Mouse Pharmacodynamic Assay To Test GIPR Antibodies - Study Design

- Mice: Diet-induced obese C57BL/6 from Jackson Labs, 18 weeks of age
- Assay: To test GIPR antibody on inhibition of insulin secretion induced by exogenous GIP ([D-Ala2]-GIP) and glucose
- Readout
  - Insulin (T = 0, 30 min from [D-Ala2]-GIP and glucose dose)
  - Glucose (T = 0, 60 min from [D-Ala2]-GIP and glucose dose)
- Study groups
  - Negative control: Vehicle, [D-Ala2]-GIP (50 nmol/kg)
  - Antibody 2.63.1 at 25, 5, 1, 0.2, 0.04 mg/kg
  - Positive control: Vehicle, no [D-Ala2]-GIP

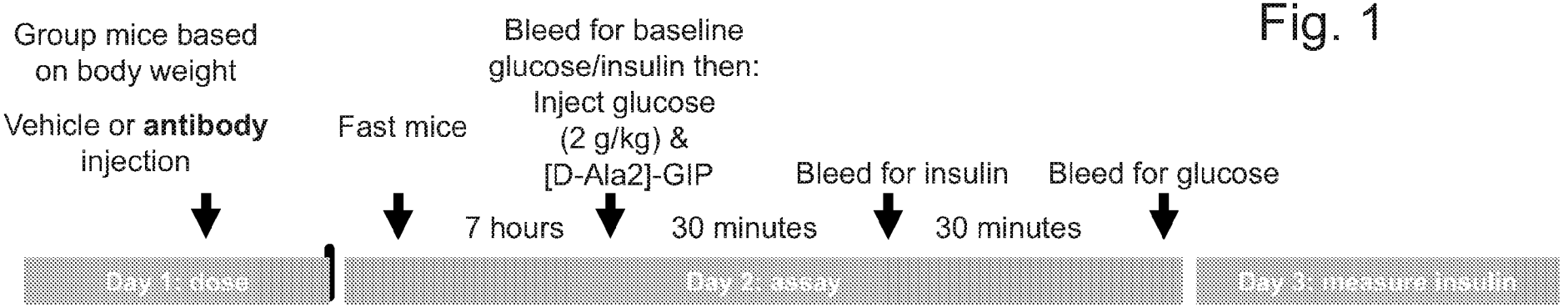


Fig. 1

GIPR Antibody 2.63.1 Antagonized GIP Induced Insulin Secretion

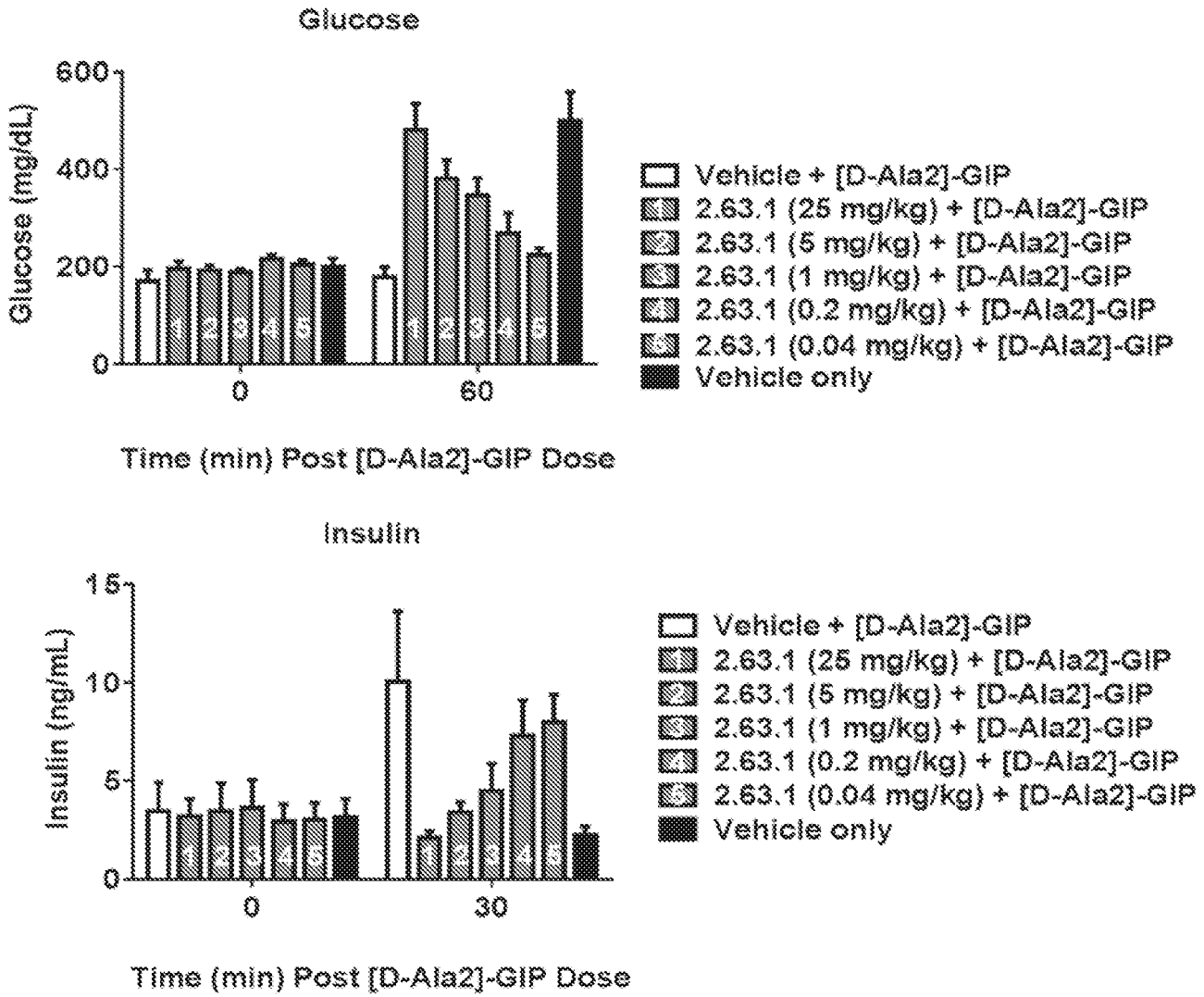
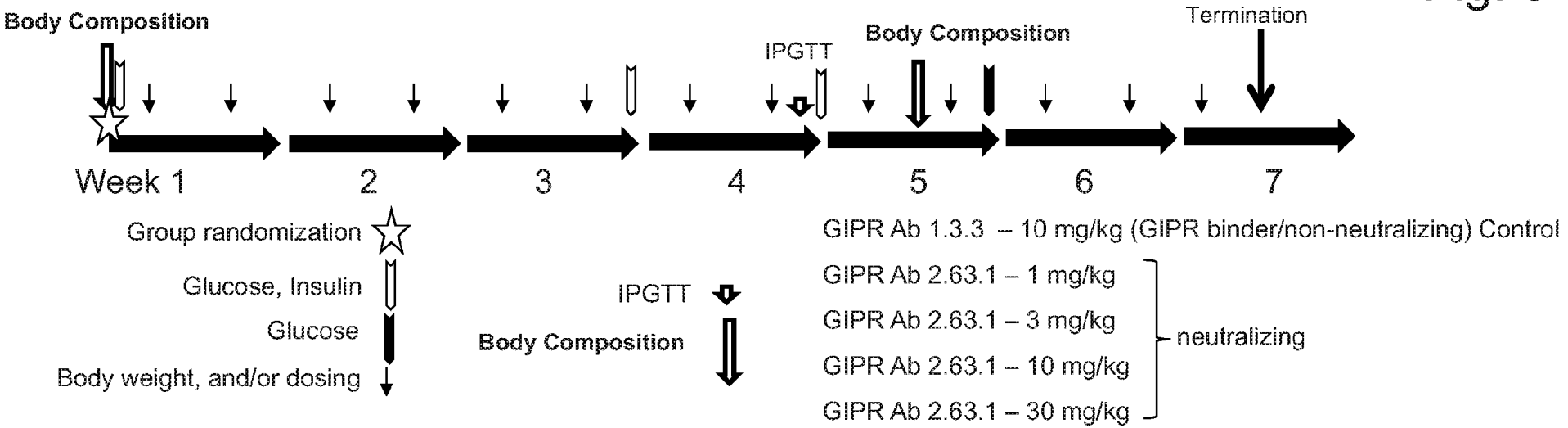


Fig. 2

Chronic Treatment Of Diet Induced Obese Mice With GIPR Antibody 2.63.1 - Study Design

- Male C57BL6 Diet-Induced Obese mice (Jackson Lab), 18 weeks old at start (on high fat diet for 12 weeks)
- Mice were randomized based on body weight, glucose and insulin (10 AM, fast for 4 hours)
- Mice were dosed twice a week for 6 weeks
- Body weights weekly; fasting glucose measured at study start and week 3, week 4, week 5
- Blood collected at study start and week 3. Terminal blood collected for measurement of insulin, total cholesterol, and triglycerides.
- Intraperitoneal glucose tolerance test (IPGTT) was performed at week 4 with 4 hour fast with 1 g/kg of glucose
- Body composition analysis of fat/lean mass was measured at beginning of the study and week 4.5
- At week 6.5, study was terminated.
  - Terminal blood
  - Liver and epididymal white adipose tissue (EpiWAT) weight
  - Collected liver and EpiWAT for pathology

Fig. 3



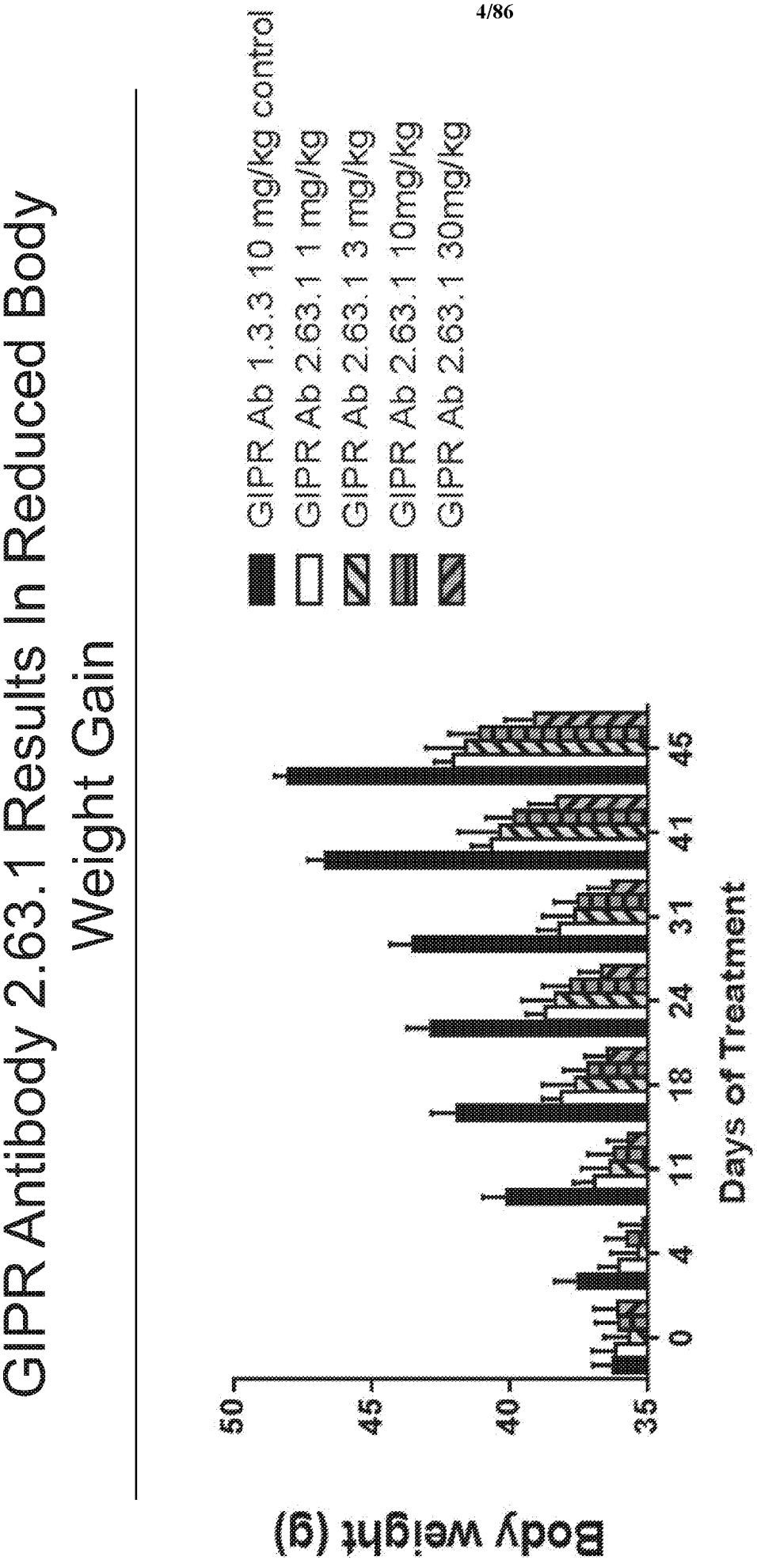

GIPR Antibody 2.63.1 Results In Reduced Body Weight Gain
GIPR Ab 1.3.3 10 mg/kg control
GIPR Ab 2.63.1 1 mg/kg
GIPR Ab 2.63.1 3 mg/kg
GIPR Ab 2.63.1 10mg/kg
GIPR Ab 2.63.1 30mg/kg
Body weight (g)
50
45
40
35
0
4
11
18
24
31
41
45
Days of Treatment

Fig. 4

GIPR Antibody 2.63.1 Results In Lower Fat Mass

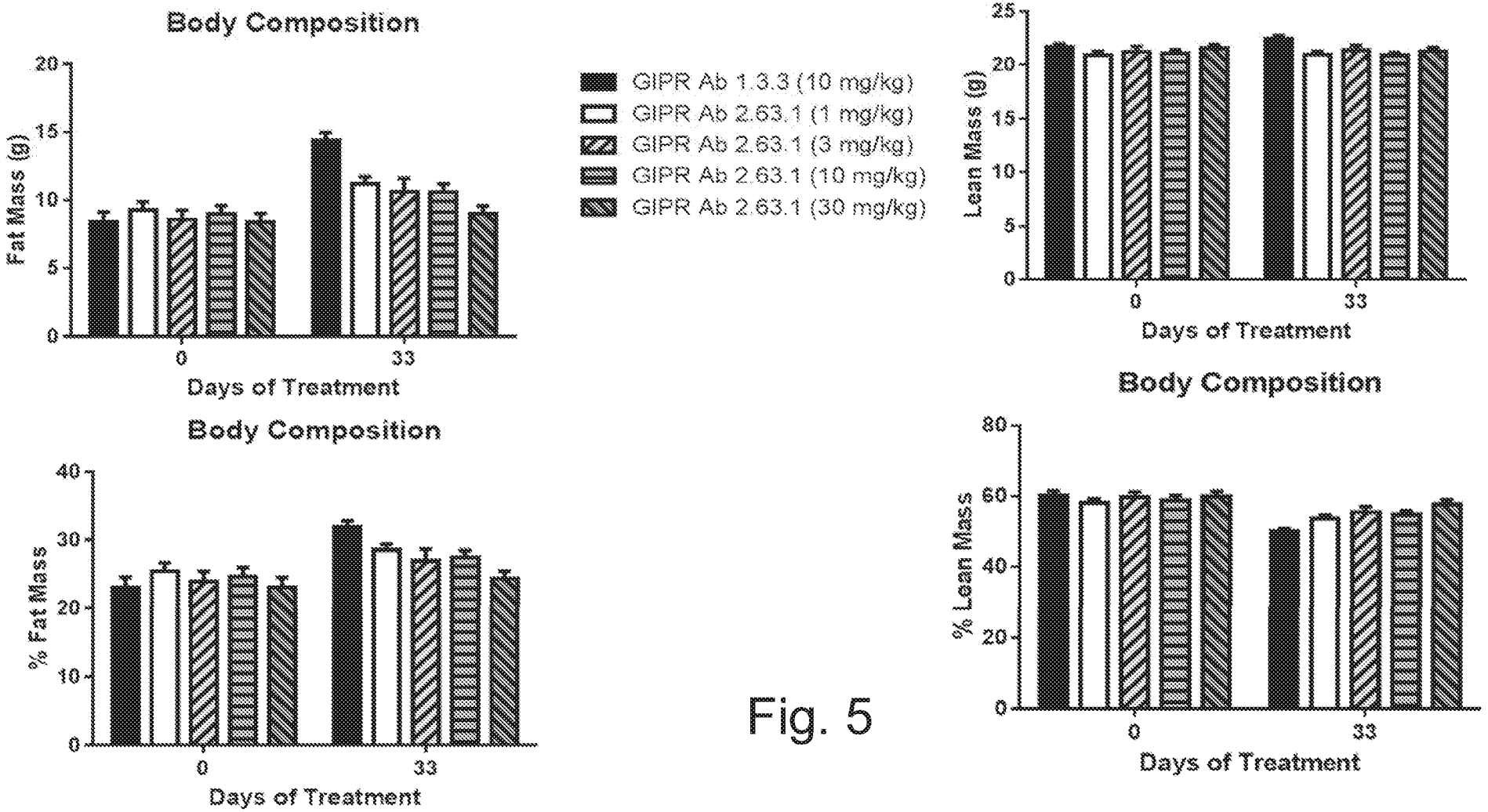


Fig. 5

GIPR Antibody 2.63.1 Results In Lower Epididymal White Adipose Tissue Weights

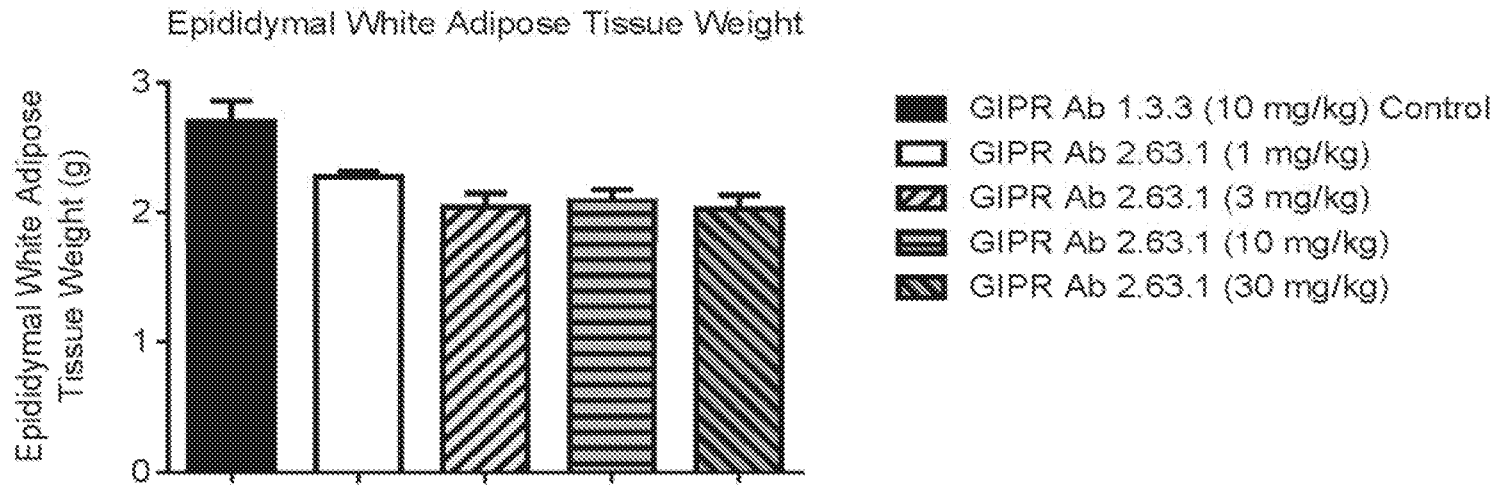


Fig. 6

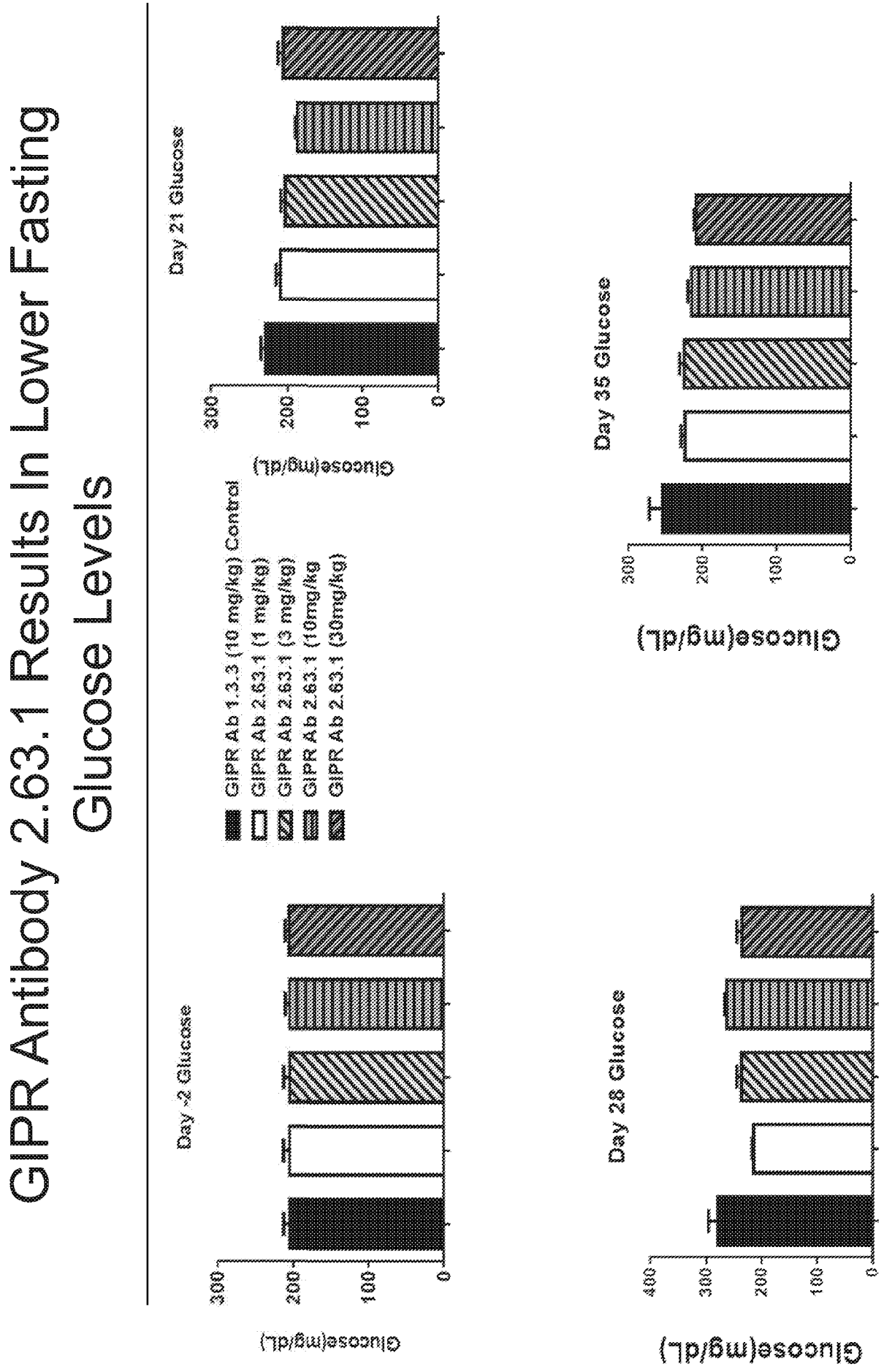

GIPR Antibody 2.63.1 Results In Lower Fasting Glucose Levels
Day -2 Glucose
Day 21 Glucose
Day 28 Glucose
Day 35 Glucose
Glucose(mg/dL)
GIPR Ab 1.3.3 (10 mg/kg) Control
GIPR Ab 2.63.1 (1 mg/kg)
GIPR Ab 2.63.1 (3 mg/kg)
GIPR Ab 2.63.1 (10mg/kg
GIPR Ab 2.63.1 (30mg/kg)

Fig. 7

GIPR Antibody 2.63.1 Results In Lower Insulin Levels

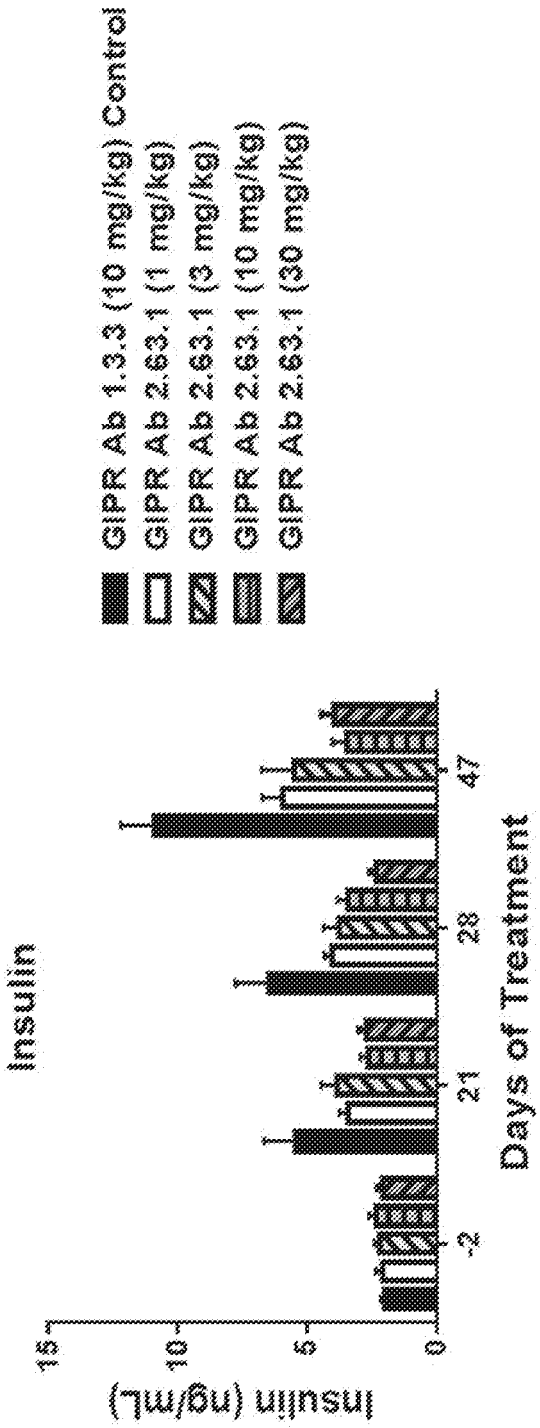


Fig. 8

GIPR Antibody 2.63.1 Results In Improved Glucose Tolerance

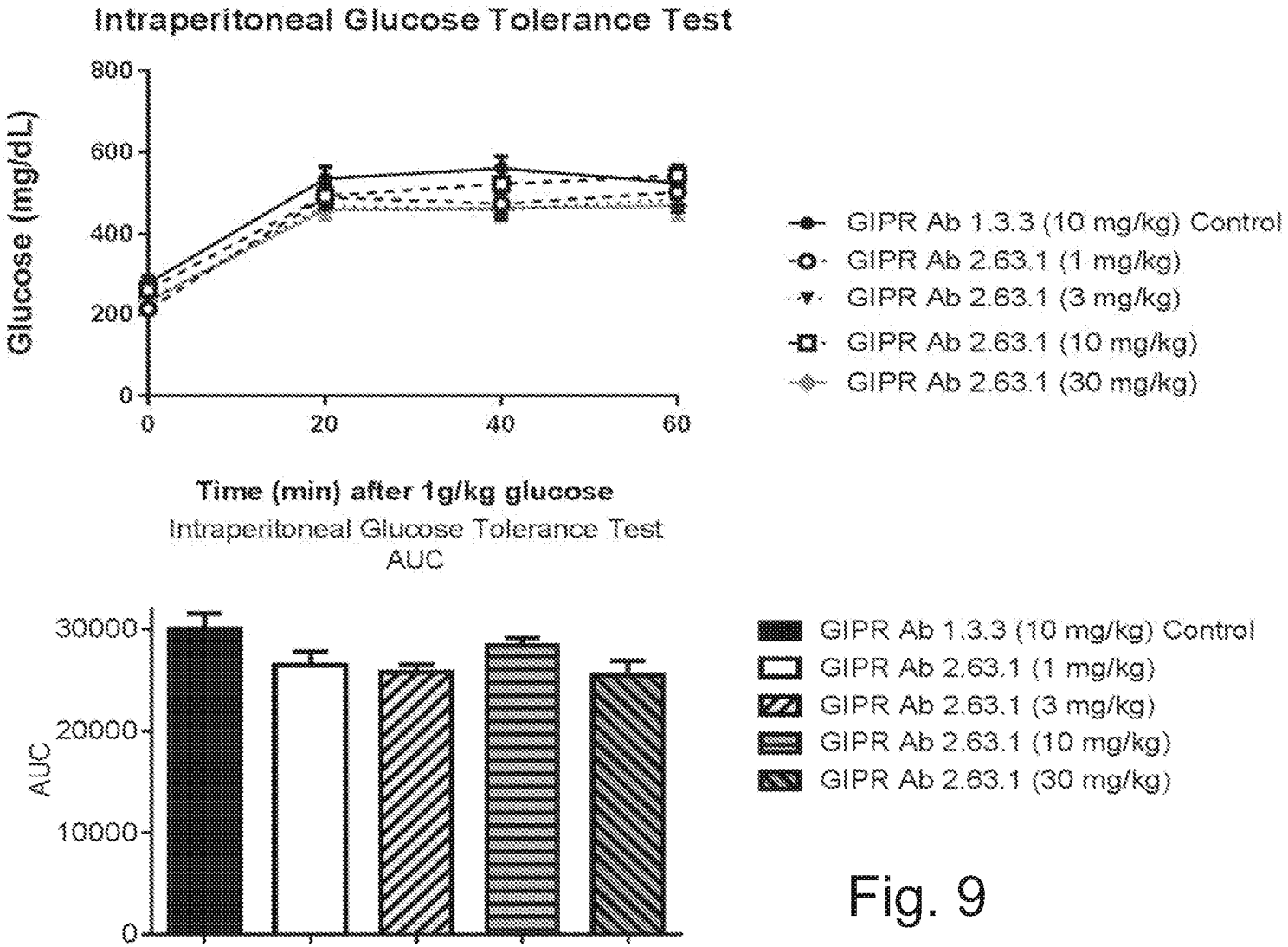


Fig. 9

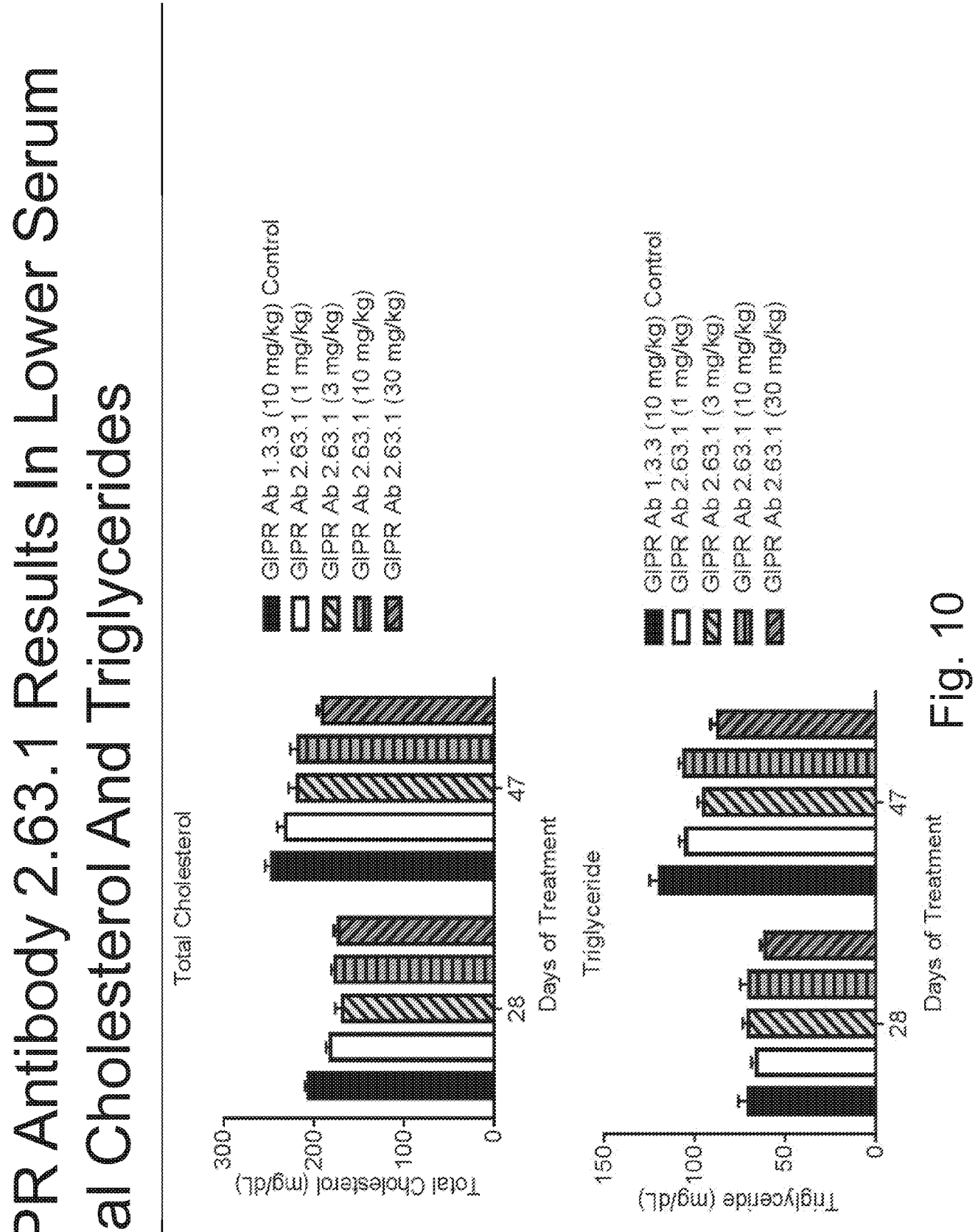

GIPR Antibody 2.63.1 Results In Lower Serum Total Cholesterol And Triglycerides
Total Cholesterol
Total Cholesterol (mg/dL)
300
200
100
0
28
47
Days of Treatment
GIPR Ab 1.3.3 (10 mg/kg) Control
GIPR Ab 2.63.1 (1 mg/kg)
GIPR Ab 2.63.1 (3 mg/kg)
GIPR Ab 2.63.1 (10 mg/kg)
GIPR Ab 2.63.1 (30 mg/kg)
Triglyceride
Triglyceride (mg/dL)
150
100
50
0
28
47
Days of Treatment
GIPR Ab 1.3.3 (10 mg/kg) Control
GIPR Ab 2.63.1 (1 mg/kg)
GIPR Ab 2.63.1 (3 mg/kg)
GIPR Ab 2.63.1 (10 mg/kg)
GIPR Ab 2.63.1 (30 mg/kg)

