03
0.01
OXM177 (mg/kg)

FIG. 12

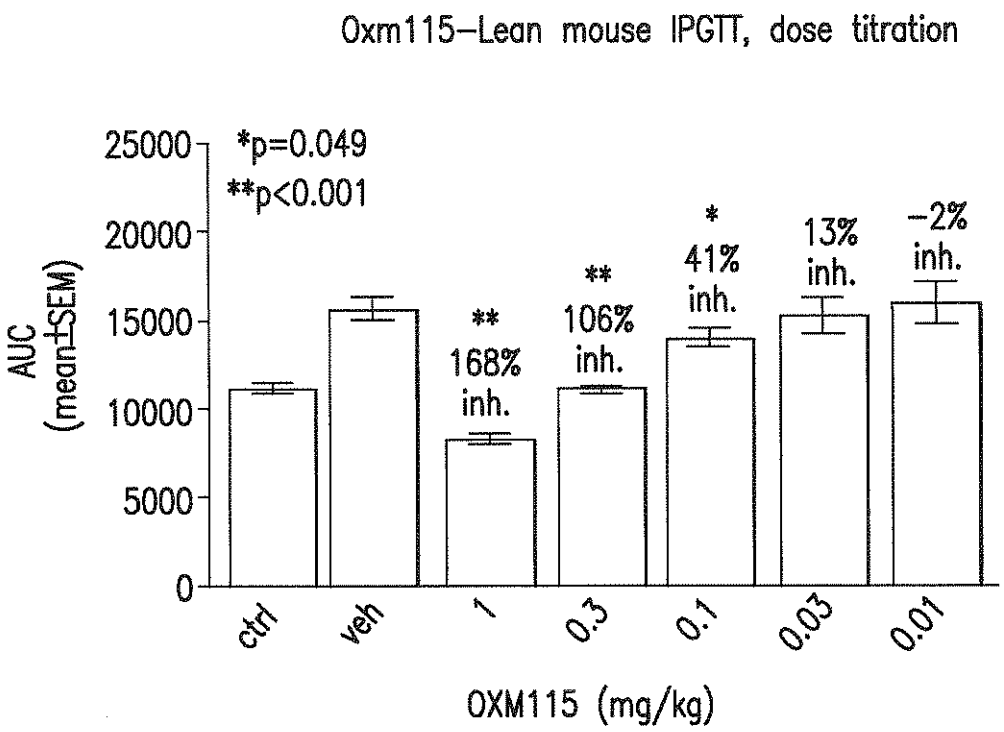

Oxm115–Lean mouse IPGTT, dose titration
*p=0.049
**p<0.001
AUC (mean±SEM)
25000
20000
15000
10000
5000
0
** 168% inh.
** 106% inh.
* 41% inh.
13% inh.
–2% inh.
ctrl
veh
1
0.3
0.1
0.03
0.01
OXM115 (mg/kg)

