WO 2025/207644 PCT/US2025/021357

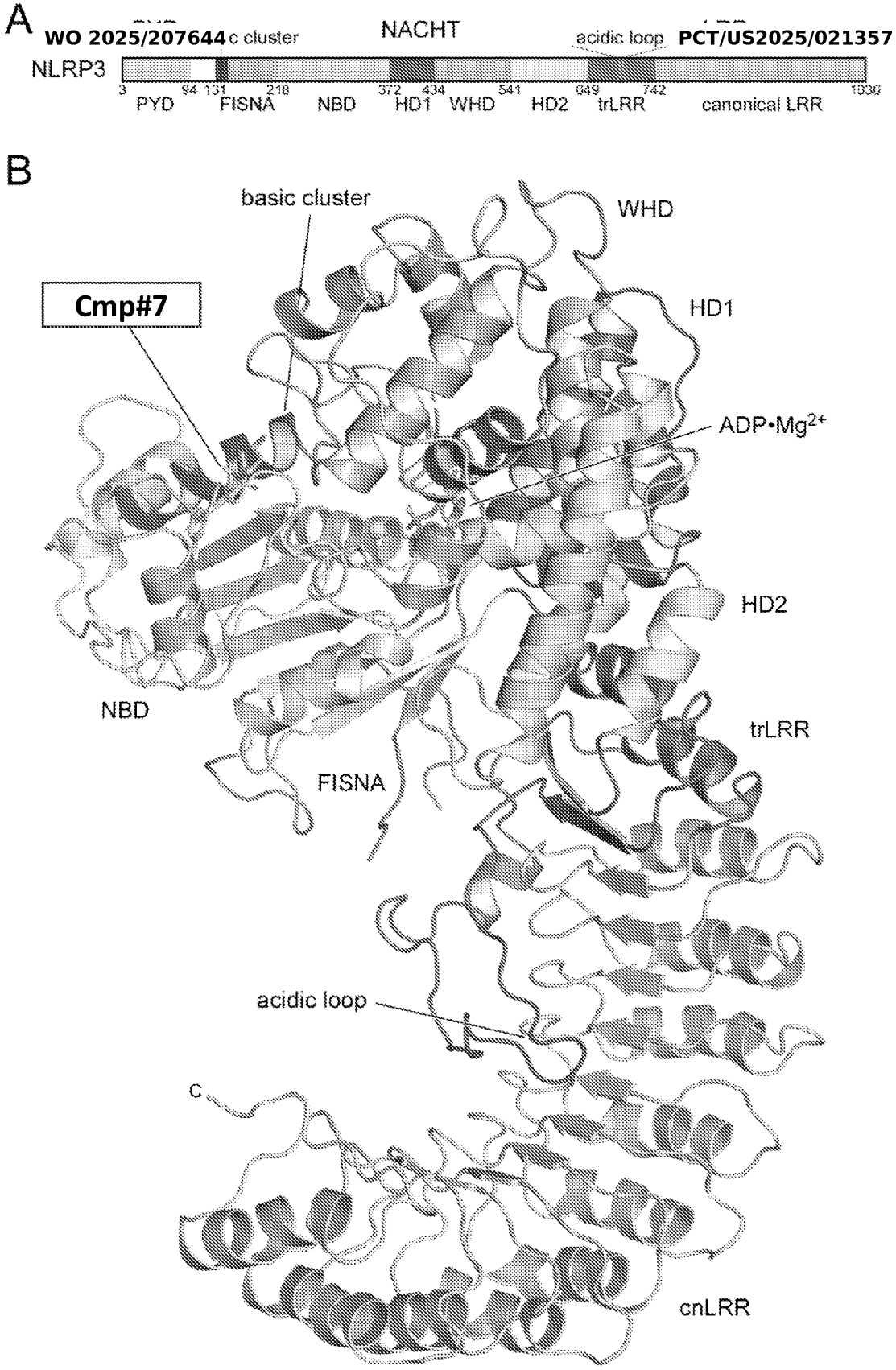


Fig. 1

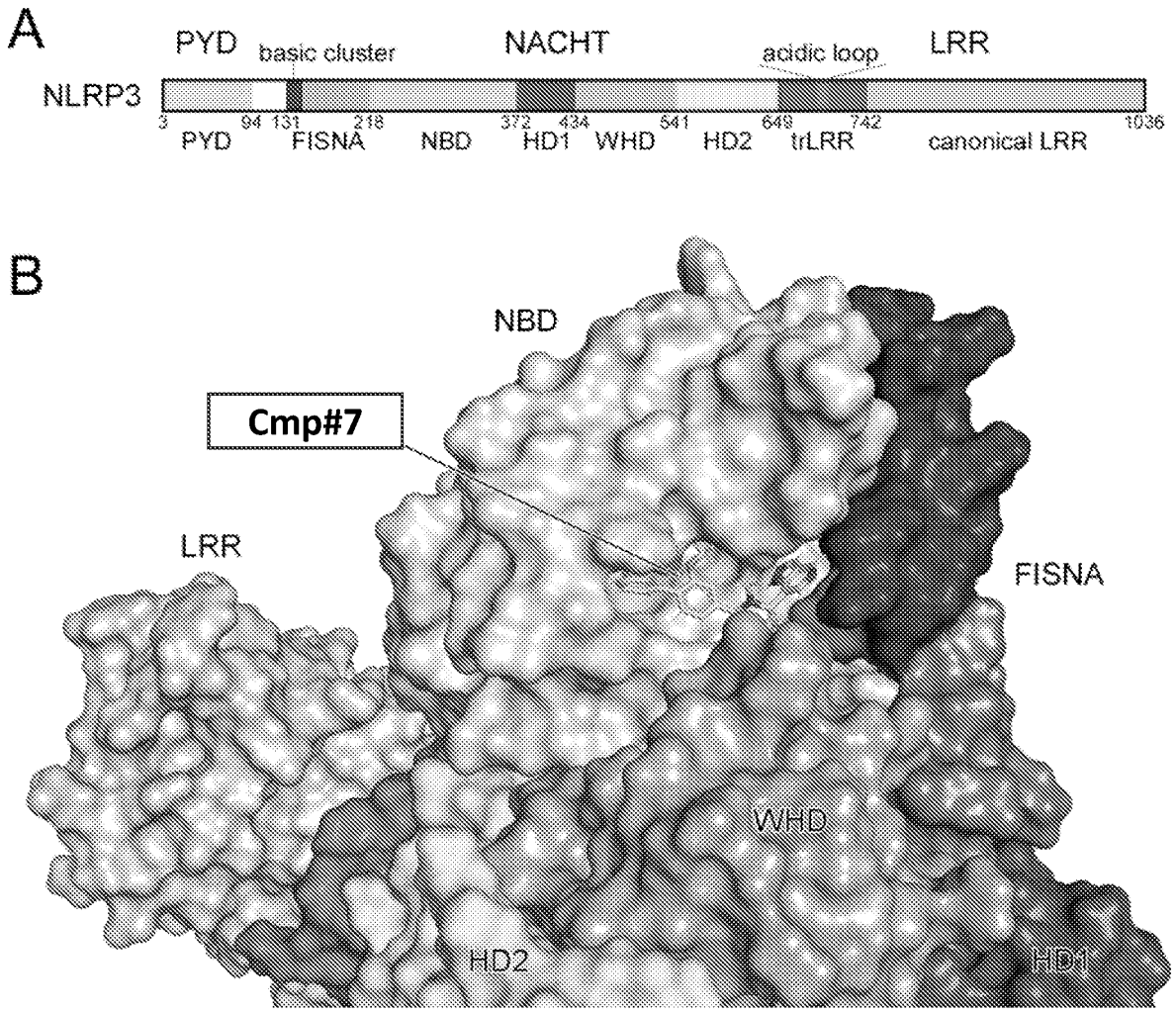

A
PYD
basic cluster
NACHT
acidic loop
LRR
NLRP3
3
94
131
218
372
434
541
649
742
1036
PYD
FISNA
NBD
HD1
WHD
HD2
trLRR
canonical LRR
B
NBD
Cmp#7
LRR
FISNA
WHD
HD2
HD1

Fig. 1 cont.

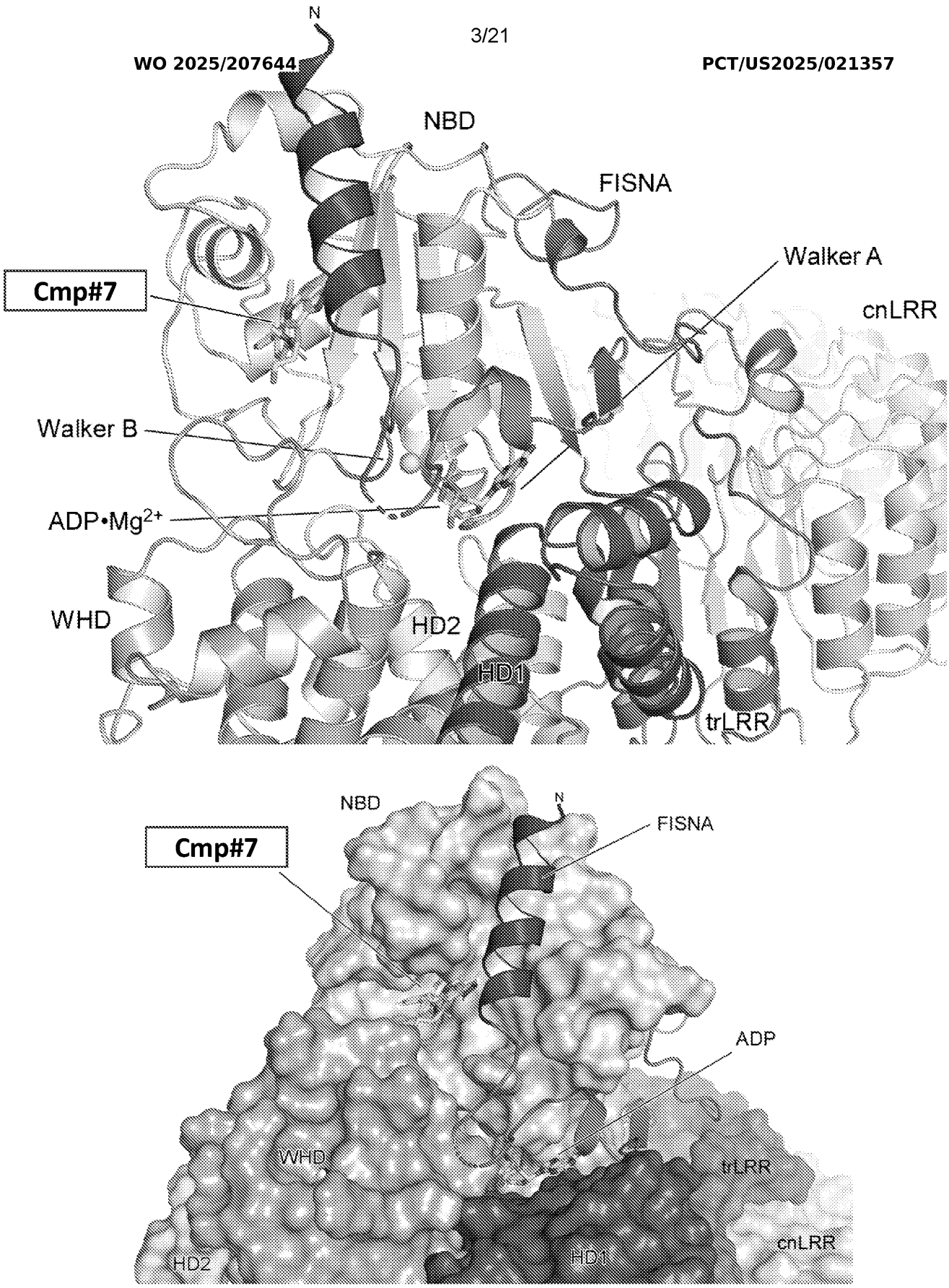

N
NBD
FISNA
Walker A
Cmp#7
cnLRR
Walker B
ADP•Mg2+
WHD
HD2
HD1
trLRR
NBD
N
FISNA
Cmp#7
ADP
WHD
trLRR
cnLRR
HD2
HD1