Fig. 10

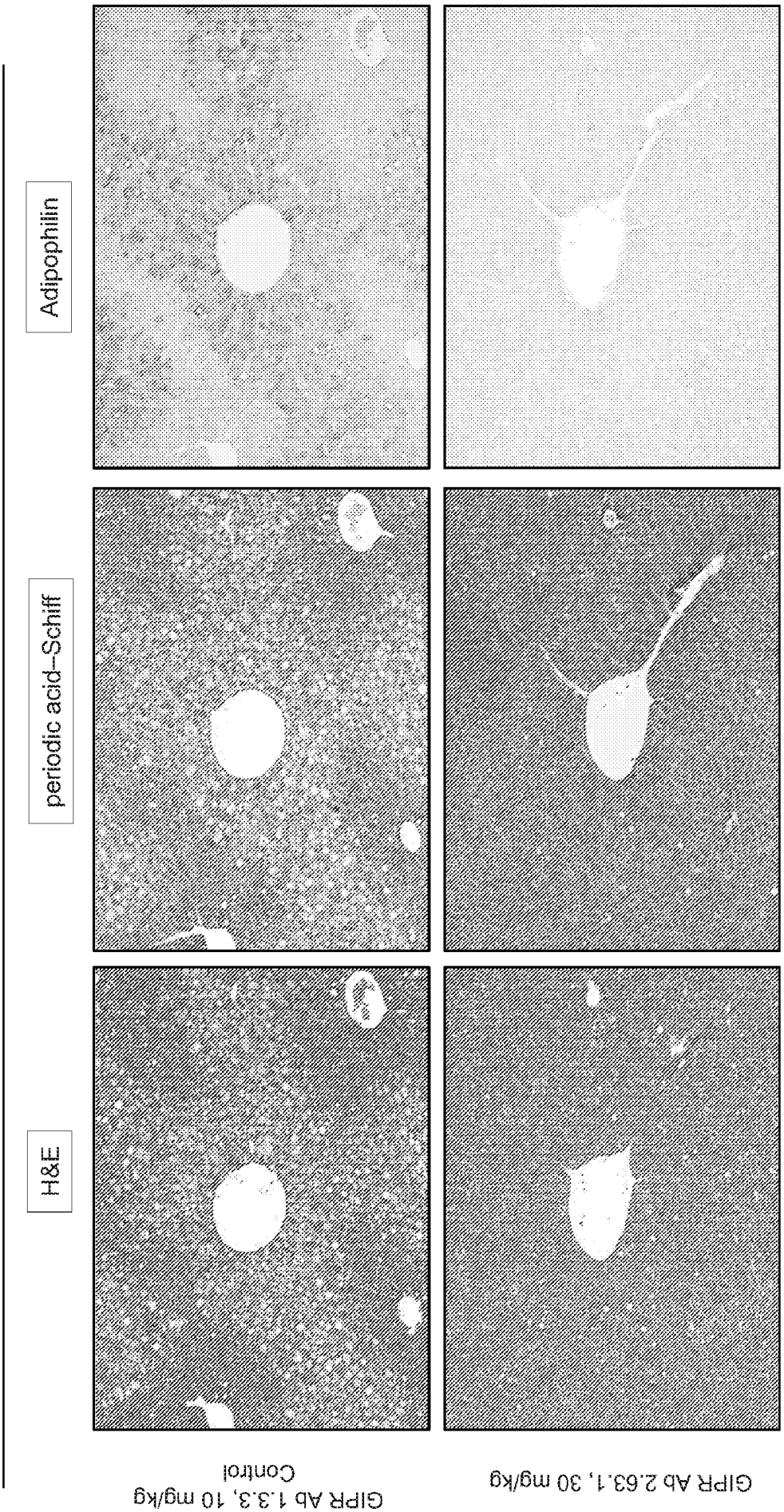

GIPR Antibody 2.63.1 Results In A Reduction In Hepatocyte Microvesicular Change And Corresponding Lipid Accumulation
H&E
periodic acid–Schiff
Adipophilin
GIPR Ab 1.3.3, 10 mg/kg Control
GIPR Ab 2.63.1, 30 mg/kg

Fig. 11

GIPR Antibody 2.63.1 Results In Reduced Liver Weight And Triglyceride Content

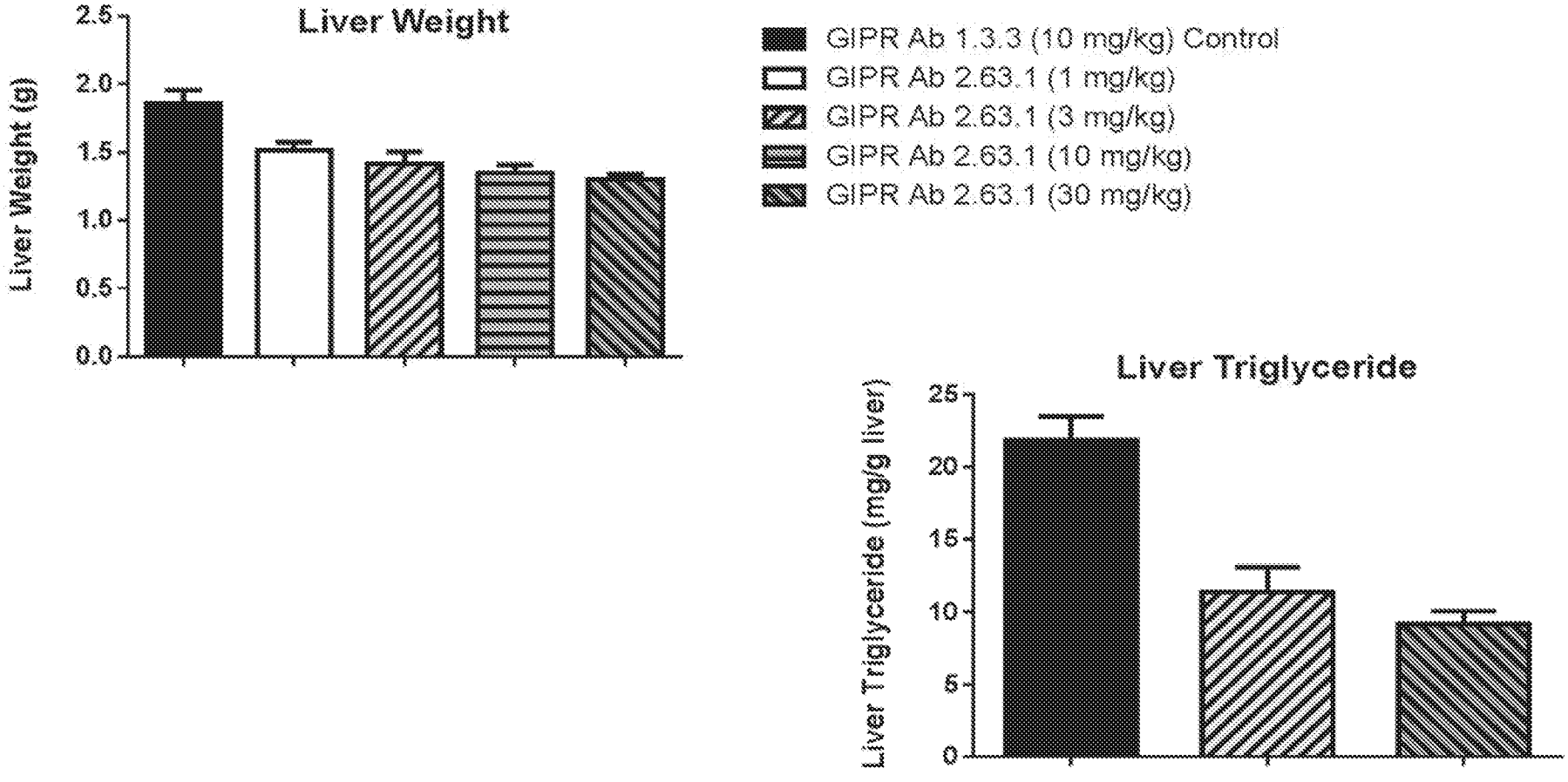


Fig. 12

Reduced Inflammation And Reduced Infiltrating Macrophages Cells Surrounding Adipocytes In Epididymal White Adipose Tissue With GIPR Antibody 2.63.1 Treatment

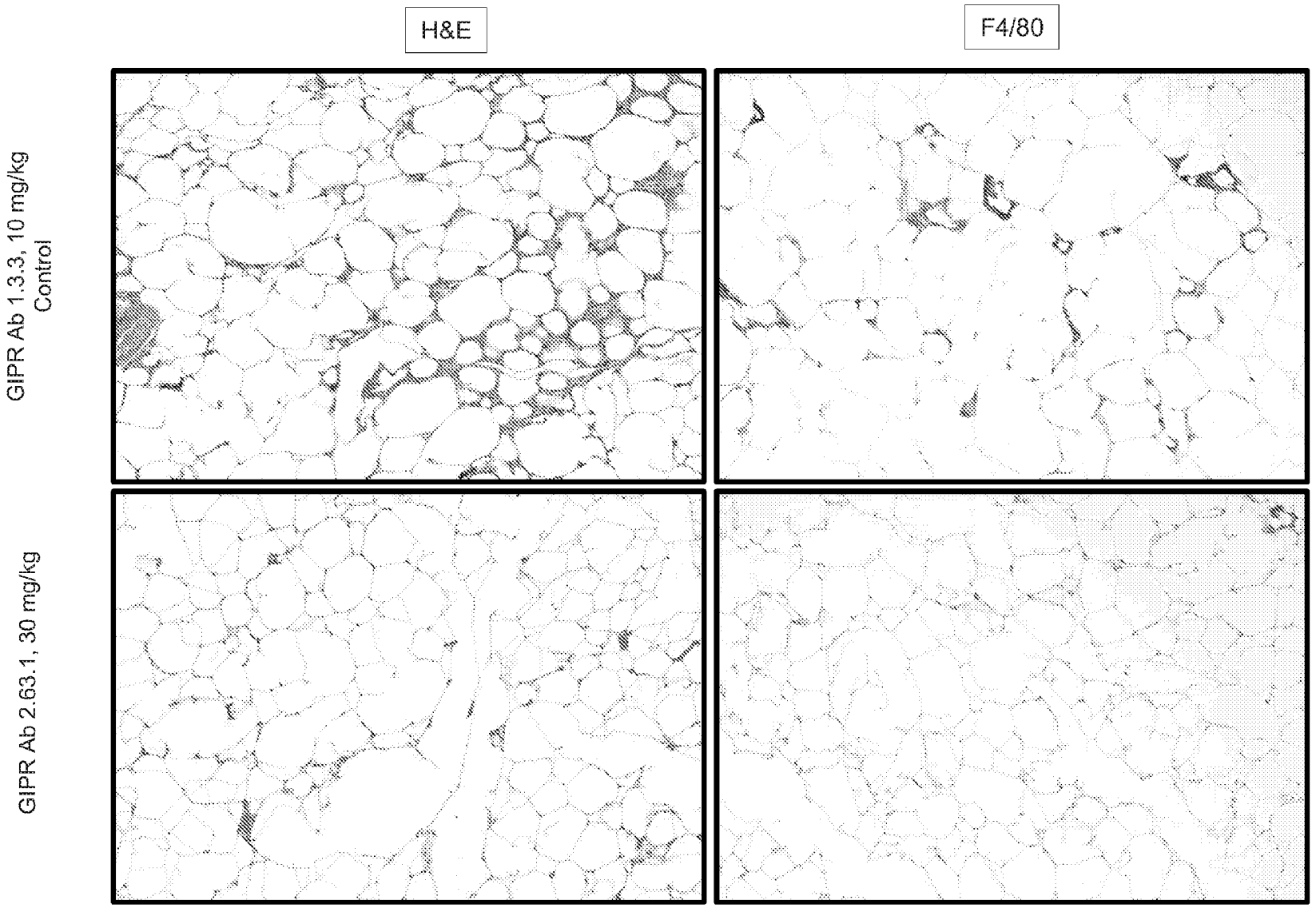


Fig. 13

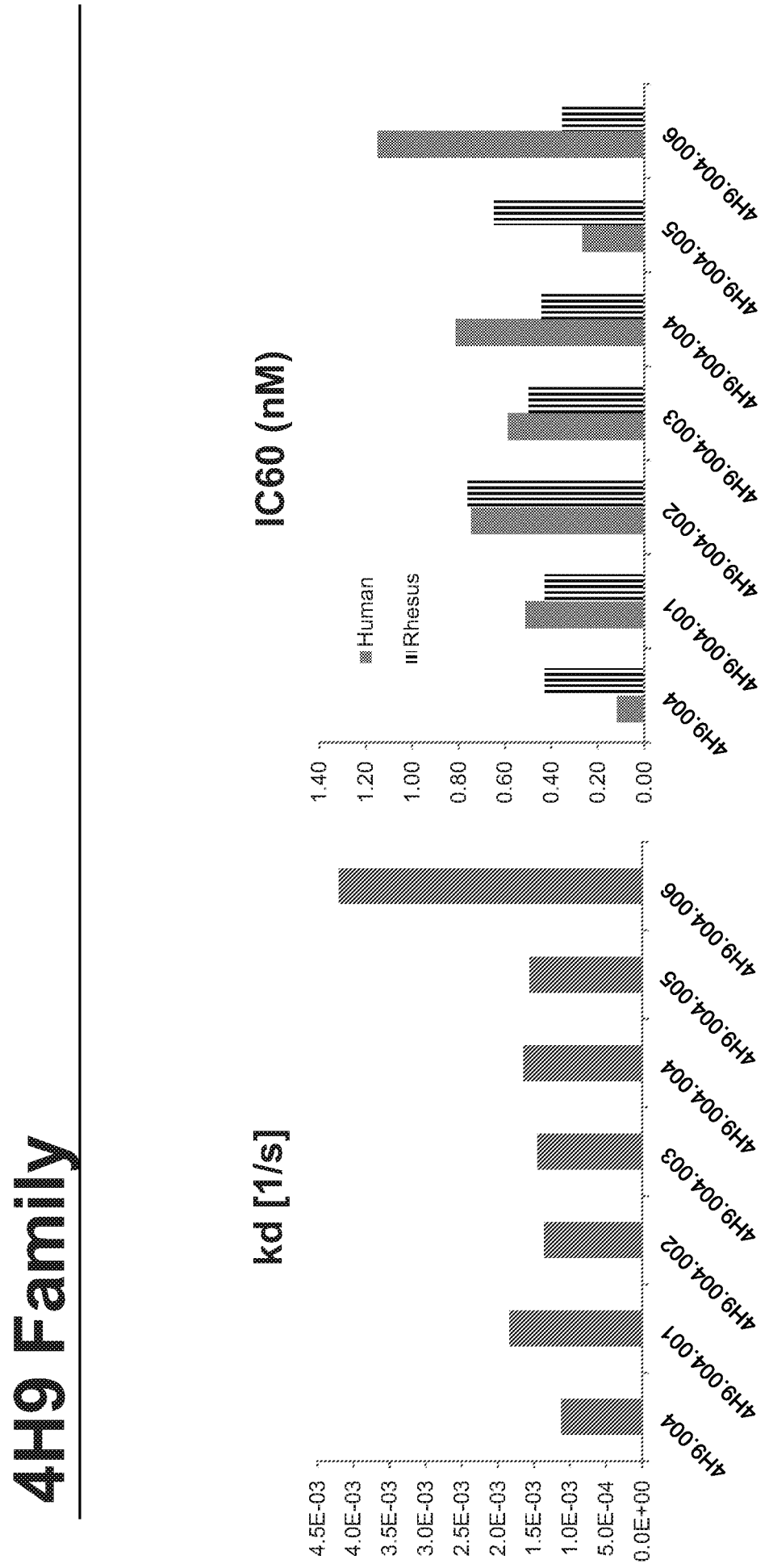

4H9 Family
kd [1/s]
4.5E-03
4.0E-03
3.5E-03
3.0E-03
2.5E-03
2.0E-03
1.5E-03
1.0E-03
5.0E-04
0.0E+00
4H9.004
4H9.004.001
4H9.004.002
4H9.004.003
4H9.004.004
4H9.004.005
4H9.004.006
IC60 (nM)
Human
Rhesus
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
4H9.004
4H9.004.001
4H9.004.002
4H9.004.003
4H9.004.004
4H9.004.005
4H9.004.006

Fig. 14A

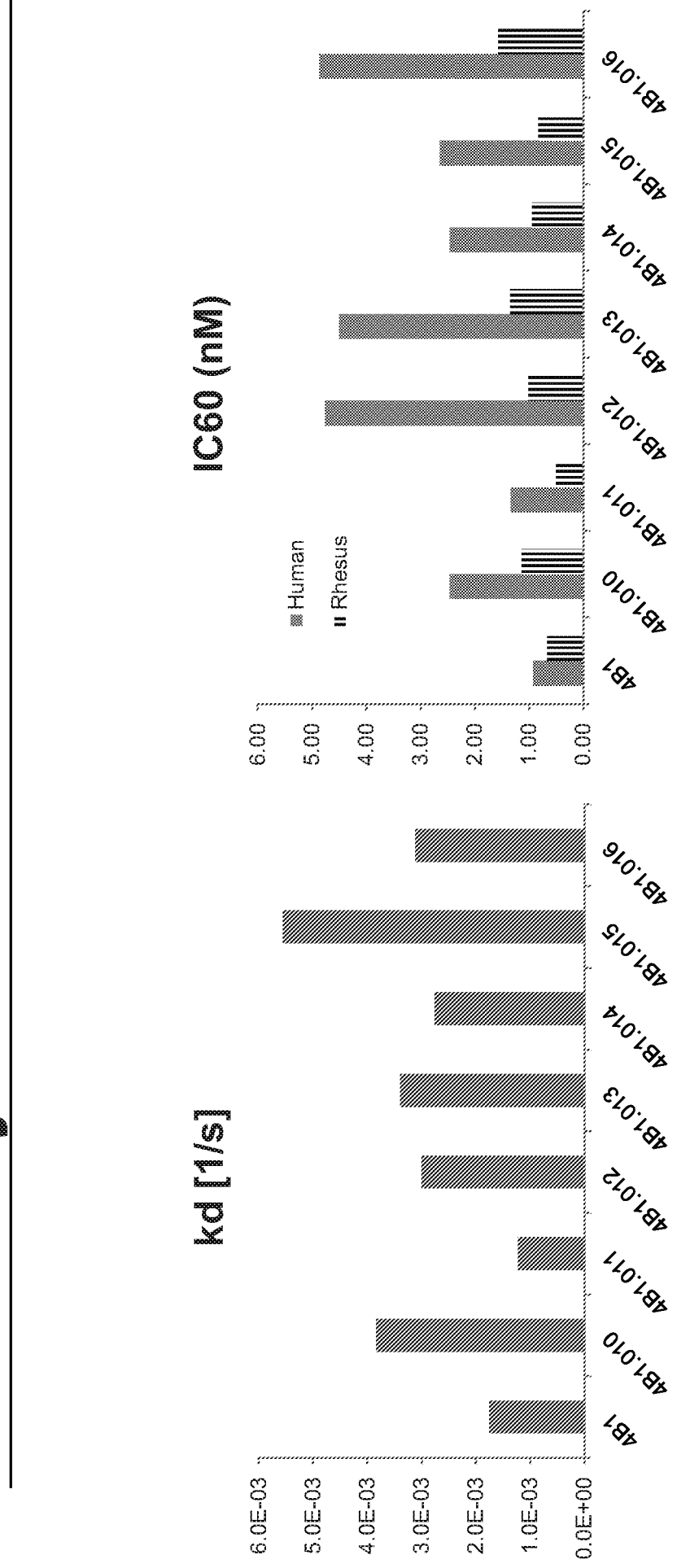

4B1 Family
kd [1/s]
6.0E-03
5.0E-03
4.0E-03
3.0E-03
2.0E-03
1.0E-03
0.0E+00
4B1
4B1.010
4B1.011
4B1.012
4B1.013
4B1.014
4B1.015
4B1.016
IC60 (nM)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Human
Rhesus
4B1
4B1.010
4B1.011
4B1.012
4B1.013
4B1.014
4B1.015
4B1.016

Fig. 14B

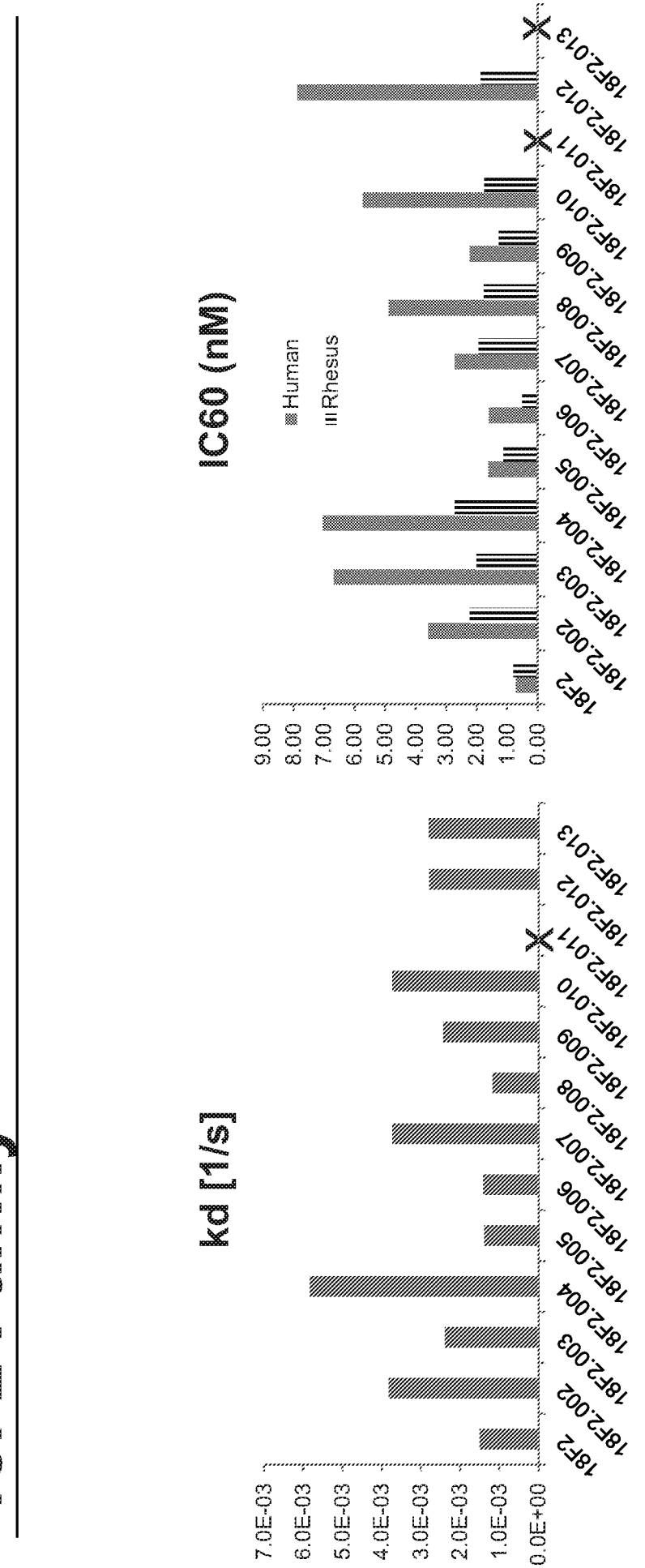

18F2 Family
kd [1/s]
7.0E-03
6.0E-03
5.0E-03
4.0E-03
3.0E-03
2.0E-03
1.0E-03
0.0E+00
18F2
18F2.002
18F2.003
18F2.004
18F2.005
18F2.006
18F2.007
18F2.008
18F2.009
18F2.010
18F2.011
18F2.012
18F2.013
IC60 (nM)
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Human
Rhesus
18F2
18F2.002
18F2.003
18F2.004
18F2.005
18F2.006
18F2.007
18F2.008
18F2.009
18F2.010
18F2.011
18F2.012
18F2.013
X No Inhibition/Binding

Fig. 14C

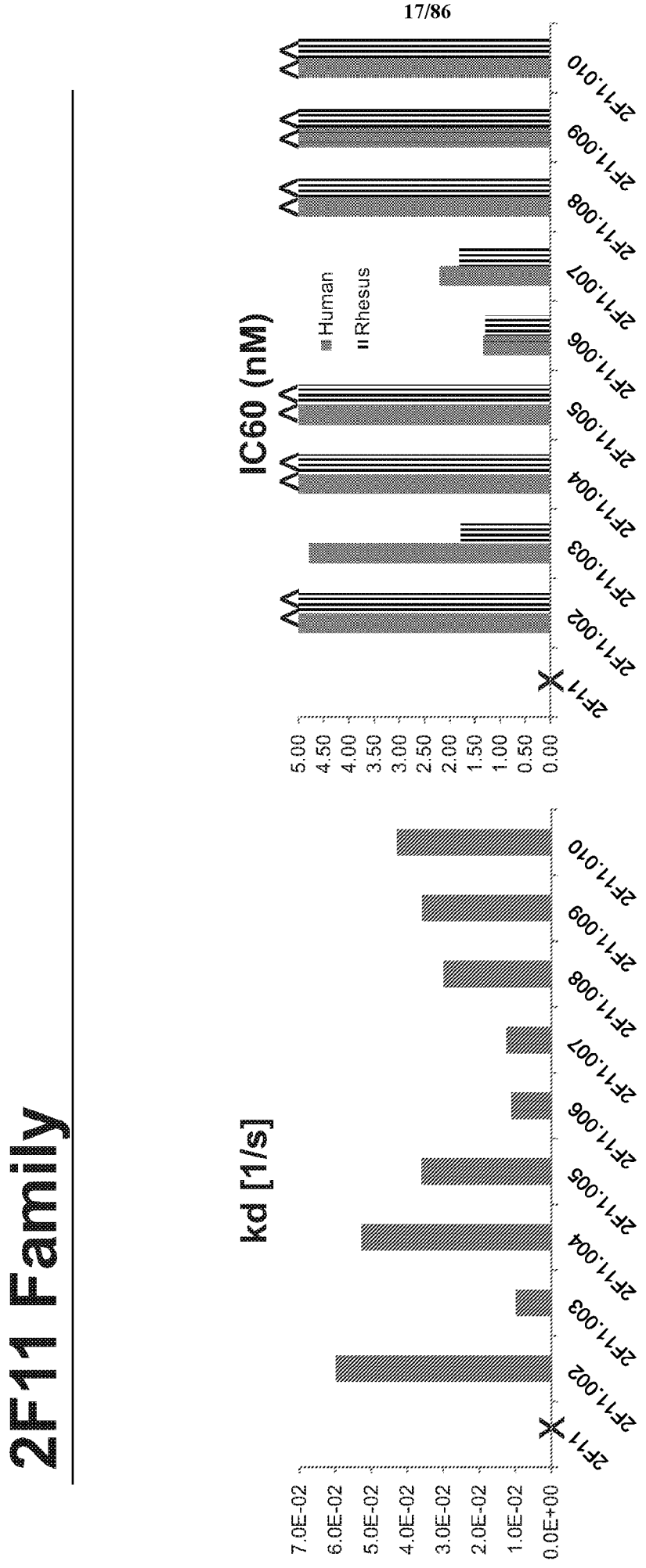

2F11 Family
kd [1/s]
7.0E-02
6.0E-02
5.0E-02
4.0E-02
3.0E-02
2.0E-02
1.0E-02
0.0E+00
2F11
2F11.002
2F11.003
2F11.004
2F11.005
2F11.006
2F11.007
2F11.008
2F11.009
2F11.010
IC60 (nM)
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14D

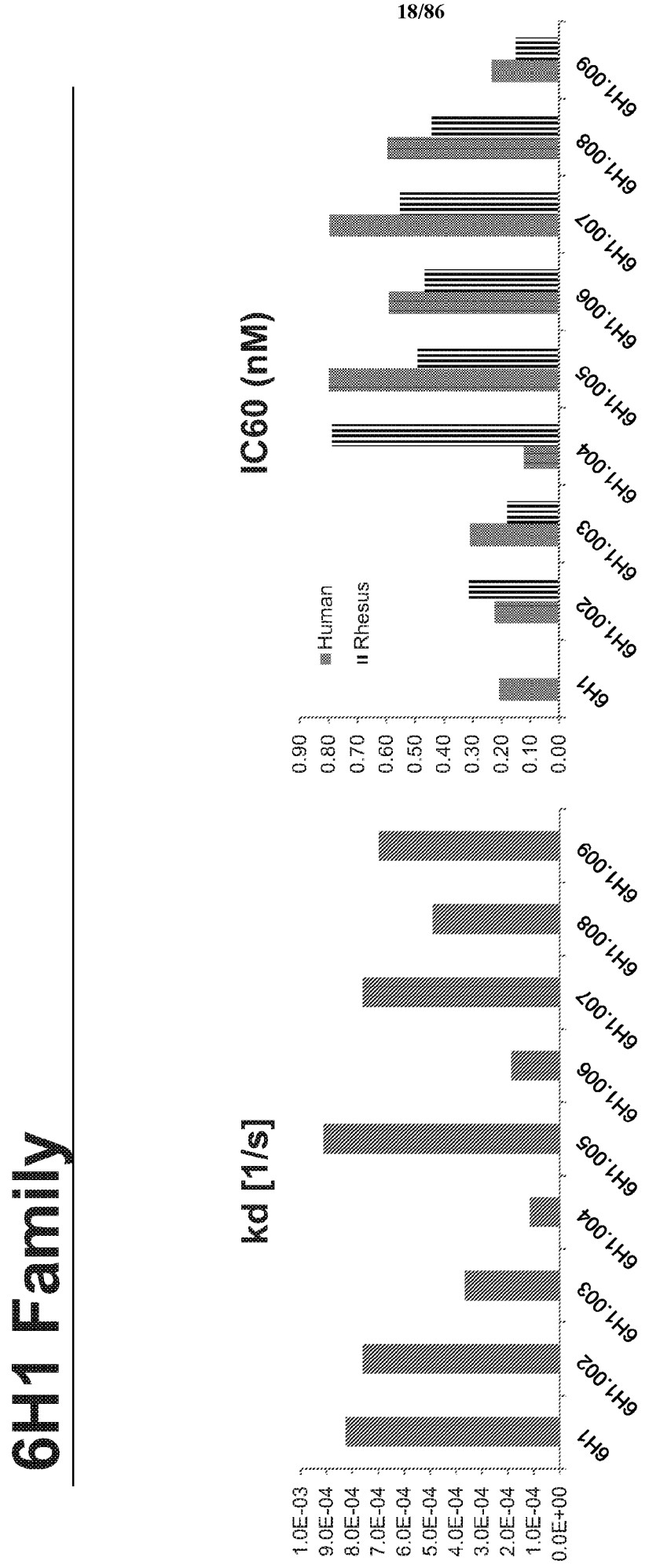

6H1 Family
kd [1/s]
1.0E-03
9.0E-04
8.0E-04
7.0E-04
6.0E-04
5.0E-04
4.0E-04
3.0E-04
2.0E-04
1.0E-04
0.0E+00
6H1
6H1.002
6H1.003
6H1.004
6H1.005
6H1.006
6H1.007
6H1.008
6H1.009
IC60 (nM)
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Human
Rhesus
6H1
6H1.002
6H1.003
6H1.004
6H1.005
6H1.006
6H1.007
6H1.008
6H1.009

Fig. 14E

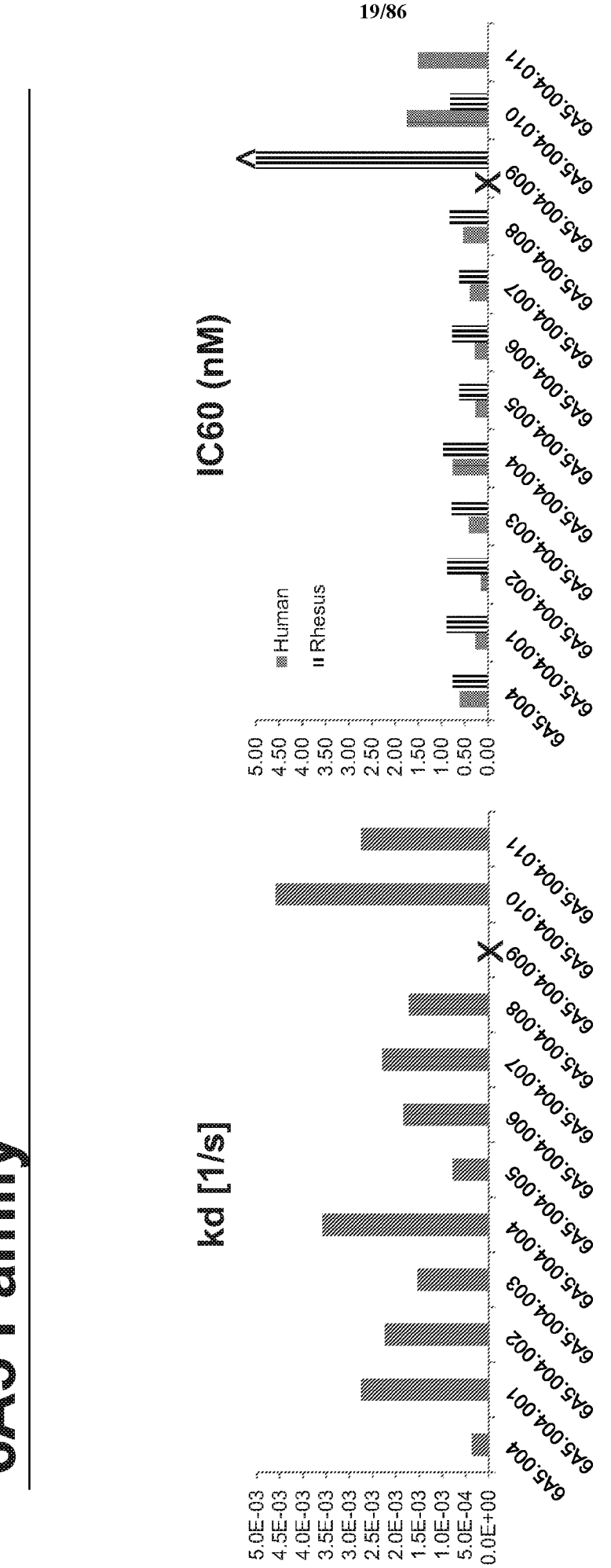

6A5 Family
kd [1/s]
5.0E-03
4.5E-03
4.0E-03
3.5E-03
3.0E-03
2.5E-03
2.0E-03
1.5E-03
1.0E-03
5.0E-04
0.0E+00
6A5.004
6A5.004.001
6A5.004.002
6A5.004.003
6A5.004.004
6A5.004.005
6A5.004.006
6A5.004.007
6A5.004.008
6A5.004.009
6A5.004.010
6A5.004.011
IC60 (nM)
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14F

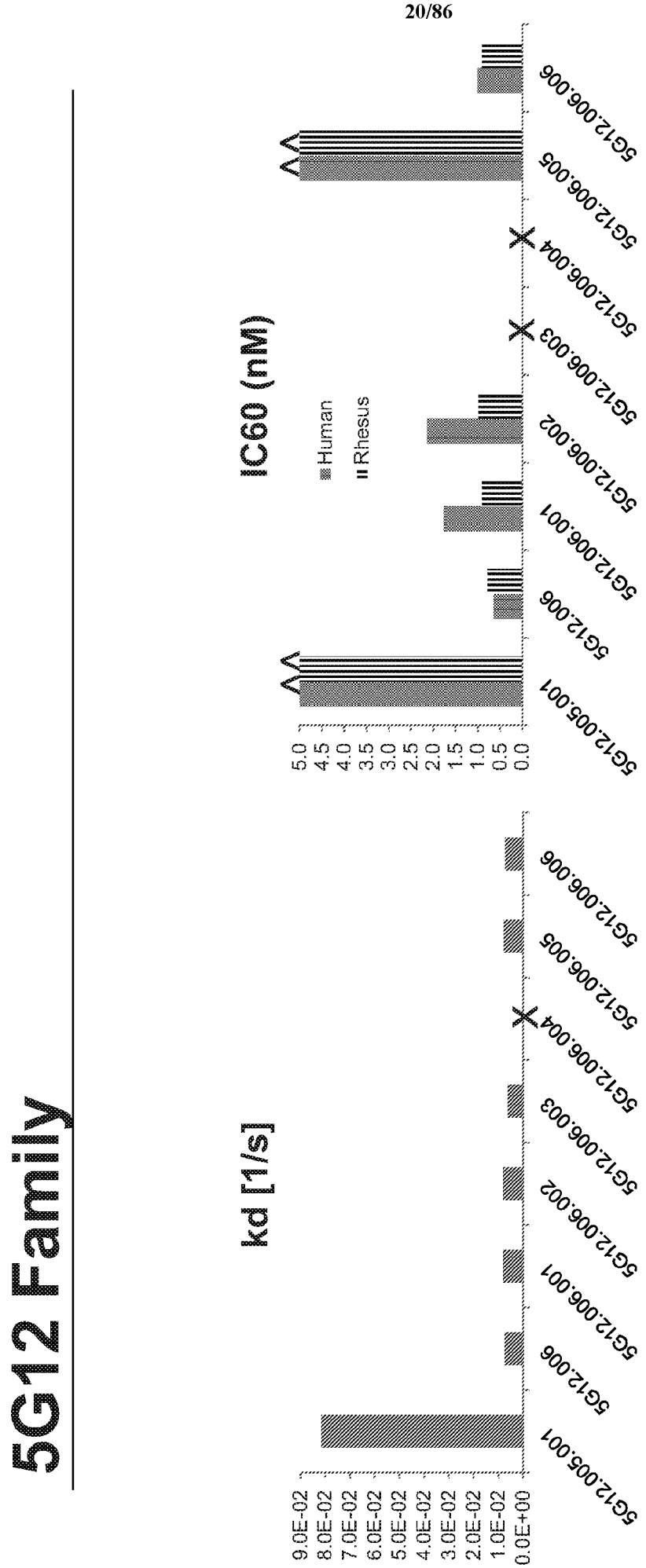

5G12 Family
kd [1/s]
9.0E-02
8.0E-02
7.0E-02
6.0E-02
5.0E-02
4.0E-02
3.0E-02
2.0E-02
1.0E-02
0.0E+00
IC60 (nM)
Human
Rhesus
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
5G12.006.001
5G12.006
5G12.006.001
5G12.006.002
5G12.006.003
5G12.006.004
5G12.006.005
5G12.006.006
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14G

