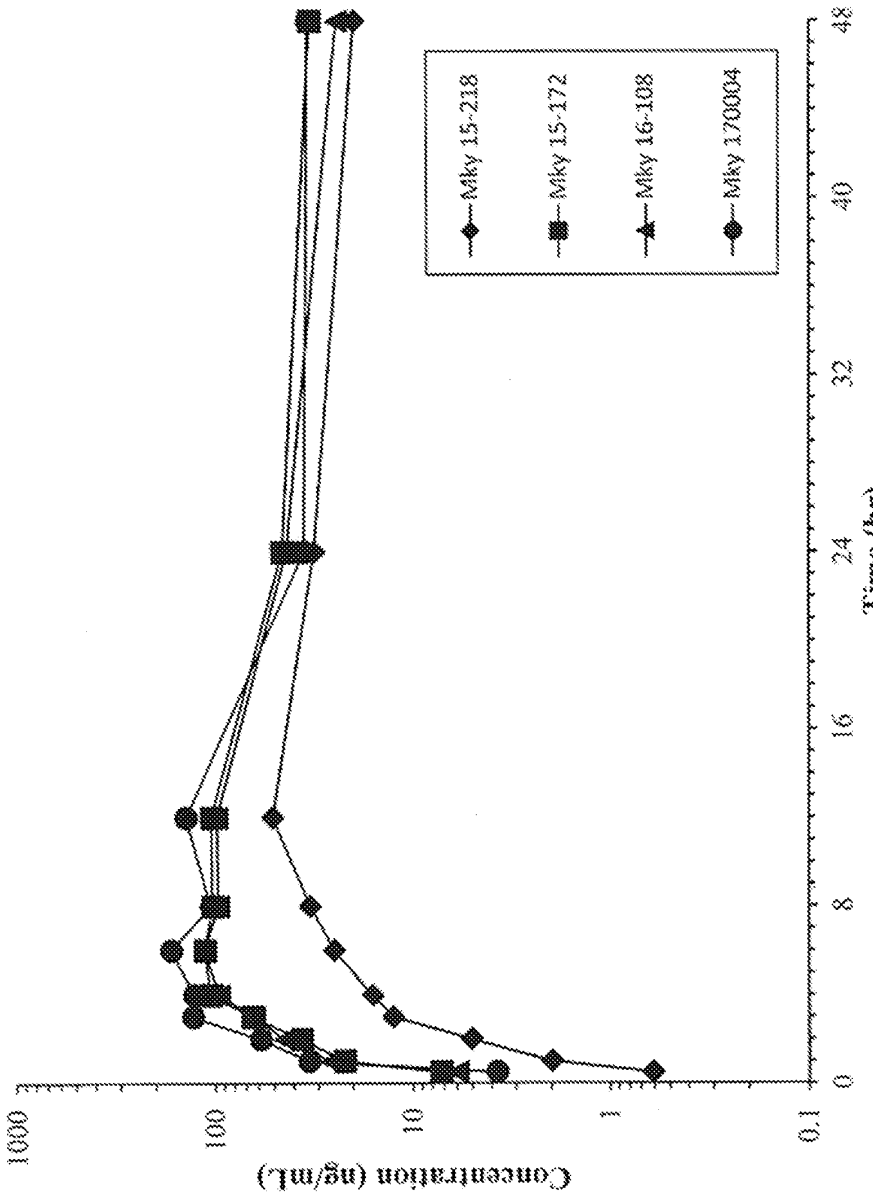

Concentration (ng/mL)
1000
100
10
1
0.1
0
8
16
24
32
40
48
Time (hr)
Mky 15-218
Mky 15-172
Mky 16-108
Mky 170004