Fig. 2

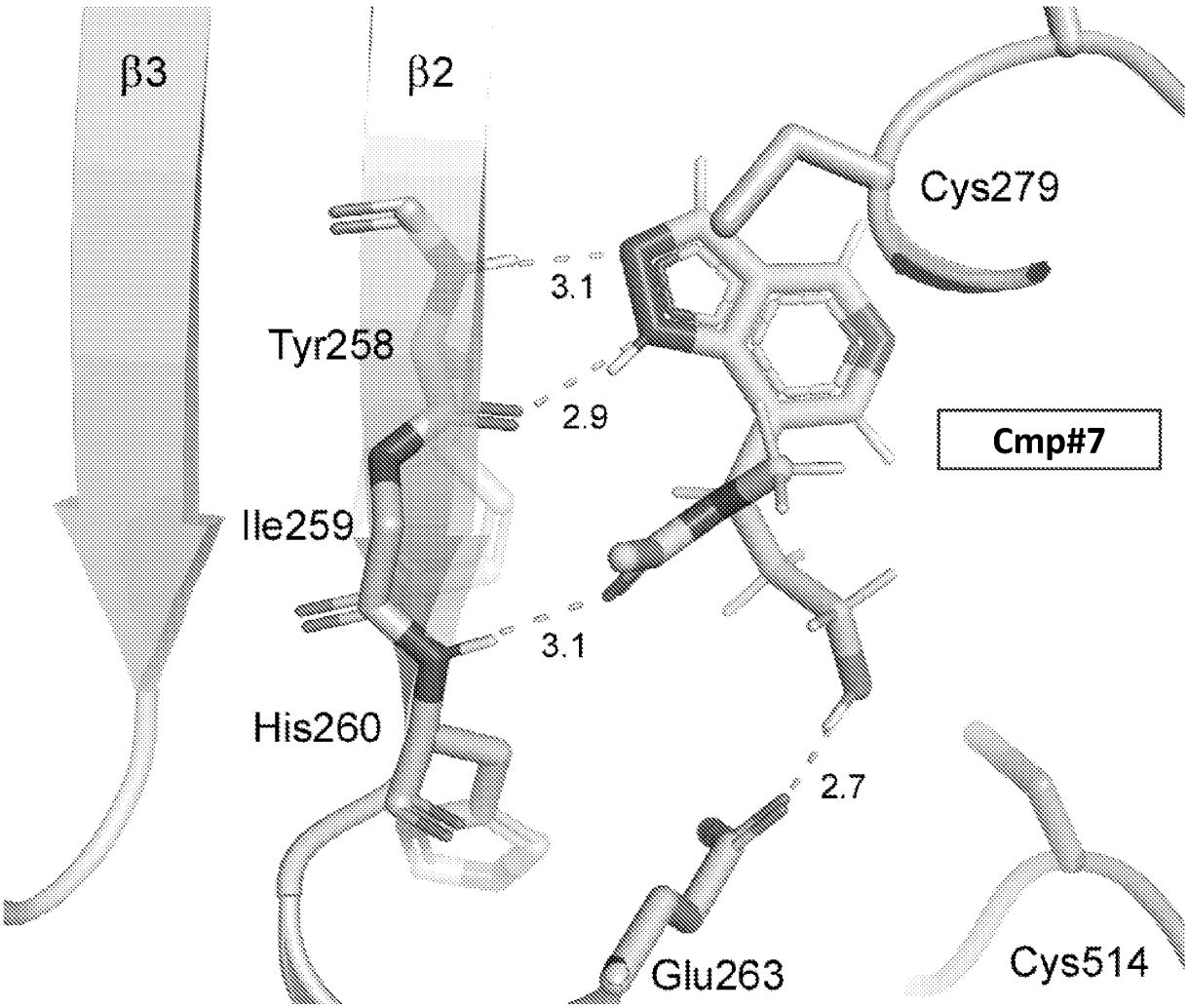

β3
β2
Cys279
3.1
Tyr258
2.9
Cmp#7
Ile259
3.1
His260
2.7
Glu263
Cys514

Fig. 3

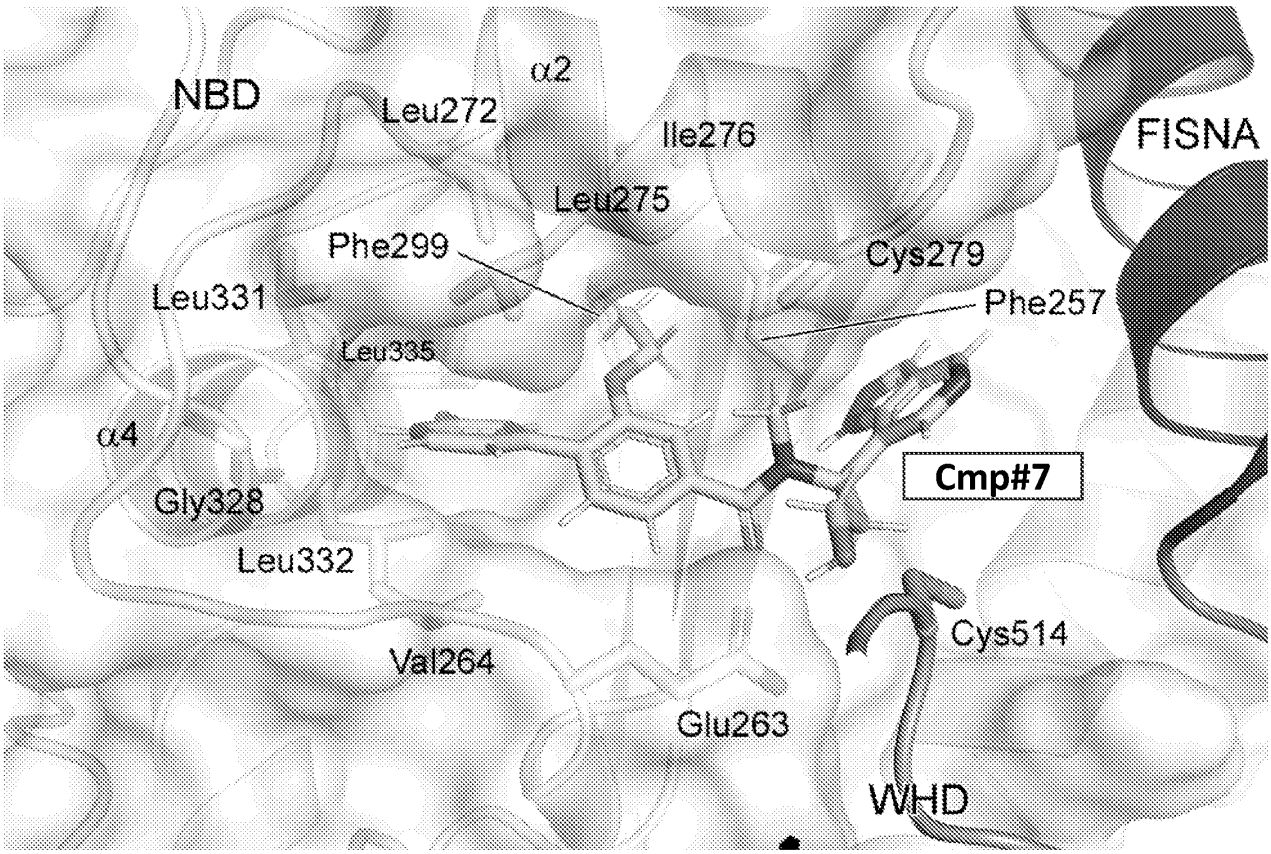

NBD
α2
Leu272
Ile276
FISNA
Leu275
Phe299
Cys279
Leu331
Phe257
Leu335
α4
Cmp#7
Gly328
Leu332
Cys514
Val264
Glu263
WHD

