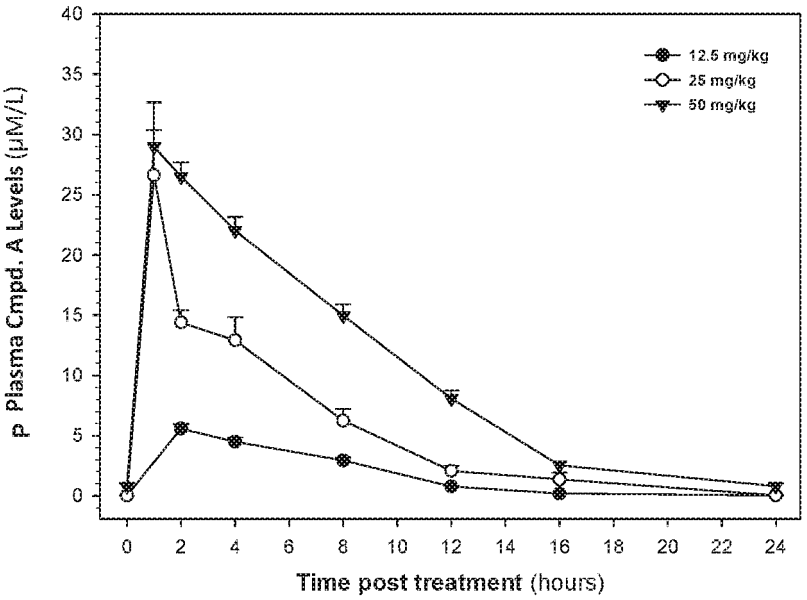
Fig. 1

A.


12.5 mg/kg
25 mg/kg
50 mg/kg
p Plasma Cmpd. A Levels (µM/L)
Time post treatment (hours)

B.

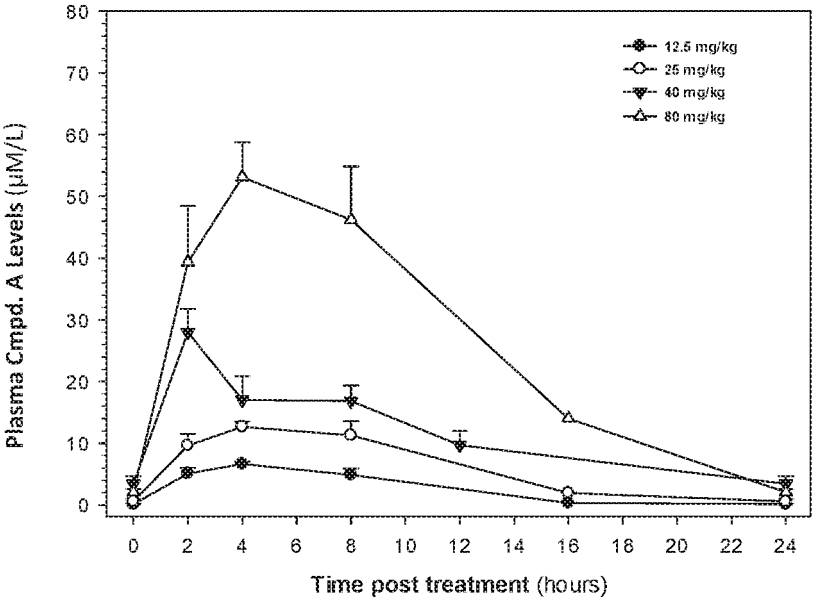
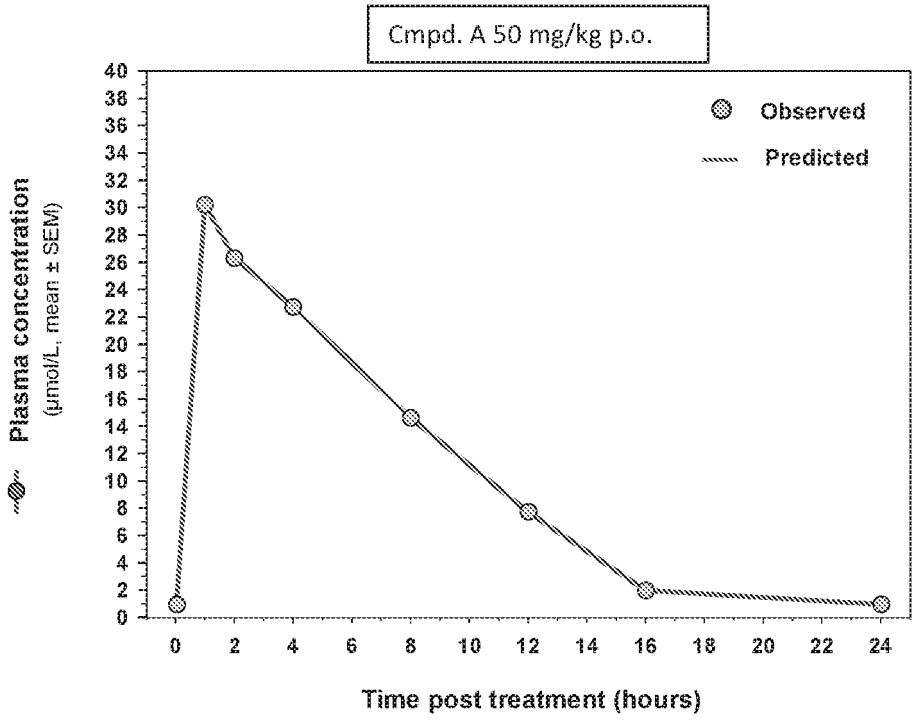

12.5 mg/kg
25 mg/kg
40 mg/kg
80 mg/kg
Plasma Cmpd. A Levels (µM/L)
Time post treatment (hours)

Fig. 2

A.


Cmpd. A 50 mg/kg p.o.
Observed
Predicted
Plasma concentration
(µmol/L, mean ± SEM)
Time post treatment (hours)

B.