FIG. 1

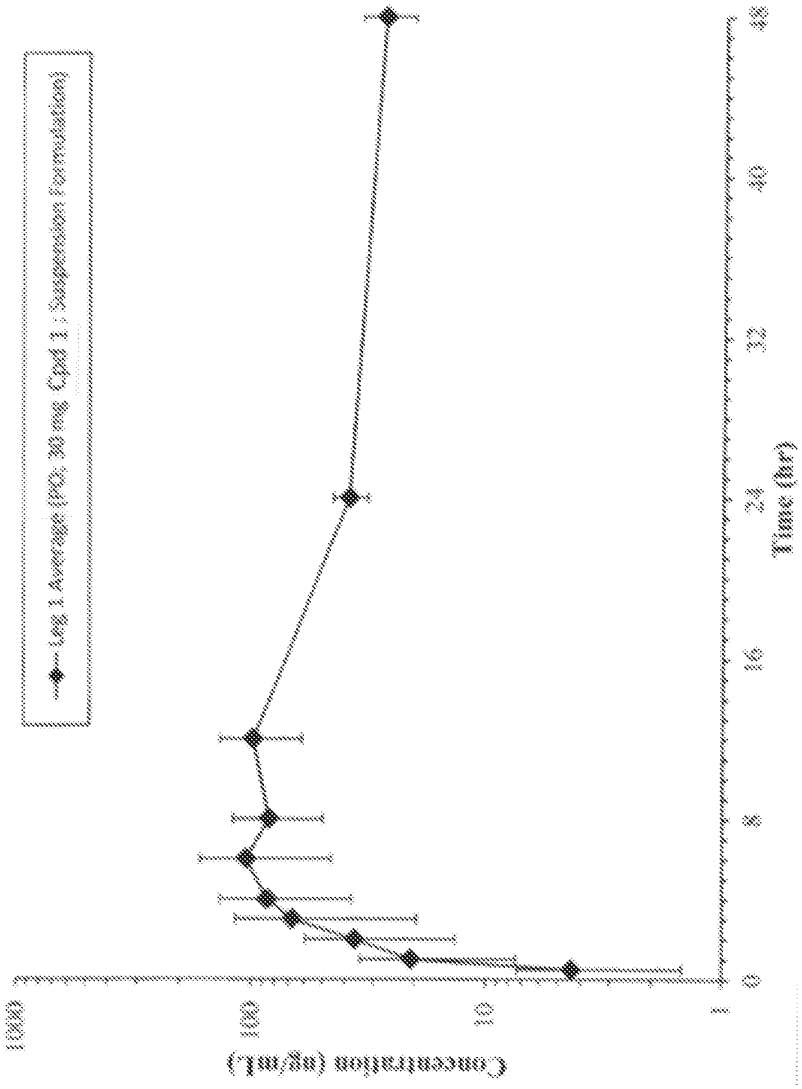

Leg 1 Average (PO, 30 mg Cpd 1 : Suspension Formulation)
Concentration (ng/mL)
1000
100
10
1
0
8
16
24
32
40
48
Time (hr)