Fig. 4

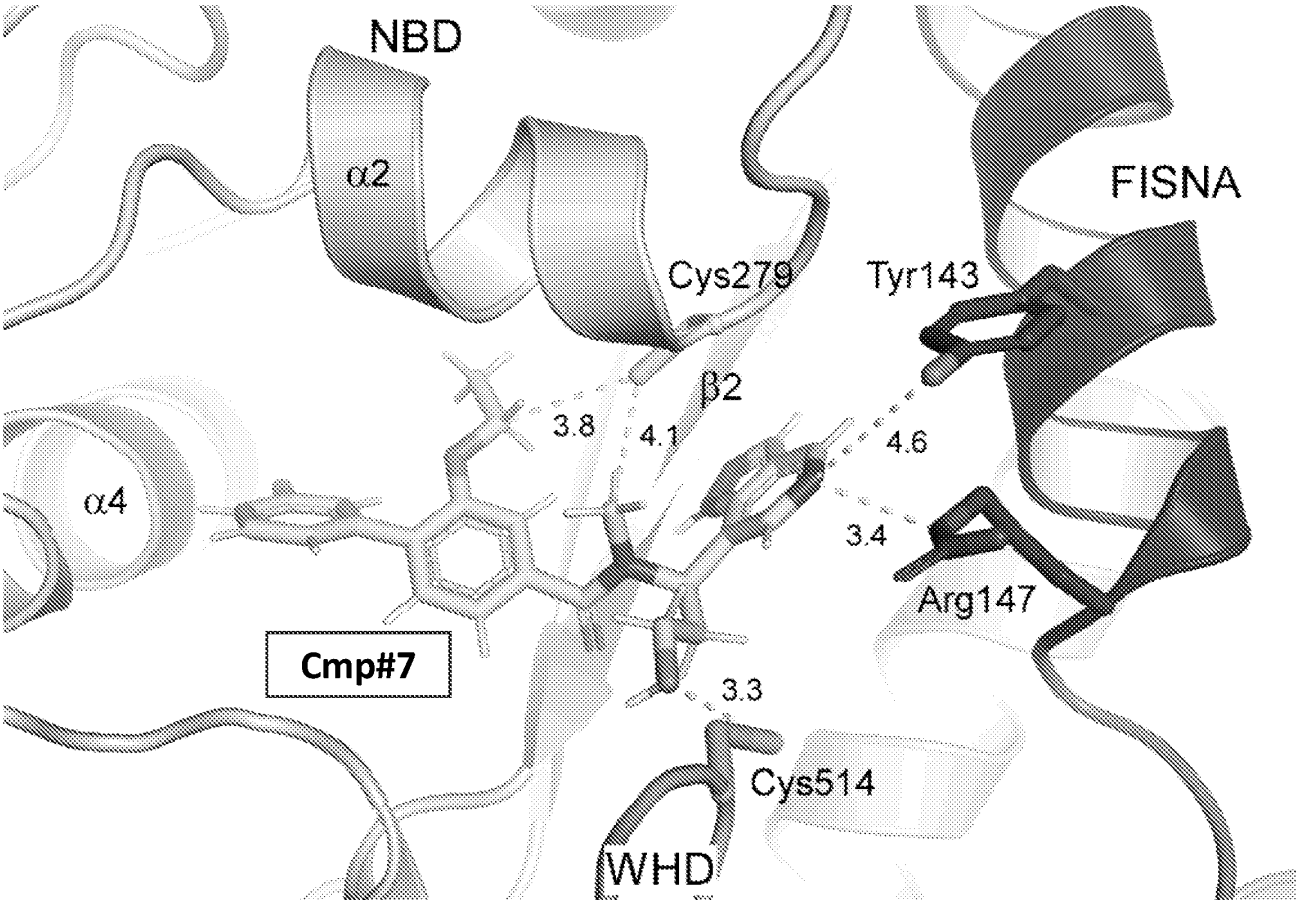

NBD
α2
FISNA
Cys279
Tyr143
β2
3.8
4.1
4.6
α4
3.4
Arg147
Cmp#7
3.3
Cys514
WHD

Fig. 5

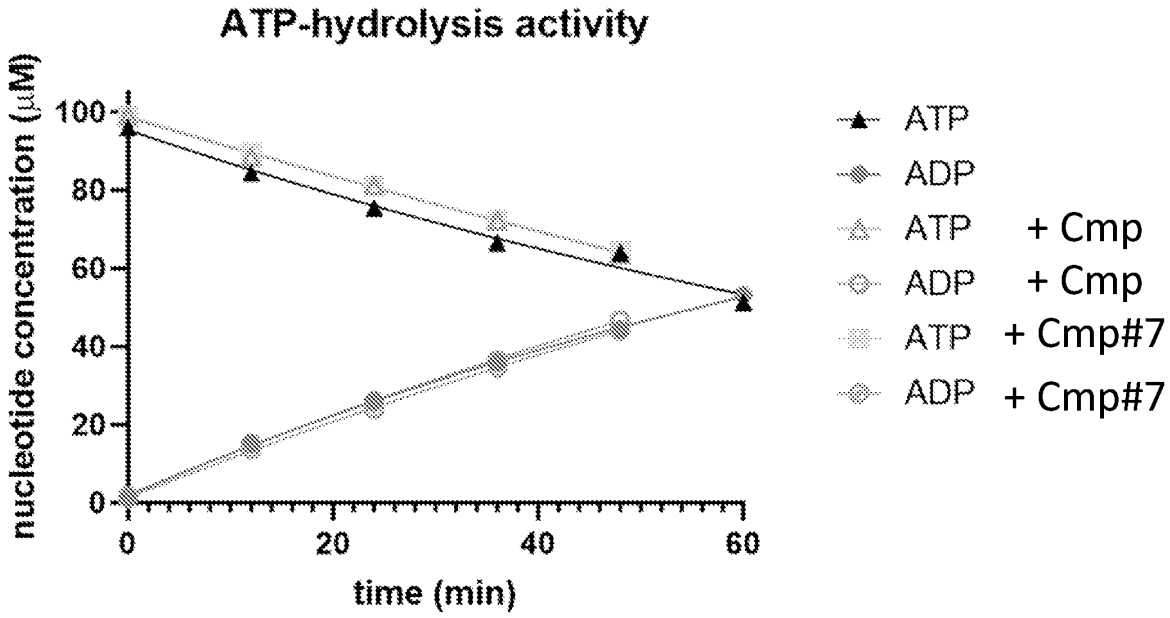

ATP-hydrolysis activity
nucleotide concentration (μM)
100
80
60
40
20
0
0
20
40
60
time (min)
ATP
ADP
ATP + Cmp
ADP + Cmp
ATP + Cmp#7
ADP + Cmp#7

Fig. 6

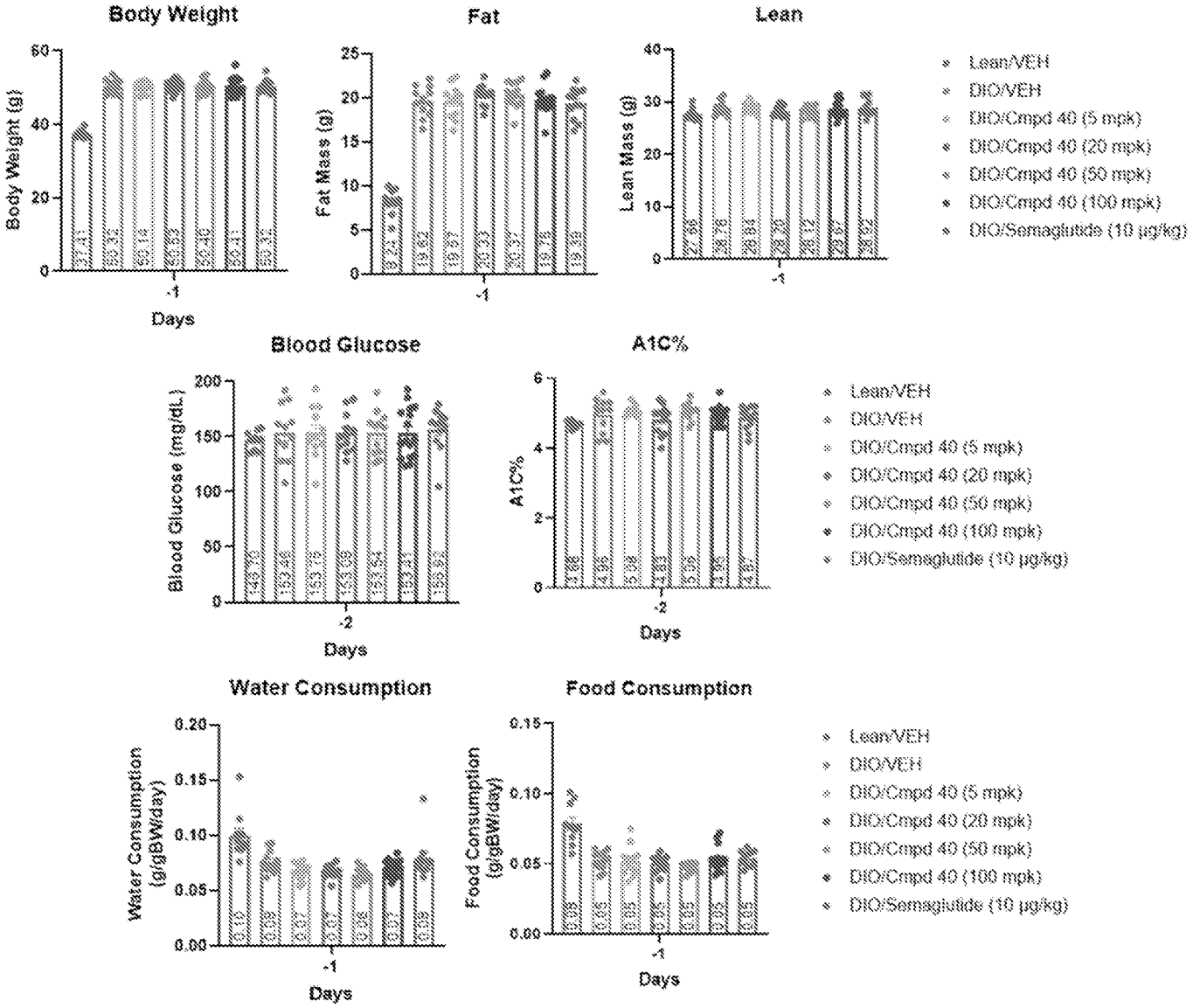

Body Weight
Body Weight (g)
Days
Fat
Fat Mass (g)
Lean
Lean Mass (g)
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100 mpk)
DIO/Semaglutide (10 µg/kg)
Blood Glucose
Blood Glucose (mg/dL)
A1C%
Water Consumption
Water Consumption (g/gBW/day)
Food Consumption
Food Consumption (g/gBW/day)