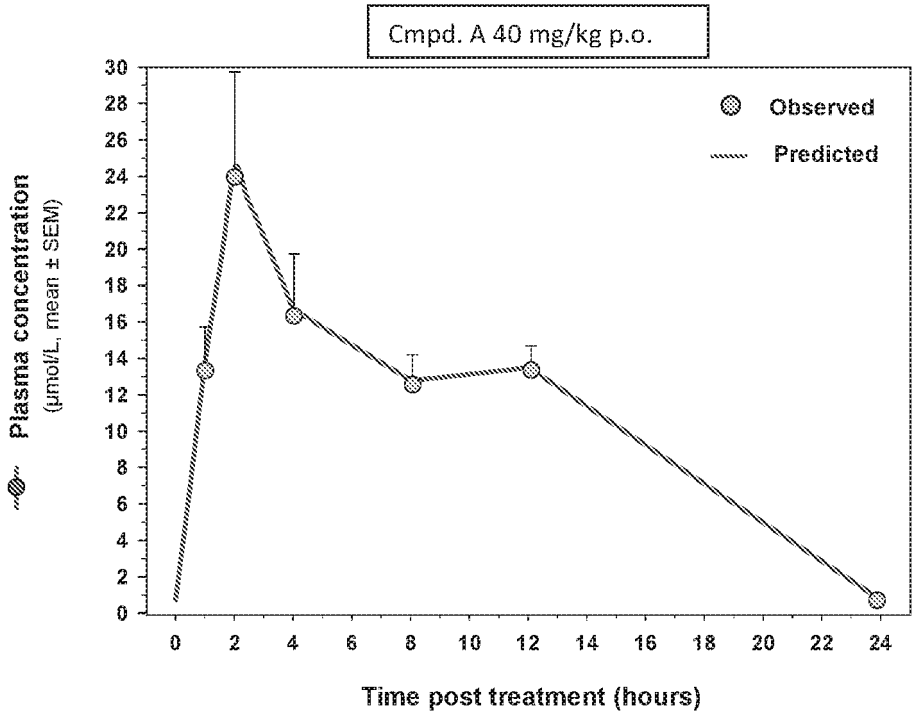
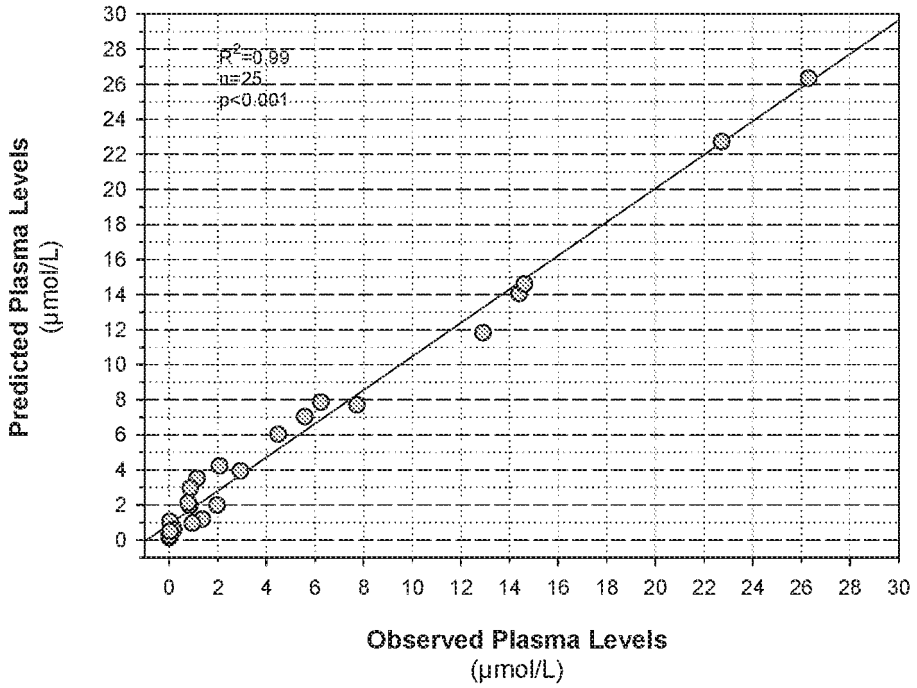

Cmpd. A 40 mg/kg p.o.
Observed
Predicted
Plasma concentration
(µmol/L, mean ± SEM)
Time post treatment (hours)

Fig. 3

A.


R²=0.99
n=25
p<0.001
Predicted Plasma Levels
(µmol/L)
Observed Plasma Levels
(µmol/L)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30

B.

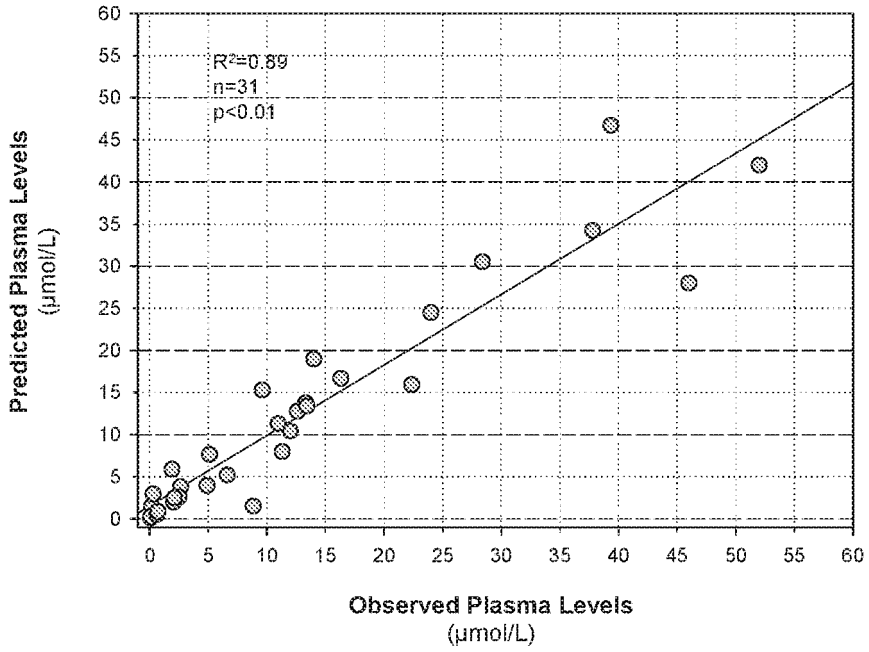
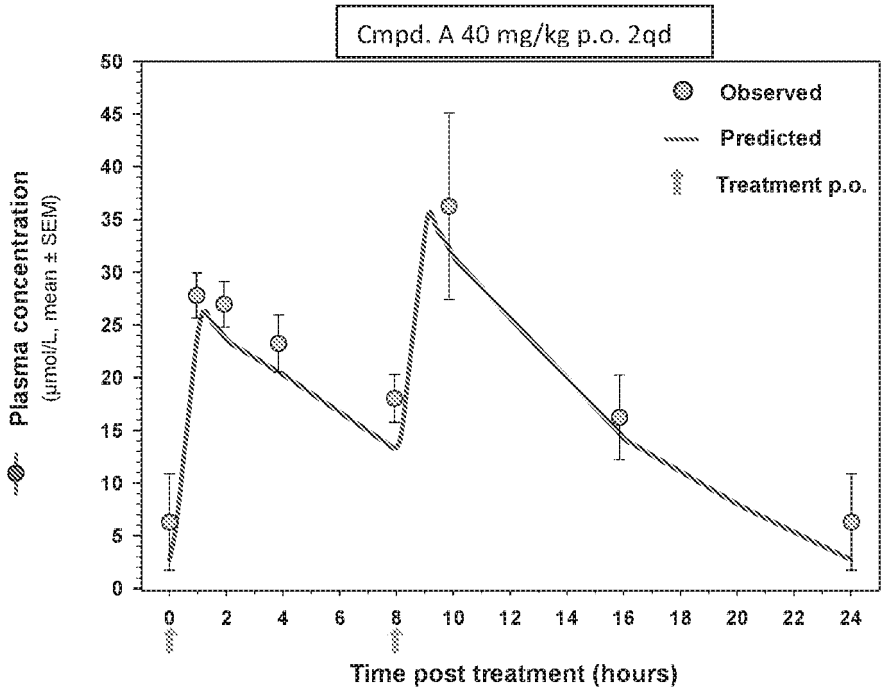

R²=0.89
n=31
p<0.01
Predicted Plasma Levels
(µmol/L)
Observed Plasma Levels
(µmol/L)
0
5
10
15
20
25
30
35
40
45
50
55
60

Fig. 4

A.