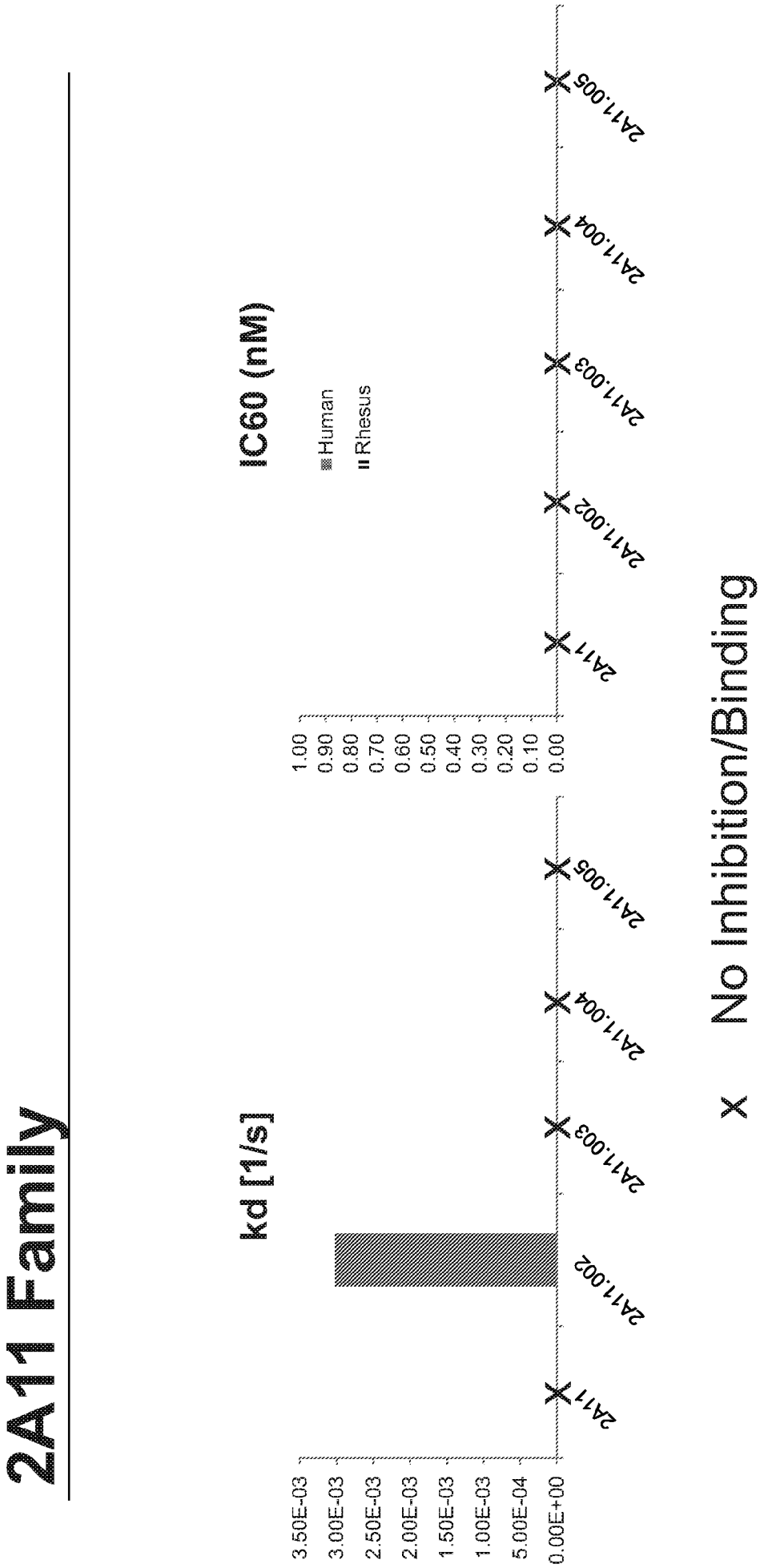

2A11 Family
kd [1/s]
3.50E-03
3.00E-03
2.50E-03
2.00E-03
1.50E-03
1.00E-03
5.00E-04
0.00E+00
2A11
2A11.002
2A11.003
2A11.004
2A11.005
IC60 (nM)
Human
Rhesus
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
2A11
2A11.002
2A11.003
2A11.004
2A11.005
x No Inhibition/Binding

Fig. 14H

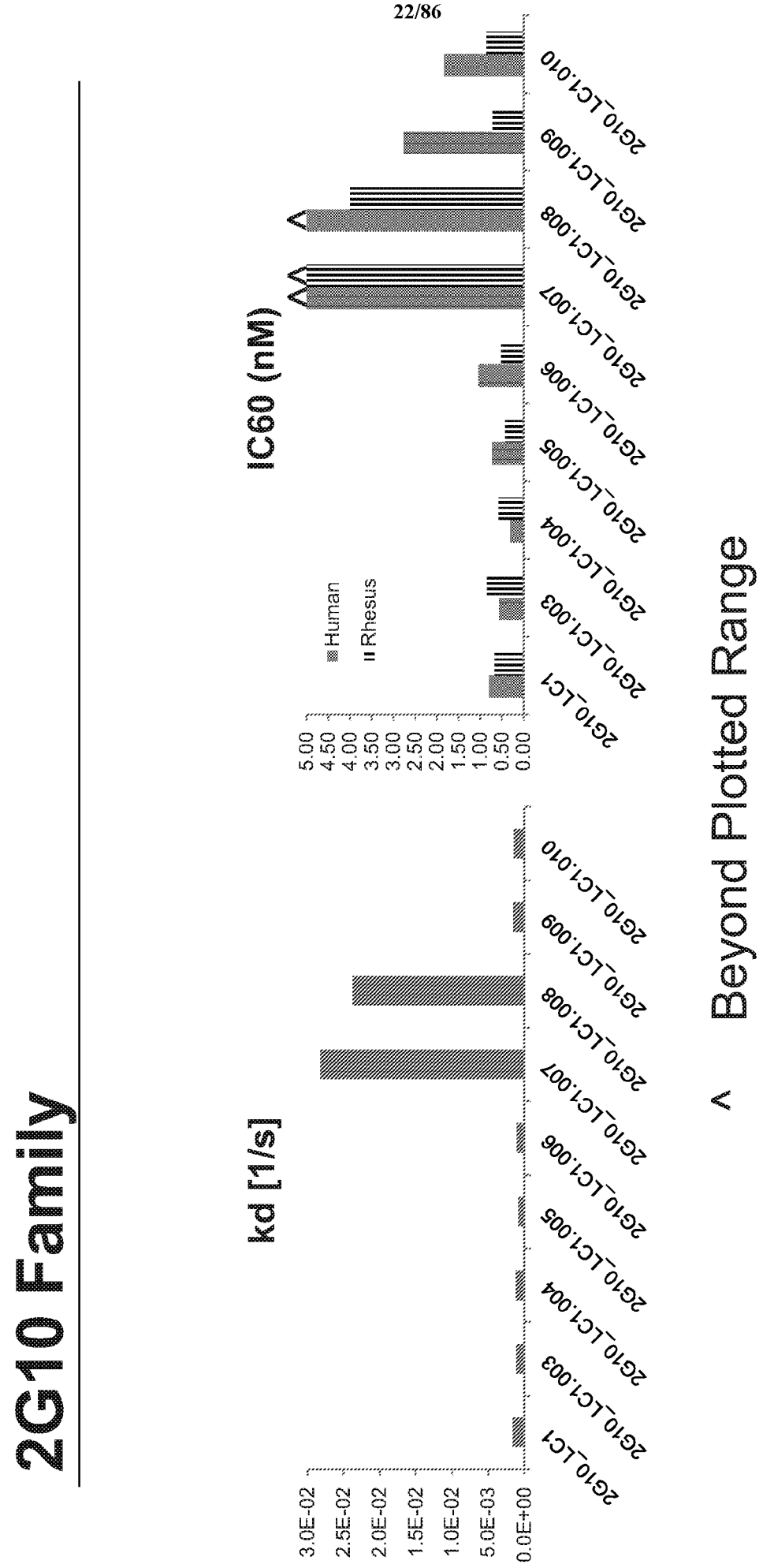

2G10 Family
kd [1/s]
3.0E-02
2.5E-02
2.0E-02
1.5E-02
1.0E-02
5.0E-03
0.0E+00
2G10_LC1
2G10_LC1.003
2G10_LC1.004
2G10_LC1.005
2G10_LC1.006
2G10_LC1.007
2G10_LC1.008
2G10_LC1.009
2G10_LC1.010
IC60 (nM)
Human
Rhesus
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
> Beyond Plotted Range

Fig. 14I

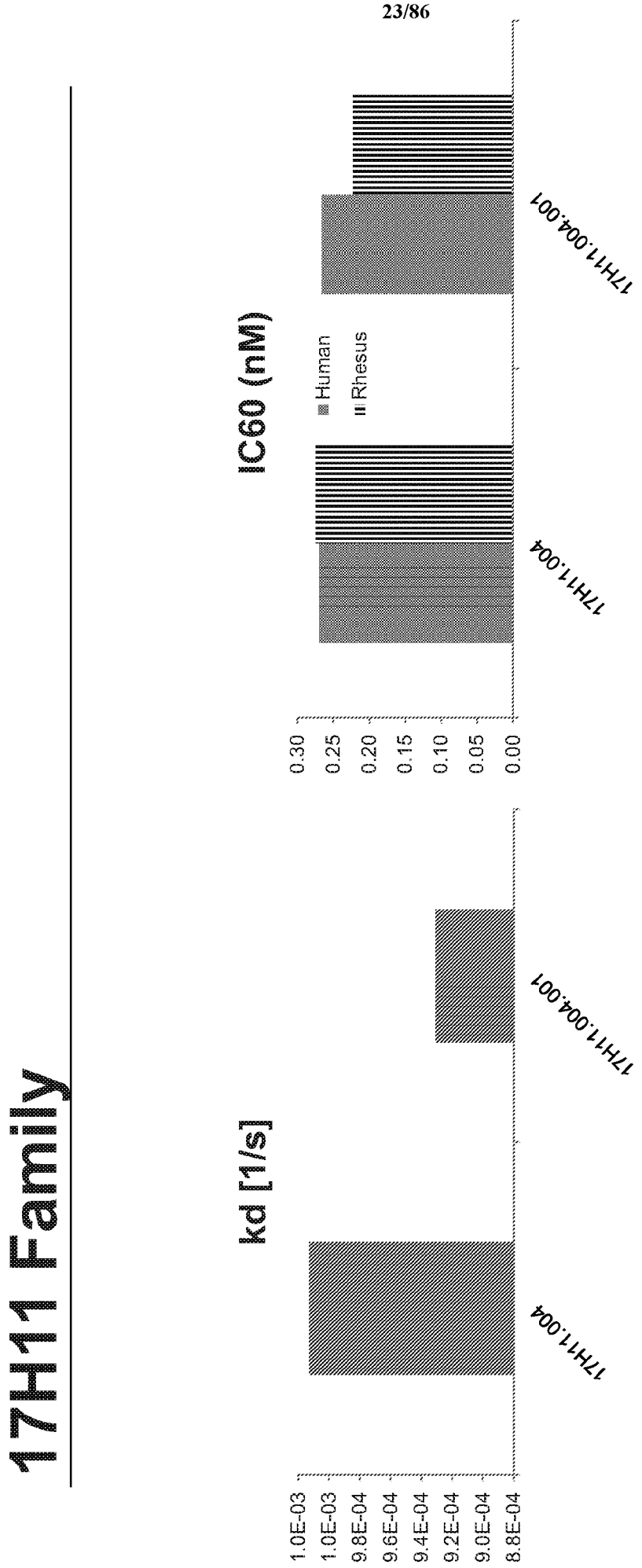

17H11 Family
kd [1/s]
1.0E-03
1.0E-03
9.8E-04
9.6E-04
9.4E-04
9.2E-04
9.0E-04
8.8E-04
17H11.004
17H11.004.001
IC60 (nM)
Human
Rhesus
0.30
0.25
0.20
0.15
0.10
0.05
0.00
17H11.004
17H11.004.001

Fig. 14J

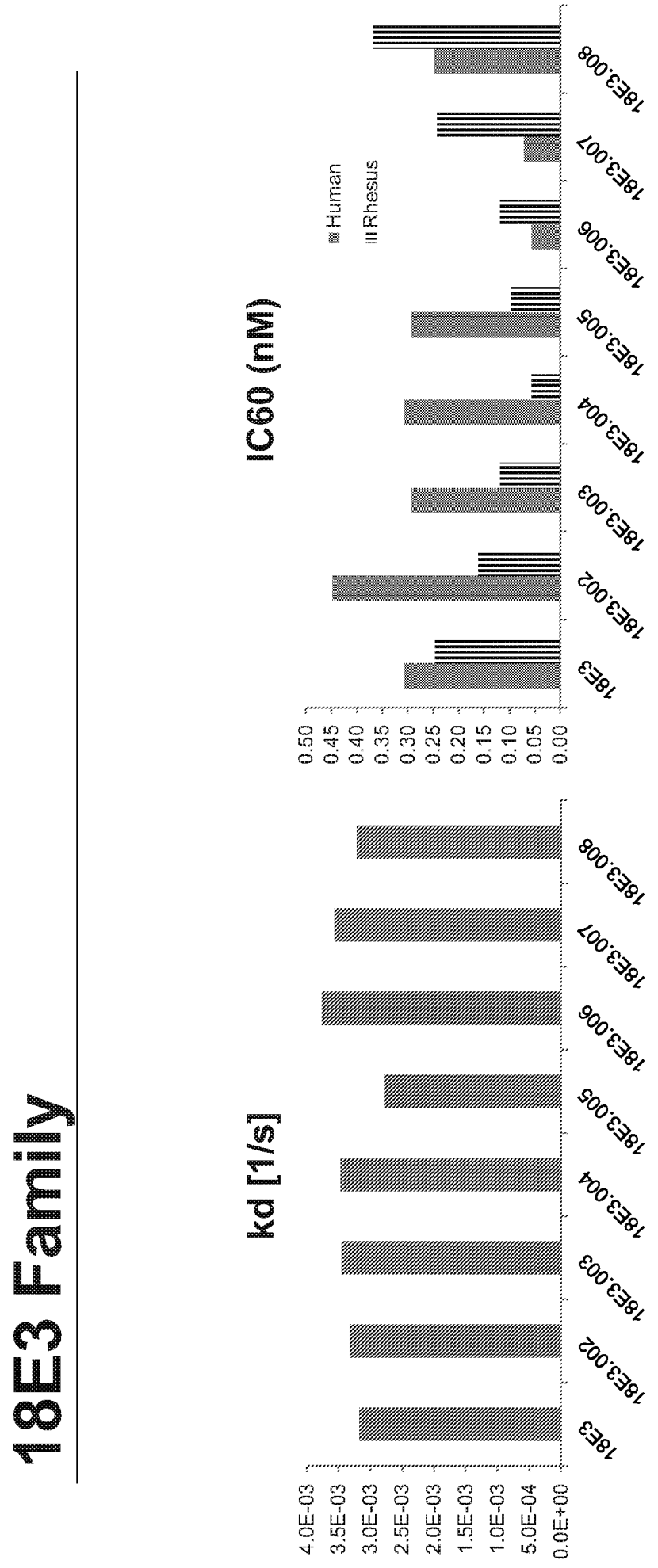

18E3 Family
kd [1/s]
4.0E-03
3.5E-03
3.0E-03
2.5E-03
2.0E-03
1.5E-03
1.0E-03
5.0E-04
0.0E+00
18E3
18E3.002
18E3.003
18E3.004
18E3.005
18E3.006
18E3.007
18E3.008
IC60 (nM)
Human
Rhesus
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
18E3
18E3.002
18E3.003
18E3.004
18E3.005
18E3.006
18E3.007
18E3.008

Fig. 14K

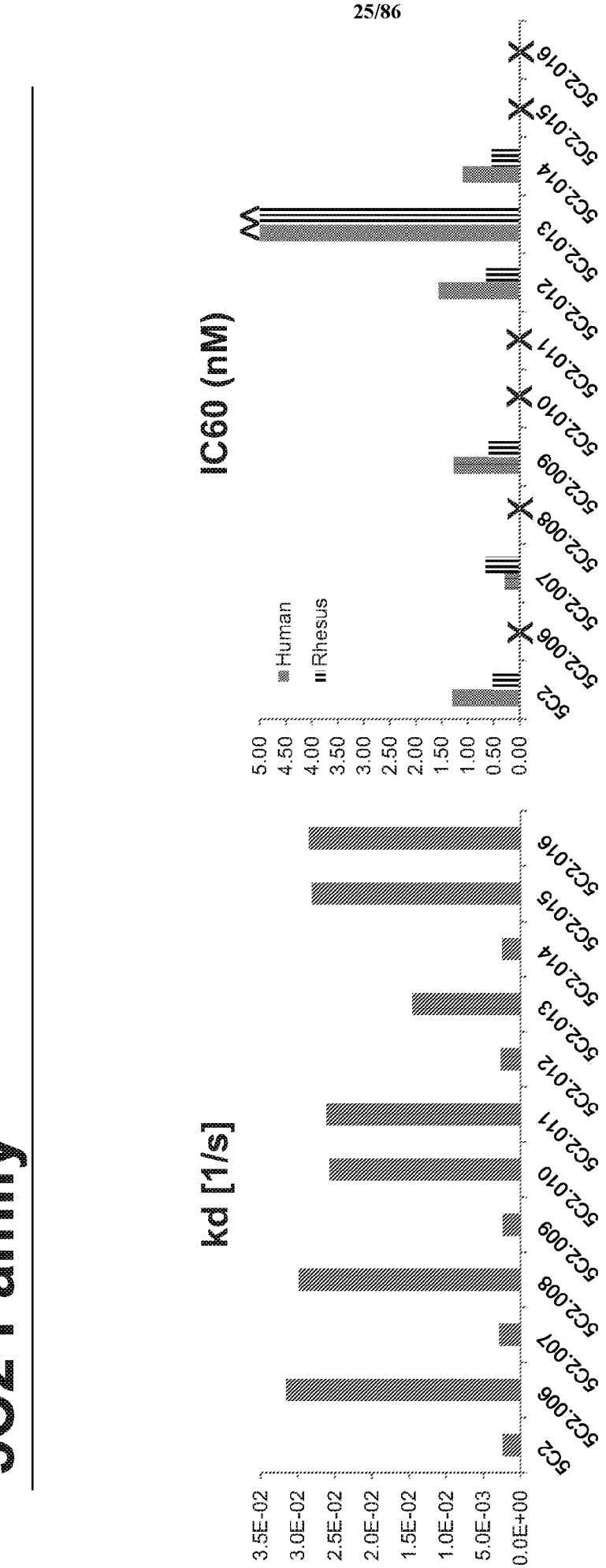

5C2 Family
kd [1/s]
3.5E-02
3.0E-02
2.5E-02
2.0E-02
1.5E-02
1.0E-02
5.0E-03
0.0E+00
5C2
5C2.006
5C2.007
5C2.008
5C2.009
5C2.010
5C2.011
5C2.012
5C2.013
5C2.014
5C2.015
5C2.016
IC60 (nM)
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14L

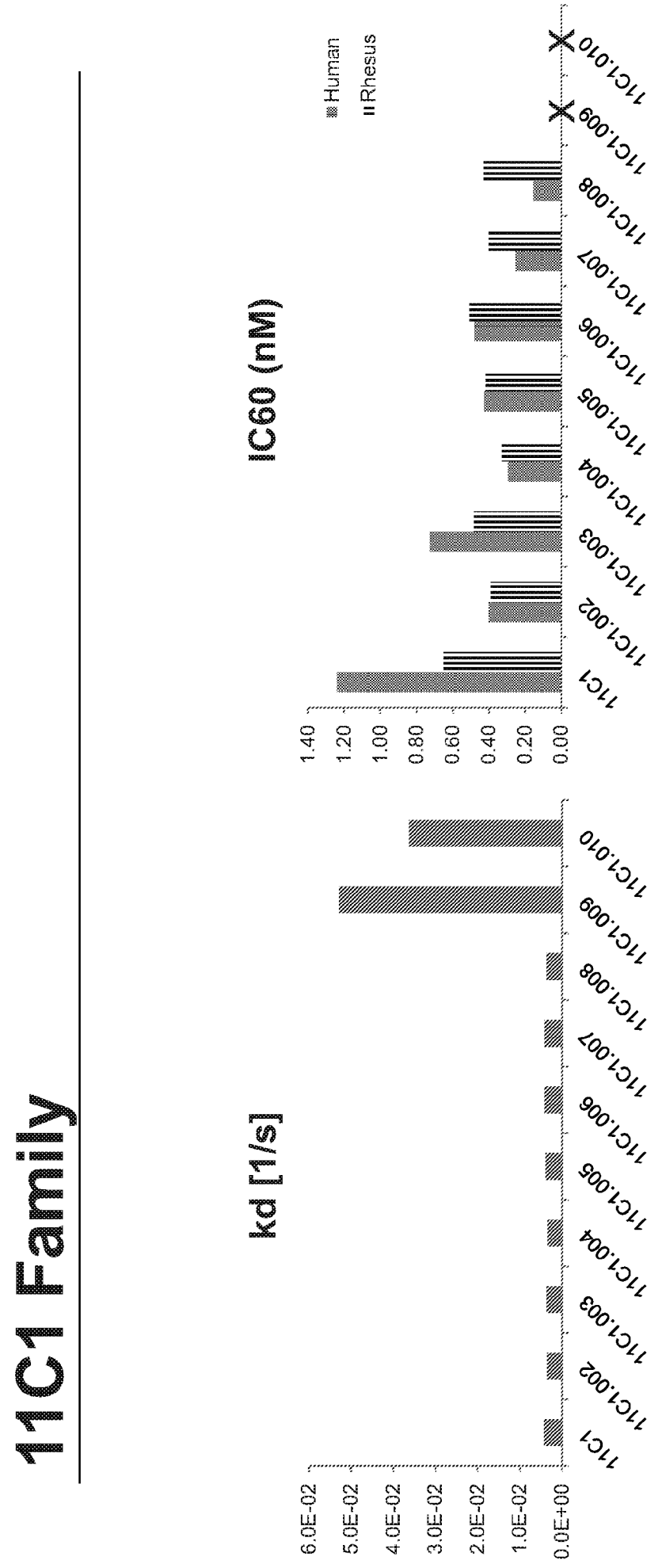

11C1 Family
kd [1/s]
6.0E-02
5.0E-02
4.0E-02
3.0E-02
2.0E-02
1.0E-02
0.0E+00
11C1
11C1.002
11C1.003
11C1.004
11C1.005
11C1.006
11C1.007
11C1.008
11C1.009
11C1.010
IC60 (nM)
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Human
Rhesus
11C1
11C1.002
11C1.003
11C1.004
11C1.005
11C1.006
11C1.007
11C1.008
11C1.009
11C1.010
X No Inhibition/Binding

Fig. 14M

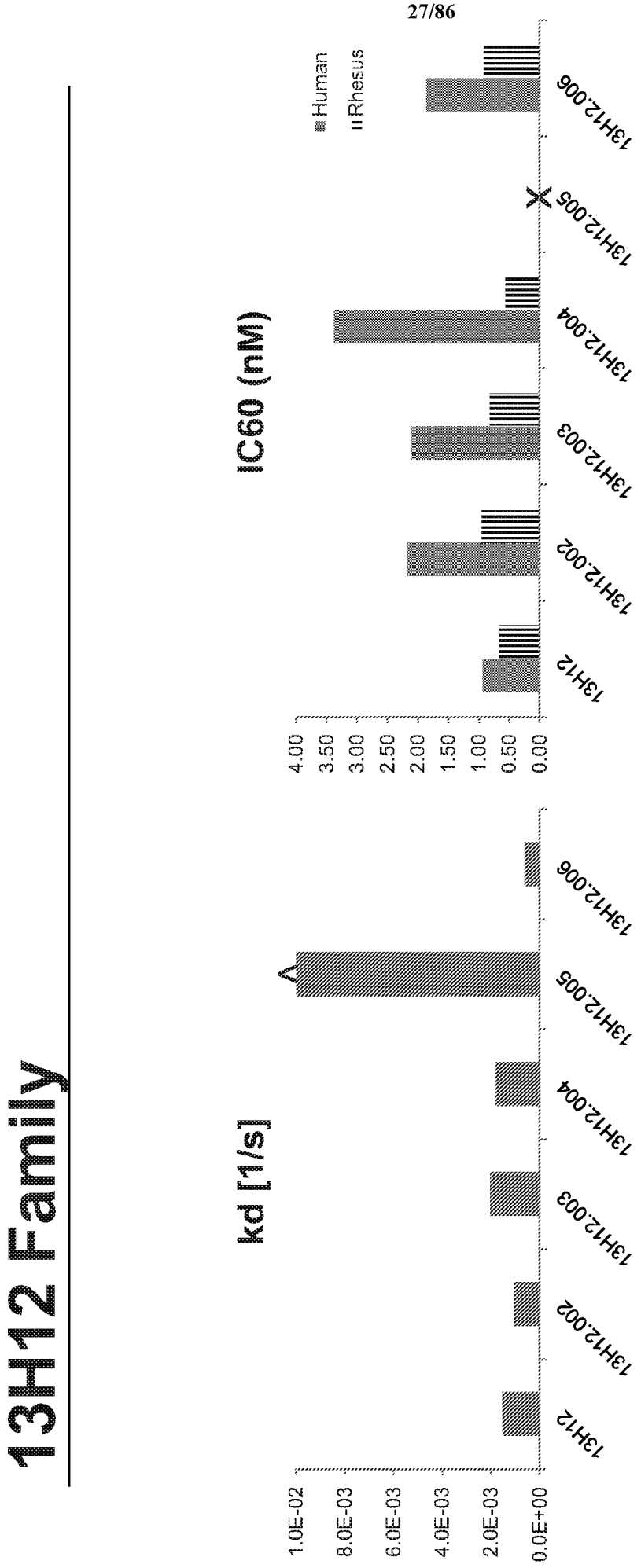

13H12 Family
kd [1/s]
1.0E-02
8.0E-03
6.0E-03
4.0E-03
2.0E-03
0.0E+00
13H12
13H12.002
13H12.003
13H12.004
13H12.005
13H12.006
IC60 (nM)
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
13H12
13H12.002
13H12.003
13H12.004
13H12.005
13H12.006
X No Inhibition/Binding
> Beyond Plotted Range

Fig. 14N

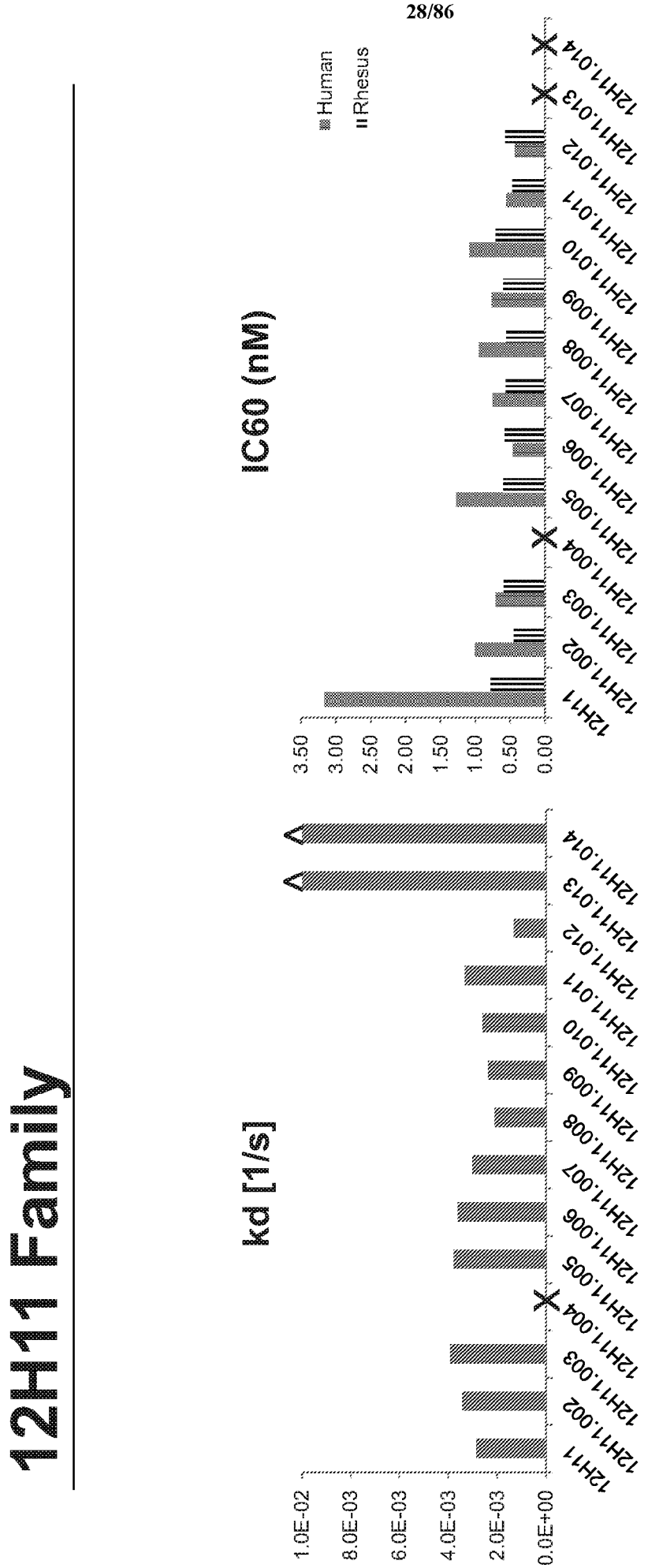

12H11 Family
kd [1/s]
1.0E-02
8.0E-03
6.0E-03
4.0E-03
2.0E-03
0.0E+00
IC60 (nM)
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
12H11
12H11.002
12H11.003
12H11.004
12H11.005
12H11.006
12H11.007
12H11.008
12H11.009
12H11.010
12H11.011
12H11.012
12H11.013
12H11.014
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14O

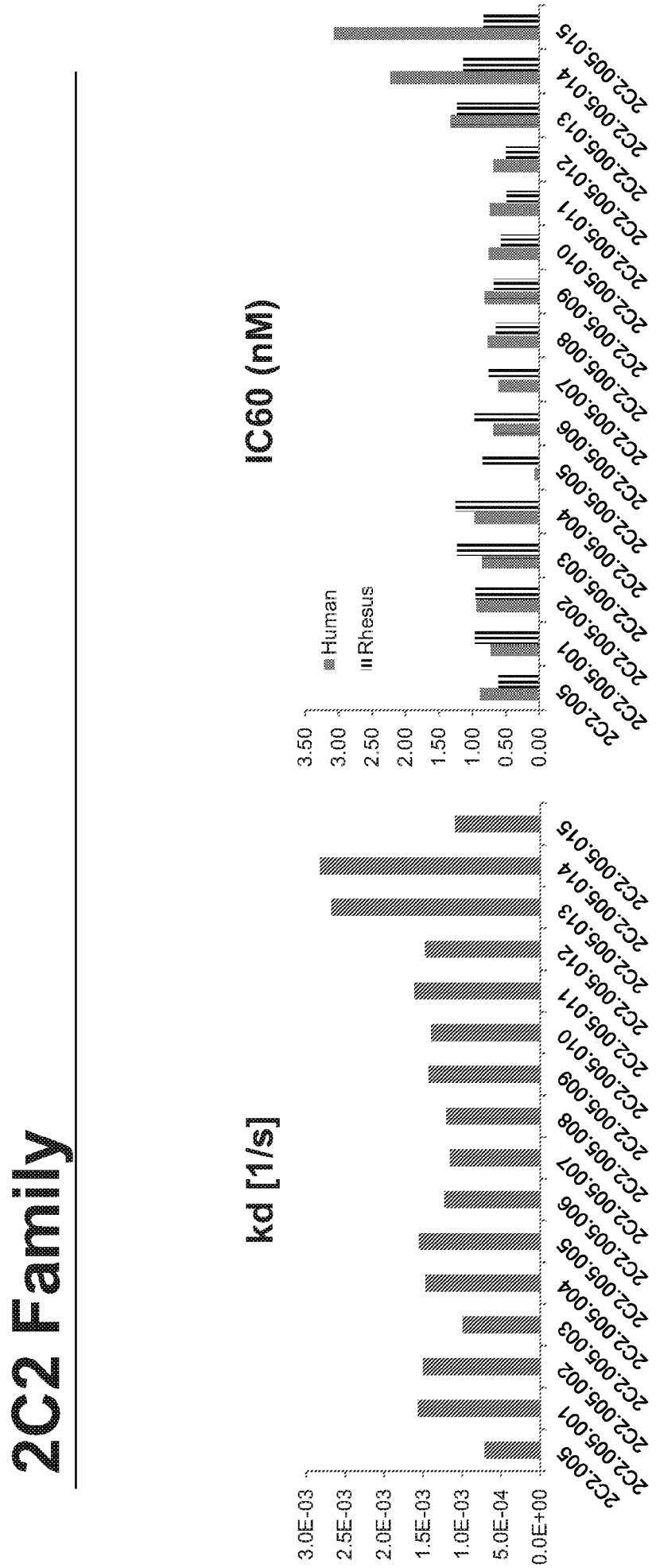

2C2 Family
kd [1/s]
3.0E-03
2.5E-03
2.0E-03
1.5E-03
1.0E-03
5.0E-04
0.0E+00
IC60 (nM)
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Human
Rhesus
2C2.005
2C2.005.001
2C2.005.002
2C2.005.003
2C2.005.004
2C2.005.005
2C2.005.006
2C2.005.007
2C2.005.008
2C2.005.009
2C2.005.010
2C2.005.011
2C2.005.012
2C2.005.013
2C2.005.014
2C2.005.015