Fig. 7

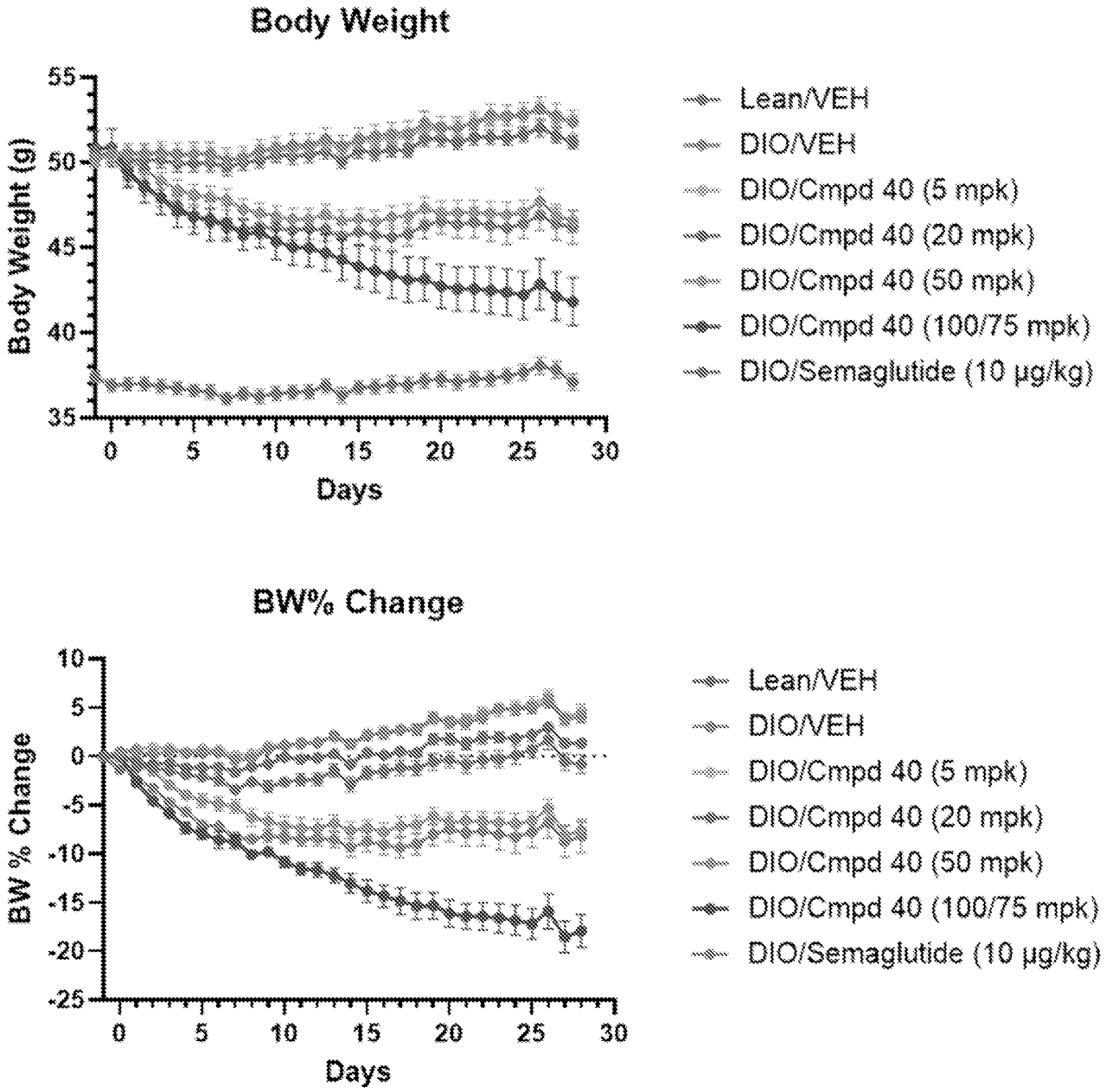

Body Weight
Body Weight (g)
55
50
45
40
35
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
BW% Change
BW % Change
10
5
0
-5
-10
-15
-20
-25
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)

Fig. 8

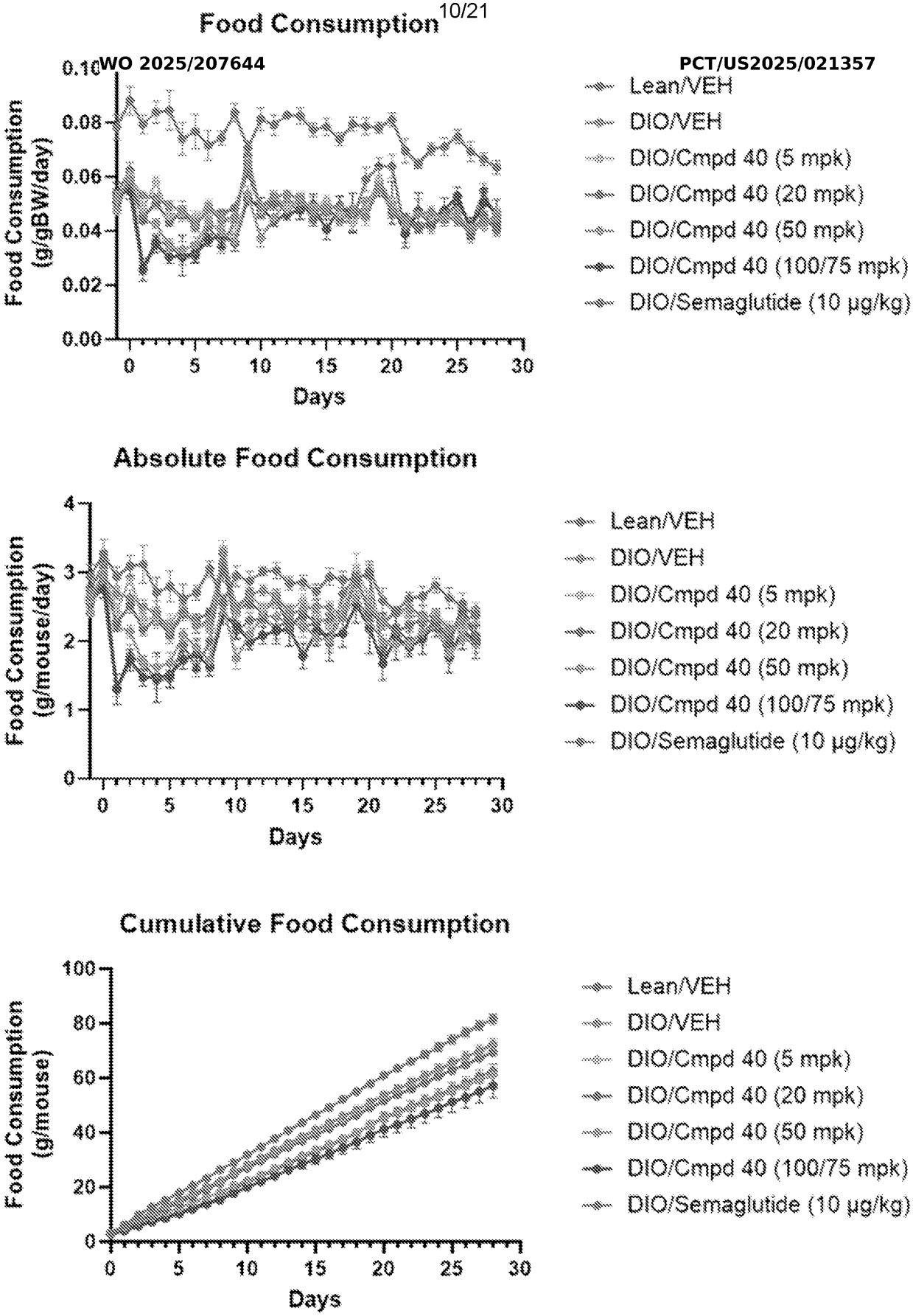
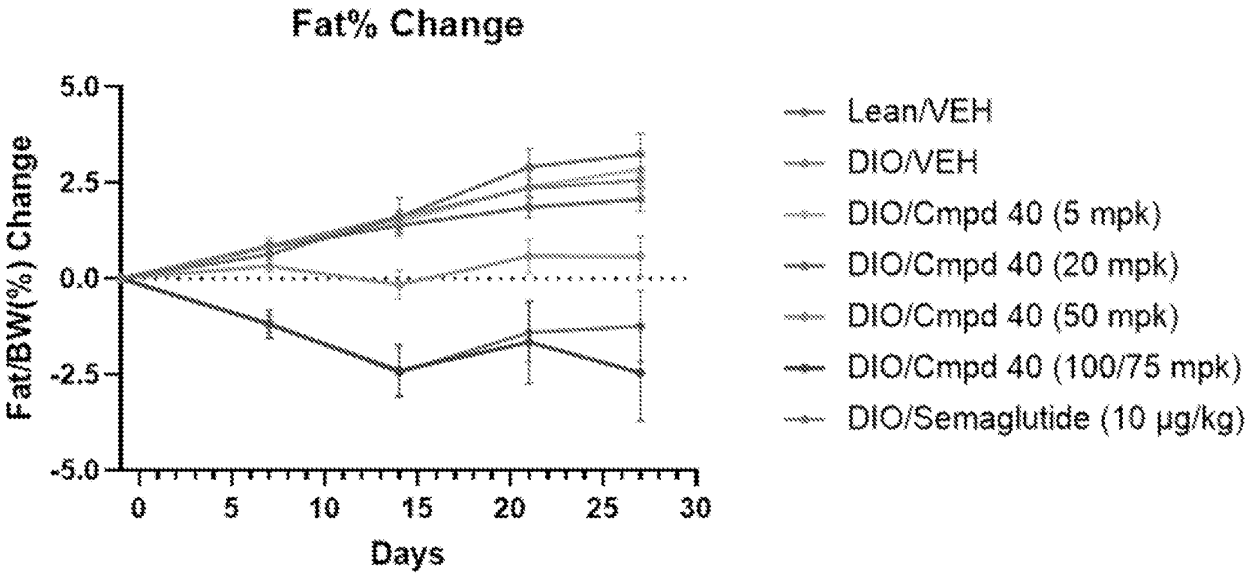

Food Consumption
Food Consumption (g/gBW/day)
0.10
0.08
0.06
0.04
0.02
0.00
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
Absolute Food Consumption
Food Consumption (g/mouse/day)
4
3
2
1
0
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
Cumulative Food Consumption
Food Consumption (g/mouse)
100
80
60
40
20
0
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)

Fig. 9


Fat% Change
Fat/BW(%) Change
5.0
2.5
0.0
-2.5
-5.0
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)

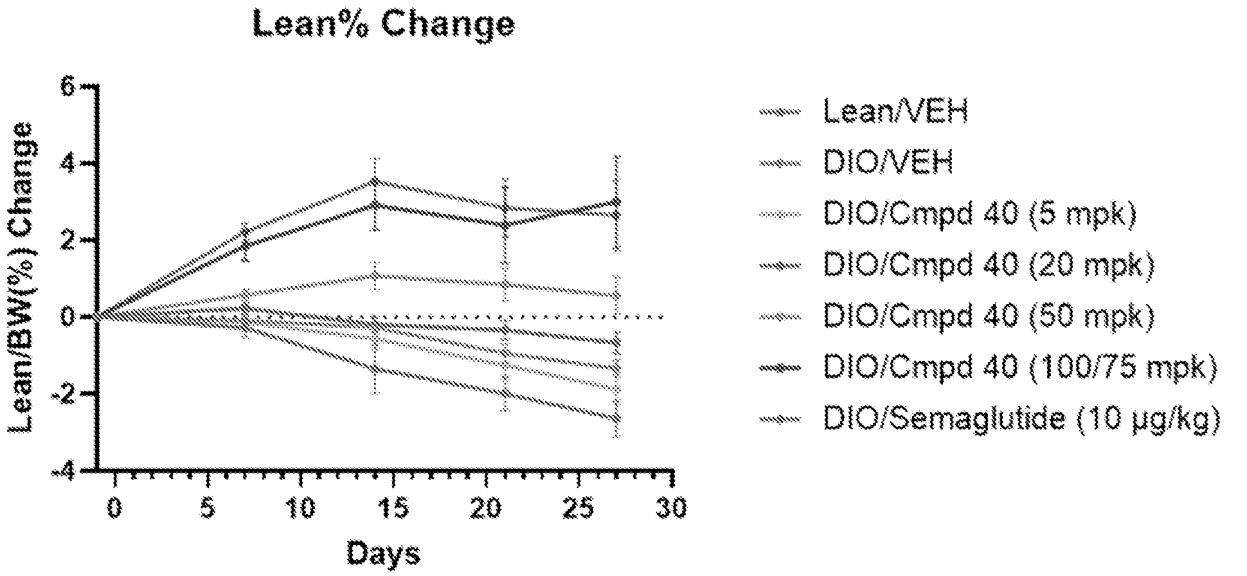

Lean% Change
Lean/BW(%) Change
6
4
2
0
-2
-4
0
5
10
15
20
25
30
Days
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)