Cmpd. A 40 mg/kg p.o. 2qd
Observed
Predicted
Treatment p.o.
Plasma concentration
(µmol/L, mean ± SEM)
Time post treatment (hours)

B.

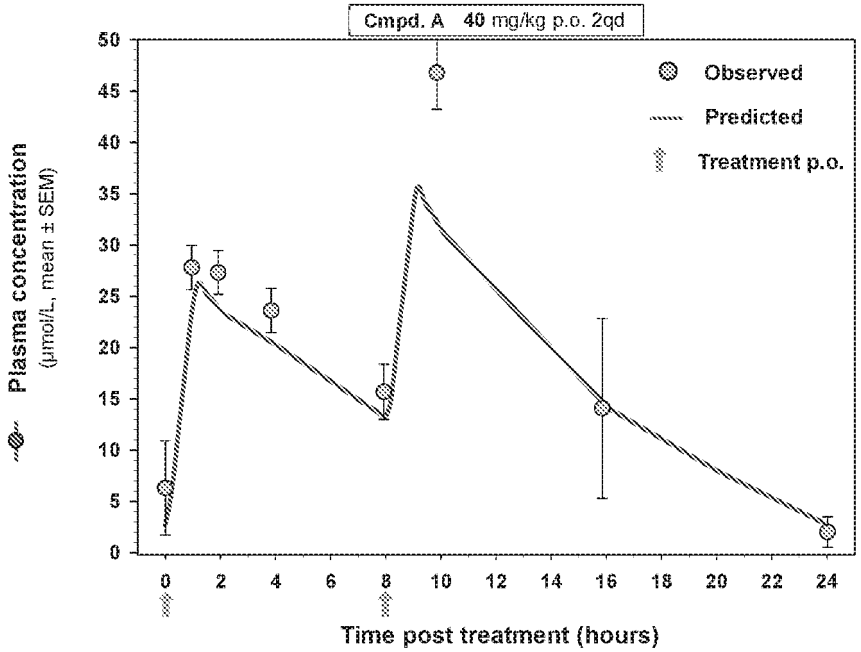

Cmpd. A 40 mg/kg p.o. 2qd
Observed
Predicted
Treatment p.o.
Plasma concentration
(µmol/L, mean ± SEM)
Time post treatment (hours)

Fig. 5

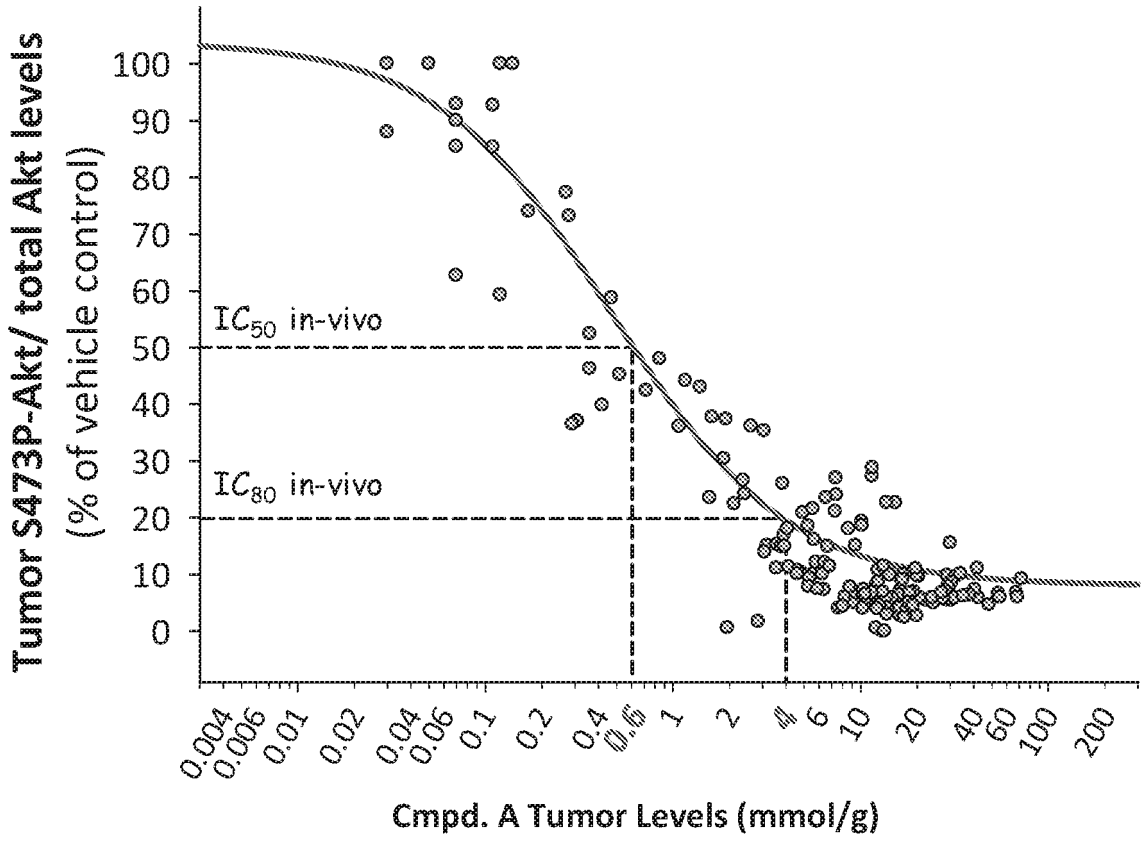

Tumor S473P-Akt/ total Akt levels
(% of vehicle control)
100
90
80
70
60
50
40
30
20
10
0
IC50 in-vivo
IC80 in-vivo
0.004
0.006
0.01
0.02
0.04
0.06
0.1
0.2
0.4
0.6
1
2
4
6
10
20
40
60
100
200
Cmpd. A Tumor Levels (mmol/g)