Fig. 14P

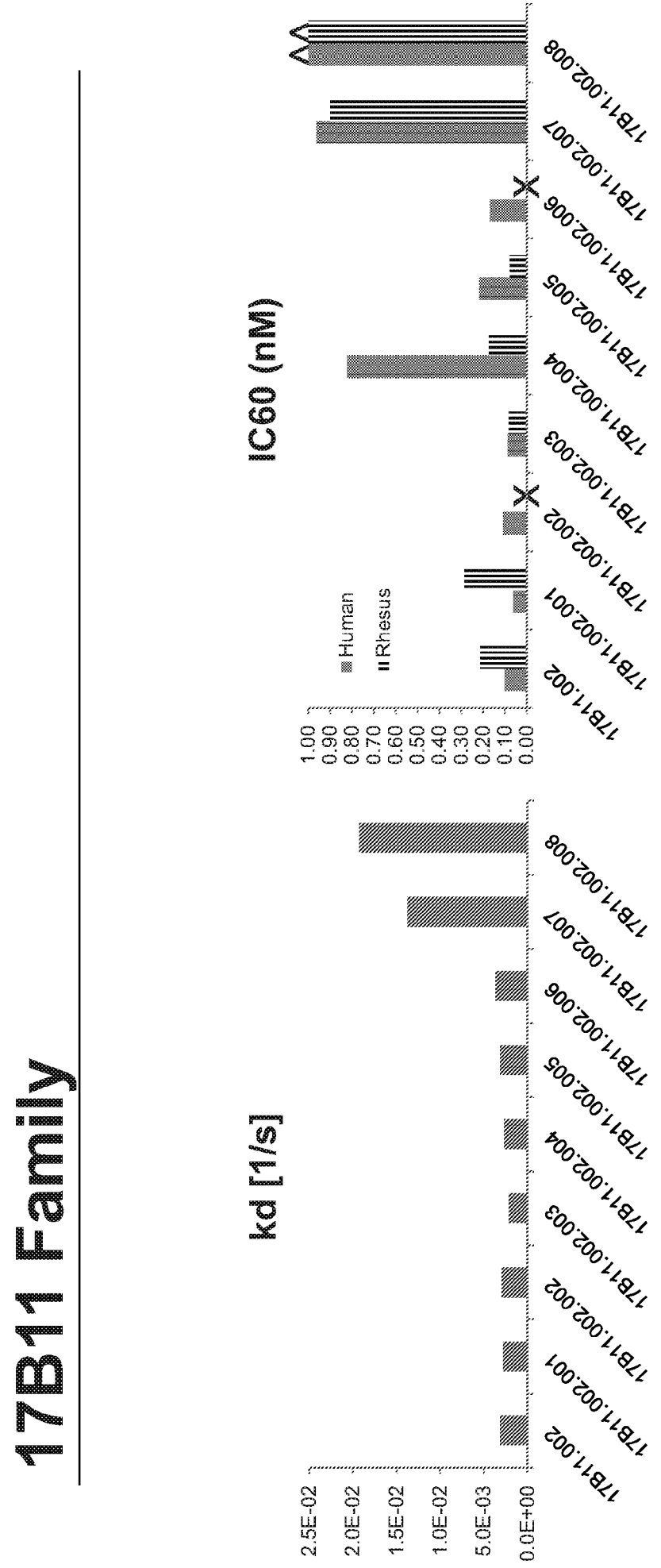

17B11 Family
kd [1/s]
2.5E-02
2.0E-02
1.5E-02
1.0E-02
5.0E-03
0.0E+00
17B11.002
17B11.002.001
17B11.002.002
17B11.002.003
17B11.002.004
17B11.002.005
17B11.002.006
17B11.002.007
17B11.002.008
IC60 (nM)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Human
Rhesus
17B11.002
17B11.002.001
17B11.002.002
17B11.002.003
17B11.002.004
17B11.002.005
17B11.002.006
17B11.002.007
17B11.002.008
X No Inhibition/Binding
^ Beyond Plotted Range

Fig. 14Q

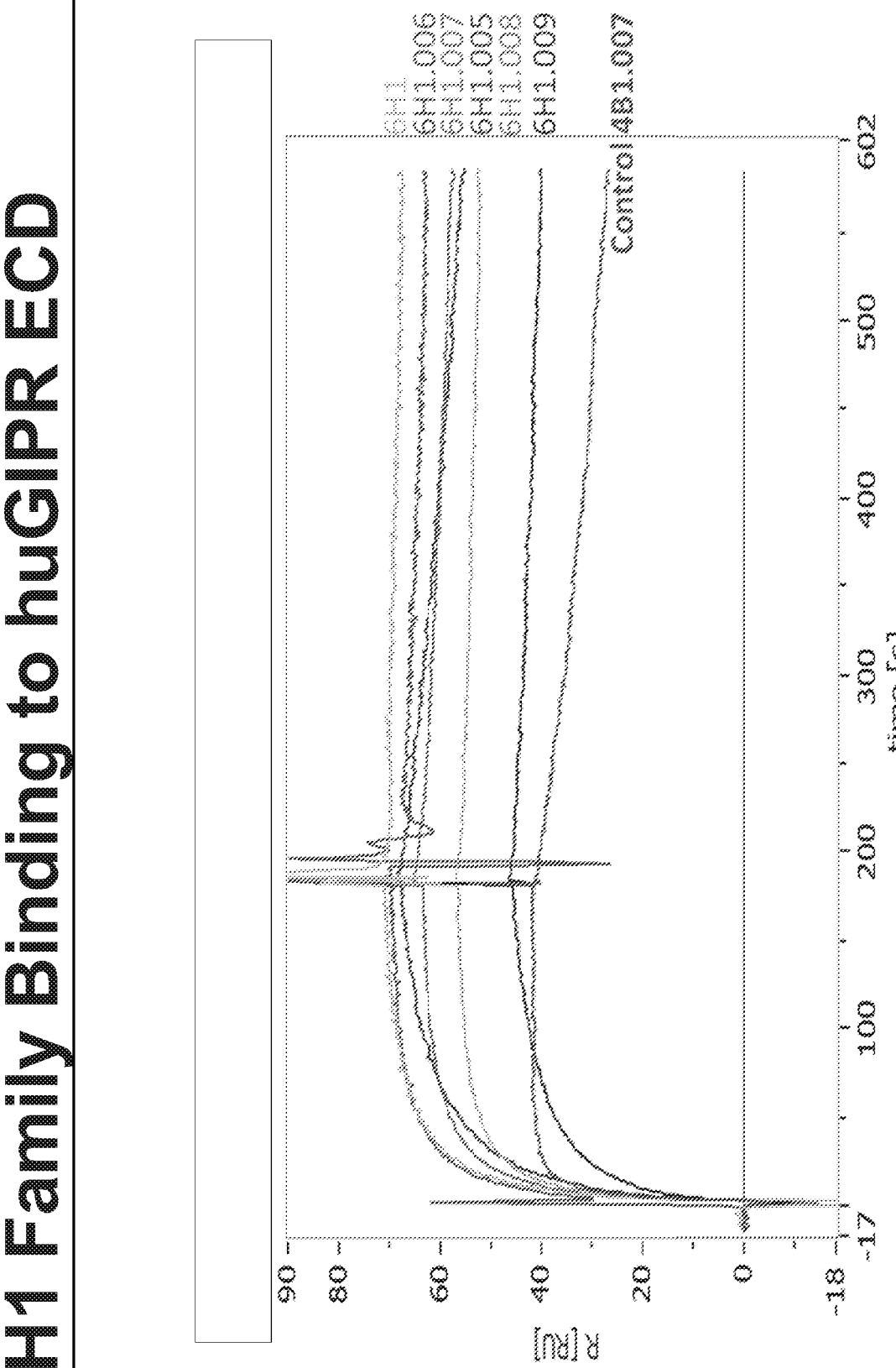

16H1 Family Binding to huGIPR ECD
16H1
6H1.006
6H1.007
6H1.005
6H1.008
6H1.009
Control 481.007
R [RU]
time [s]
90
80
60
40
20
0
-18
-17
100
200
300
400
500
602

Fig. 15

Mouse Pharmacodynamic Assay To Test GIPR Antibodies - Study Design

- Mice: Diet-induced obese C57BL/6 from Jackson Labs, age 18 weeks of age
- Assay: To test GIPR antibody on inhibition of insulin secretion induced by exogenous GIP ([D-Ala2]-GIP) and glucose
- Readout
  - Insulin (T = 0, 30 min from [D-Ala2]-GIP and glucose dose)
  - Glucose (T = 0, 60 min from [D-Ala2]-GIP and glucose dose)
- Study groups
  - Negative control: Vehicle, [D-Ala2]-GIP (50 nmol/kg)
  - Antibody 5G12.006 at 0.008, 0.04, 0.2,1, 5 mg/kg
  - Positive control: Vehicle, no [D-Ala2]-GIP

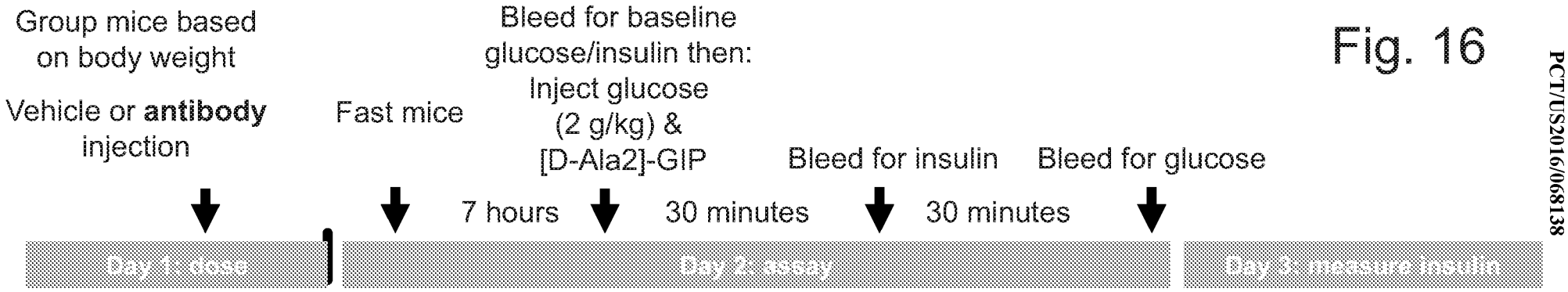


Fig. 16

GIPR Antibody 5G12.006 Antagonized GIP Induced Insulin Secretion

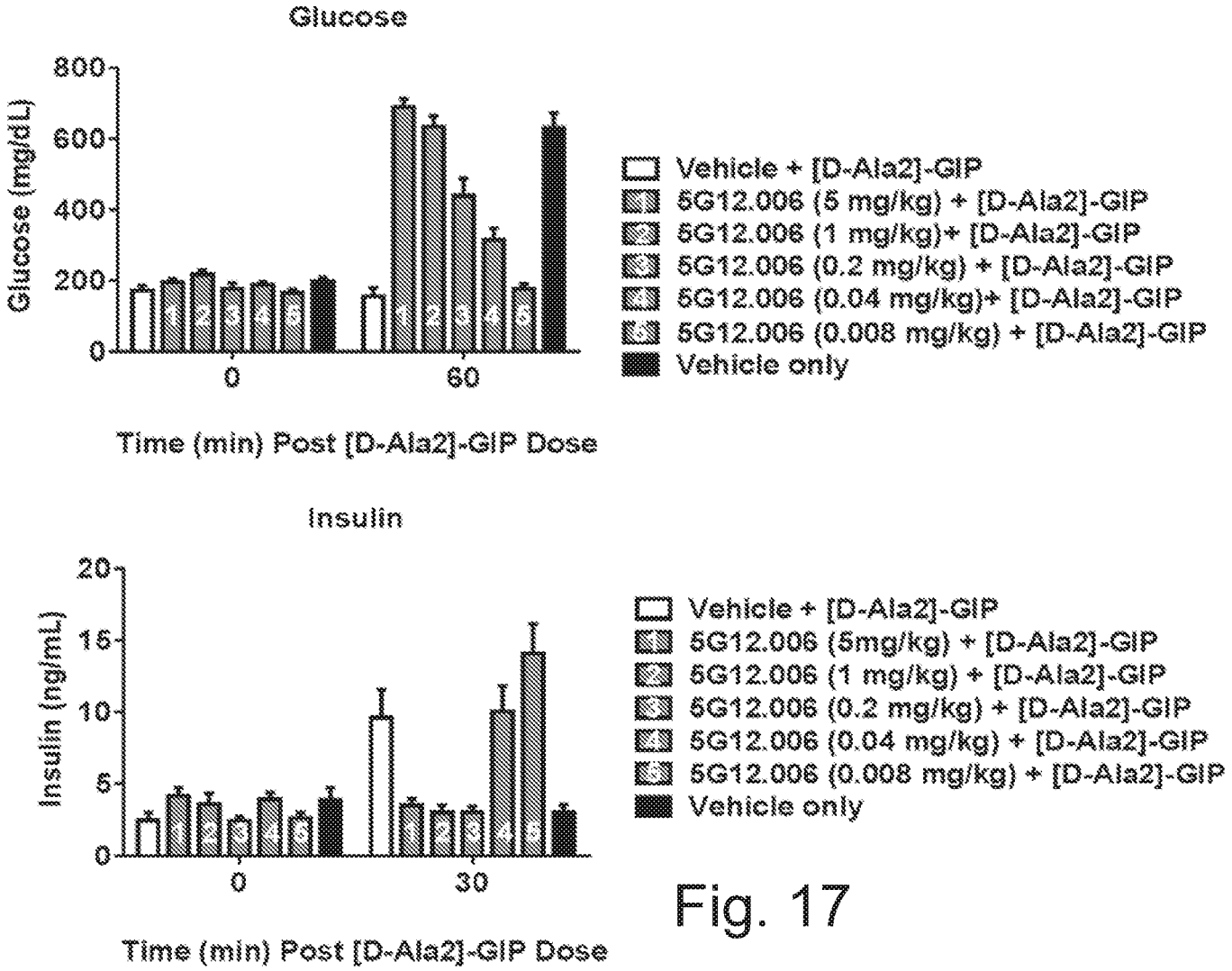


Fig. 17

Chronic Treatment Of Diet Induced Obese Mice With GIPR Antibody 5G12.006 - Study Design

- Male C57BL/6 Diet-Induced Obese mice (Jackson Lab), 18 weeks old at start (on high fat diet for 12 weeks)
- Mice were randomized based on body weight
- Mice were dosed each week for 4 weeks
- Body weights were recorded twice a week; not fasted glucose measured on day 18 and fasted insulin measured on day 29
- Terminal blood collected for measurement of total cholesterol, and triglycerides
- Intraperitoneal glucose tolerance test (IPGTT) was performed on day 25 with 4 hour fast with 1 g/kg of glucose
- After 4 weeks, study was terminated following a 4 hour fast. Serum samples were collected and livers were weighed

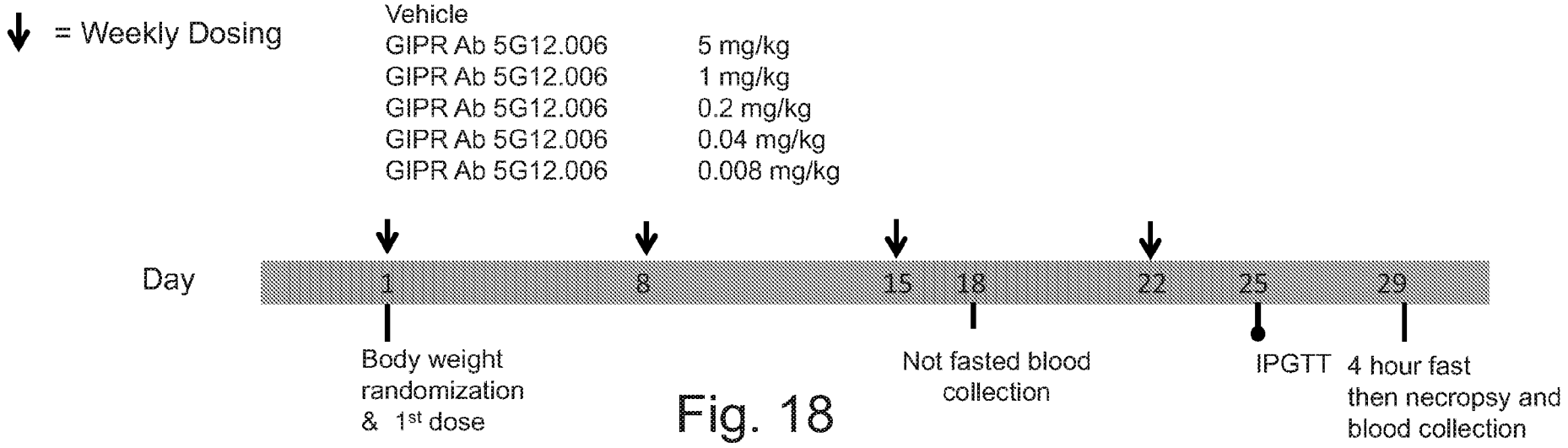


Fig. 18

GIPR Antibody 5G12.006 Results In Reduced Body Weight Gain

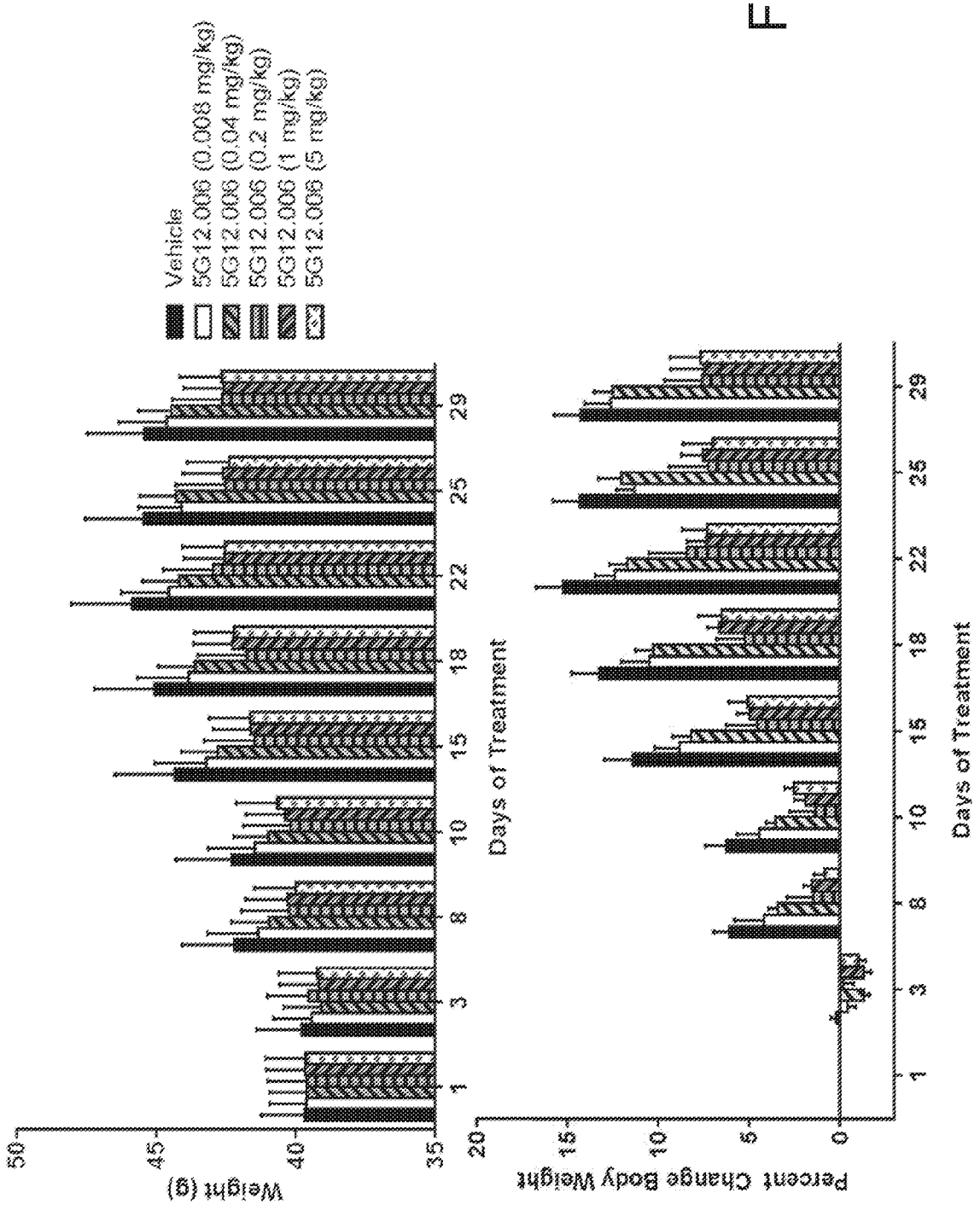
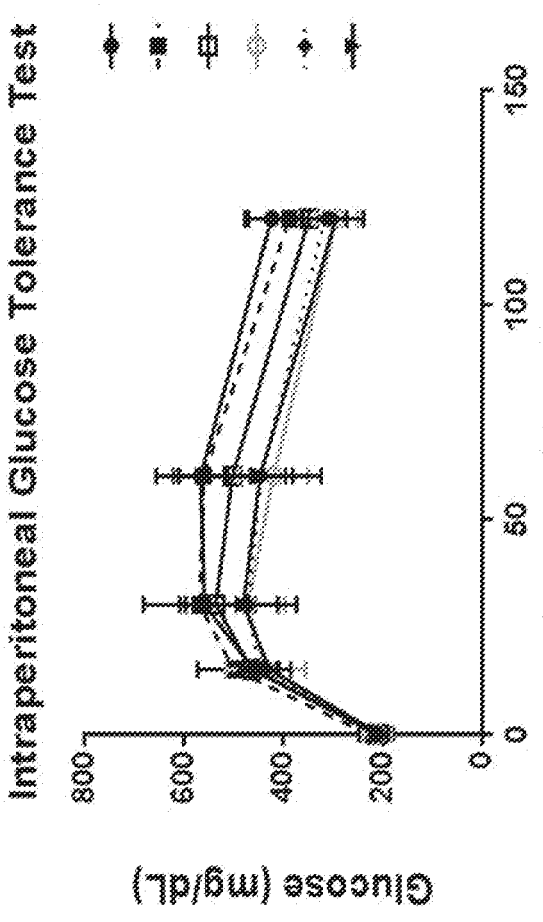


Fig. 19

GIPR Antibody 5G12.006 Results In Improved Glucose Tolerance



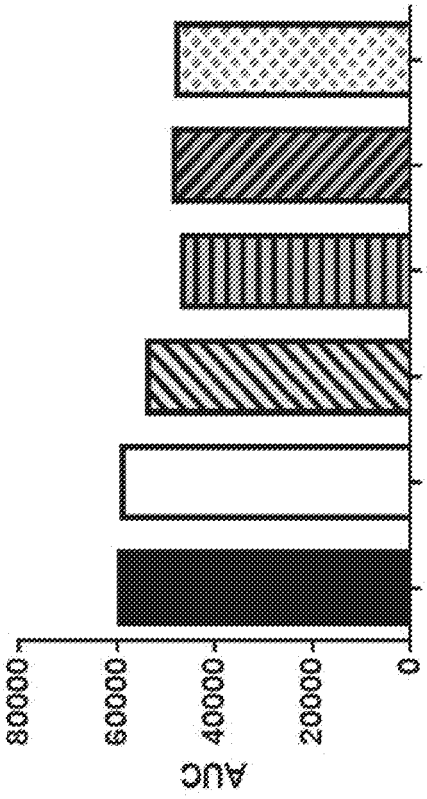


Fig. 20

GIPR Antibody 5G12.006 Results In Lower Glucose and Insulin Levels

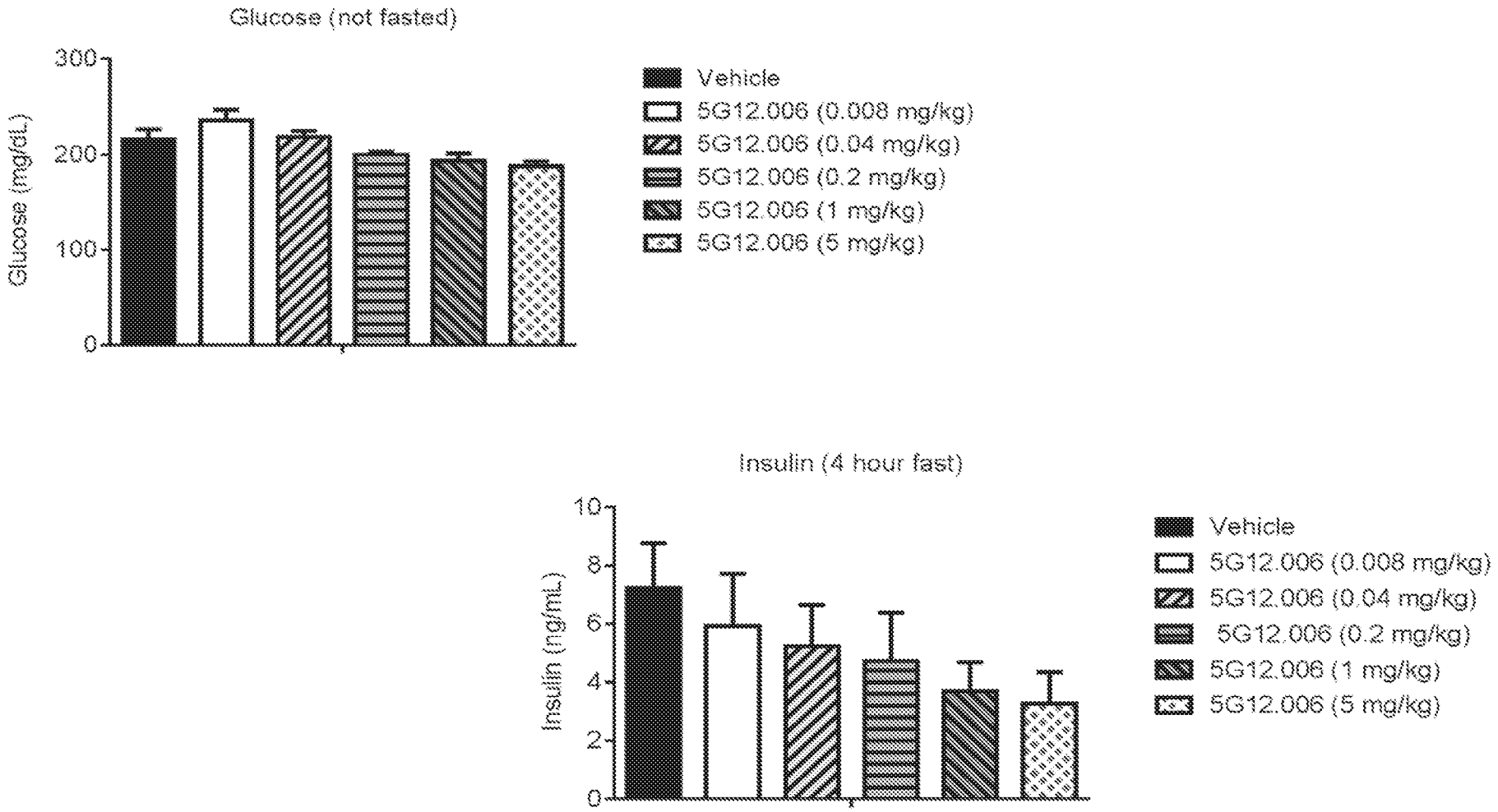


Fig. 21

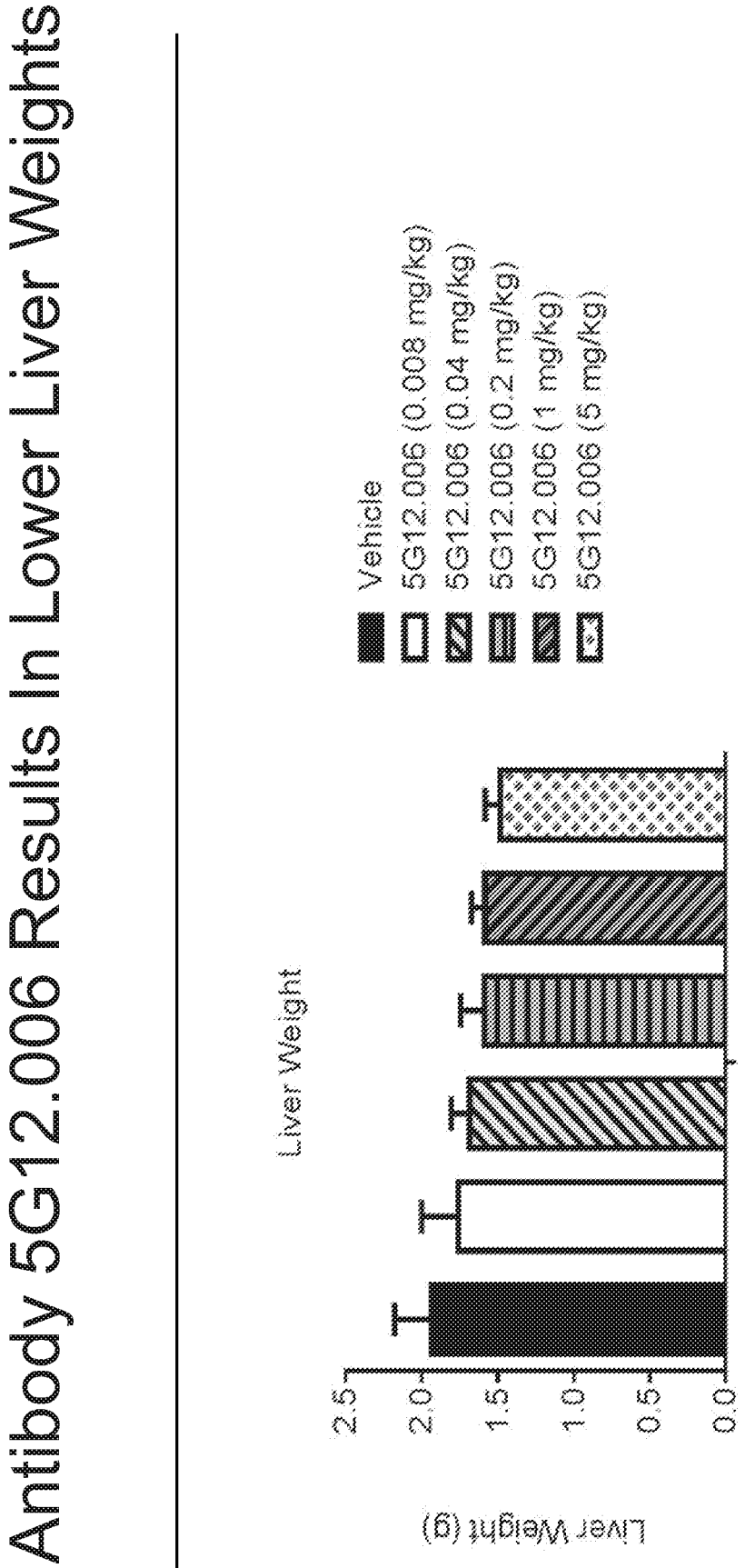

GIPR Antibody 5G12.006 Results In Lower Liver Weights
Liver Weight
Liver Weight (g)
2.5
2.0
1.5
1.0
0.5
0.0
Vehicle
5G12.006 (0.008 mg/kg)
5G12.006 (0.04 mg/kg)
5G12.006 (0.2 mg/kg)
5G12.006 (1 mg/kg)
5G12.006 (5 mg/kg)

Fig. 22

GIPR Antibody 5G12.006 Results In Lower Total Cholesterol Levels

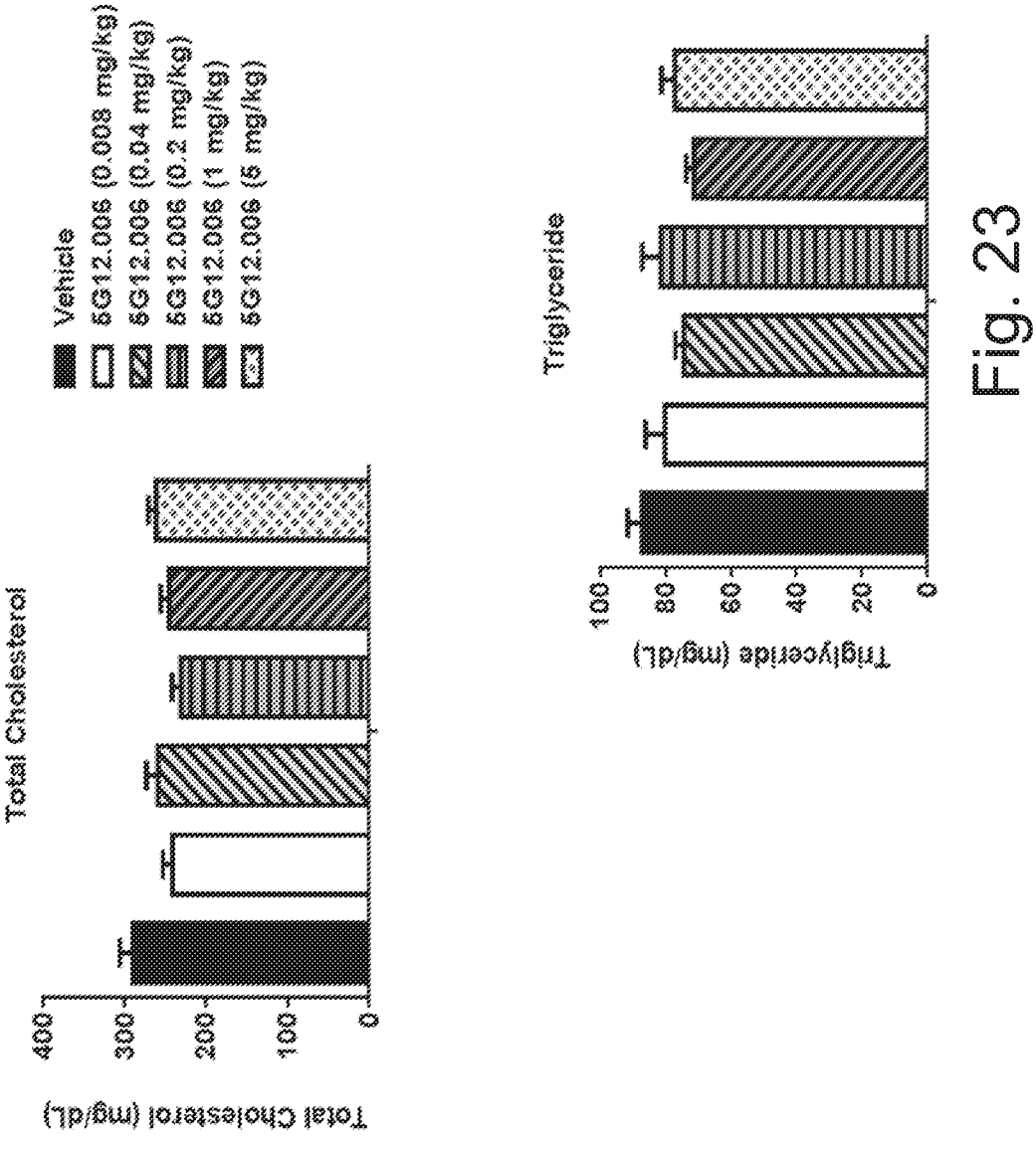
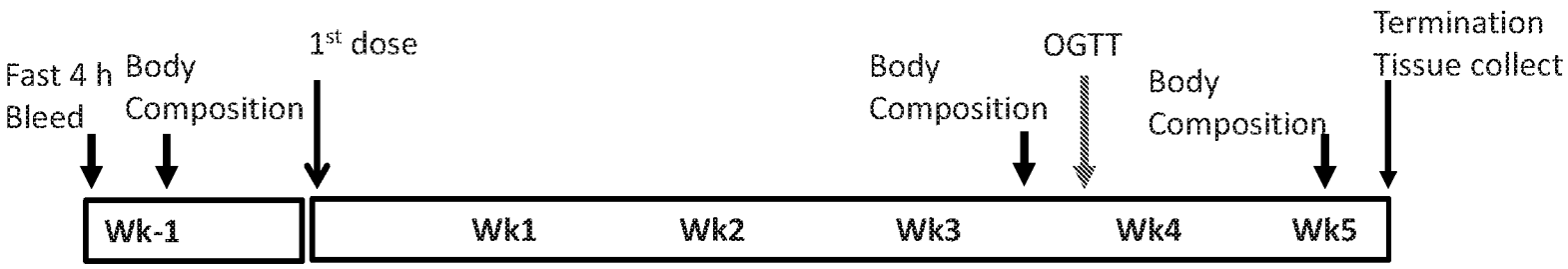