Fig. 10

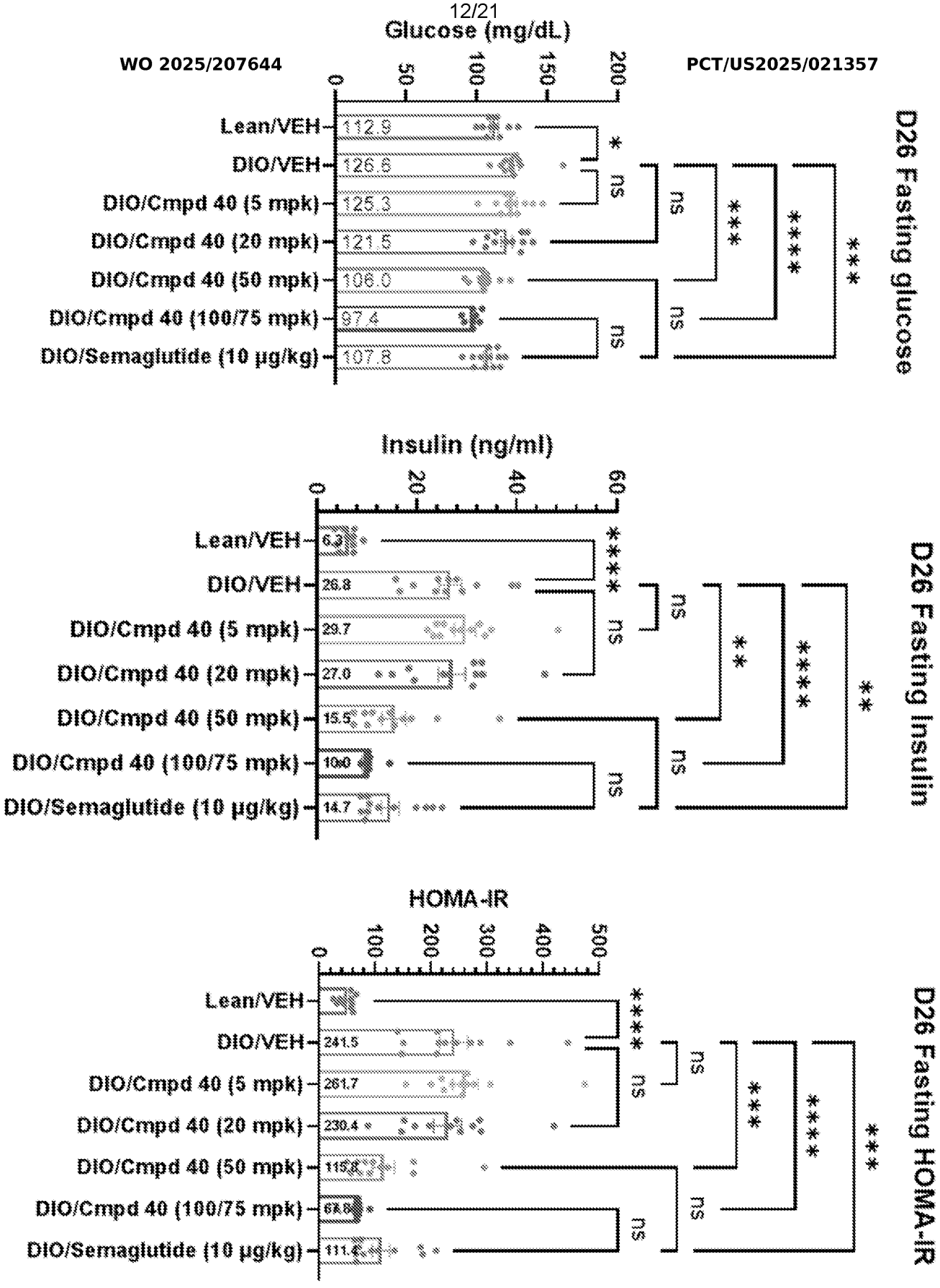

Glucose (mg/dL)
0
50
100
150
200
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
112.9
126.6
125.3
121.5
106.0
97.4
107.8
D26 Fasting glucose
Insulin (ng/ml)
0
20
40
60
6.3
26.8
29.7
27.0
15.5
10.0
14.7
D26 Fasting Insulin
HOMA-IR
0
100
200
300
400
500
241.5
261.7
230.4
115.8
68.8
111.4
D26 Fasting HOMA-IR
ns
*
**
***
****

Fig. 11

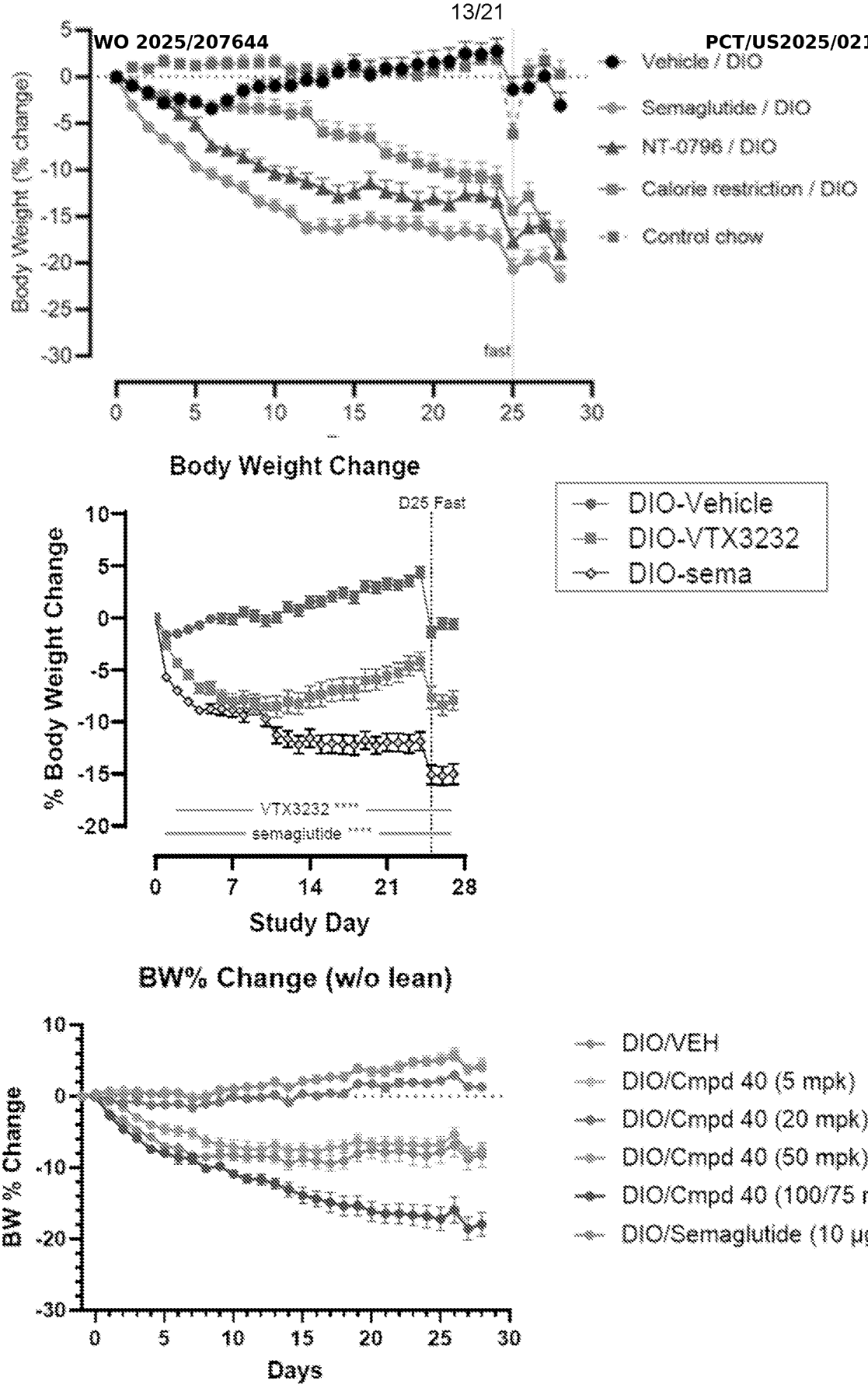

Body Weight (% change)
5
0
-5
-10
-15
-20
-25
-30
fast
0
5
10
15
20
25
30
Vehicle / DIO
Semaglutide / DIO
NT-0796 / DIO
Calorie restriction / DIO
Control chow
Body Weight Change
% Body Weight Change
D25 Fast
10
5
0
-5
-10
-15
-20
VTX3232 ****
semaglutide ****
0
7
14
21
28
Study Day
DIO-Vehicle
DIO-VTX3232
DIO-sema
BW% Change (w/o lean)
BW % Change
10
0
-10
-20
-30
0
5
10
15
20
25
30
Days
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)