Fig. 6

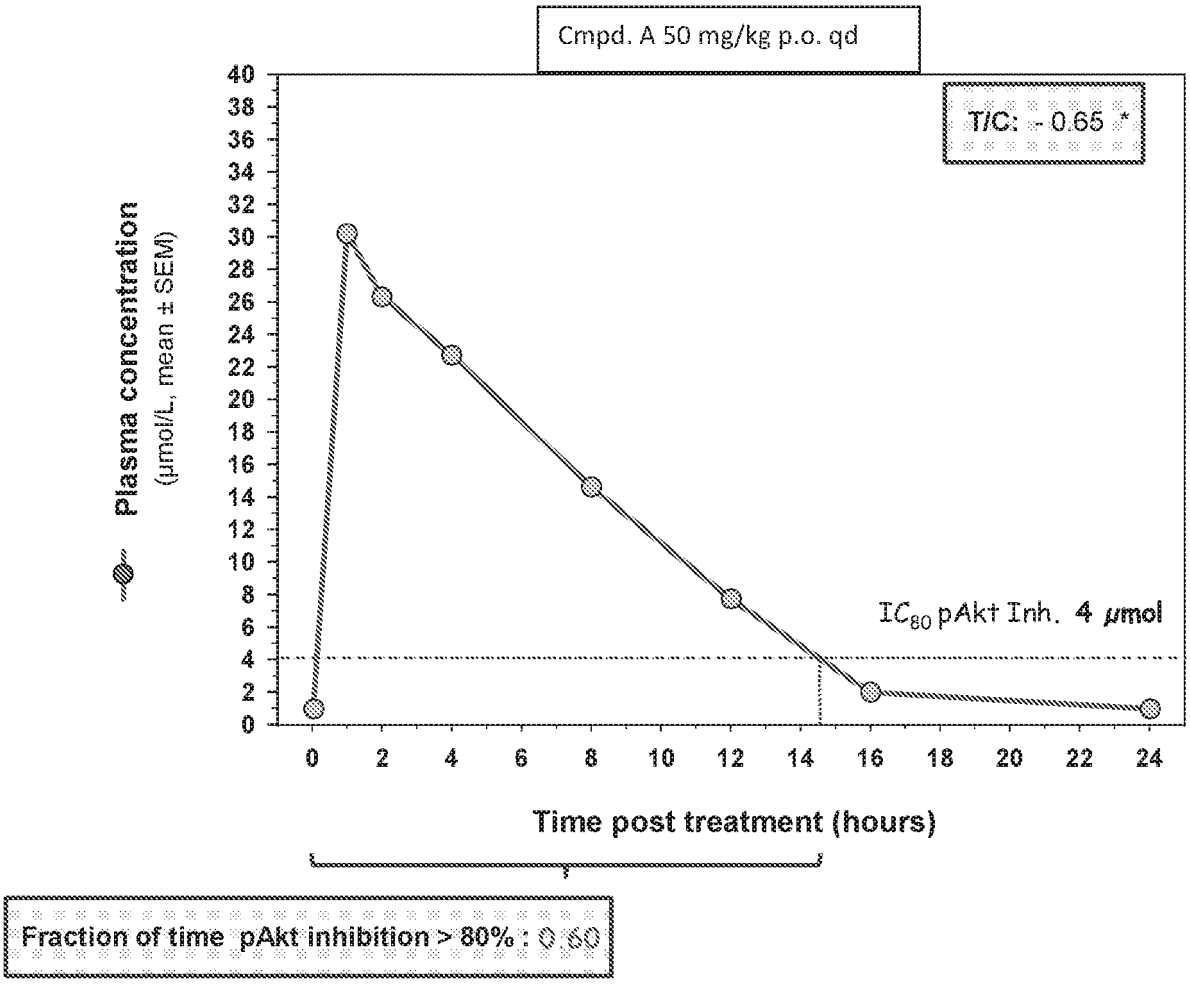

Cmpd. A 50 mg/kg p.o. qd
T/C: - 0.65 *
Plasma concentration
(µmol/L, mean ± SEM)
IC80 pAkt Inh. 4 µmol
Time post treatment (hours)
Fraction of time pAkt inhibition > 80% : 0.60

Fig. 7

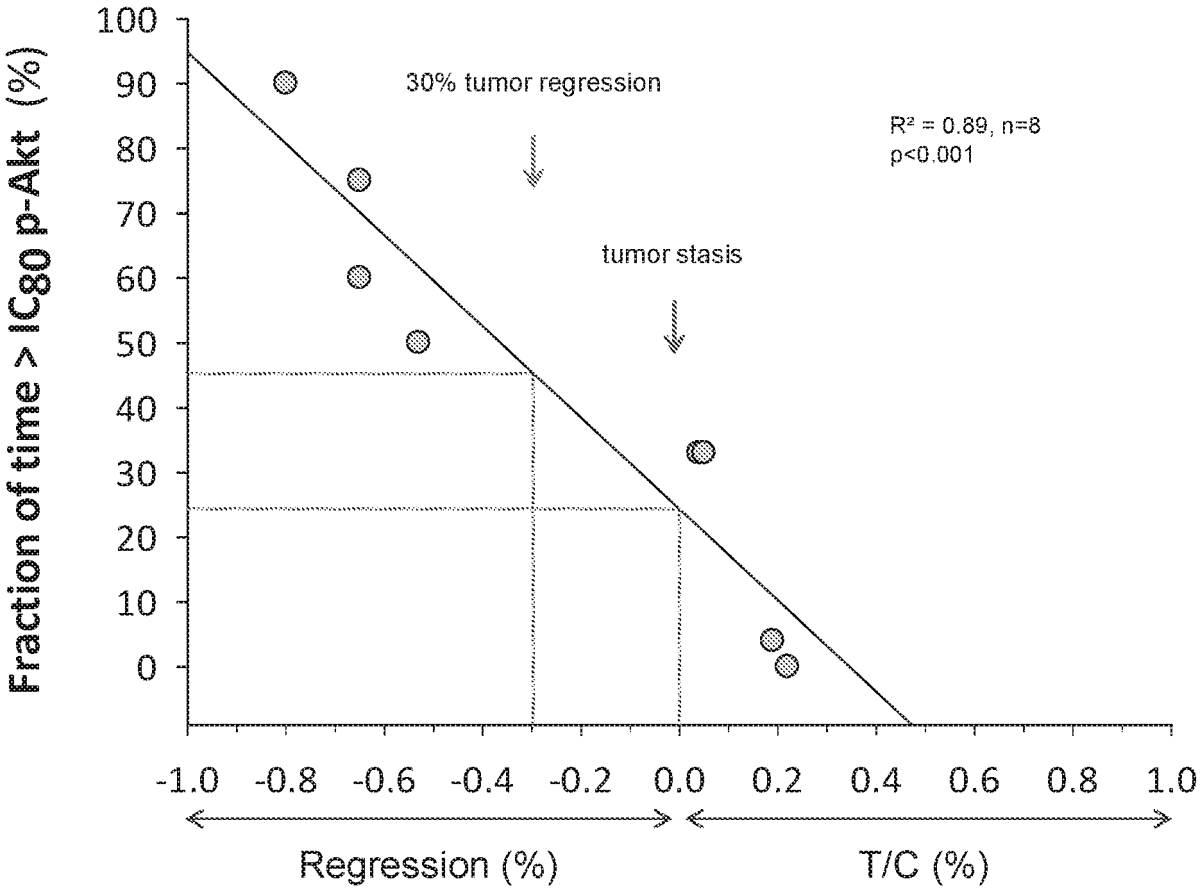

Fraction of time > IC80 p-Akt (%)
100
90
80
70
60
50
40
30
20
10
0
30% tumor regression
tumor stasis
R² = 0.89, n=8
p<0.001
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Regression (%)
T/C (%)