Fig. 23

Treatment Of Mice With Anti-GIPR 2.63.1 In Combination With Liraglutide - Study Design

- Mice: Jackson Labs C57BL/6 DIO, 35 weeks of age (on high fat diet for 29 weeks) at study start
- Group and treatment, N=10/group, dose vol ume is 5 ml/kg, study duration is 5 weeks on treatment
  - A. Vehicle, daily
  - B. Anti-GIPR mAb 2.63.1, 30 mg/kg, twice a week
  - C. Liraglutide, 0.3 mg/kg, once a day
  - D. Anti-GIPR mAb 2.63.1 (30 mg/kg, twice a week) + Liraglutide (0.3 mg/kg, once a day)
- Procedures:
  - Day -10: fast 4 hours, body weight, glucose and serum analysis
  - Day -7 to day -1: Acclimation by dosing with vehicle daily for all groups
  - Day -6: Body composition
  - Day 1: Body weight, grouping and first dose
- Efficacy readout:
  - Body weight daily
  - Food intake
  - Body composition measurement at beginning and end
  - Glucose, insulin, OGTT and serum lipid levels at termination

Fig. 24



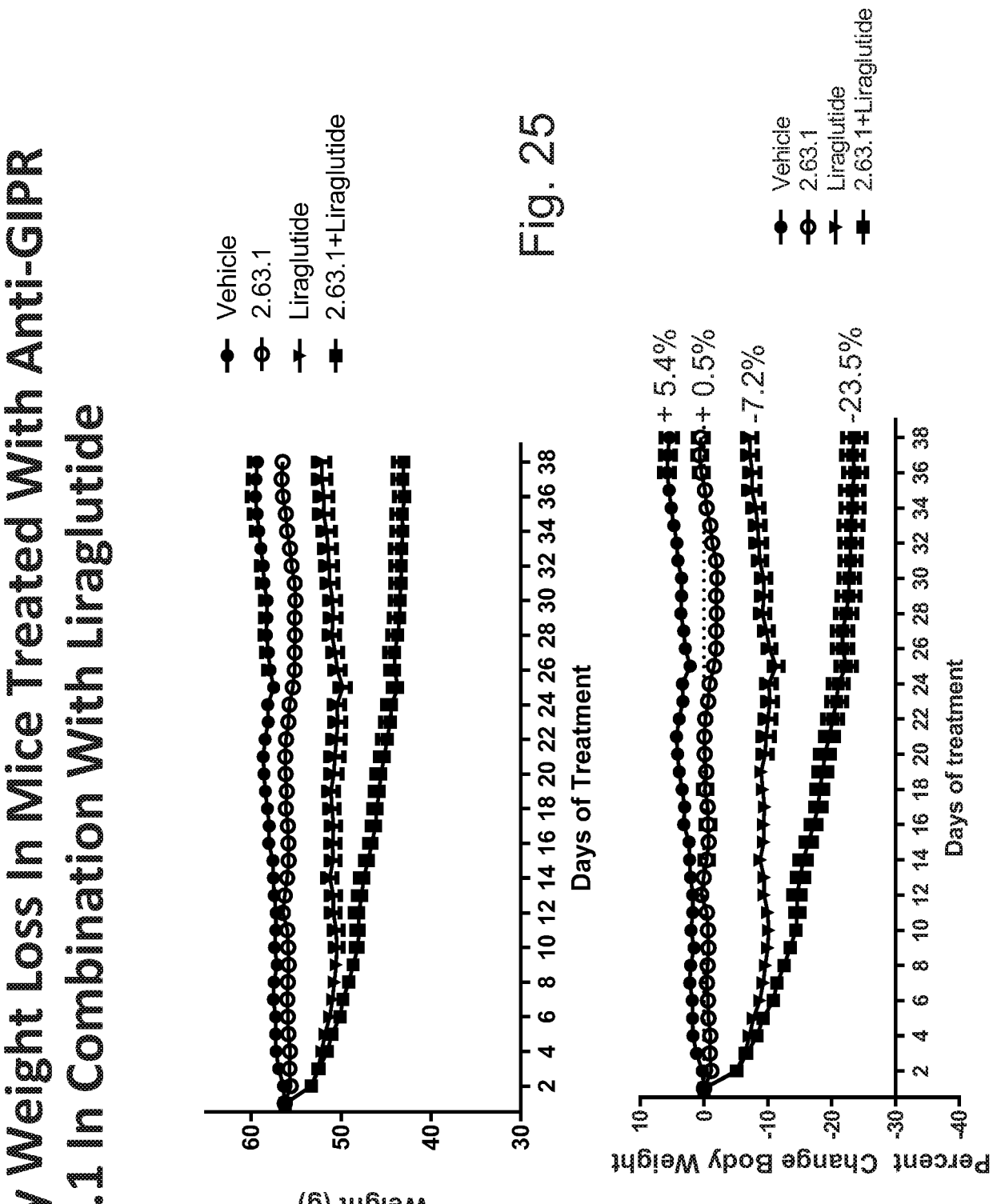

Body Weight Loss In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide
Weight (g)
Days of Treatment
Percent Change Body Weight
+ 5.4%
+ 0.5%
-7.2%
-23.5%
Days of treatment

Fig. 25

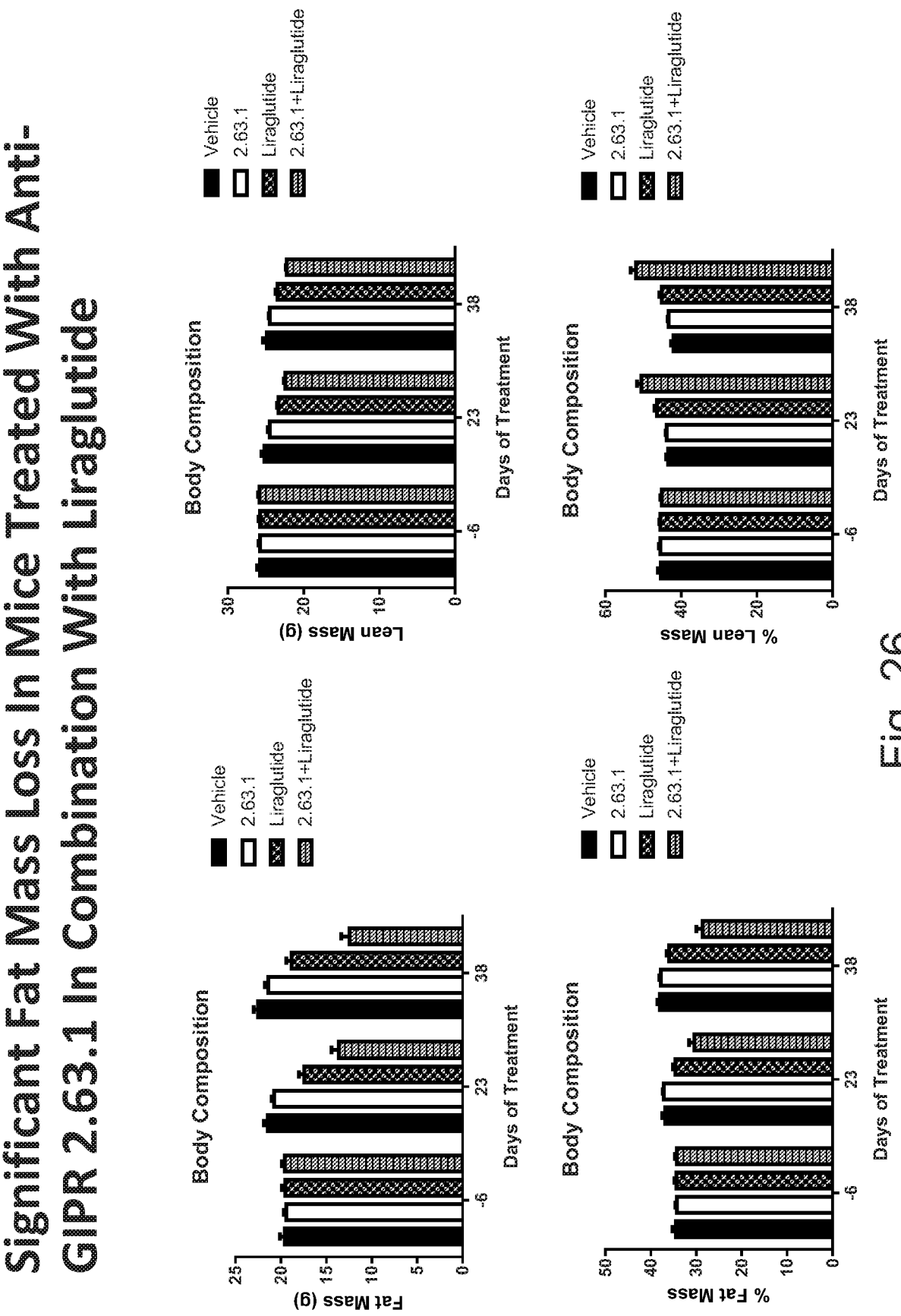
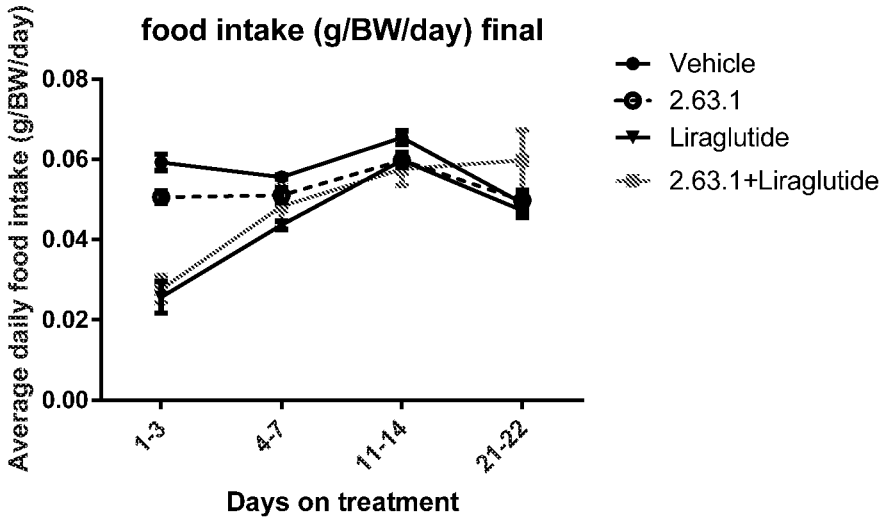
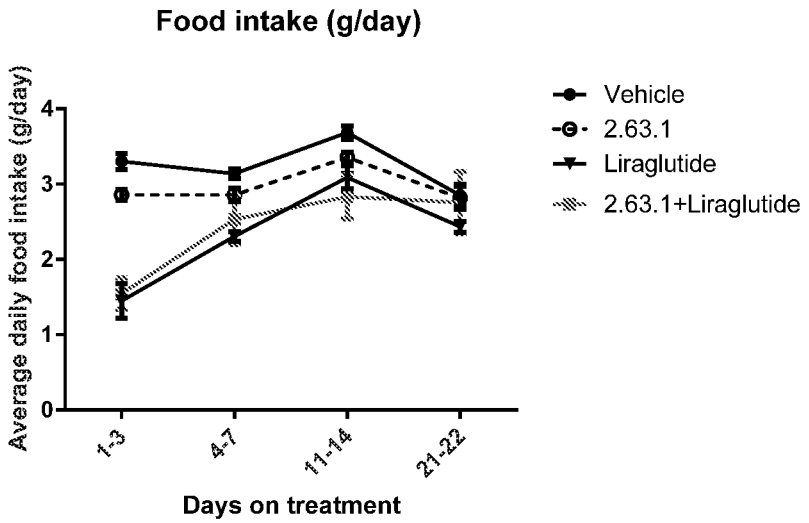

Significant Fat Mass Loss In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Body Composition
Fat Mass (g)
Lean Mass (g)
% Fat Mass
% Lean Mass
Days of Treatment
-6
23
38
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide

Fig. 26

Food Intake In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide





Note:
Food intake data is from the following numbers animals each group
Vehicle: N=6
2.63.1: N=8
Liraglutide: N=4
2.63.1 + Liraglutide: N=3

The other animals played with the food during some of the time points and food intake could not be accurately measured. These animals are not included.

Fig. 27

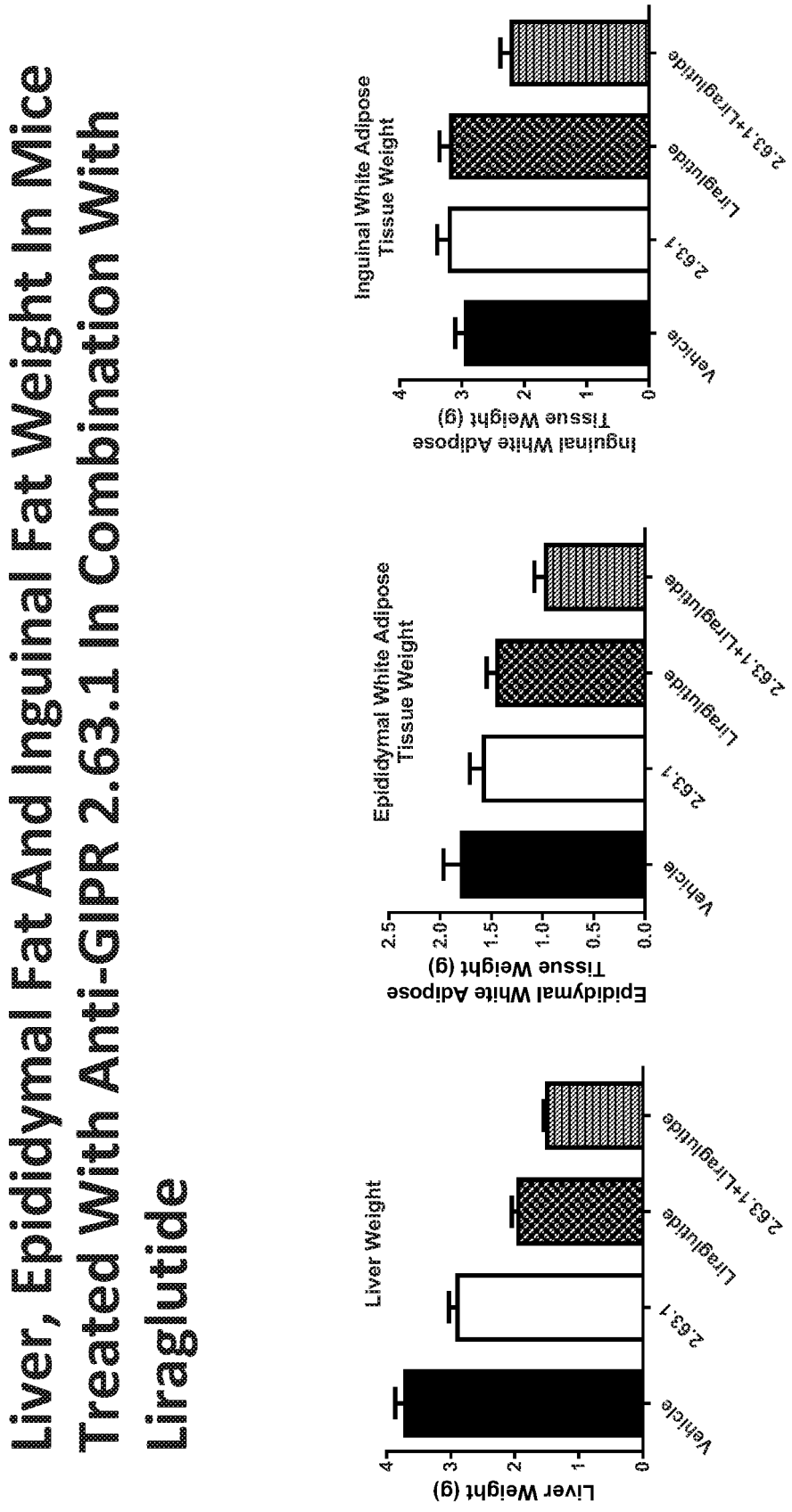

Liver, Epididymal Fat And Inguinal Fat Weight In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Liver Weight
Liver Weight (g)
Epididymal White Adipose Tissue Weight
Epididymal White Adipose Tissue Weight (g)
Inguinal White Adipose Tissue Weight
Inguinal White Adipose Tissue Weight (g)
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide

Fig. 28

Glucose Tolerance In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide

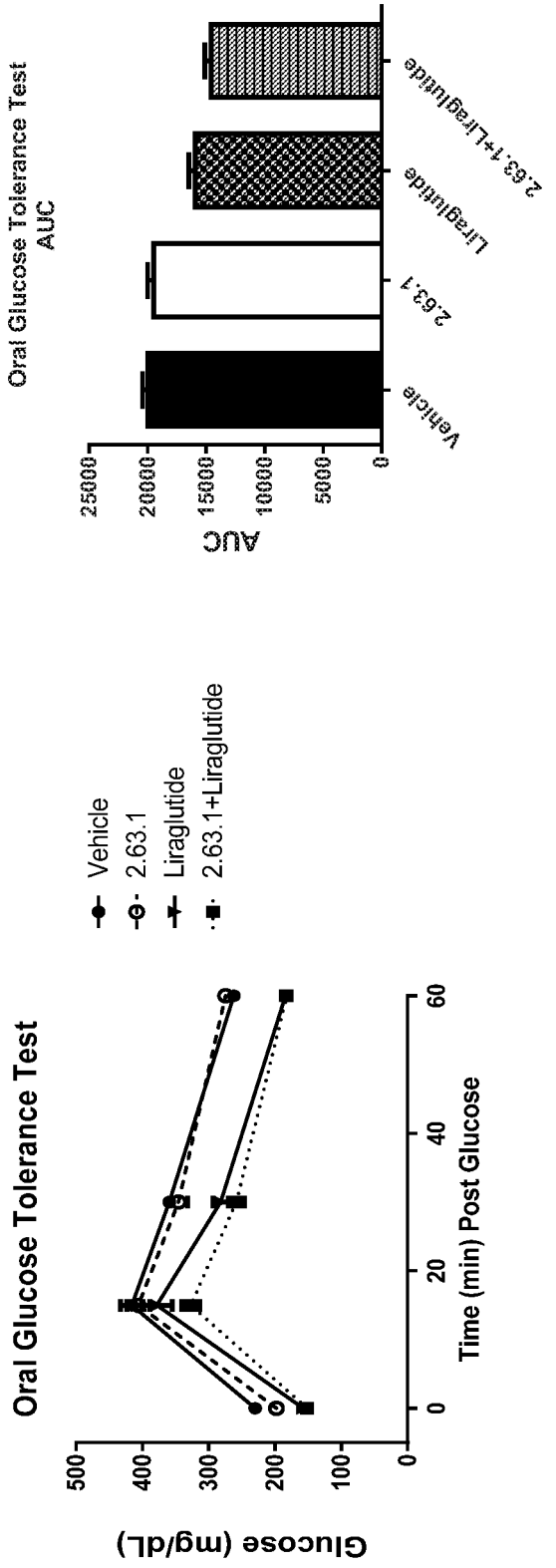


Fig. 29

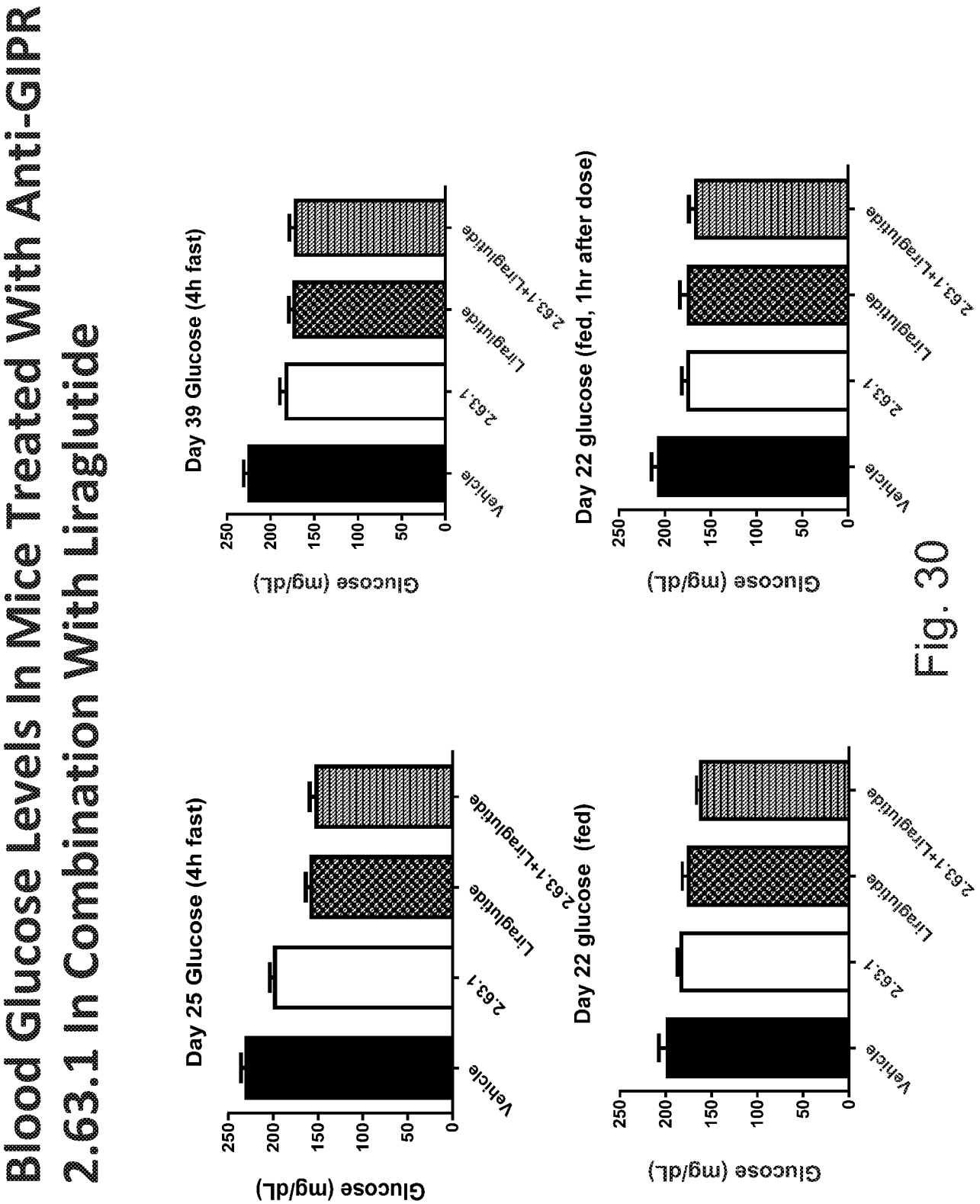

Blood Glucose Levels In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Day 25 Glucose (4h fast)
Day 39 Glucose (4h fast)
Day 22 glucose (fed)
Day 22 glucose (fed, 1hr after dose)
Glucose (mg/dL)
0
50
100
150
200
250
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide

Fig. 30

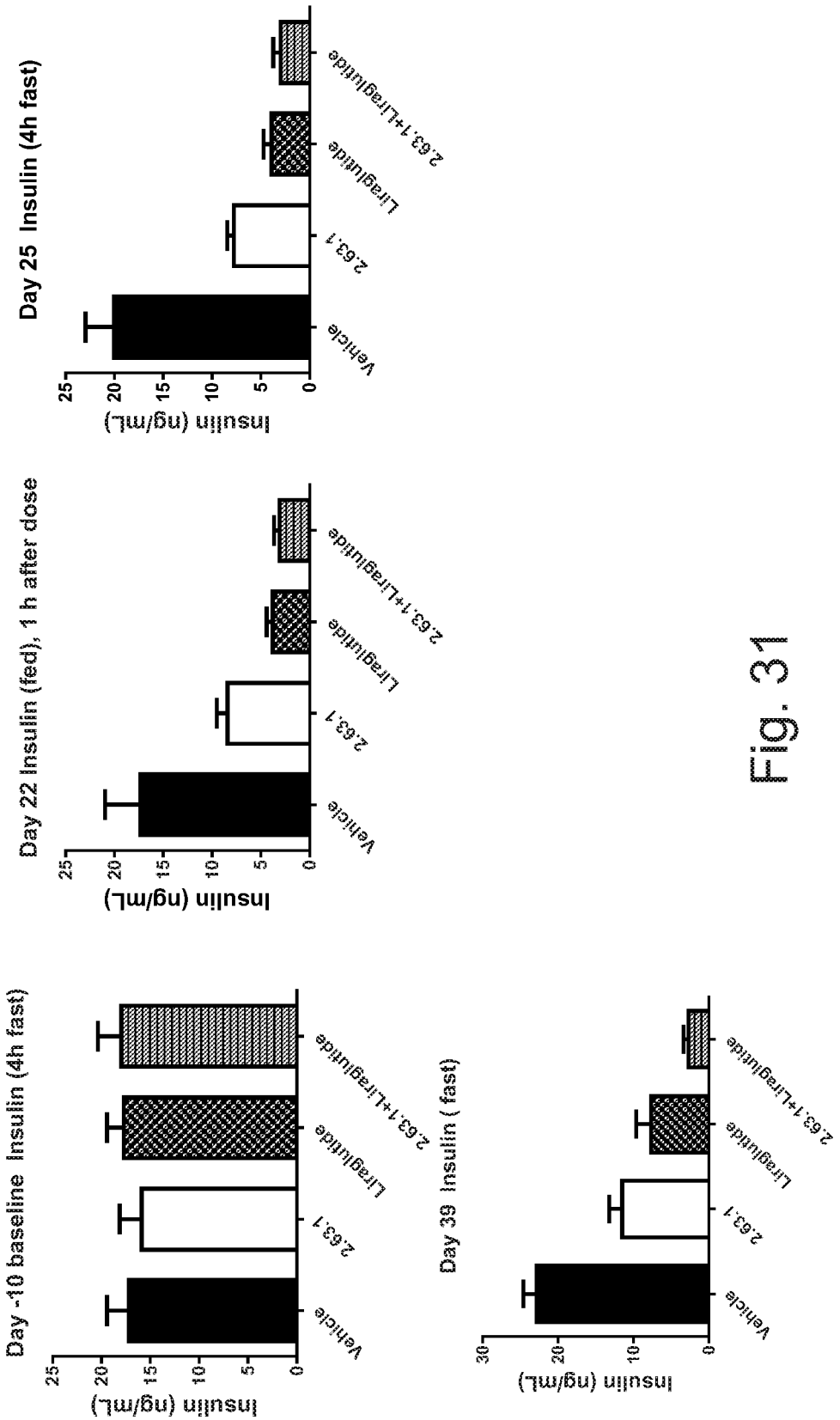

Plasma Insulin Levels In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Day -10 baseline Insulin (4h fast)
Day 22 Insulin (fed), 1 h after dose
Day 25 Insulin (4h fast)
Day 39 Insulin (fast)
Insulin (ng/mL)
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide

Fig. 31

Serum Total Cholesterol Levels In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide

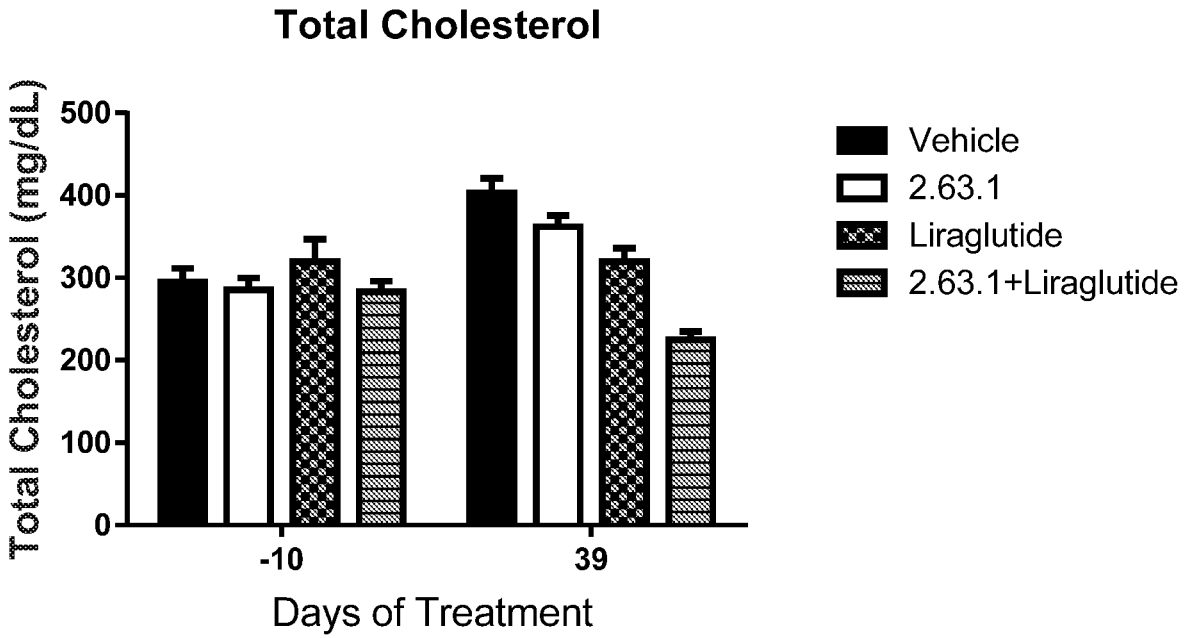


Fig. 32

Serum Leptin Level In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide

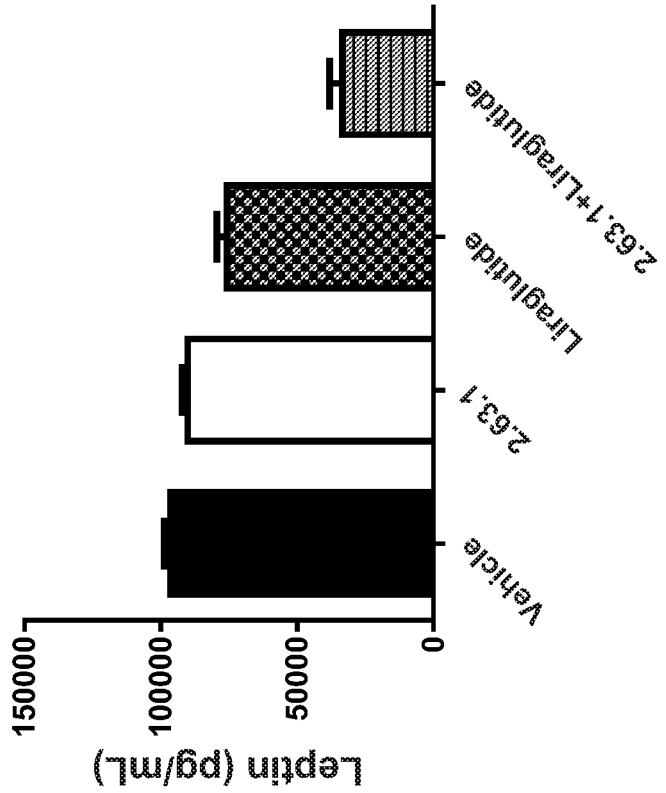


Fig. 33

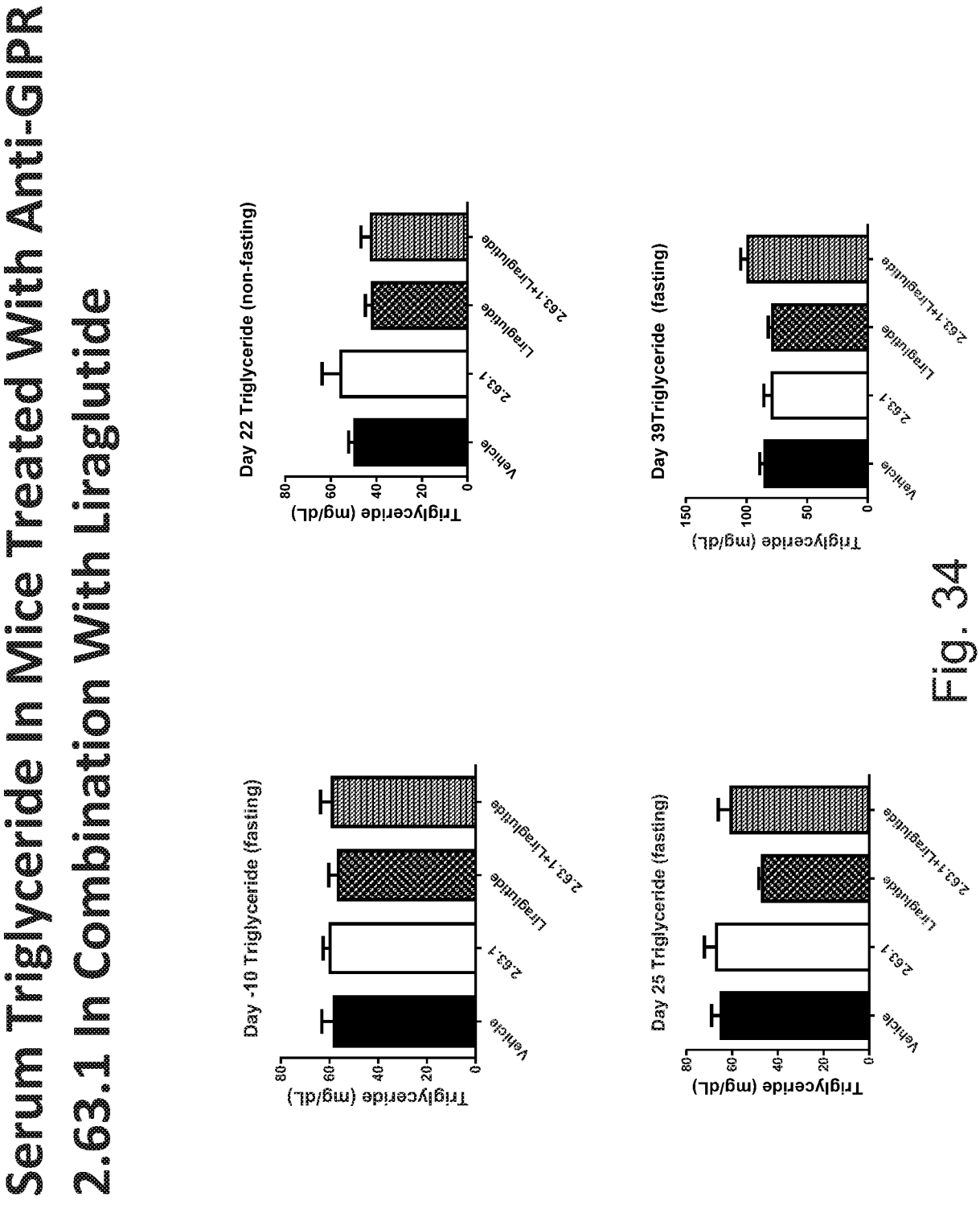

Serum Triglyceride In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide
Day -10 Triglyceride (fasting)
Triglyceride (mg/dL)
0
20
40
60
80
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide
Day 22 Triglyceride (non-fasting)
Triglyceride (mg/dL)
0
20
40
60
80
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide
Day 25 Triglyceride (fasting)
Triglyceride (mg/dL)
0
20
40
60
80
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide
Day 39Triglyceride (fasting)
Triglyceride (mg/dL)
0
50
100
150
Vehicle
2.63.1
Liraglutide
2.63.1+Liraglutide

Fig. 34

Study In Mice Treated With Anti-GIPR 2.63.1 In Combination with Liraglutide, Dulaglutide Or Exendin IV