Fig. 12

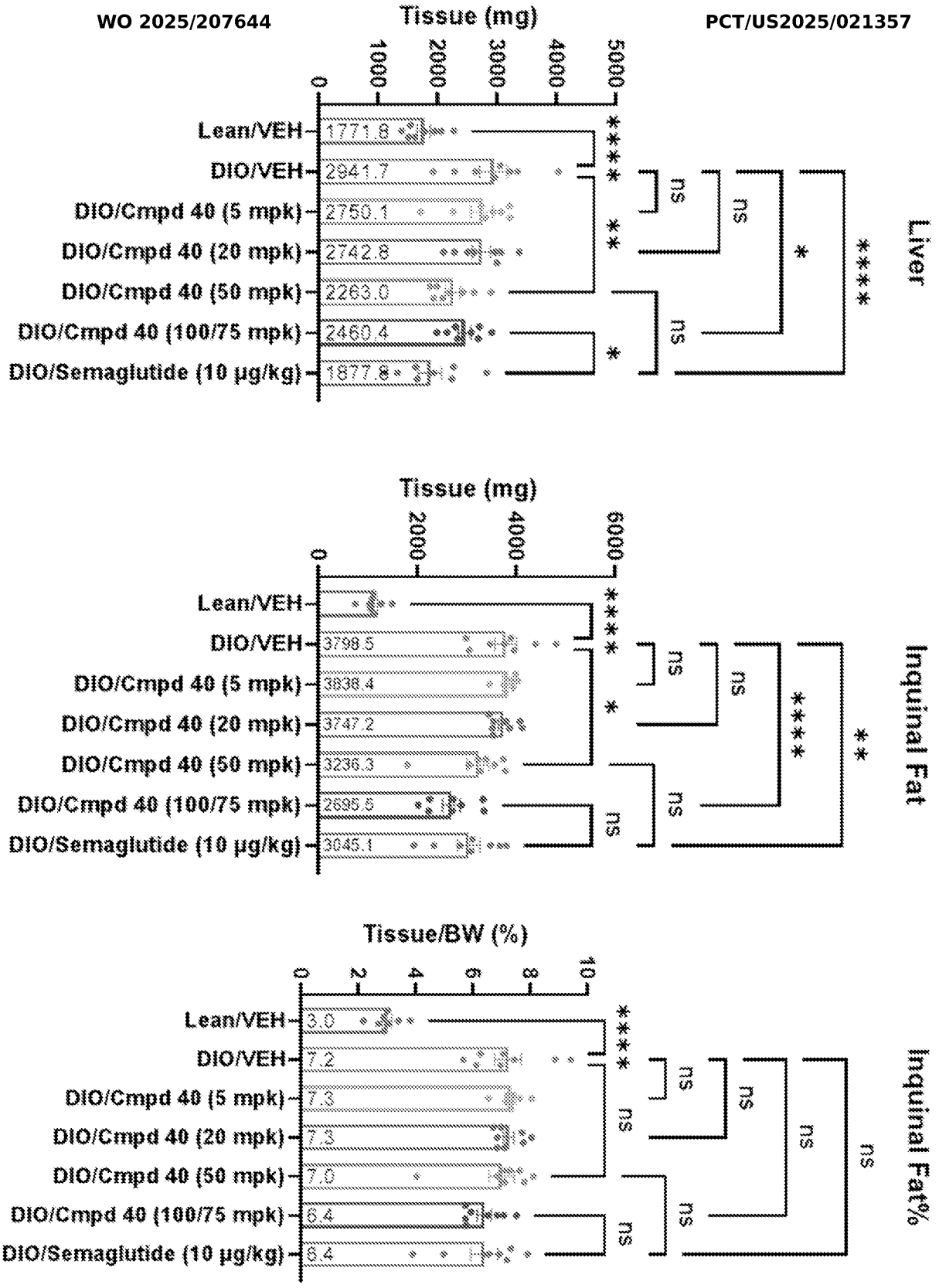

Liver
Tissue (mg)
0
1000
2000
3000
4000
5000
Lean/VEH
1771.8
DIO/VEH
2941.7
DIO/Cmpd 40 (5 mpk)
2750.1
DIO/Cmpd 40 (20 mpk)
2742.8
DIO/Cmpd 40 (50 mpk)
2263.0
DIO/Cmpd 40 (100/75 mpk)
2460.4
DIO/Semaglutide (10 µg/kg)
1877.8
****
**
*
ns
ns
*
****
Inquinal Fat
Tissue (mg)
0
2000
4000
6000
Lean/VEH
DIO/VEH
3798.5
DIO/Cmpd 40 (5 mpk)
3836.4
DIO/Cmpd 40 (20 mpk)
3747.2
DIO/Cmpd 40 (50 mpk)
3236.3
DIO/Cmpd 40 (100/75 mpk)
2695.6
DIO/Semaglutide (10 µg/kg)
3045.1
****
*
ns
ns
ns
****
**
Inquinal Fat%
Tissue/BW (%)
0
2
4
6
8
10
Lean/VEH
3.0
DIO/VEH
7.2
DIO/Cmpd 40 (5 mpk)
7.3
DIO/Cmpd 40 (20 mpk)
7.3
DIO/Cmpd 40 (50 mpk)
7.0
DIO/Cmpd 40 (100/75 mpk)
6.4
DIO/Semaglutide (10 µg/kg)
6.4
****
ns
ns
ns
ns
ns
ns

Fig. 13

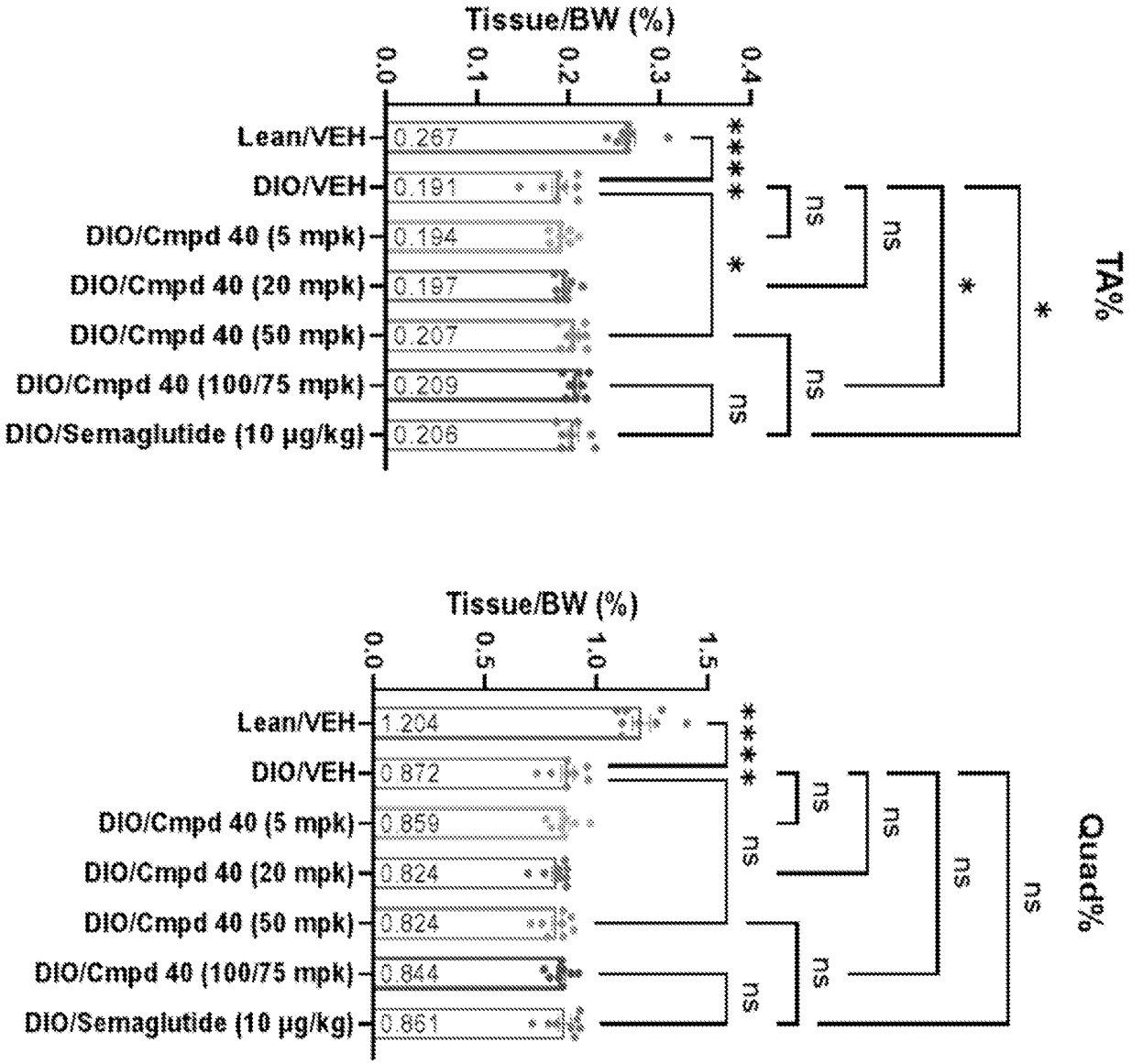
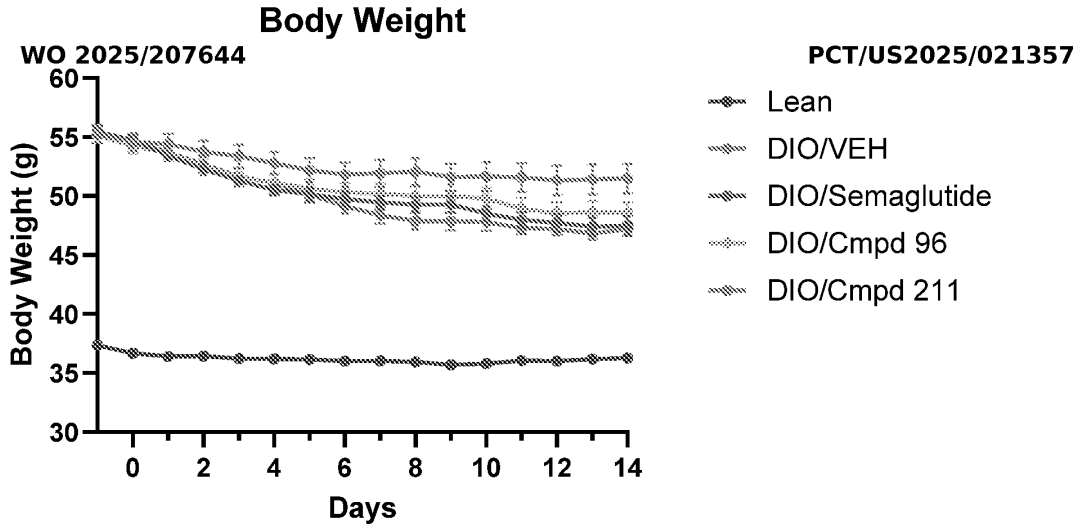
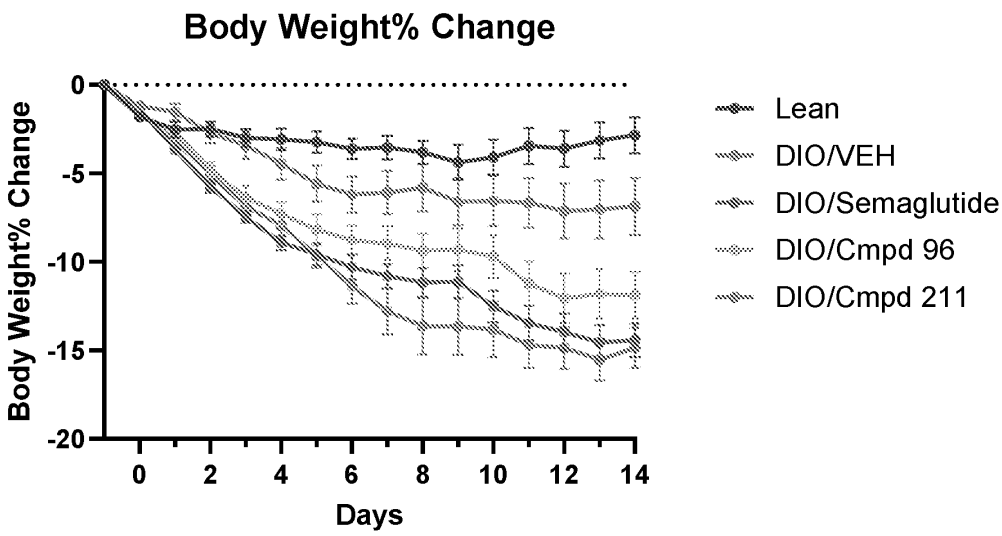