Fig. 8

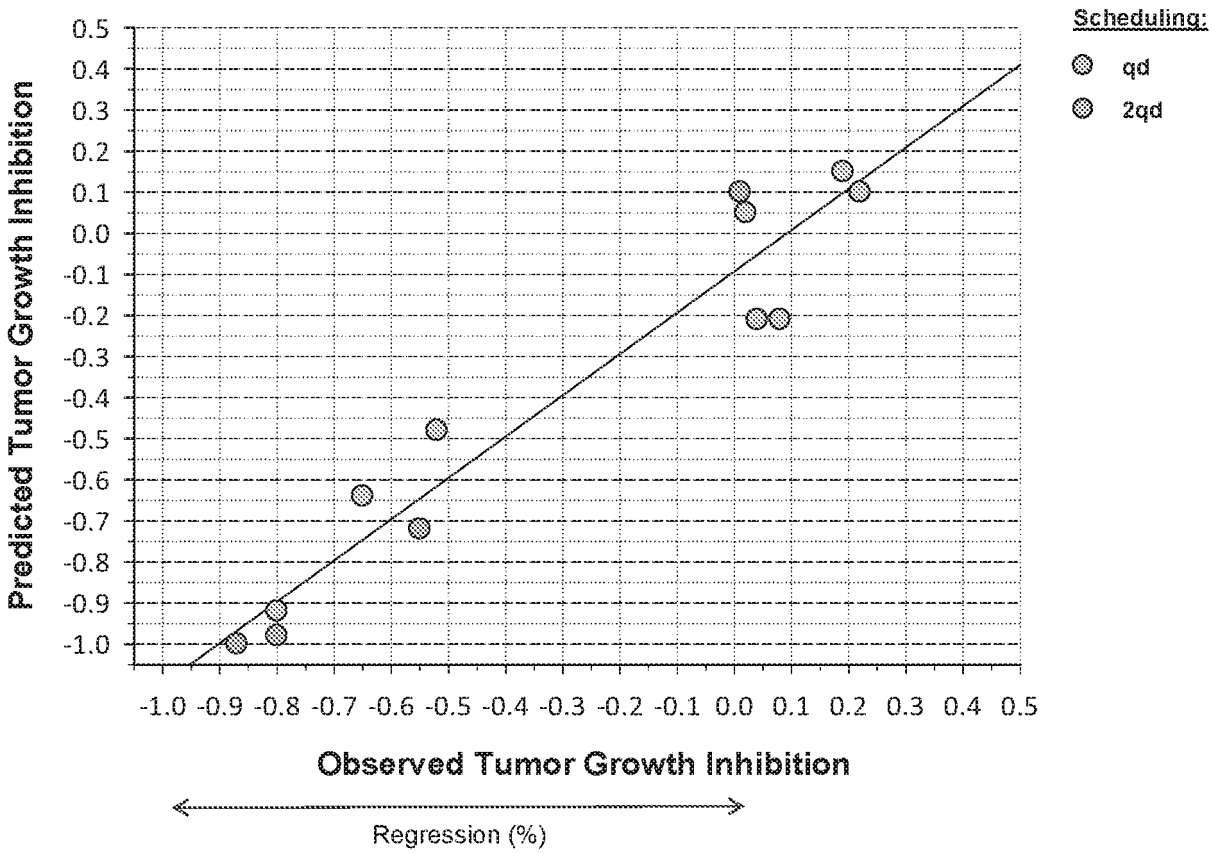
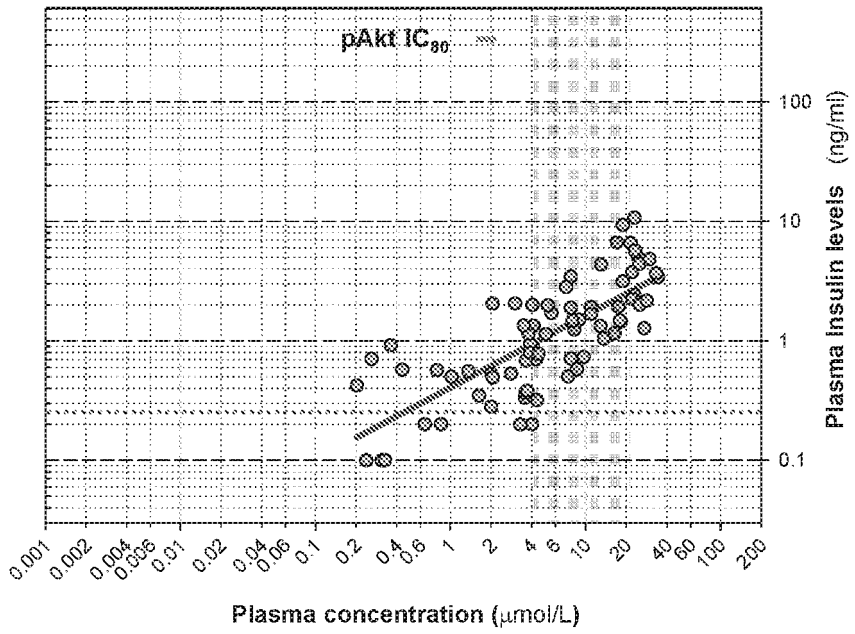

Predicted Tumor Growth Inhibition
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1.0
-1.0 -0.9 -0.8 -0.7 -0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4 0.5
Observed Tumor Growth Inhibition
Regression (%)
Scheduling:
qd
2qd

Fig. 9

A.


pAkt IC80
100
10
1
0.1
Plasma insulin levels (ng/ml)
0.001
0.002
0.004
0.006
0.01
0.02
0.04
0.06
0.1
0.2
0.4
0.6
1
2
4
6
10
20
40
60
100
200
Plasma concentration (µmol/L)

B.

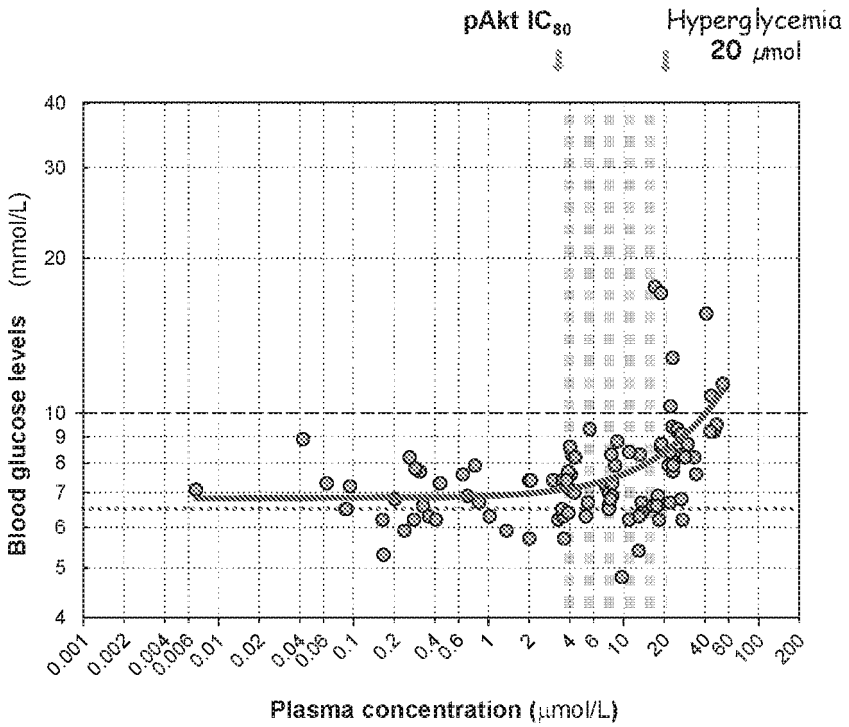
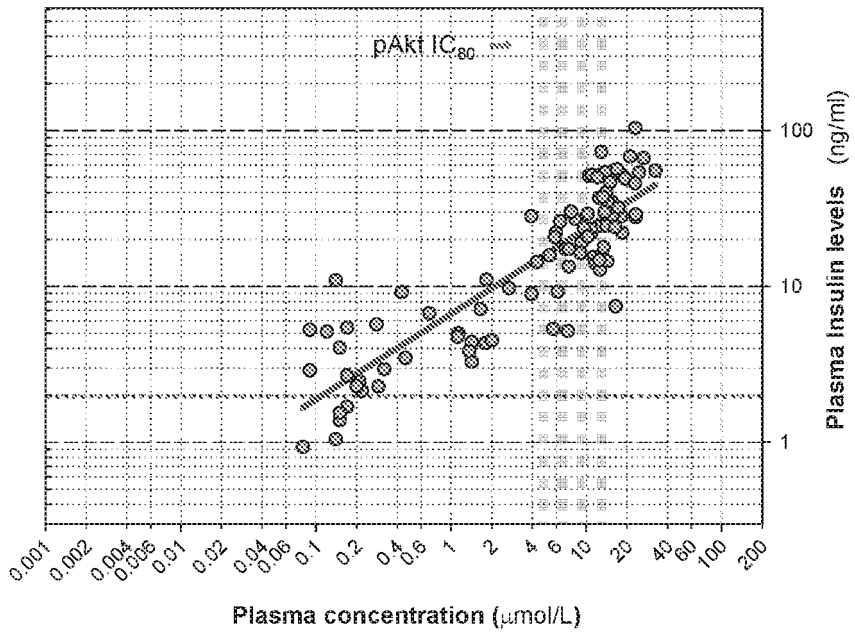