- Mice: Jackson Labs C57BL/6 DIO, 37 weeks of age (on high fat diet for 31 weeks) at study start
- Group and treatment: N=8/group, dose volume is 5 ml/kg
  - A. Vehicle
  - B. Anti-GIPR mAb 2.63.1 (25 mg/kg, once a week)
  - C. Dulaglutide (1mg/kg, twice a week)
  - D. Anti-GIPR mAb 2.63.1 (25 mg/kg, once a week) + Dulaglutide (1mg/kg, twice a week)
  - E. Liraglutide (0.3 mg/kg, once a day)
  - F. Anti-GIPR mAb 2.63.1 (25 mg/kg, once a week) + Liraglutide (0.3 mg/kg, once a day)
  - G. Exendin IV (0.01 mg/kg, once a day)
  - H. Anti-GIPR mAb 2.63.1 (25 mg/kg, once a week) + Exendin IV (0.01 mg/kg, once a day)
- Procedures:
  - Day -7 to day -1: Acclimation by dosing with vehicle daily for all groups. Body weight, glucose and serum (fast 4 h)
  - Day 1: Body weight, grouping and first dose
- Efficacy readout:
  - Body weight daily
  - Food intake
  - Body composition at beginning and end
  - Glucose, insulin, OGTT at day 23

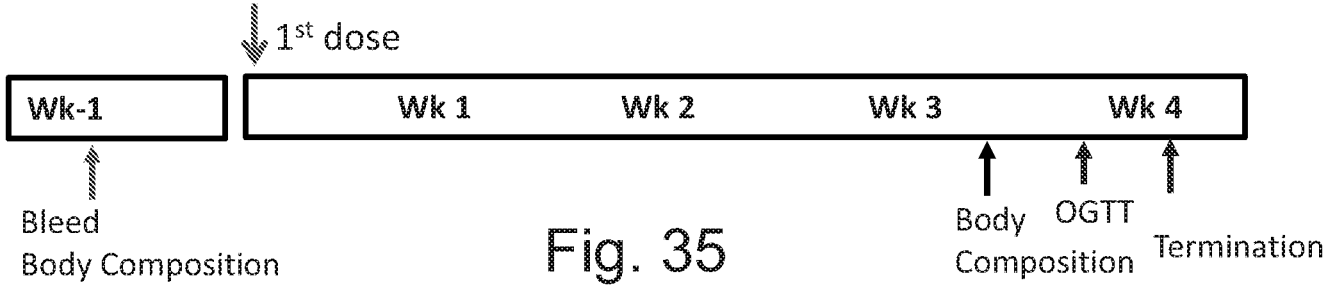


Fig. 35

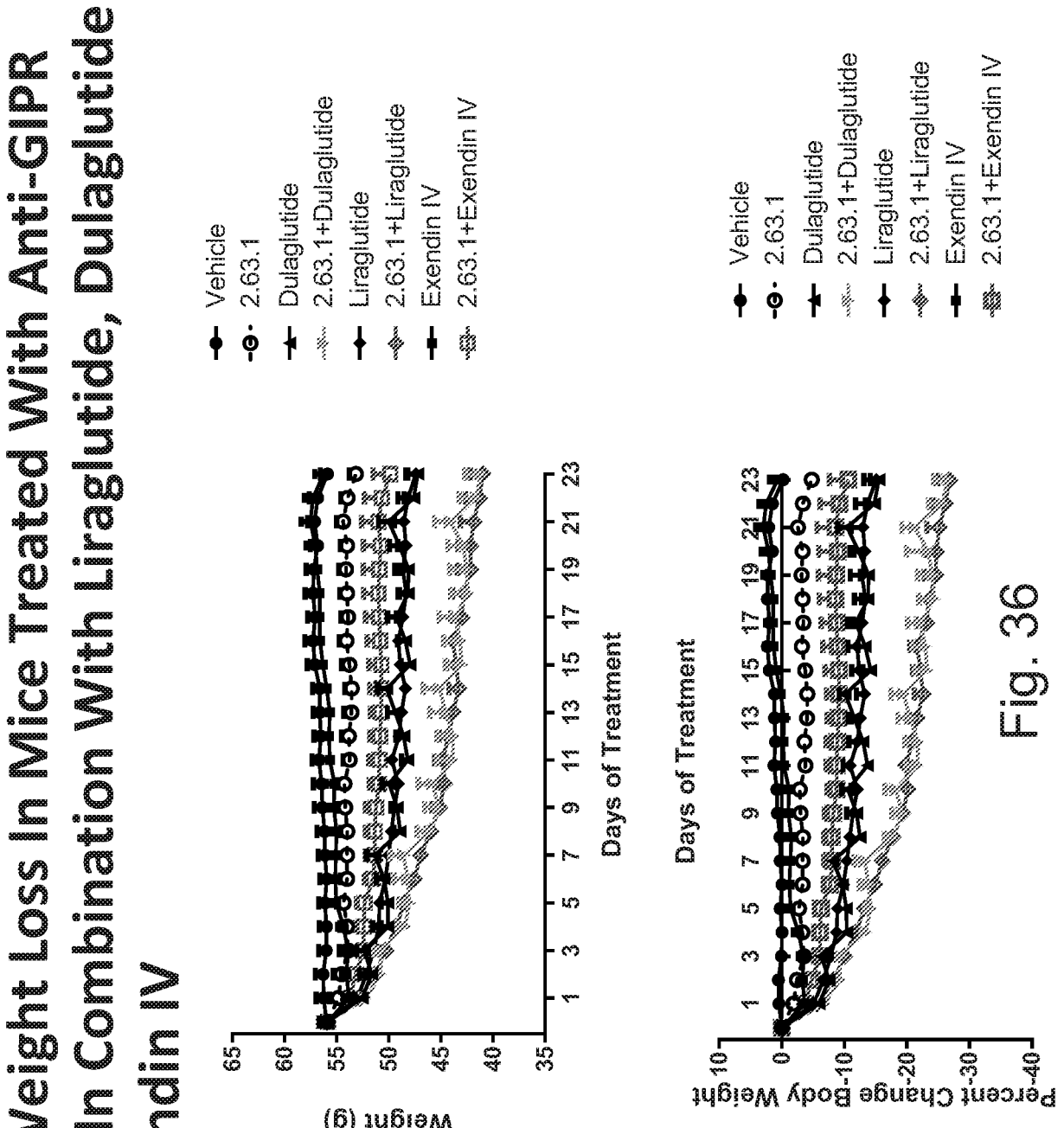

Body Weight Loss In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide, Dulaglutide Or Exendin IV
Vehicle
2.63.1
Dulaglutide
2.63.1+Dulaglutide
Liraglutide
2.63.1+Liraglutide
Exendin IV
2.63.1+Exendin IV
Weight (g)
Days of Treatment
Percent Change Body Weight
Days of Treatment

Fig. 36

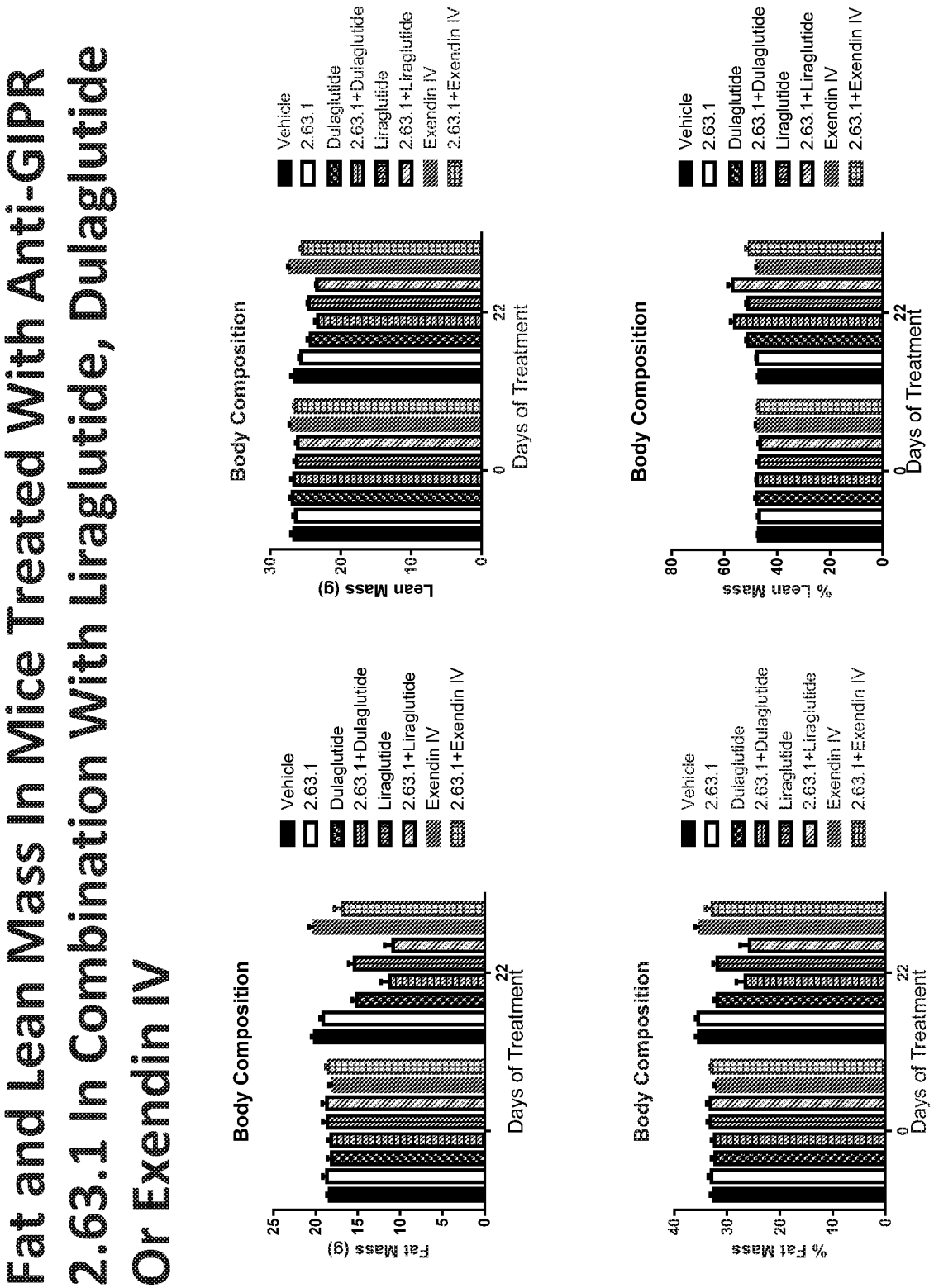
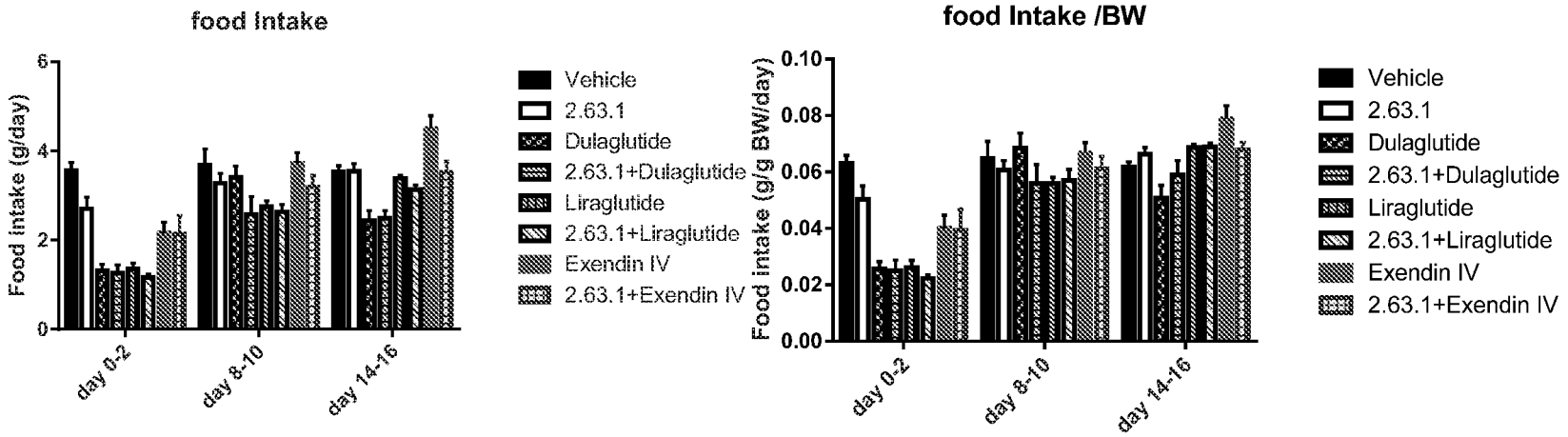

Fat and Lean Mass In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide, Dulaglutide Or Exendin IV
Body Composition
Fat Mass (g)
Lean Mass (g)
% Fat Mass
% Lean Mass
Days of Treatment
0
22
Vehicle
2.63.1
Dulaglutide
2.63.1+Dulaglutide
Liraglutide
2.63.1+Liraglutide
Exendin IV
2.63.1+Exendin IV

Fig. 37

Food Intake In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide, Dulaglutide Or Exendin IV



Food intake data is from the following numbers animals each group
Vehicle: N=6
2.63.1: N=6
Dulaglutide: N=8
2.63.1 + Dulaglutide: N=6
Liraglutide: N=6
2.63.1 + Liraglutide: N=4
Exendin IV: N=7
2.63.1 + Exendin IV: N=4

Fig. 38

Insulin, Glucose And Glucose Tolerance In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide, Dulaglutide Or Exendin IV

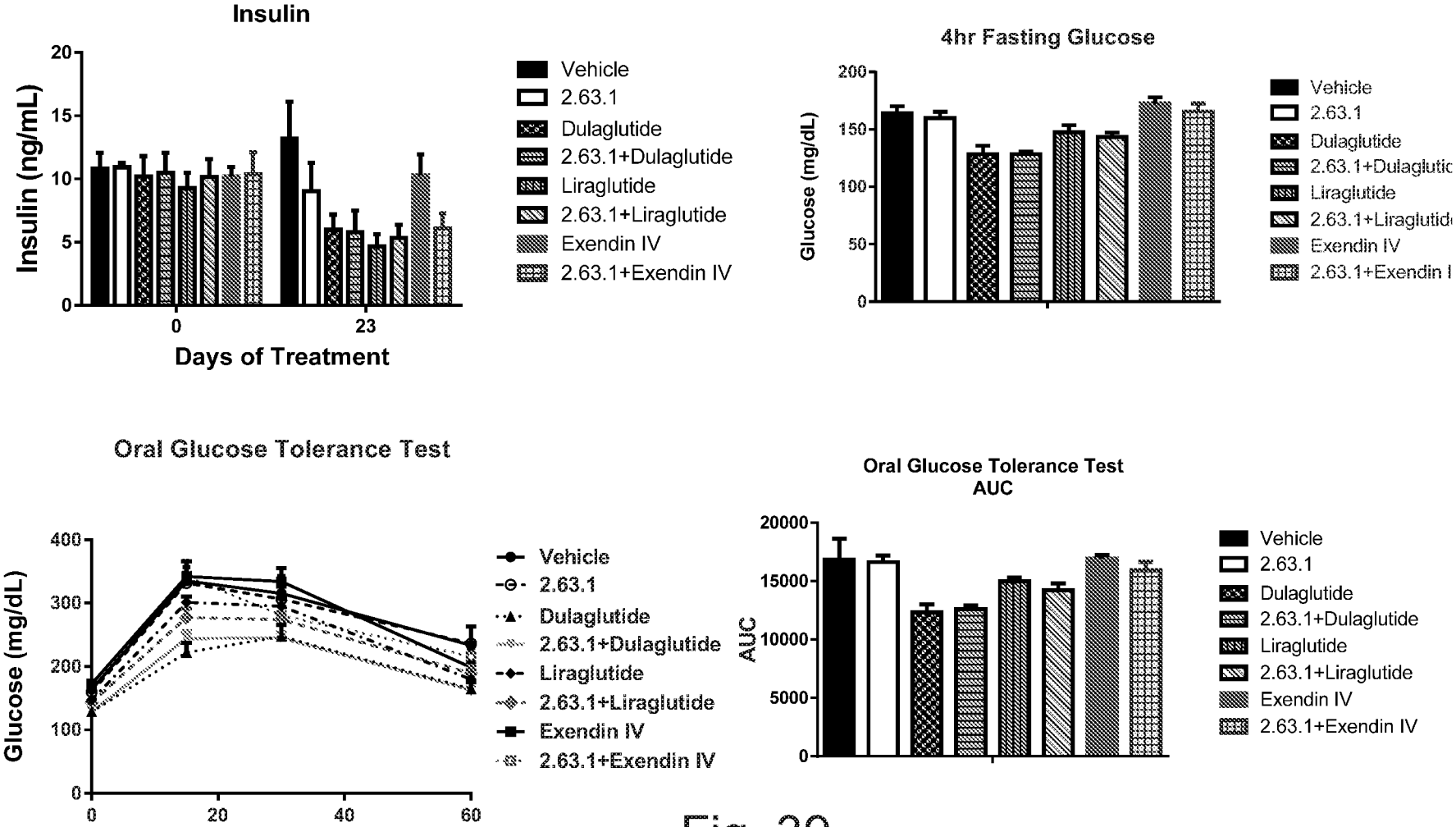


Fig. 39

Serum Total Cholesterol And Triglyceride In Mice Treated With Anti-GIPR 2.63.1 In Combination With Liraglutide, Dulaglutide Or Exendin IV

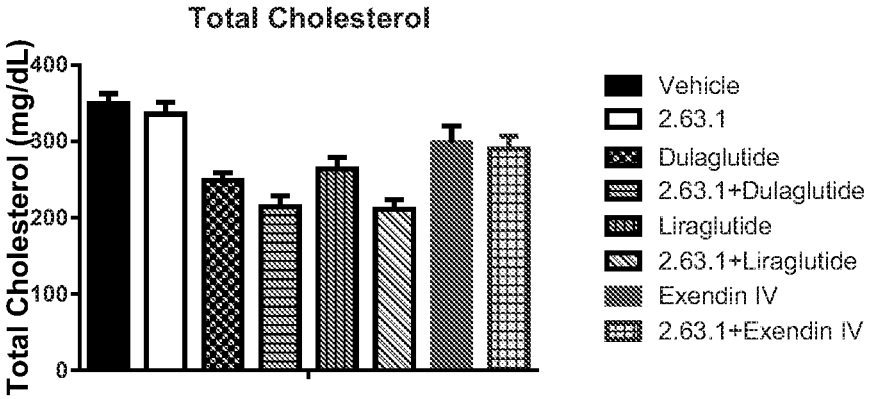
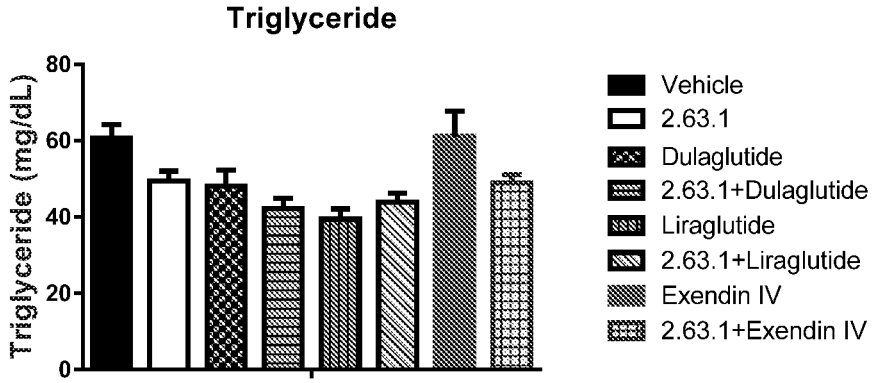


Fig. 40



Anti-GIPR Treatment In Mice Pre-treated To A GLP-1 Analog – Study Design

- Mice: Harlan C57BL/6 male DIO mice, 17 weeks of age (on high fat diet for 13 weeks) at study start
- Group and treatment, N=8/group, dose volume is 4ml/kg, study duration is 4 weeks (each phase is 2 weeks)

Phase 1	Phase 2
A. Saline daily + Vehicle weekly	Saline daily + Vehicle weekly
B. Liraglutide 0.05mg/kg daily + Vehicle weekly	Liraglutide 0.05mg/kg daily + Vehicle weekly
C. Liraglutide 0.05mg/kg daily + Vehicle weekly	Liraglutide 0.05mg/kg daily+ GIPR Ab 2.63.1 25mg/kg weekly
D. Liraglutide 0.3mg/kg daily + Vehicle weekly	Liraglutide 0.3mg/kg daily + Vehicle weekly
E. Liraglutide 0.3mg/kg daily + Vehicle weekly	Liraglutide 0.3mg/kg daily + GIPR Ab 2.63.1 1mg/kg weekly
F. Liraglutide 0.3mg/kg daily + Vehicle weekly	Liraglutide 0.3mg/kg daily + GIPR Ab 2.63.1 25mg/kg weekly
G. Liraglutide 0.3mg/kg daily + Vehicle weekly	Saline daily + Vehicle weekly
H. Liraglutide 0.3mg/kg daily + Vehicle weekly	Saline daily + GIPR Ab 2.63.1 25mg/kg weekly
I. Liraglutide 0.3mg/kg daily + GIPR Ab 2.63.1 25mg/kg weekly	Liraglutide 0.3mg/kg daily + GIPR Ab 2.63.1 25mg/kg weekly

- Procedures:
  - Day -8 to -1: dosing acclimation
  - Day -1: 4h fasted blood collection, body weight
  - Day -1: randomize on body weight
  - Day 1: 1st dose phase 1
  - Day 1-3; 15-17; 25-27: Food intake measured
  - Day 14: 2wk 4hr fasted blood collection
  - Day 15: 1st dose phase 2
  - Day 28: 4hr fasted final blood collection
  - Day 29: Termination tissue collection
- Endpoints:
  - Body weights
  - Mouse hormones, liver enzymes, lipid levels, glucose and insulin
  - Food Intake

Fig. 41

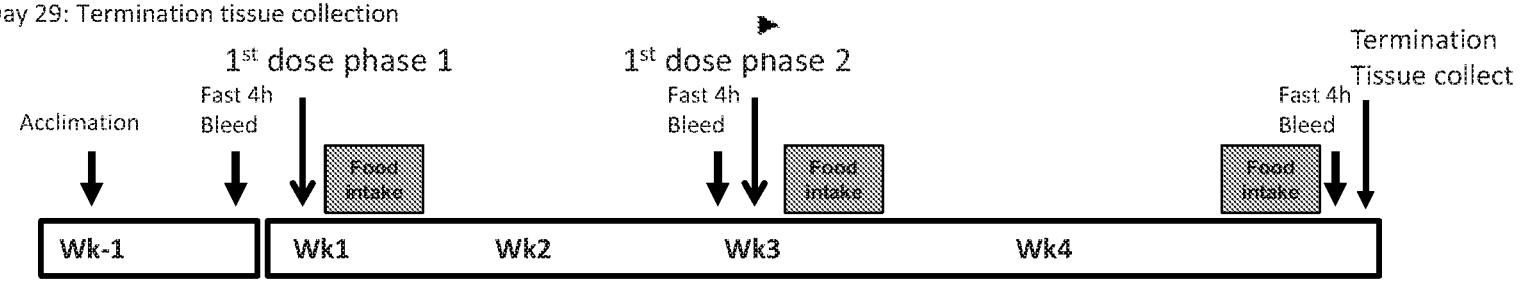
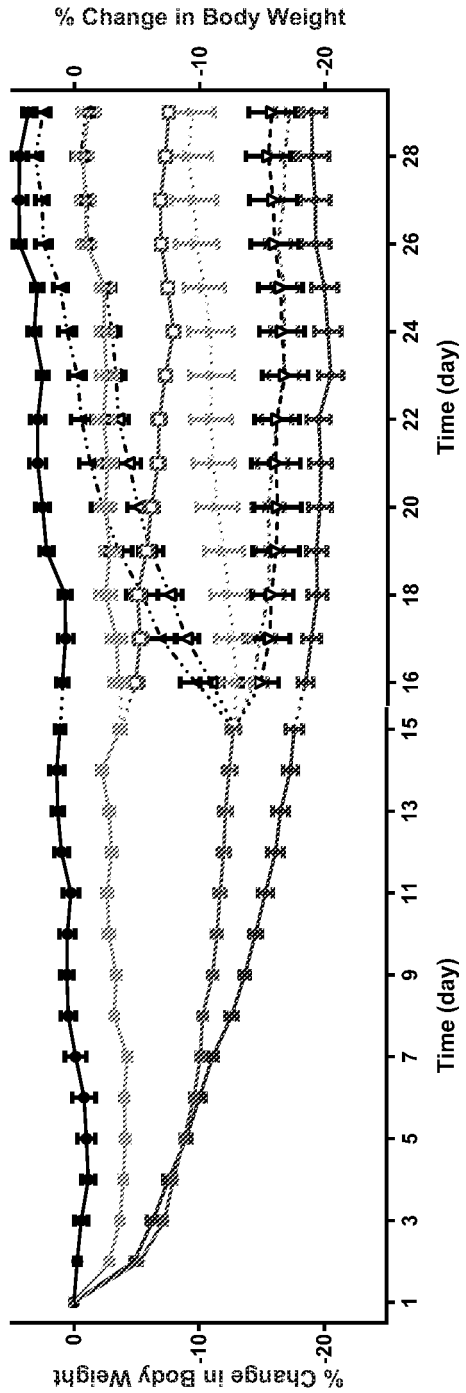


Fig. 42A

Body Weights – Combined Graphs



Phase 1

ANCOVA				
A vs	B	C	D
Day 1	***	***	***
2	***	***	***
3	**	***	***
4	**	***	***
5	*	***	***
6	**	***	***
7	***	***	***
8	***	***	***
9	***	***	***
10	**	***	***
11	***	***	***
12	***	***	***
13	***	***	***
14	***	***	***
15	***	***	***

Phase 1
QD (Ira) / QW (GIPR Ab)

A. Saline / Vehicle n=8
B. Ira 0.05mg/kg / Vehicle n=16
C. Ira 0.3mg/kg / Vehicle n=40
I. Ira 0.3mg/kg / GIPR Ab 25mg/kg n=8

Phase 2
QD (Ira) / QW (GIPR Ab)

A. Saline / Vehicle
B. Ira 0.05mg/kg / Vehicle
C. Ira 0.05mg/kg / GIPR Ab 25mg/kg
D. Ira 0.3mg/kg / Vehicle
E. Ira 0.3mg/kg / GIPR Ab 1mg/kg
F. Ira 0.3mg/kg / GIPR Ab 25mg/kg
G. Saline / Vehicle
H. Saline / GIPR Ab 25mg/kg
I. Ira 0.3mg/kg / GIPR Ab 25mg/kg

pvalues
p<0.05 *
p<0.01 **
p<0.001 ***

Phase 2

ANCOVA						
A vs	I	B vs	C	D vs	E	F	G vs	H
Day 16	***		ns		ns	ns		ns
17	***		ns		ns	ns		ns
18	***		ns		ns	ns		ns
19	***		ns		ns	ns		ns
20	***		ns		ns	ns		ns
21	***		ns		ns	ns		ns
22	***		ns		ns	*		ns
23	***		ns		ns	*		ns
24	***		ns		ns	*		ns
25	***		*		ns	*		ns
26	***		*		ns	*		ns
27	***		*		ns	**		ns
28	***		*		ns	**		ns
29	***		*		ns	**		ns

Fig. 42B

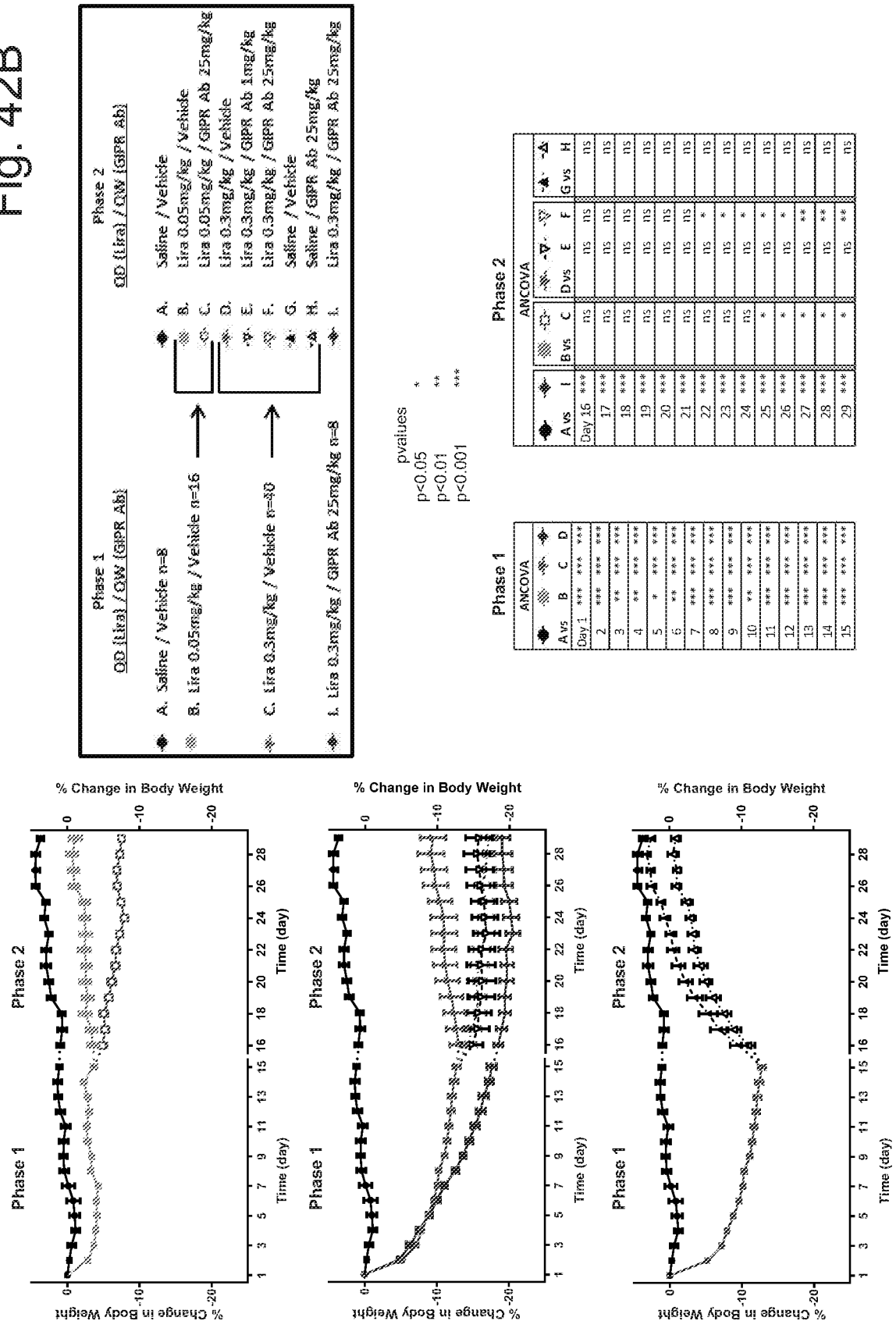

Body Weights – Separated Graphs
Phase 1
QD (lira) / QW (GPR Ab)
A. Saline / Vehicle n=8
B. Lira 0.05mg/kg / Vehicle n=16
C. Lira 0.3mg/kg / Vehicle n=40
I. Lira 0.3mg/kg / GPR Ab 25mg/kg n=8
Phase 2
QD (lira) / QW (GPR Ab)
A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / GPR Ab 25mg/kg
D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / GPR Ab 1mg/kg
F. Lira 0.3mg/kg / GPR Ab 25mg/kg
G. Saline / Vehicle
H. Saline / GPR Ab 25mg/kg
I. Lira 0.3mg/kg / GPR Ab 25mg/kg
pvalues
p<0.05 *
p<0.01 **
p<0.001 ***
Phase 1
ANCOVA
A vs B C D
Day 1 *** *** ***
2 *** *** ***
3 ** *** ***
4 ** *** ***
5 * *** ***
6 ** *** ***
7 *** *** ***
8 *** *** ***
9 *** *** ***
10 ** *** ***
11 *** *** ***
12 *** *** ***
13 *** *** ***
14 *** *** ***
15 *** *** ***
Phase 2
ANCOVA
A vs I B vs C D vs E F G vs H
Day 16 *** ns ns ns ns ns
17 *** ns ns ns ns ns
18 *** ns ns ns ns ns
19 *** ns ns ns ns ns
20 *** ns ns ns ns ns
21 *** ns ns ns ns ns
22 *** ns ns * ns ns
23 *** ns ns * ns ns
24 *** ns ns * ns ns
25 *** * ns * ns ns
26 *** * ns * ns ns
27 *** * ns ** ns ns
28 *** * ns ** ns ns
29 *** * ns ** ns ns
% Change in Body Weight
% Change in Body Weight
Phase 1
Phase 2
Time (day)
% Change in Body Weight
% Change in Body Weight
Phase 1
Phase 2
Time (day)
% Change in Body Weight
% Change in Body Weight
Phase 1
Phase 2
Time (day)