FIG.13

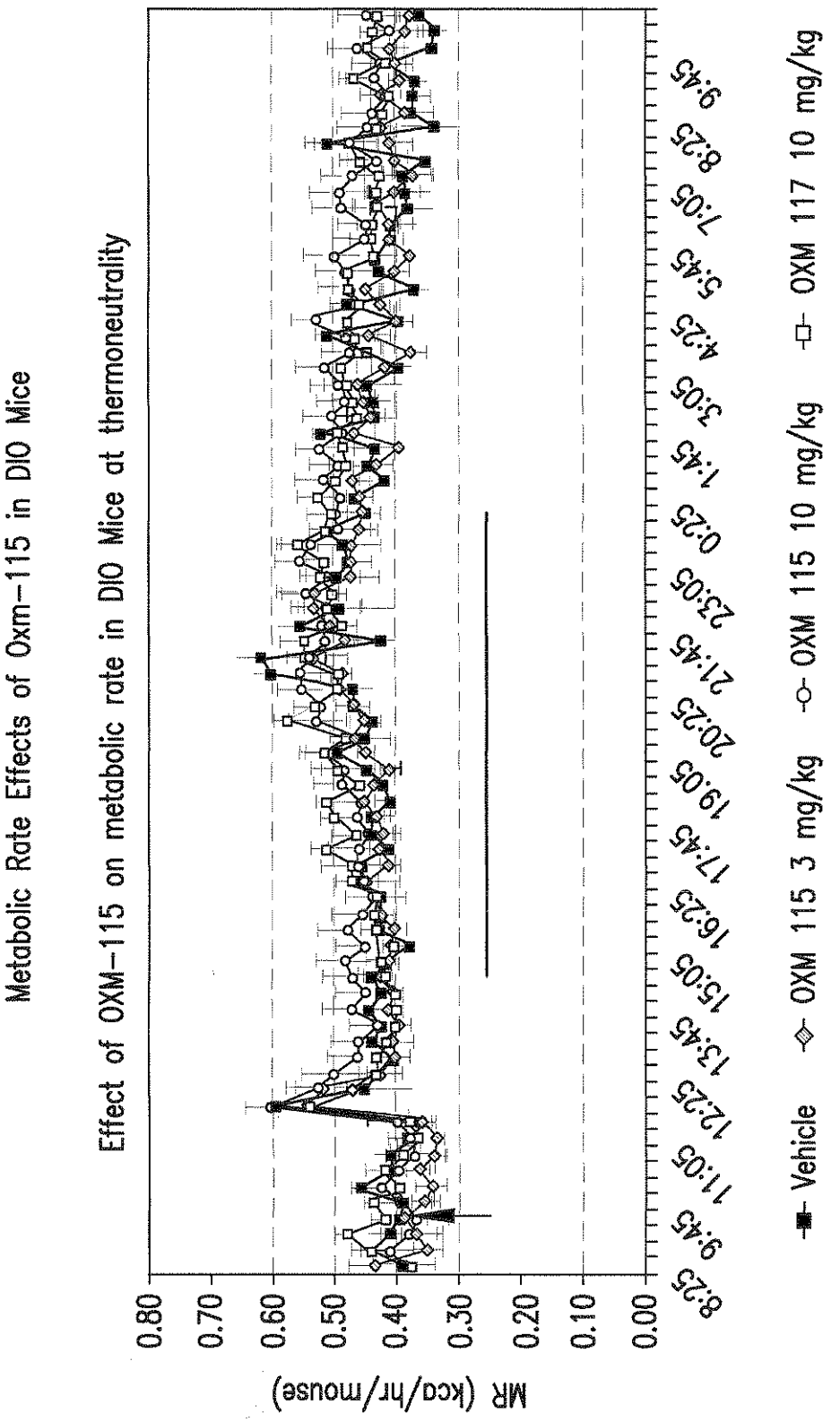

Metabolic Rate Effects of Oxm-115 in DIO Mice
Effect of OXM-115 on metabolic rate in DIO Mice at thermoneutrality
MR (kcal/hr/mouse)
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
8:25
9:45
11:05
12:25
13:45
15:05
16:25
17:45
19:05
20:25
21:45
23:05
0:25
1:45
3:05
4:25
5:45
7:05
8:25
9:45
Vehicle
OXM 115 3 mg/kg
OXM 115 10 mg/kg
OXM 117 10 mg/kg