pAkt IC80
Hyperglycemia
20 µmol
40
30
20
10
9
8
7
6
5
4
Blood glucose levels (mmol/L)
0.001
0.002
0.004
0.006
0.01
0.02
0.04
0.06
0.1
0.2
0.4
0.6
1
2
4
6
10
20
40
60
100
200
Plasma concentration (µmol/L)

Fig. 10

A.


pAkt IC80
100
10
1
Plasma Insulin levels (ng/ml)
0.001 0.002 0.004 0.006 0.01 0.02 0.04 0.06 0.1 0.2 0.4 0.6 1 2 4 6 10 20 40 60 100 200
Plasma concentration (µmol/L)

B.

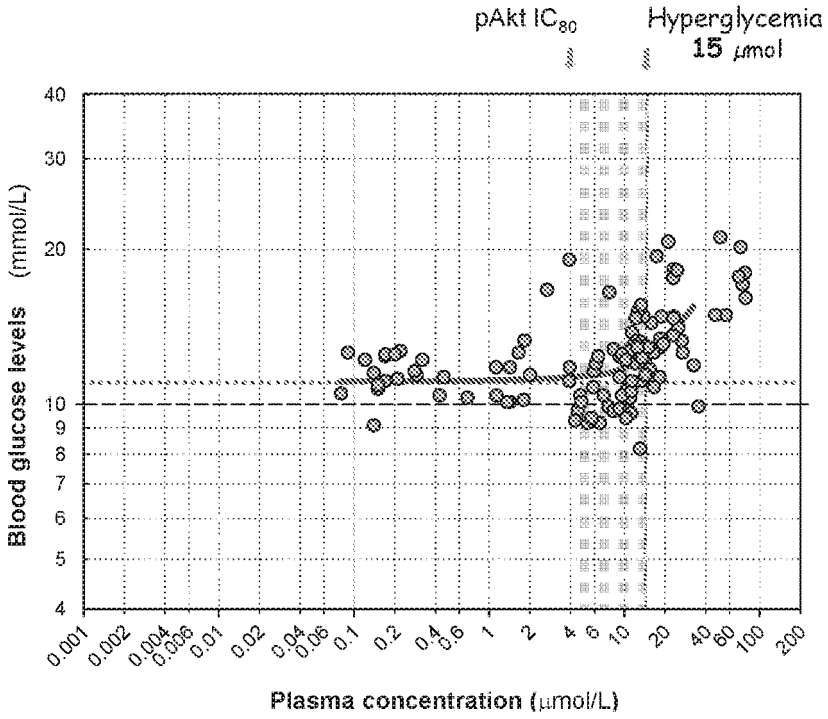

pAkt IC80
Hyperglycemia
15 µmol
40
30
20
10
9
8
7
6
5
4
Blood glucose levels (mmol/L)
0.001 0.002 0.004 0.006 0.01 0.02 0.04 0.06 0.1 0.2 0.4 0.6 1 2 4 6 10 20 40 60 100 200
Plasma concentration (µmol/L)

Fig. 11

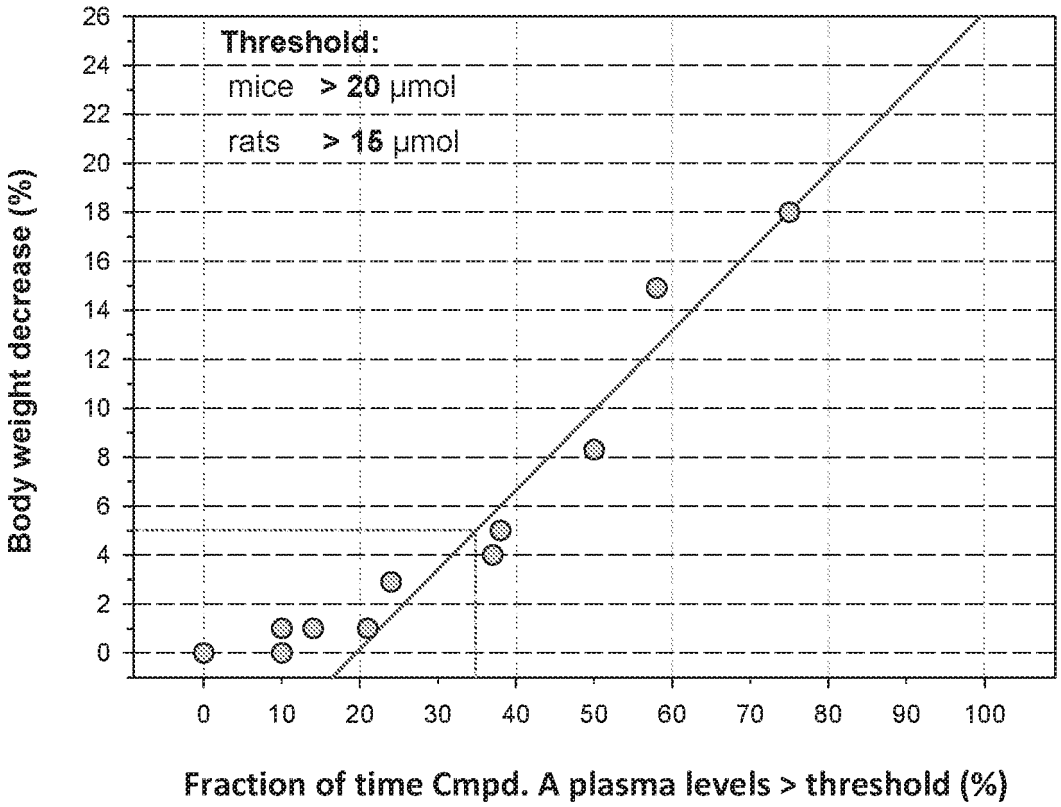

Threshold:
mice > 20 µmol
rats > 15 µmol
Body weight decrease (%)
Fraction of time Cmpd. A plasma levels > threshold (%)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
0
10
20
30
40
50
60
70
80
90
100