Fig. 43

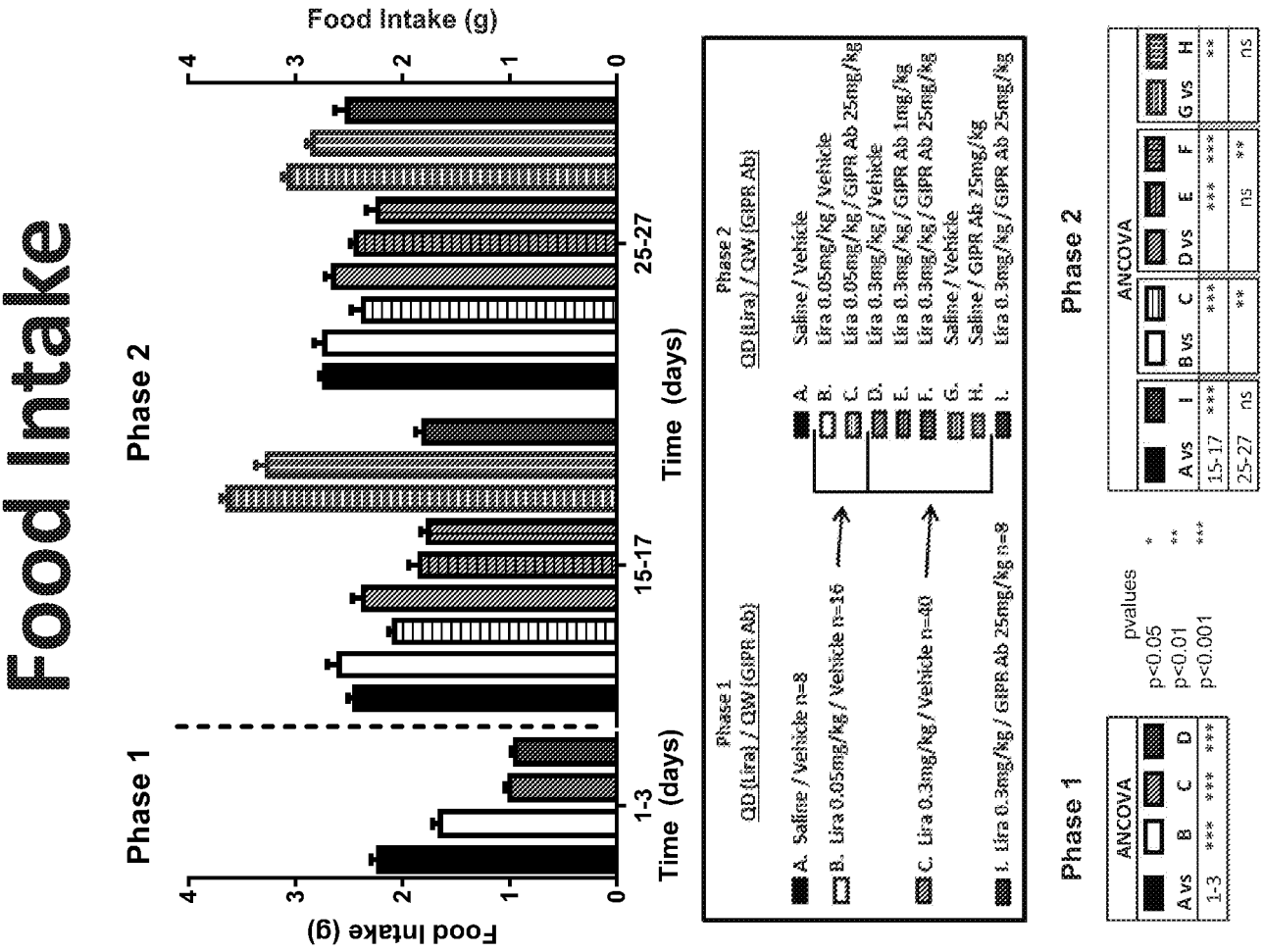
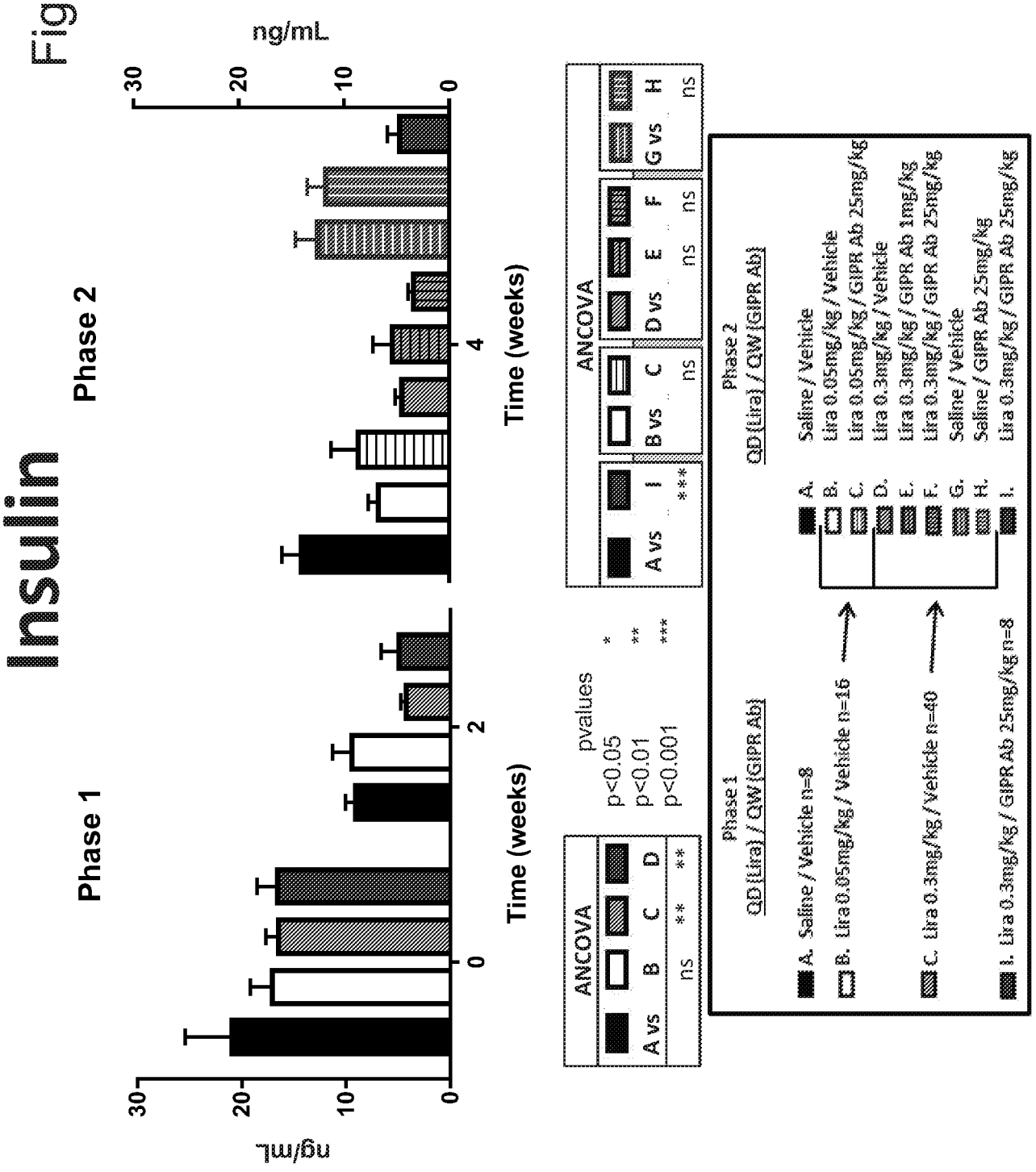
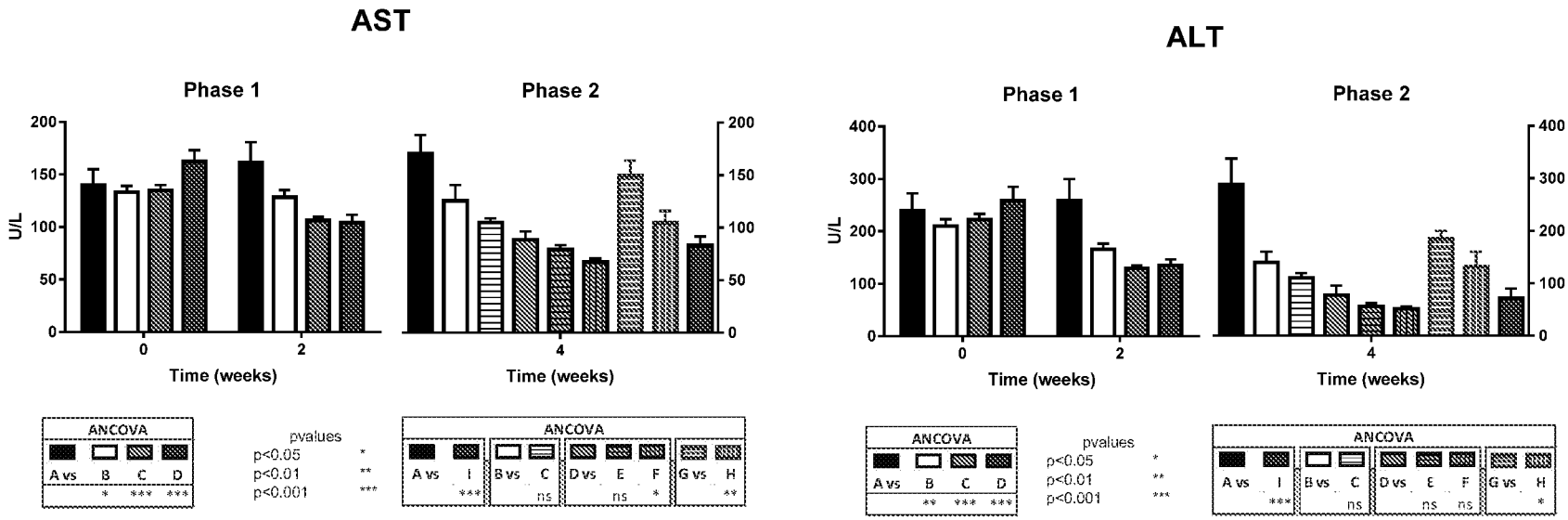

Food Intake
Phase 1
Phase 2
Food Intake (g)
Time (days)
1-3
15-17
25-27
Phase 1
QD (Lira) / QW (GIPR Ab)
A. Saline / Vehicle n=8
B. Lira 0.05mg/kg / Vehicle n=16
C. Lira 0.3mg/kg / Vehicle n=40
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg n=8
Phase 2
QD (Lira) / QW (GIPR Ab)
A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / GIPR Ab 25mg/kg
D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / GIPR Ab 1mg/kg
F. Lira 0.3mg/kg / GIPR Ab 25mg/kg
G. Saline / Vehicle
H. Saline / GIPR Ab 25mg/kg
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg
ANCOVA
A vs I
B vs C
D vs E
F vs G
H
1-3 *** *** ***
15-17 *** *** *** **
25-27 ns ** ns ns
pvalues
p<0.05 *
p<0.01 **
p<0.001 ***

Fig. 44


Insulin
Phase 1
Phase 2
ng/mL
Time (weeks)
ANCOVA
A vs B C D
ns ** **
pvalues
p<0.05 *
p<0.01 **
p<0.001 ***
ANCOVA
A vs I B vs C D vs E F G vs H
*** ns ns ns ns
Phase 1
QD (Lira) / QW (GIPR Ab)
Phase 2
QD (Lira) / QW (GIPR Ab)
A. Saline / Vehicle n=8
B. Lira 0.05mg/kg / Vehicle n=16
C. Lira 0.3mg/kg / Vehicle n=40
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg n=8
A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / GIPR Ab 25mg/kg
D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / GIPR Ab 1mg/kg
F. Lira 0.3mg/kg / GIPR Ab 25mg/kg
G. Saline / Vehicle
H. Saline / GIPR Ab 25mg/kg
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg

Clinical Chemistry – Liver Enzymes



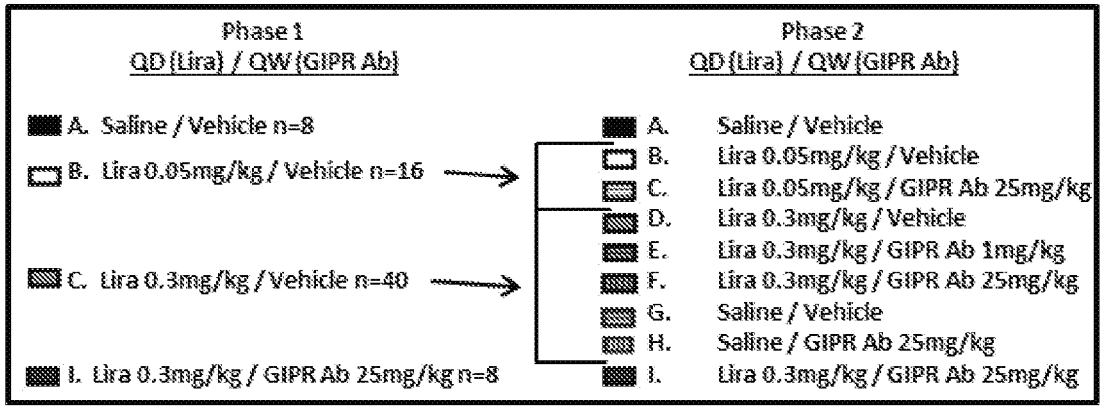
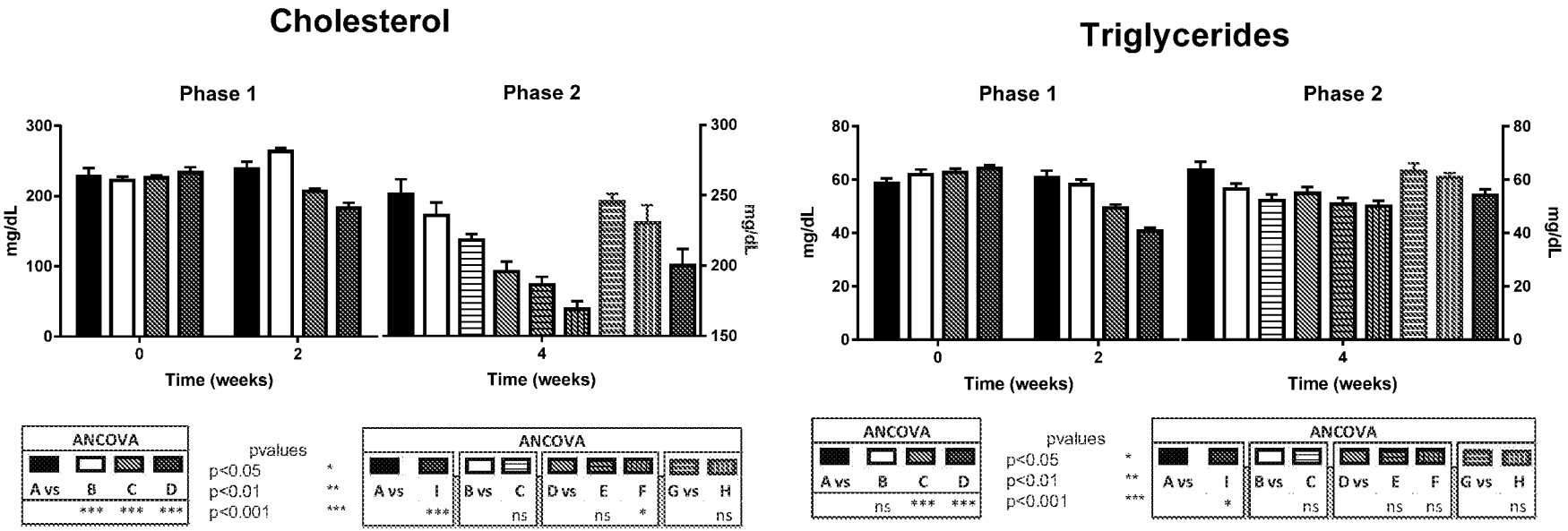


Fig. 45A

Clinical Chemistry – Plasma Cholesterol and Triglycerides



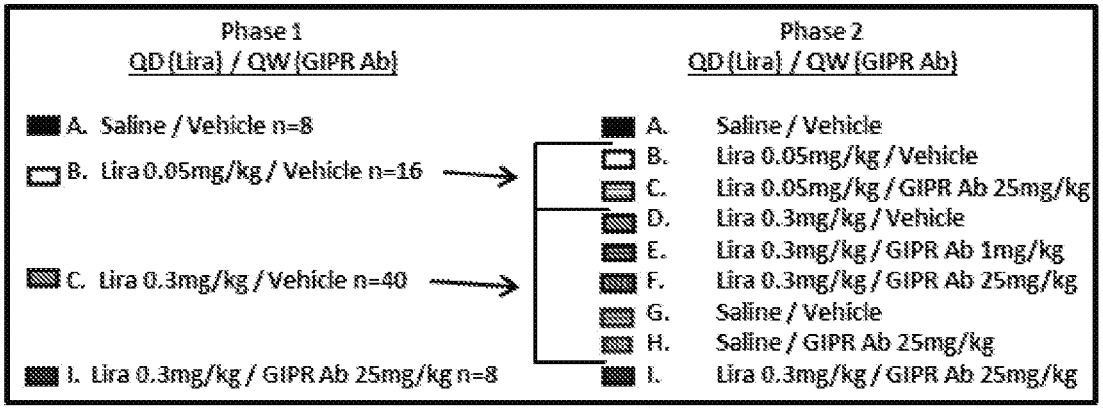
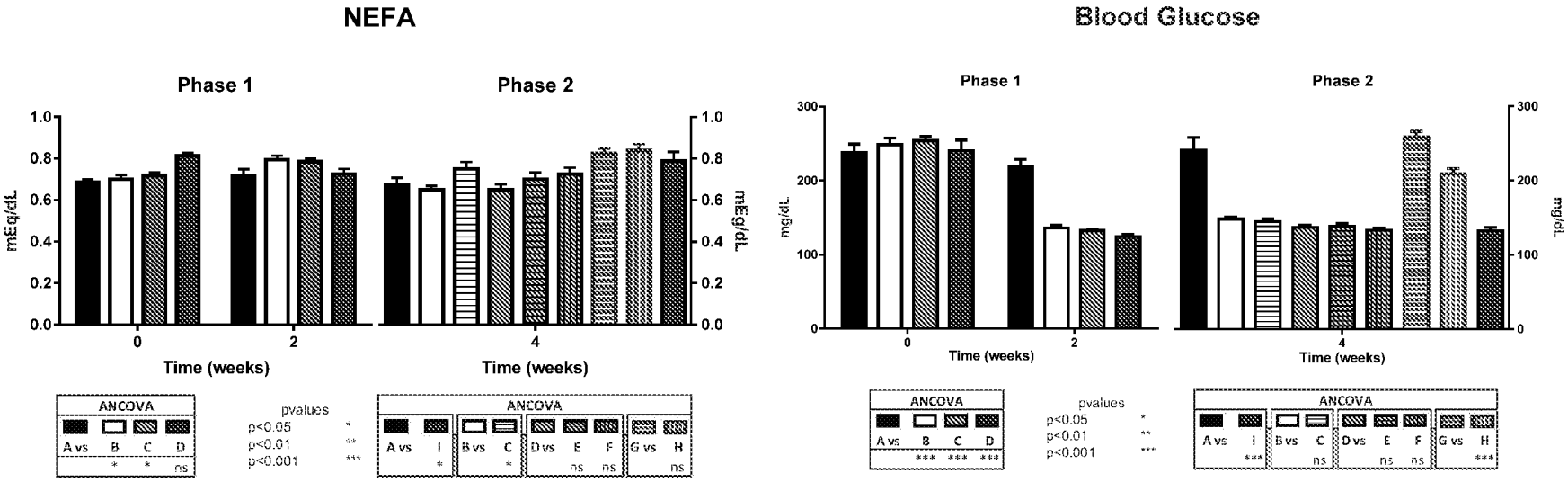


Fig. 45B

Clinical Chemistry – Plasma NEFA and Glucose



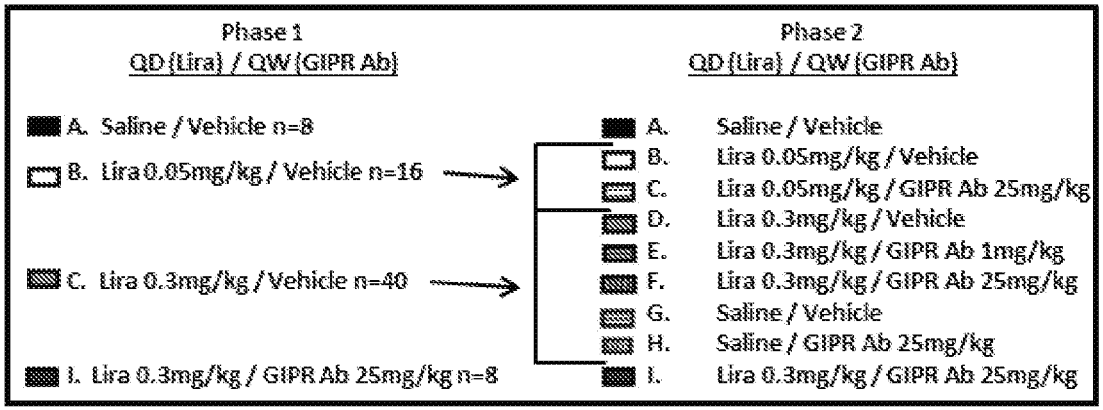
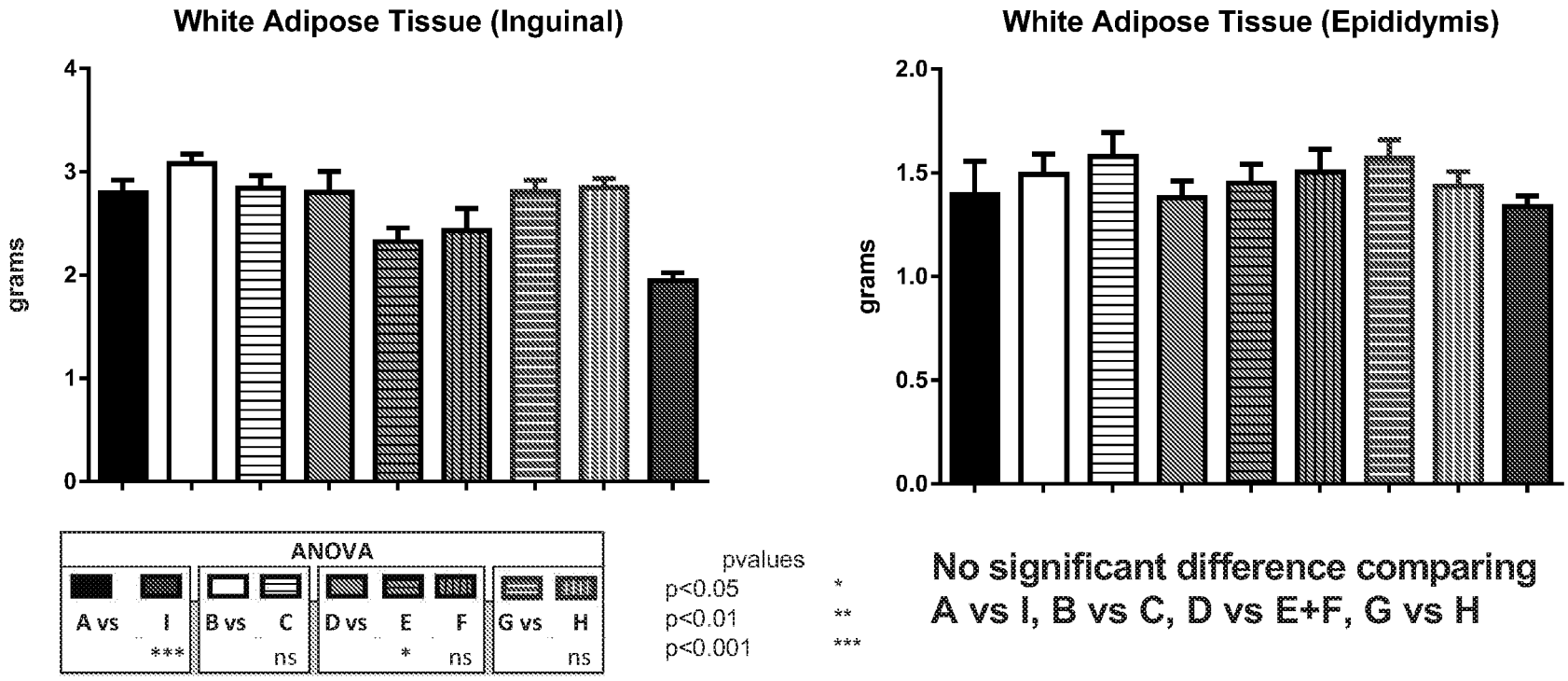


Fig. 45C

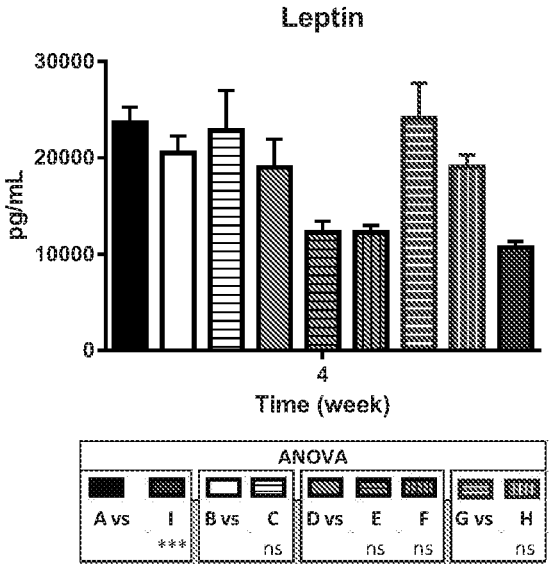
Tissue Weights

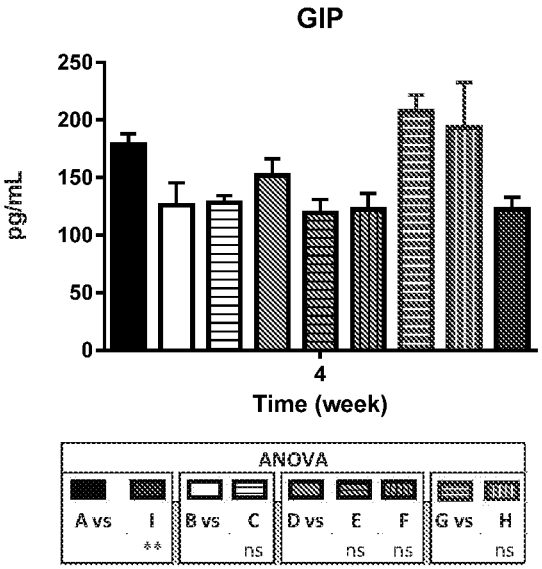


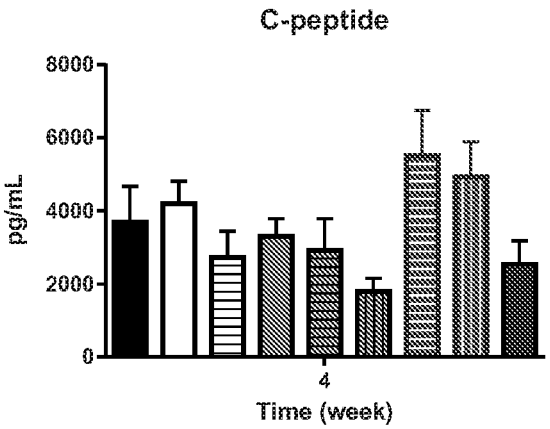
	Phase 1 QD (Lira) / QW (GIPR)	Phase 2 QD (Lira) / QW (GIPR)
A.	Saline / Vehicle	Saline / Vehicle
B.	Lira 0.05mg/kg / Vehicle	Lira 0.05mg/kg / Vehicle
C.	Lira 0.05mg/kg / Vehicle	Lira 0.05mg/kg / GIPR Ab 25mg/kg
D.	Lira 0.3mg/kg / Vehicle	Lira 0.3mg/kg / Vehicle
E.	Lira 0.3mg/kg / Vehicle	Lira 0.3mg/kg / GIPR Ab 1mg/kg
F.	Lira 0.3mg/kg / Vehicle	Lira 0.05mg/kg / GIPR Ab 25mg/kg
G.	Lira 0.3mg/kg / Vehicle	Saline / Vehicle
H.	Lira 0.3mg/kg / Vehicle	Saline / GIPR Ab 25mg/kg
I.	Lira 0.3mg/kg / GIPR Ab 25mg/kg	Lira 0.3mg/kg / GIPR Ab 25mg/kg

Fig. 46

Plasma Hormones







No significant differences comparing
A vs I, B vs C, D vs E+F, G vs H

Phase 1 QD (Lira) / QW (GIPR)	Phase 2 QD (Lira) / QW (GIPR)
A. Saline / Vehicle	A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle	B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / Vehicle	C. Lira 0.05mg/kg / GIPR Ab 25mg/kg
D. Lira 0.3mg/kg / Vehicle	D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / Vehicle	E. Lira 0.3mg/kg / GIPR Ab 1mg/kg
F. Lira 0.3mg/kg / Vehicle	F. Lira 0.05mg/kg / GIPR Ab 25mg/kg
G. Lira 0.3mg/kg / Vehicle	G. Saline / Vehicle
H. Lira 0.3mg/kg / Vehicle	H. Saline / GIPR Ab 25mg/kg
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg	I. Lira 0.3mg/kg / GIPR Ab 25mg/kg

Fig. 47A

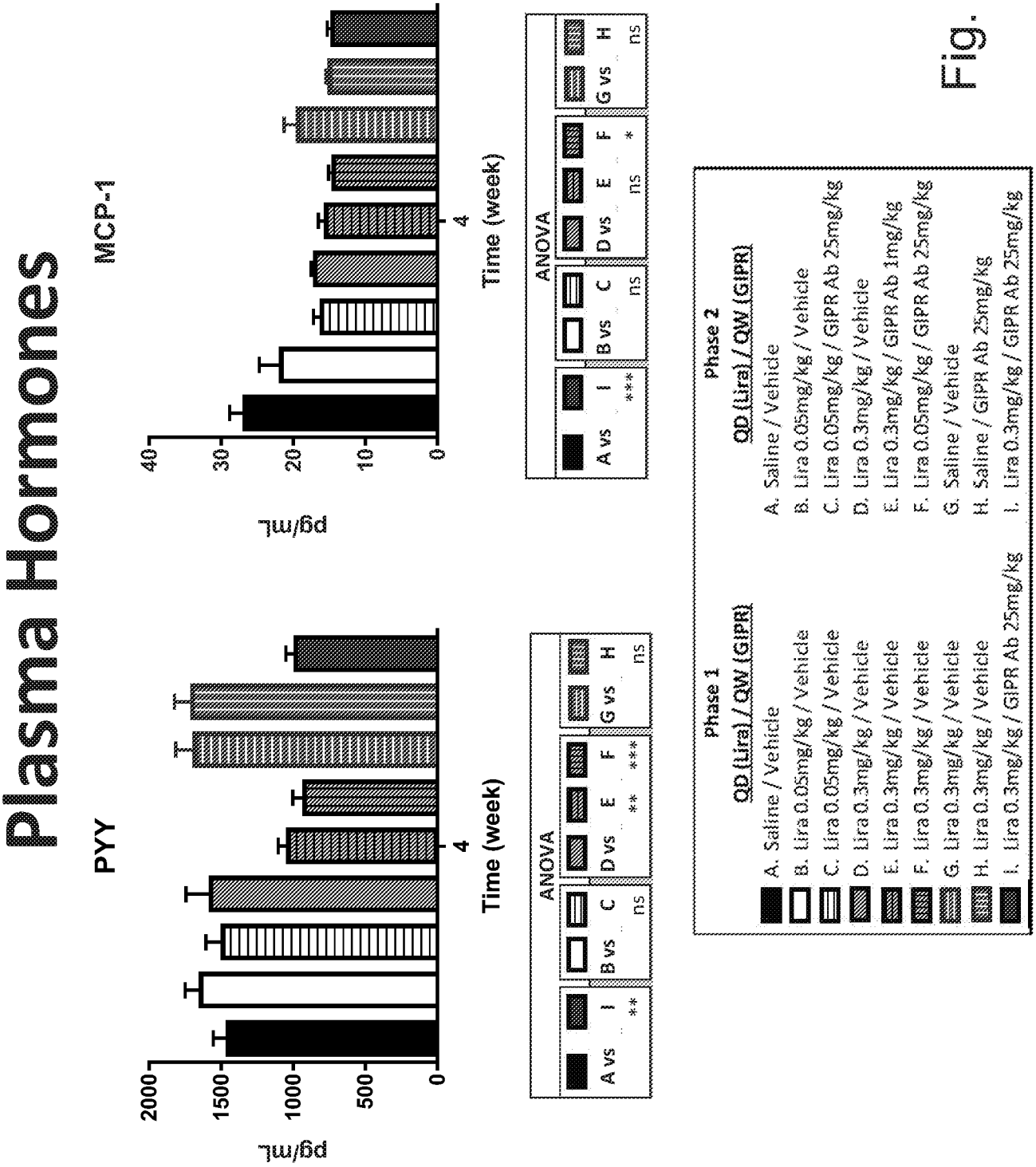

Plasma Hormones
PYY
MCP-1
pg/mL
Time (week)
ANOVA
A vs I
B vs C
D vs E
G vs H
Phase 1
QD (Lira) / QW (GIPR)
A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / Vehicle
D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / Vehicle
F. Lira 0.3mg/kg / Vehicle
G. Lira 0.3mg/kg / Vehicle
H. Lira 0.3mg/kg / Vehicle
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg
Phase 2
QD (Lira) / QW (GIPR)
A. Saline / Vehicle
B. Lira 0.05mg/kg / Vehicle
C. Lira 0.05mg/kg / GIPR Ab 25mg/kg
D. Lira 0.3mg/kg / Vehicle
E. Lira 0.3mg/kg / GIPR Ab 1mg/kg
F. Lira 0.05mg/kg / GIPR Ab 25mg/kg
G. Saline / Vehicle
H. Saline / GIPR Ab 25mg/kg
I. Lira 0.3mg/kg / GIPR Ab 25mg/kg

Fig. 47B

GIPR Ab chronic study design in spontaneously obese cynomolgus monkeys

PURPOSE: Determine efficacy of GIPR Ab 2G10 alone and in combination with Dulaglutide

GROUPS (Naïve spontaneously obese cynomolgus NHPs; n=10/gp)
1. Vehicle
2. 2G10 only (3mg/kg)
3. Dulaglutide only (0.05, 0.1, 0.25mg/kg loading)
4. 2G10 + Dulaglutide (co-injected)

ENDPOINTS:
- weekly body weight
- daily food intake
- blood chemistries (insulin and triglycerides)
- OGTT

Dosing Regimen

2G10:	every 6 days
Dulaglutide:	every 3 days
Vehicle:	matches 2G10 or Dula dose regimen

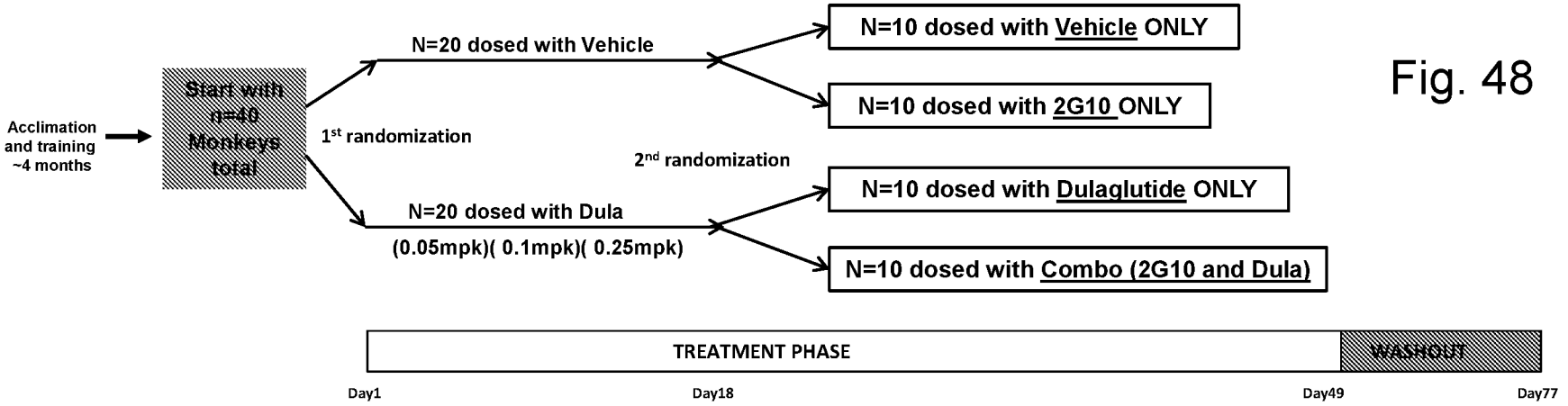


Fig. 48

2G10 causes body weight reduction in spontaneous obese cynomolgus monkeys with or without Dulaglutide

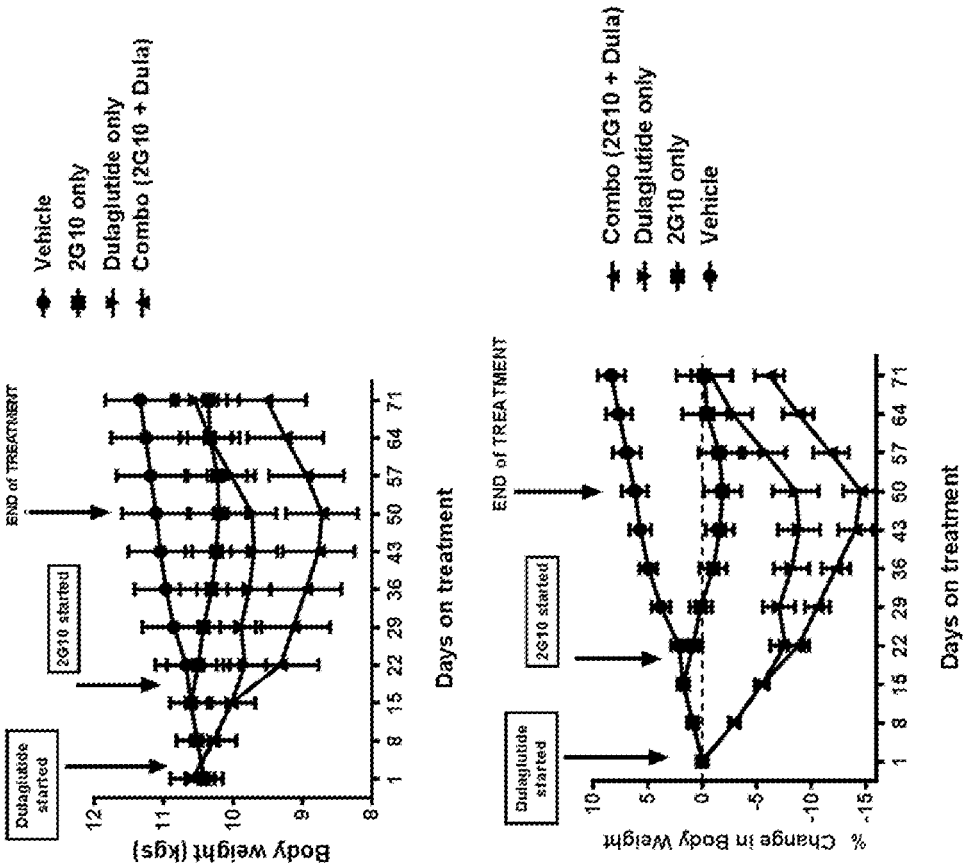


Fig. 49

2G10 alone causes body weight reduction in spontaneously obese cynomolgus monkeys (baseline reinitiated at day 15 prior starting 2G10 treatment)