FIG. 14A

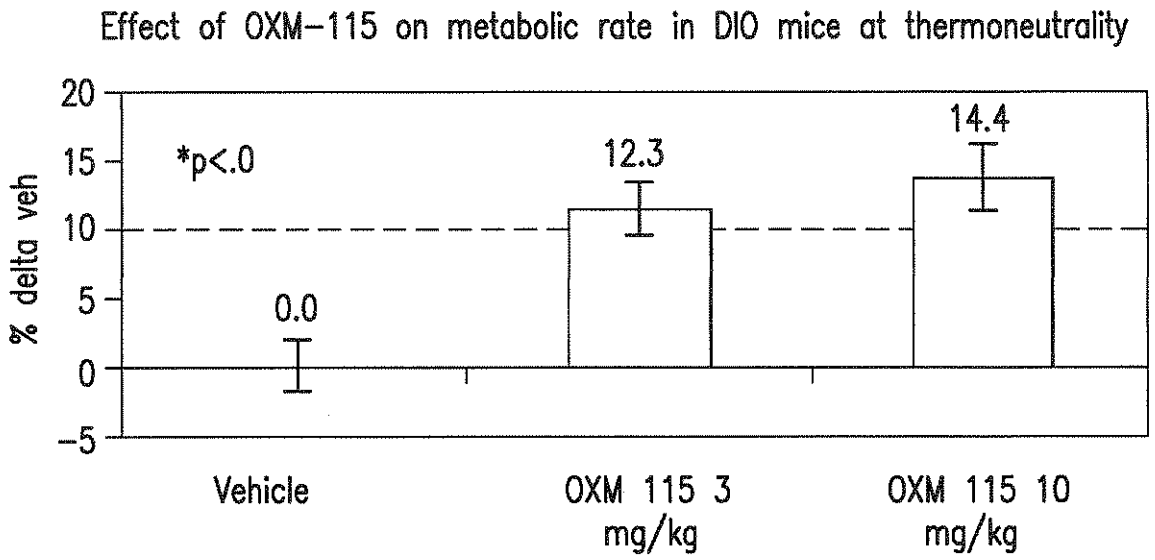

Effect of OXM-115 on metabolic rate in DIO mice at thermoneutrality
% delta veh
20
15
10
5
0
-5
*p<.0
0.0
12.3
14.4
Vehicle
OXM 115 3 mg/kg
OXM 115 10 mg/kg