Fig. 12

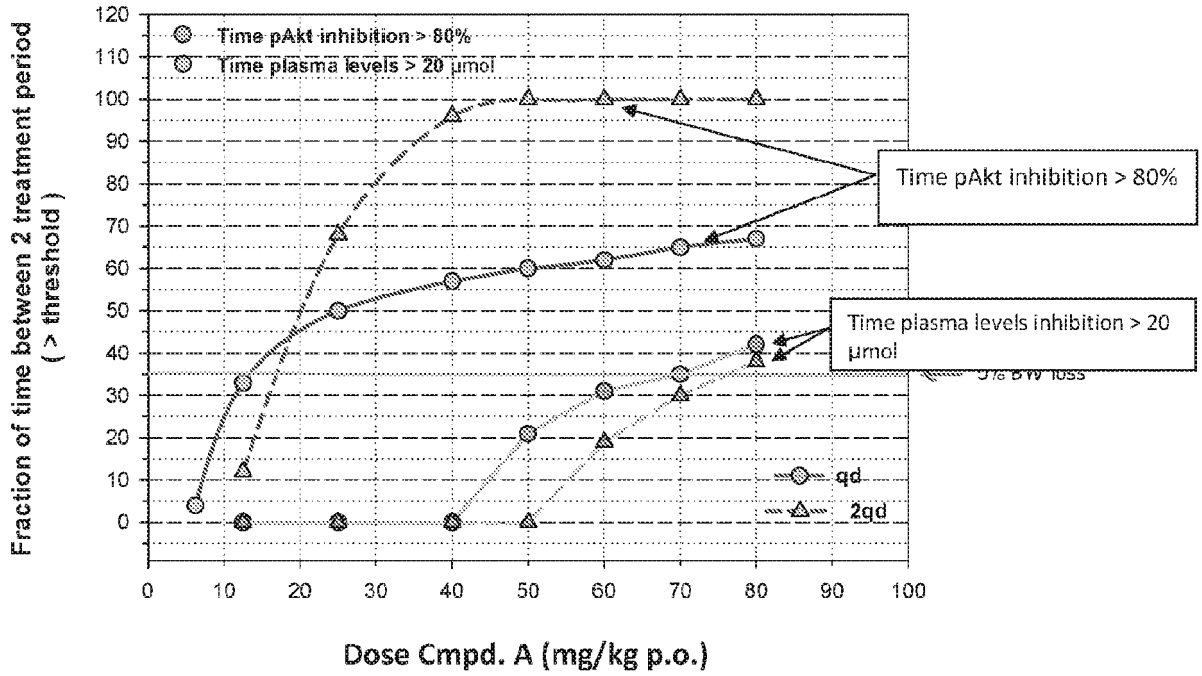

Time pAkt inhibition > 80%
Time plasma levels > 20 µmol
Fraction of time between 2 treatment period (> threshold)
Dose Cmpd. A (mg/kg p.o.)
qd
2qd
Time pAkt inhibition > 80%
Time plasma levels inhibition > 20 µmol

Fig. 13

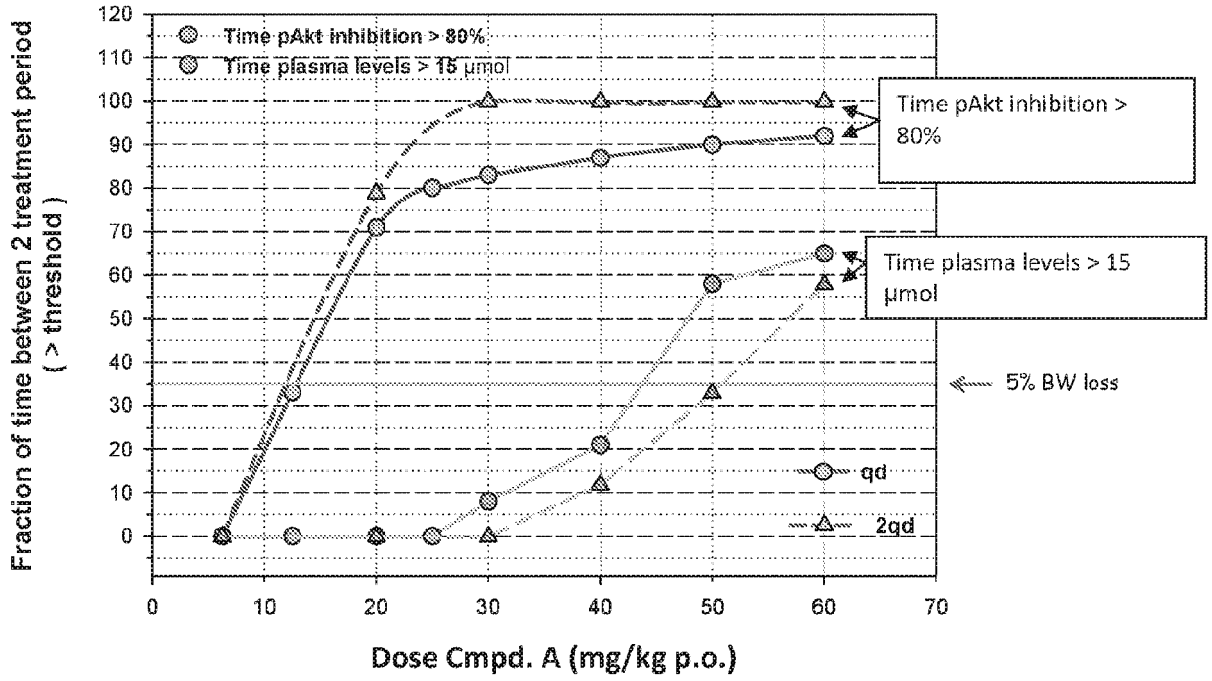
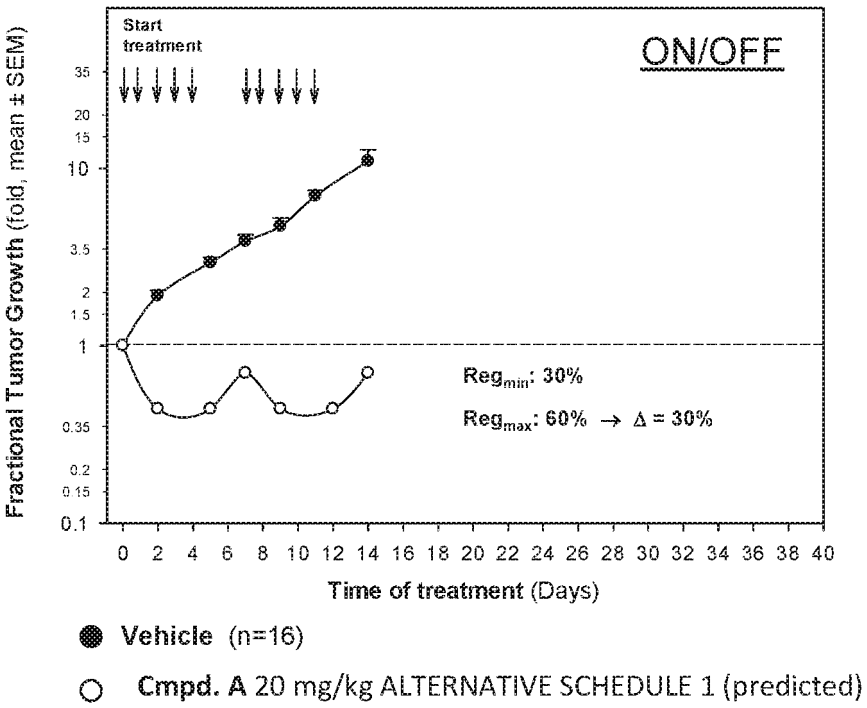