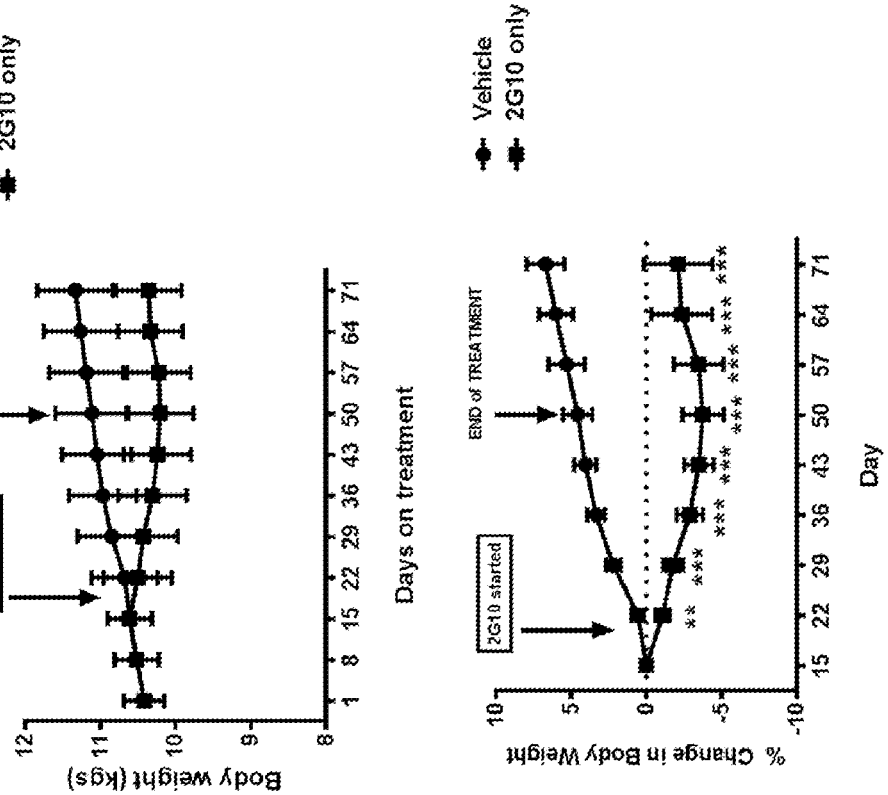
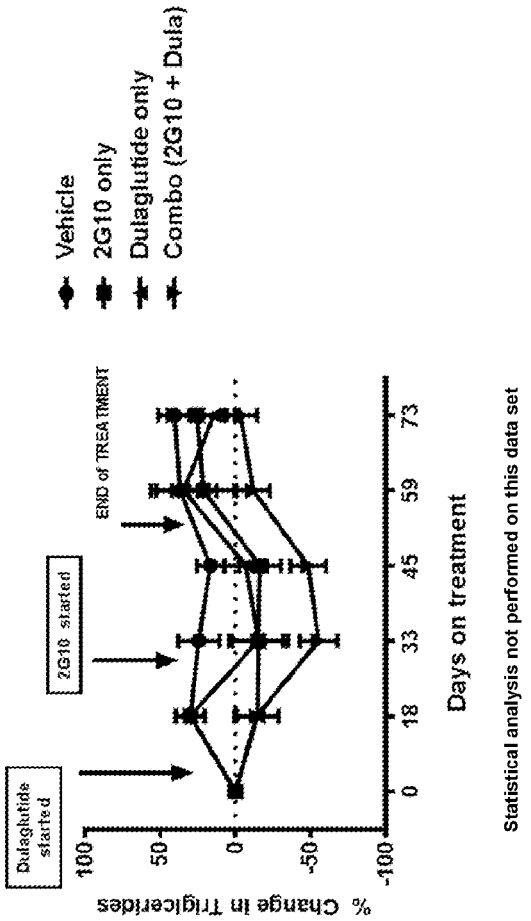


Fig. 50

2G10 prevents increase in insulin and reduces triglycerides levels with or without Dulaglutide in overnight fasted spontaneously obese cynomolgus monkeys (% change from baseline)



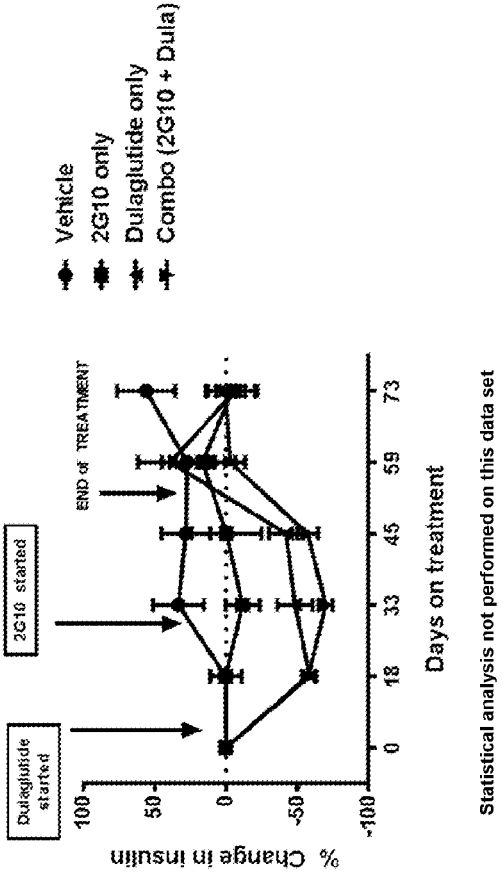


Fig. 51

2G10 prevents increase in insulin levels and reduces triglycerides levels with or without Dulaglutide in overnight fasted spontaneously obese cynomolgus monkeys (raw data) post treatment phase (day 45)

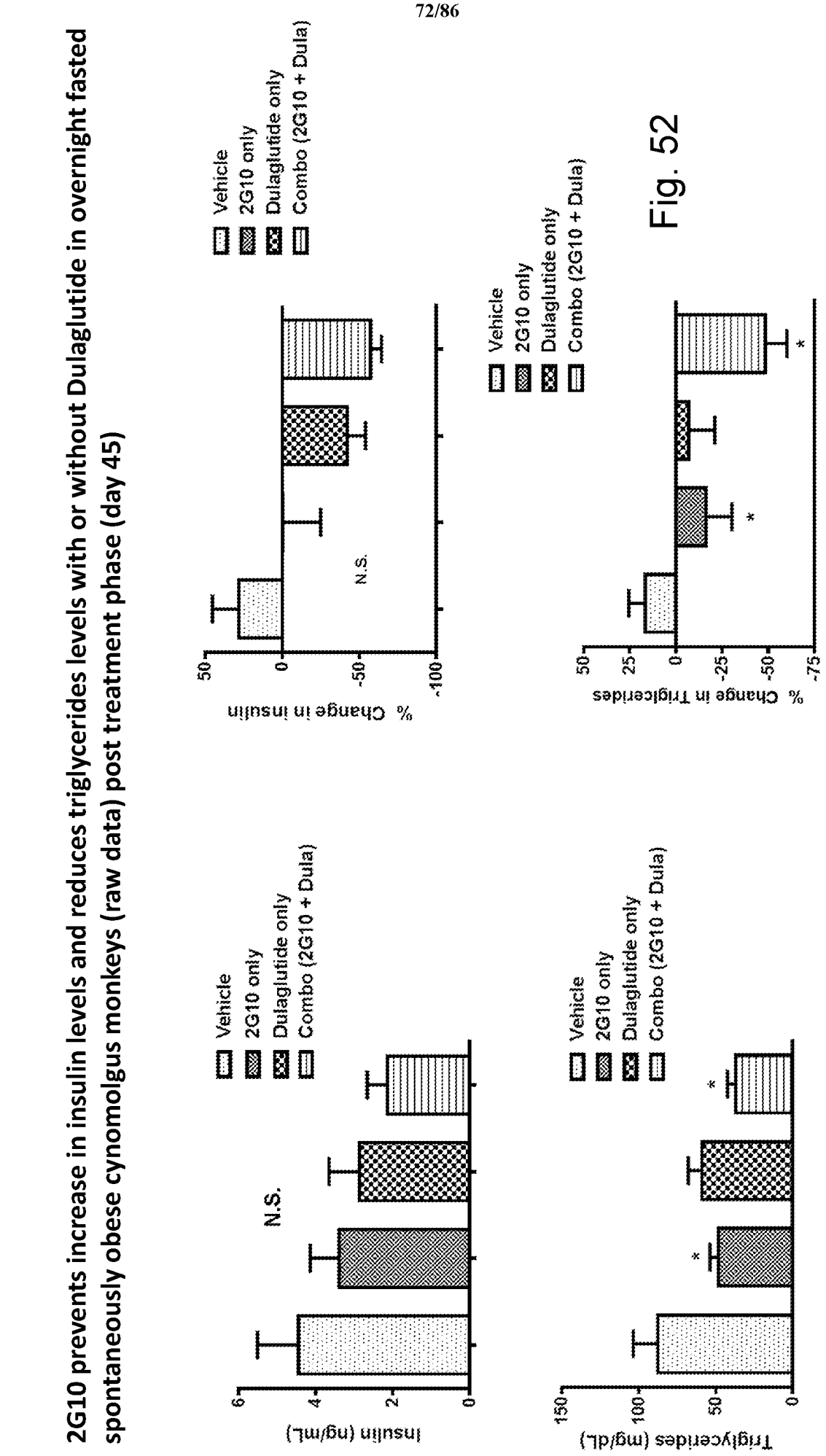


Fig. 52

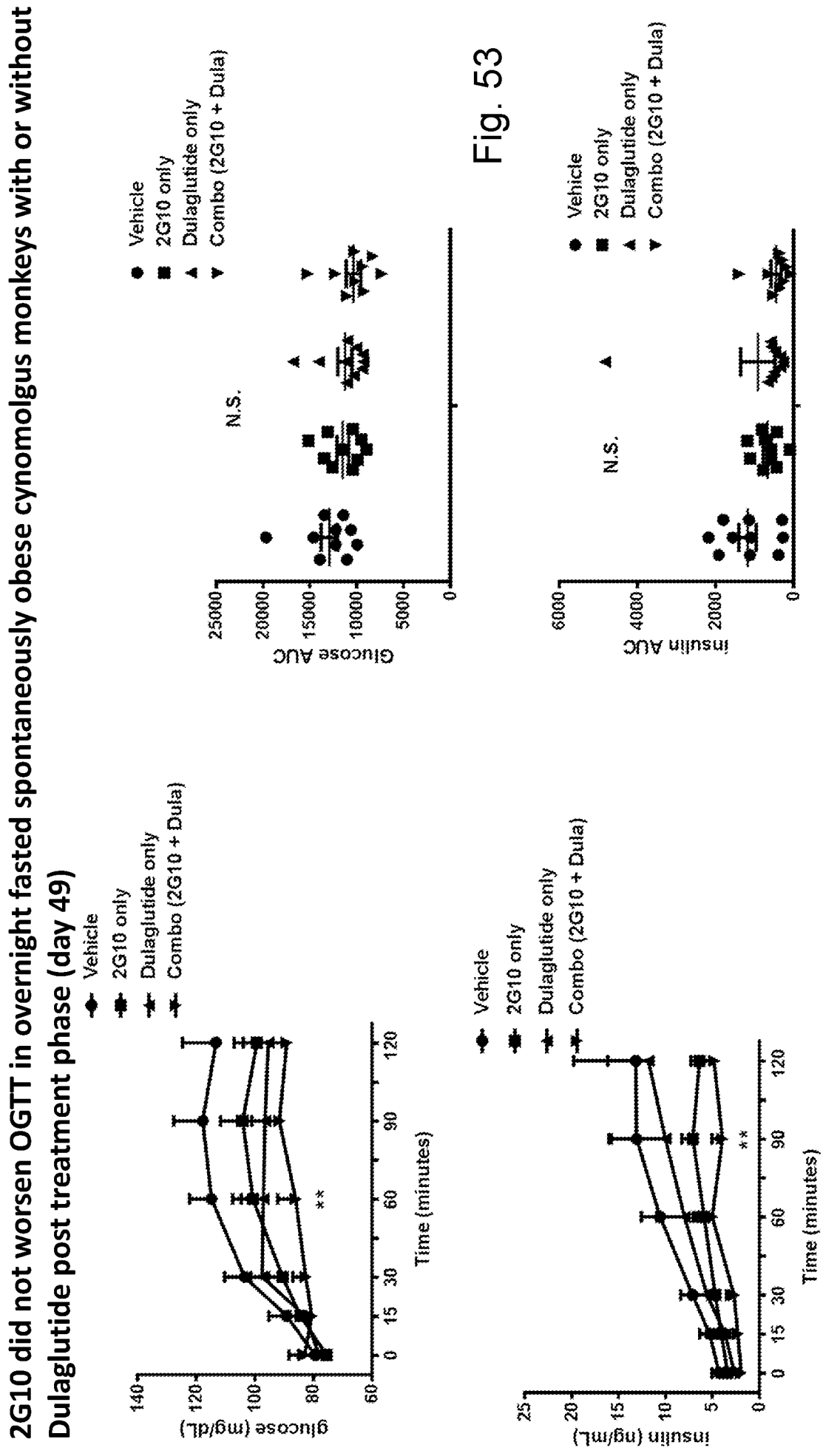

2G10 did not worsen OGTT in overnight fasted spontaneously obese cynomolgus monkeys with or without Dulaglutide post treatment phase (day 49)
Vehicle
2G10 only
Dulaglutide only
Combo (2G10 + Dula)
glucose (mg/dL)
Time (minutes)
**
Glucose AUC
N.S.
insulin (ng/mL)
Insulin AUC

Fig. 53

2G10 had no effects on total cholesterol, LDL-C and HDL-C levels in overnight fasted spontaneously obese cynomolgus monkeys post treatment phase (day 45)

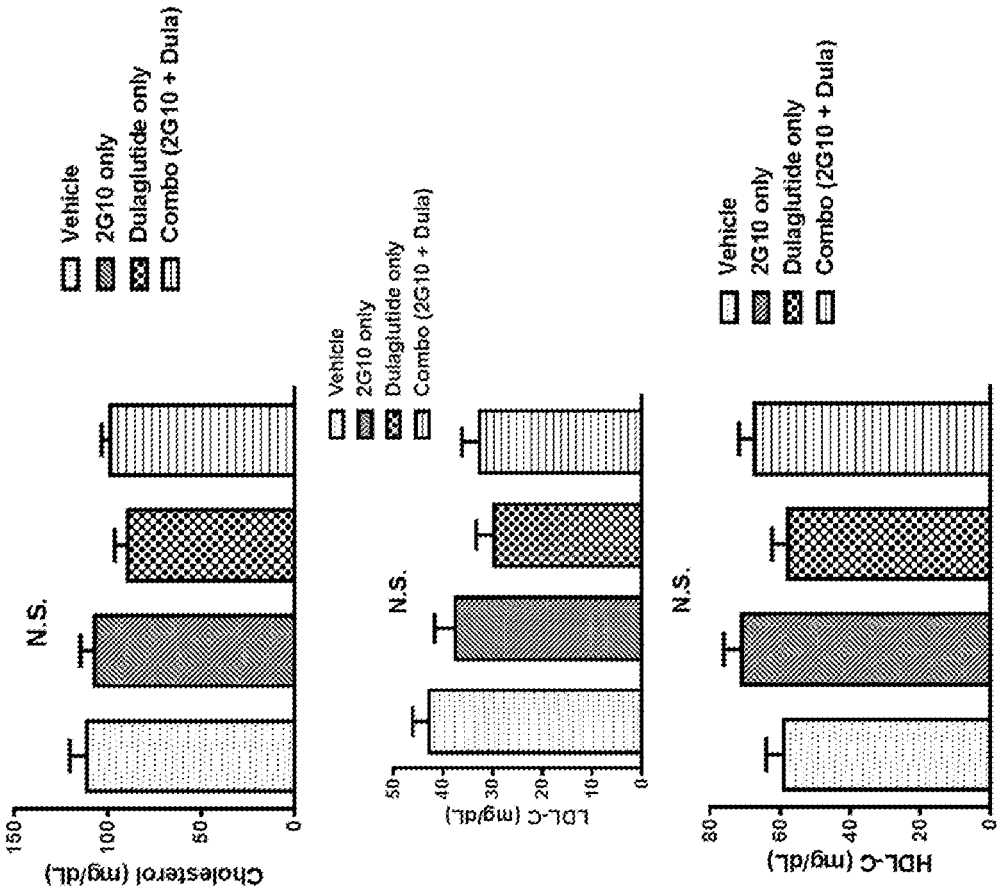


Fig. 54

2G10 had no effects glucose levels in overnight fasted normoglycemic obese cynomolgus monkeys post treatment phase (day 45)

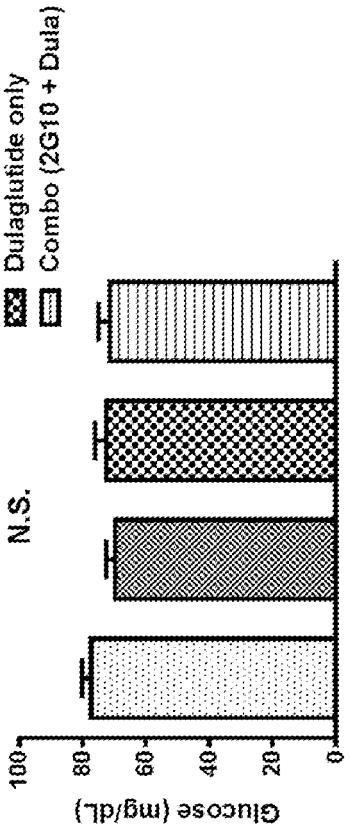


Fig. 55

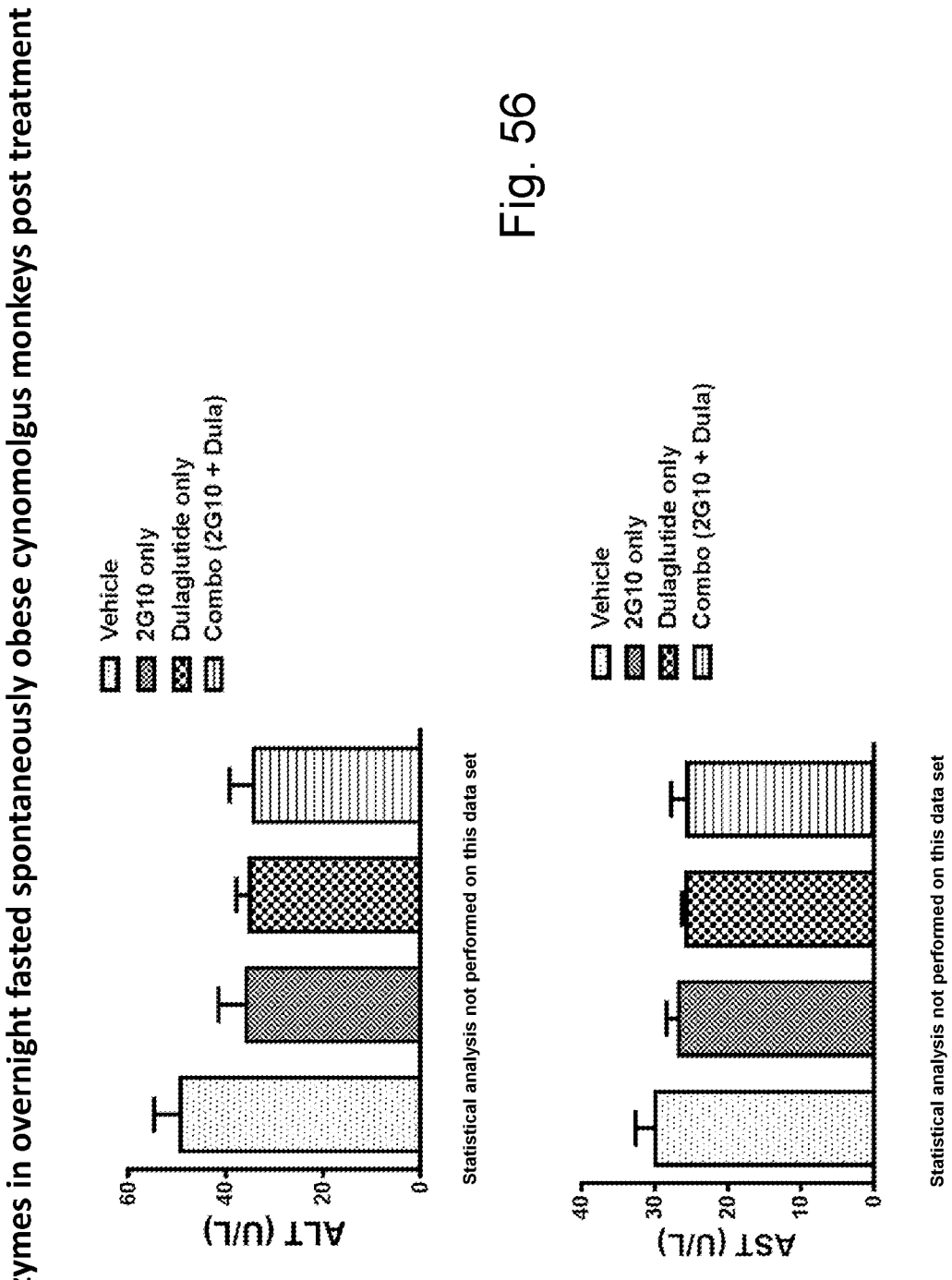

2G10 had no effect on liver enzymes in overnight fasted spontaneously obese cynomolgus monkeys post treatment phase (day 45)
Vehicle
2G10 only
Dulaglutide only
Combo (2G10 + Dula)
ALT (U/L)
0
20
40
60
Statistical analysis not performed on this data set
Vehicle
2G10 only
Dulaglutide only
Combo (2G10 + Dula)
AST (U/L)
0
10
20
30
40
Statistical analysis not performed on this data set

Fig. 56

FIG. 57

Overall structure of the huGIPR-Fab 2G10 complex

FIG. 57A

FIG. 57B

FIG. 58

Binding Interface

FIG. 58A

Binding interface highlighting the CDR loops of Fab 2G10

FIG. 58B

Binding interface highlighting the huGIPR residues

FIG. 59

Overall structure of the huGIPR-Fab 2C2 complex

FIG. 59A

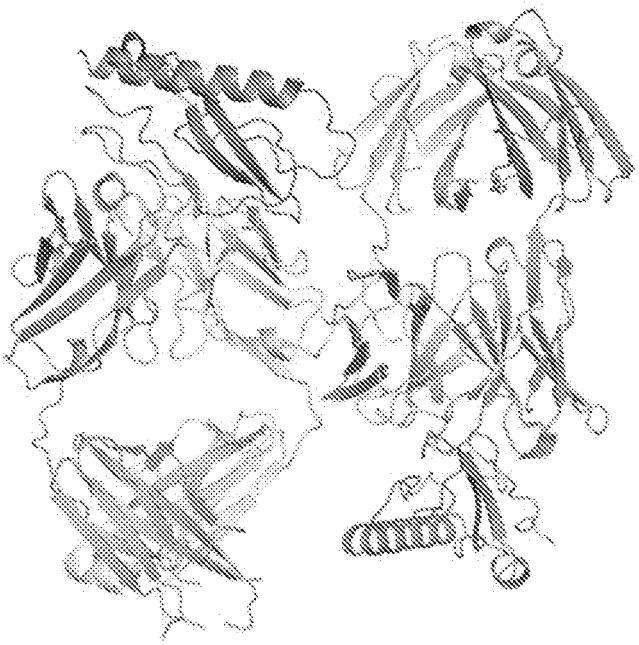


FIG. 59B

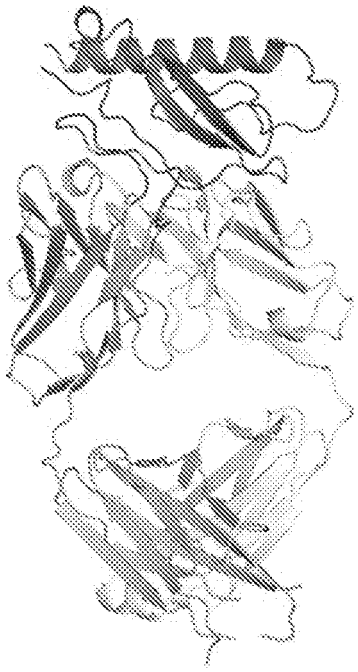


FIG. 60

Binding Interface

FIG. 60A

Binding interface highlighting the CDR loops of Fab 2C2

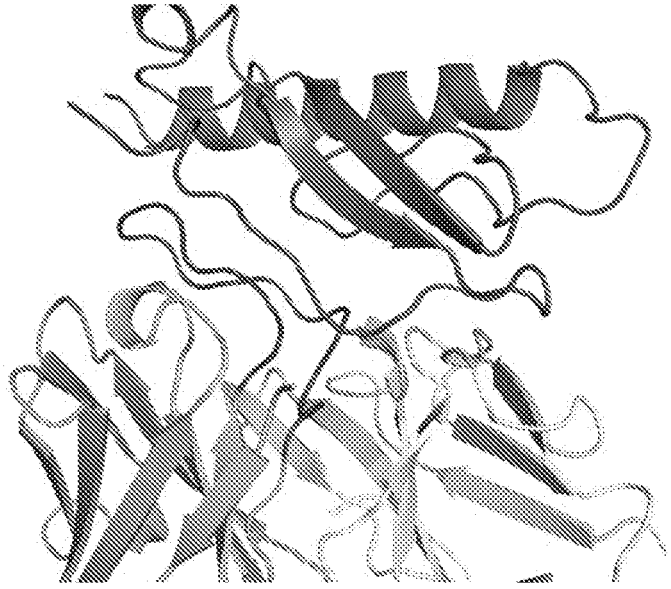


FIG. 60B

Binding interface highlighting the huGIPR residues

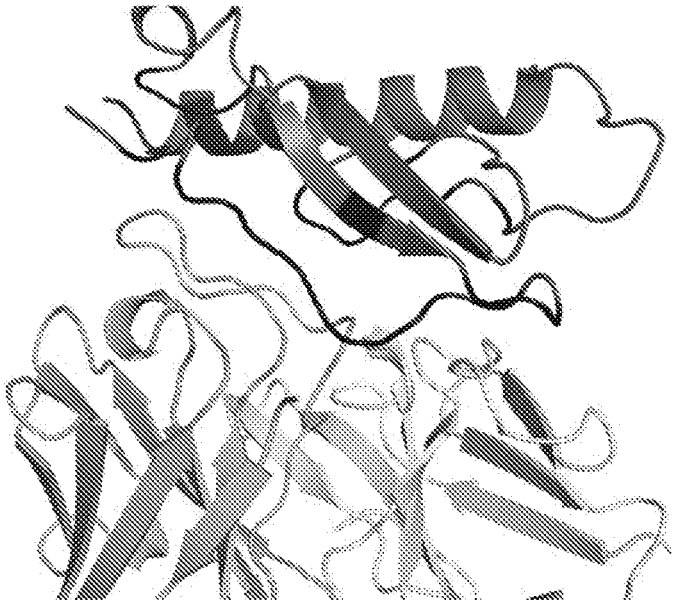


FIG. 61

Overall structure of the huGIPR-Fab 6H1 complex

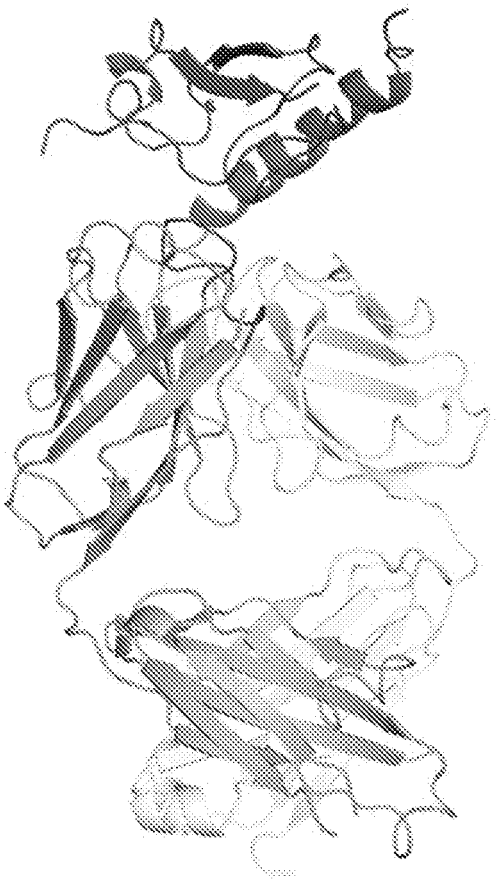


FIG. 62

Binding Interface

FIG. 62A

Binding interface highlighting the CDR loops of Fab 6H1

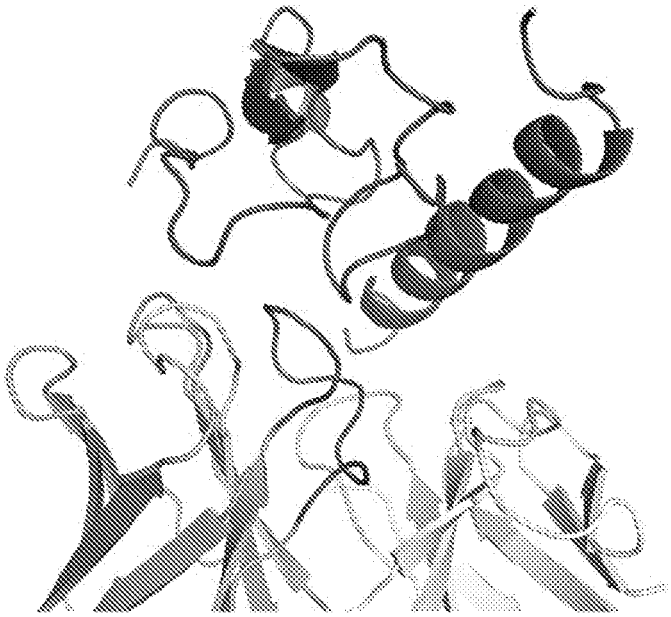


FIG. 62B

Binding interface highlighting the huGIPR residues

FIG. 63

Overall structure of the huGIPR-Fab 17H11 complex

FIG. 64

Binding Interface

FIG. 64A

Binding interface highlighting the CDR loops of Fab 17H11

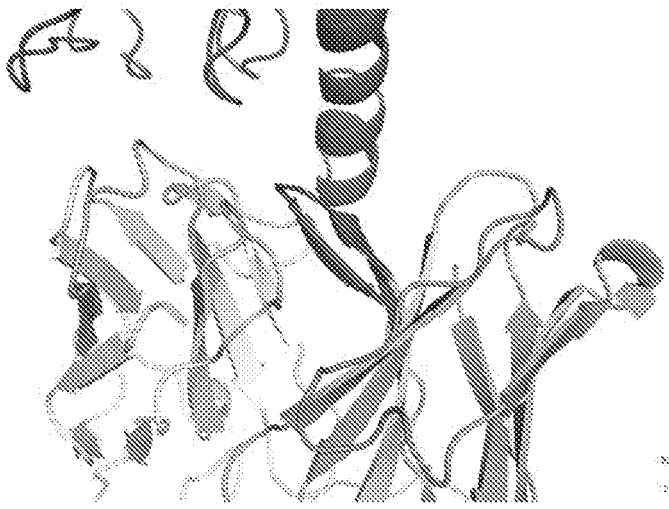


FIG. 64B

Binding interface highlighting the huGIPR residues

FIG. 65

Surface representation of antibody epitope

FIG.65A
2G10

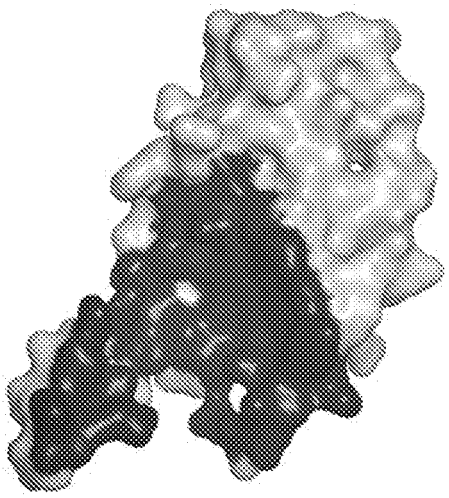


FIG. 65B
2C2

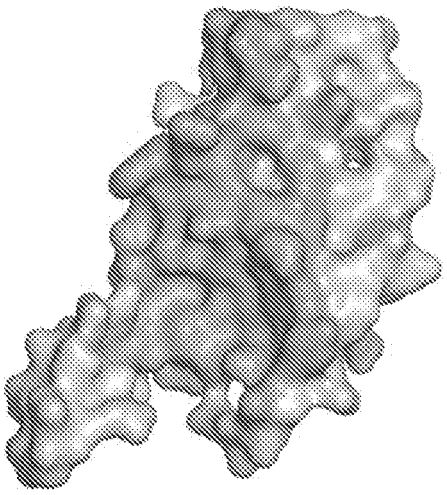


FIG. 65C
6H1

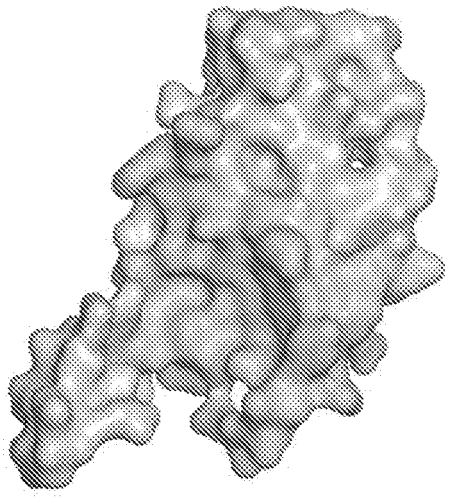


FIG. 65D
17H11

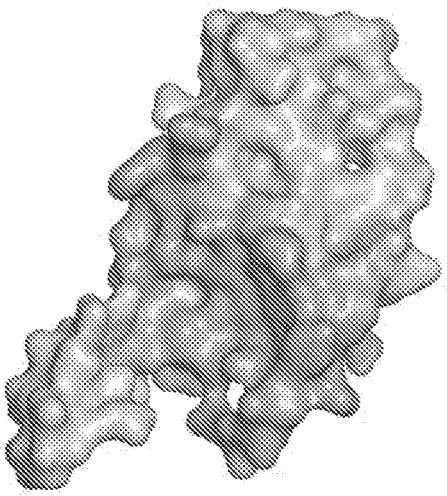


FIG. 65 (Continued)

Surface representation of antibody epitope

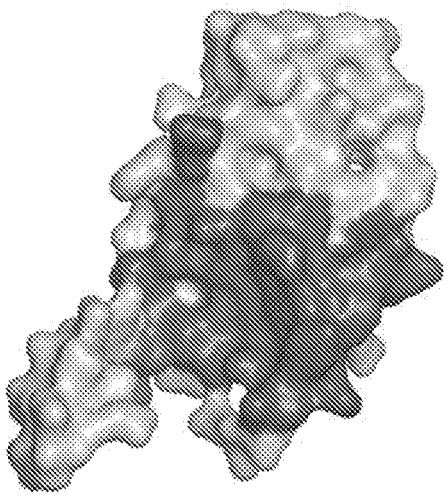



FIG. 65E – Epitope for the Gipg013 (PDB: 4JH0)