Tissue/BW (%)
0.0
0.1
0.2
0.3
0.4
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
0.267
0.191
0.194
0.197
0.207
0.209
0.208
****
*
ns
ns
*
ns
ns
*
*
TA%
Tissue/BW (%)
0.0
0.5
1.0
1.5
Lean/VEH
DIO/VEH
DIO/Cmpd 40 (5 mpk)
DIO/Cmpd 40 (20 mpk)
DIO/Cmpd 40 (50 mpk)
DIO/Cmpd 40 (100/75 mpk)
DIO/Semaglutide (10 µg/kg)
1.204
0.872
0.859
0.824
0.824
0.844
0.861
****
ns
ns
ns
ns
ns
ns
ns
Quad%

Fig. 13, cont'd

A


Body Weight
Body Weight (g)
60
55
50
45
40
35
30
0
2
4
6
8
10
12
14
Days
Lean
DIO/VEH
DIO/Semaglutide
DIO/Cmpd 96
DIO/Cmpd 211

B


Body Weight% Change
Body Weight% Change
0
-5
-10
-15
-20
0
2
4
6
8
10
12
14
Days
Lean
DIO/VEH
DIO/Semaglutide
DIO/Cmpd 96
DIO/Cmpd 211

C

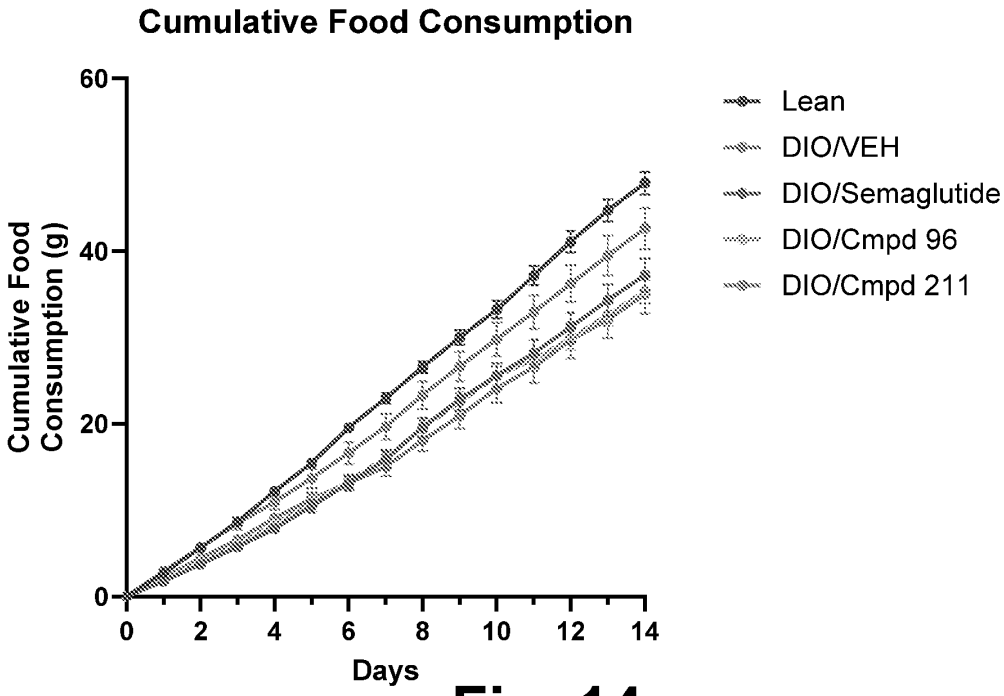

Cumulative Food Consumption
Cumulative Food Consumption (g)
60
40
20
0
0
2
4
6
8
10
12
14
Days
Lean
DIO/VEH
DIO/Semaglutide
DIO/Cmpd 96
DIO/Cmpd 211

Fig. 14

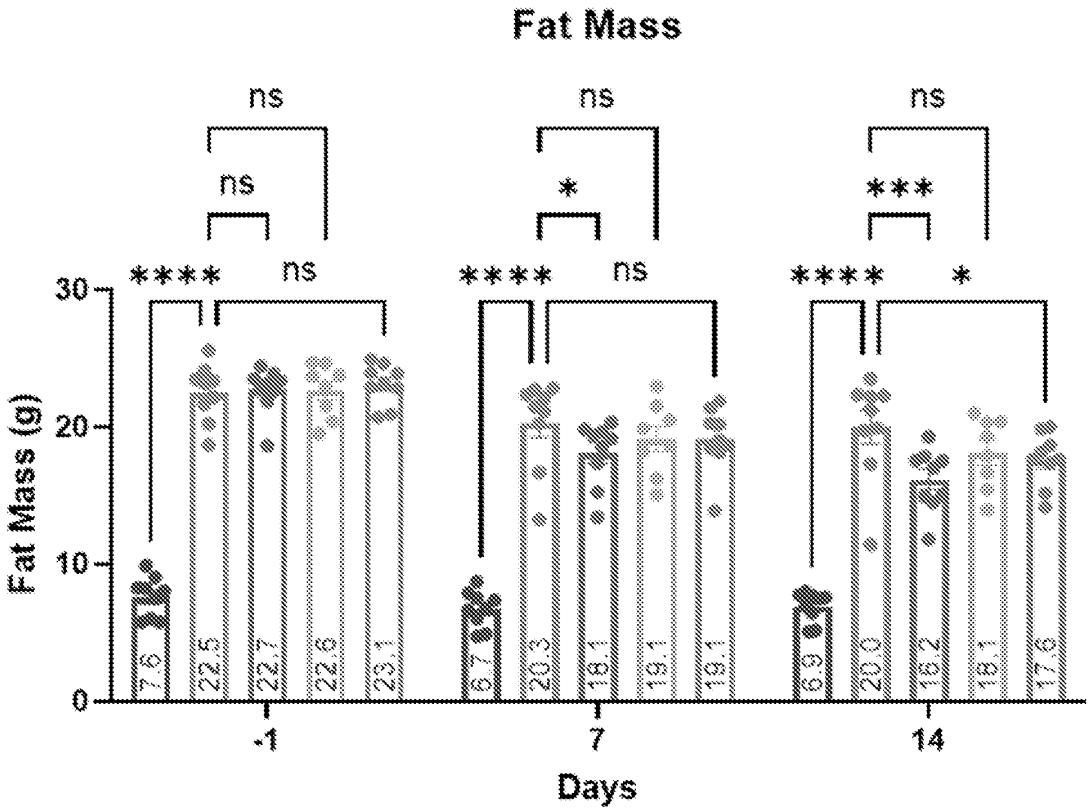

Fat Mass
ns
ns
ns
*
ns
***
****
ns
****
ns
****
*
30
20
10
0
Fat Mass (g)
7.6
22.5
22.7
22.6
23.1
6.7
20.3
18.1
19.1
19.1
6.9
20.0
16.2
18.1
17.6
-1
7
14
Days
Lean
DIO/VEH
DIO/SMG
DIO / Cmpd 096
DIO / Cmpd 211

Fig. 15

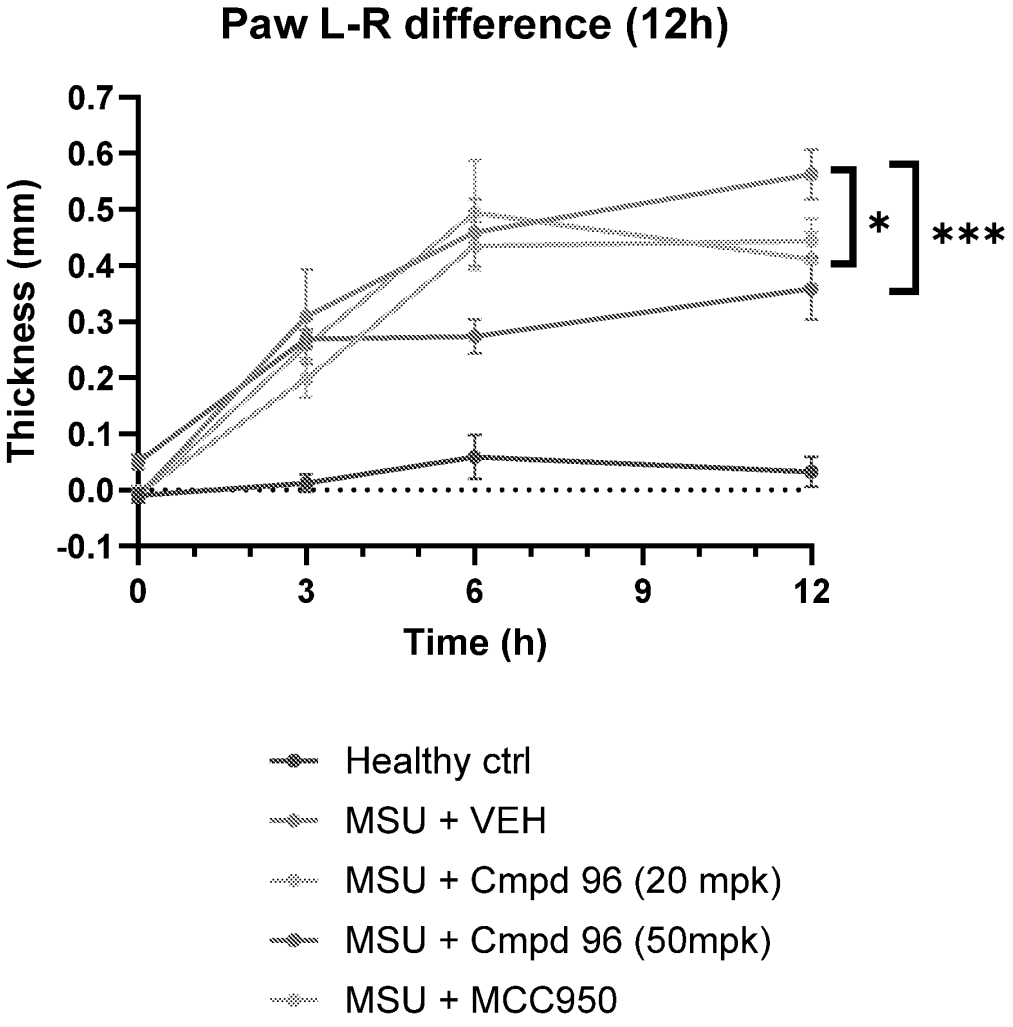

Paw L-R difference (12h)
Thickness (mm)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0
3
6
9
12
Time (h)
*
***
Healthy ctrl
MSU + VEH
MSU + Cmpd 96 (20 mpk)
MSU + Cmpd 96 (50mpk)
MSU + MCC950