Time pAkt inhibition > 80%
Time plasma levels > 15 µmol
Fraction of time between 2 treatment period (> threshold)
Dose Cmpd. A (mg/kg p.o.)
Time pAkt inhibition > 80%
Time plasma levels > 15 µmol
5% BW loss
qd
2qd

Fig. 14

A.


Start treatment
ON/OFF
Fractional Tumor Growth (fold, mean ± SEM)
35
20
15
10
3.5
2
1.5
1
0.35
0.2
0.15
0.1
Reg$_{min}$: 30%
Reg$_{max}$: 60% → Δ = 30%
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Time of treatment (Days)
Vehicle (n=16)
Cmpd. A 20 mg/kg ALTERNATIVE SCHEDULE 1 (predicted)

B.

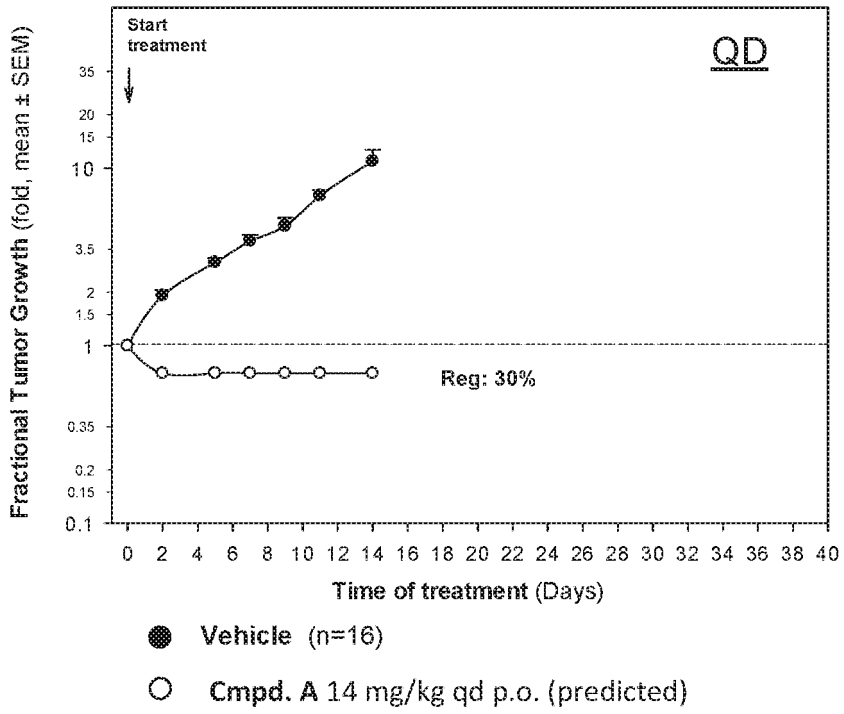
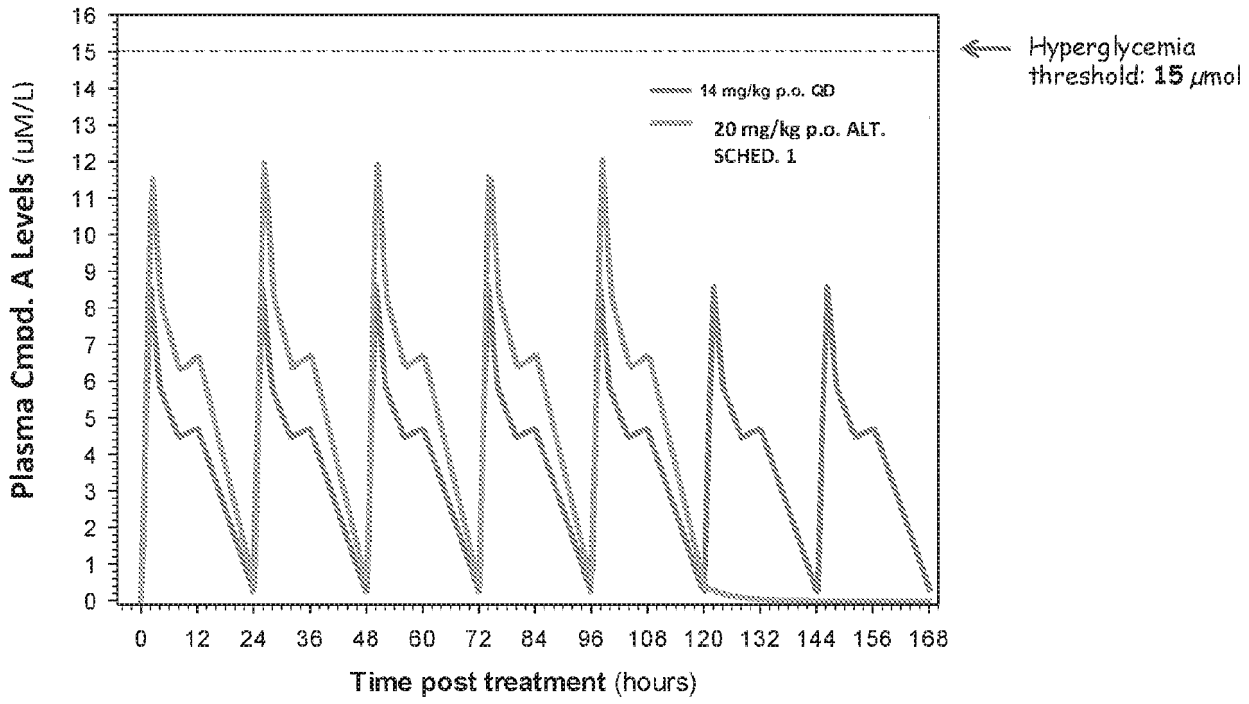

Start treatment
QD
Fractional Tumor Growth (fold, mean ± SEM)
35
20
15
10
3.5
2
1.5
1
0.35
0.2
0.15
0.1
Reg: 30%
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Time of treatment (Days)
Vehicle (n=16)
Cmpd. A 14 mg/kg qd p.o. (predicted)

Fig. 15


Plasma Cmpd. A Levels (uM/L)
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
14 mg/kg p.o. QD
20 mg/kg p.o. ALT. SCHED. 1
Hyperglycemia threshold: 15 µmol
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168
Time post treatment (hours)