FIG.14B

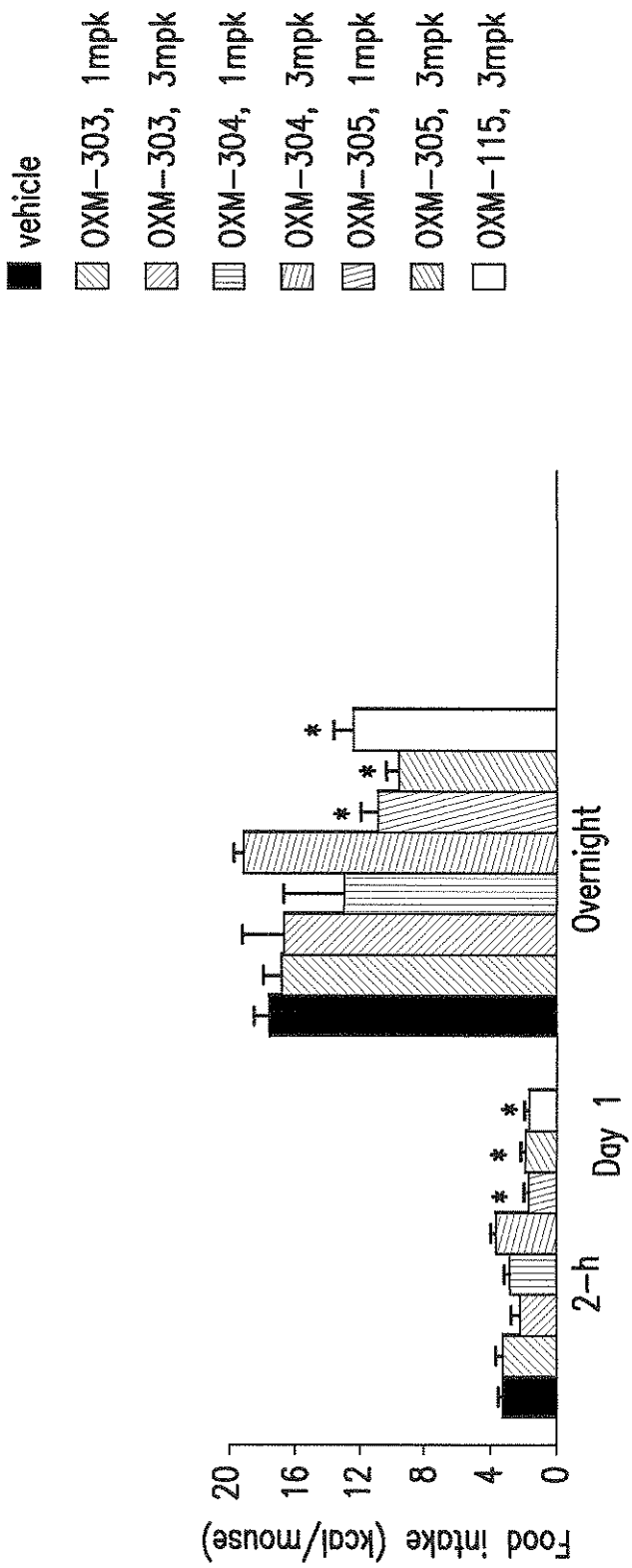

vehicle
OXM-303, 1mpk
OXM-303, 3mpk
OXM-304, 1mpk
OXM-304, 3mpk
OXM-305, 1mpk
OXM-305, 3mpk
OXM-115, 3mpk
Food intake (kcal/mouse)
0
4
8
12
16
20
2-h
Day 1
Overnight
*

FIG. 15

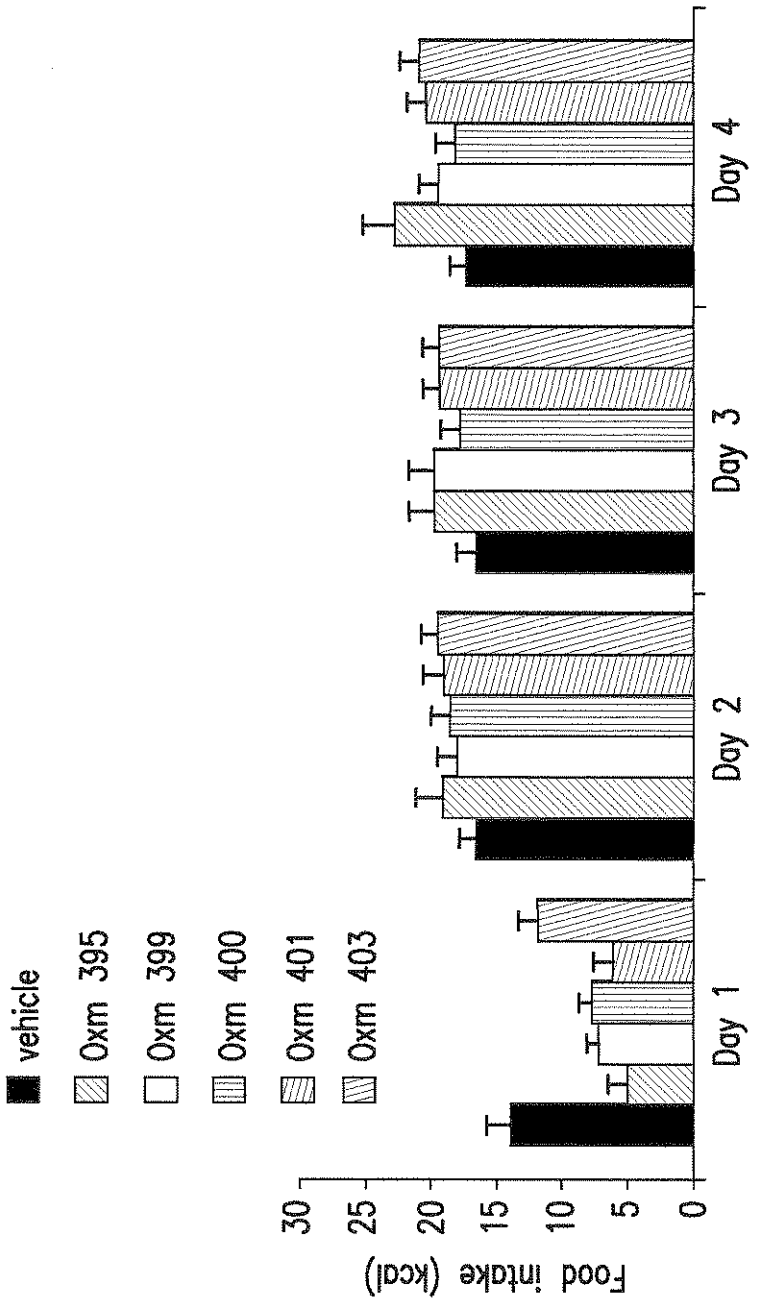

Food intake (kcal)
0
5
10
15
20
25
30
Day 1
Day 2
Day 3
Day 4
vehicle
Oxm 395
Oxm 399
Oxm 400
Oxm 401
Oxm 403

FIG.16