Fig. 16

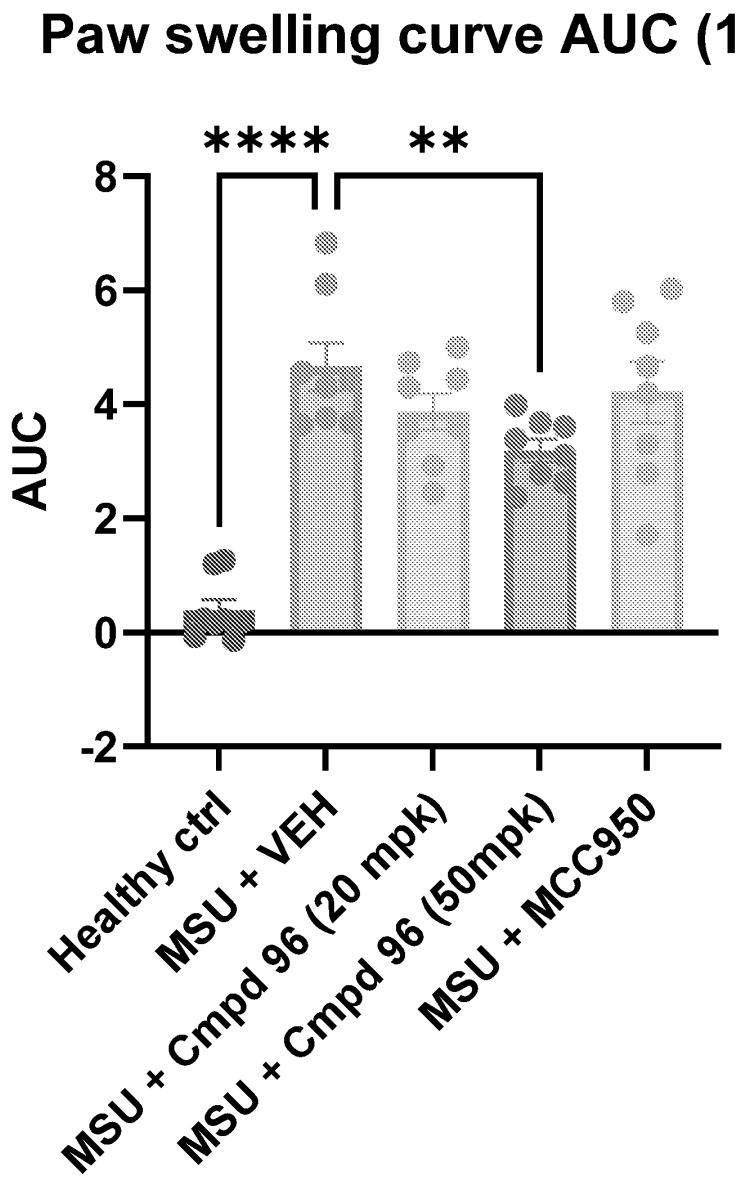

Paw swelling curve AUC (12h)
****
**
AUC
8
6
4
2
0
-2
Healthy ctrl
MSU + VEH
MSU + Cmpd 96 (20 mpk)
MSU + Cmpd 96 (50mpk)
MSU + MCC950

Fig. 16, cont'd

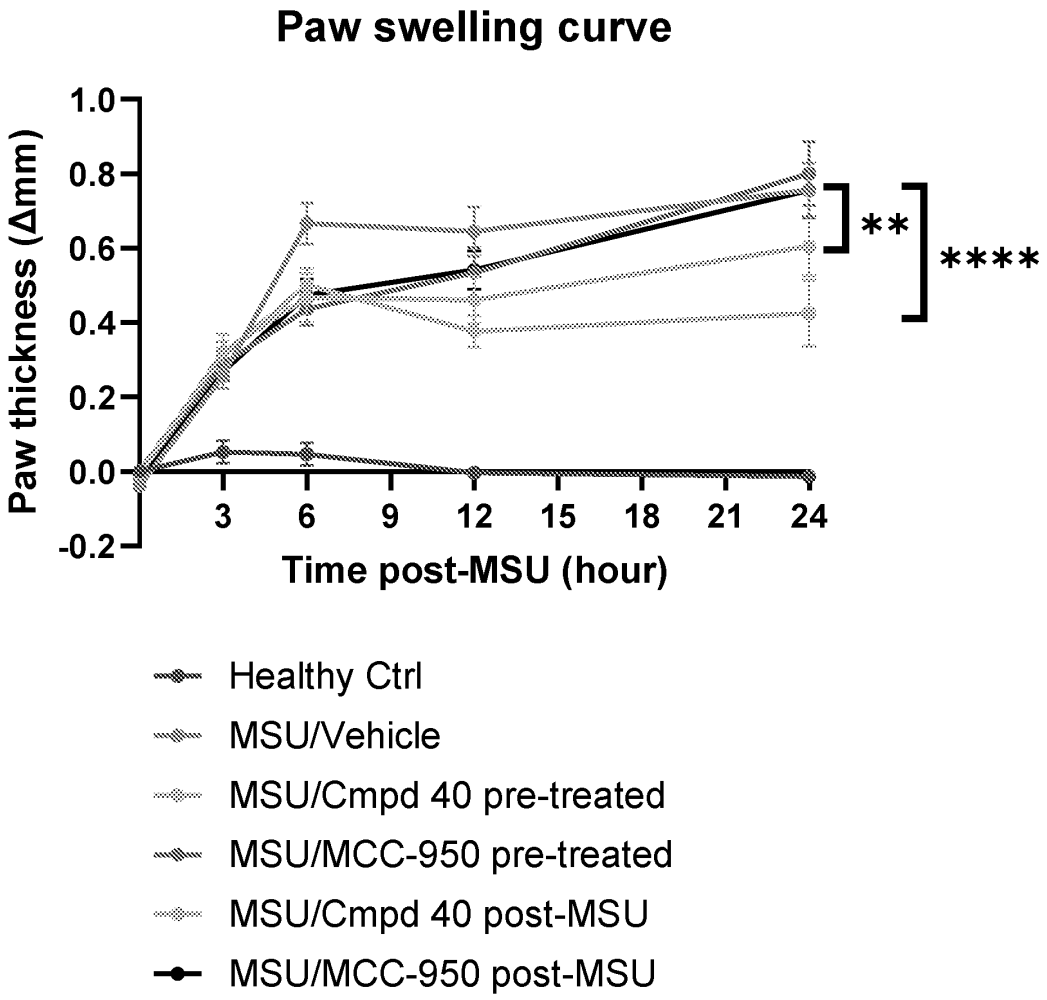

Paw swelling curve
Paw thickness (Δmm)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
3
6
9
12
15
18
21
24
Time post-MSU (hour)
**
****
Healthy Ctrl
MSU/Vehicle
MSU/Cmpd 40 pre-treated
MSU/MCC-950 pre-treated
MSU/Cmpd 40 post-MSU
MSU/MCC-950 post-MSU

Fig. 17

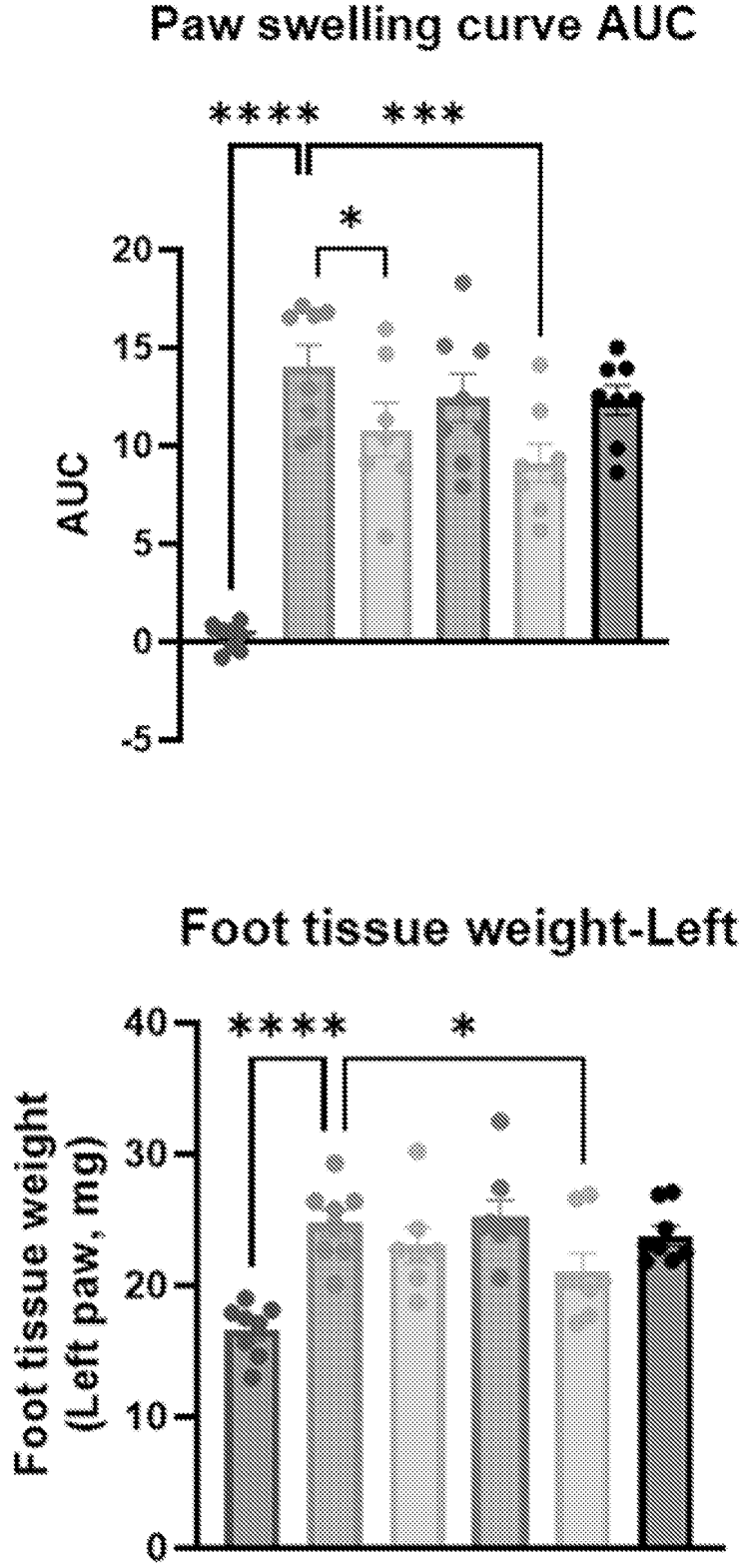

Paw swelling curve AUC
****
***
*
AUC
20
15
10
5
0
-5
Foot tissue weight-Left
****
*
Foot tissue weight (Left paw, mg)
40
30
20
10
0

Fig. 17, cont'd