FIG. 2

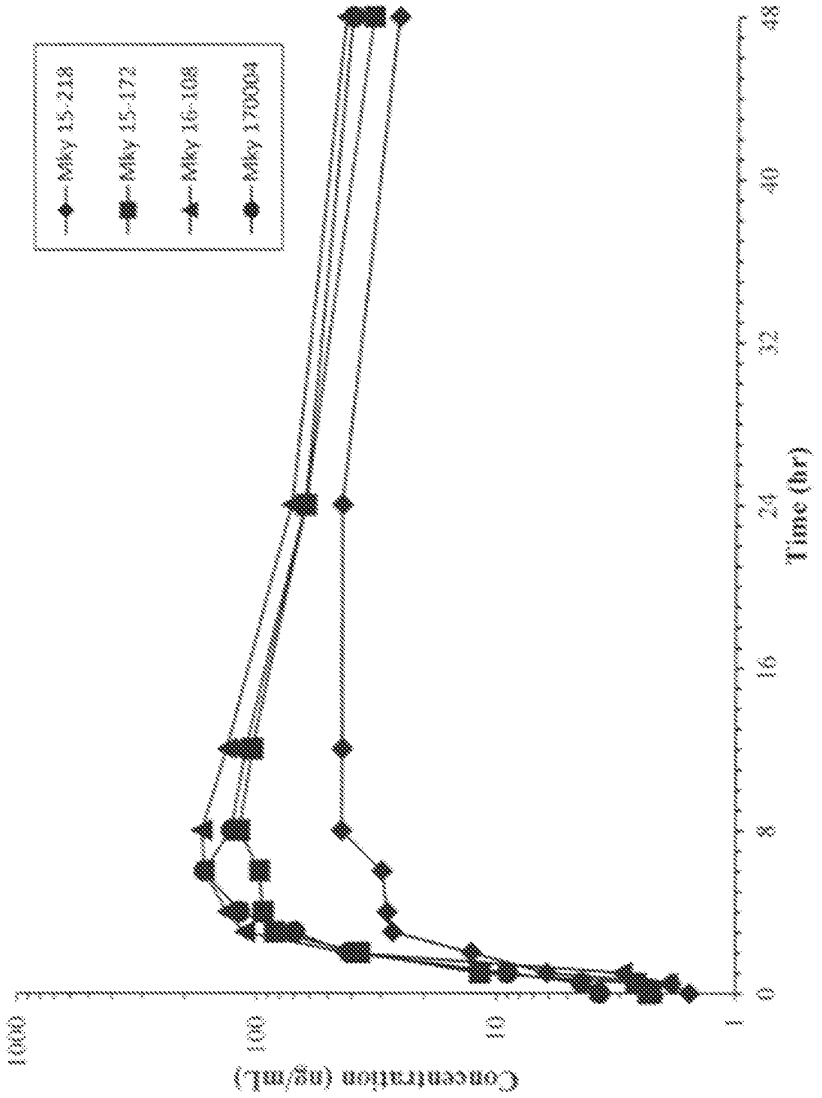

Mky 15-218
Mky 15-172
Mky 16-108
Mky 170004
Concentration (ng/mL)
1000
100
10
1
0
8
16
24
32
40
48
Time (hr)

FIG. 3

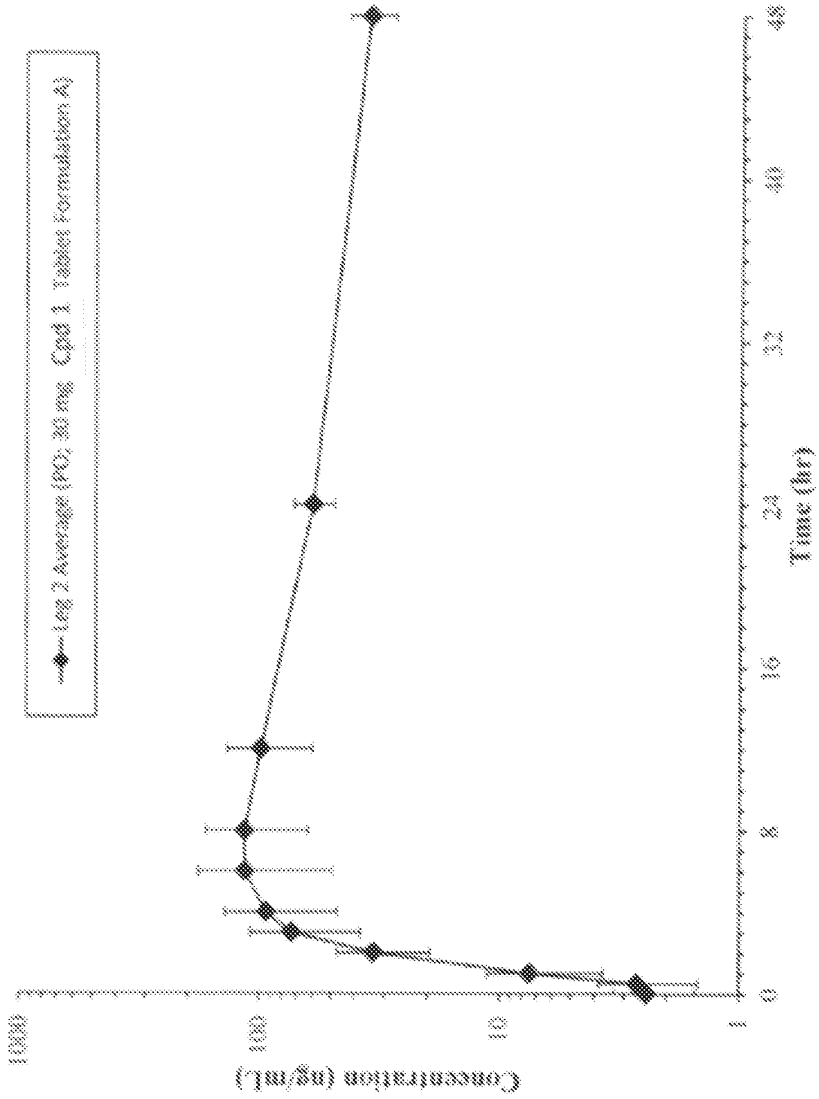

Leg 2 Average (PO; 30 mg Cpd 1 Tablet Formulation A)
Concentration (ng/mL)
1000
100
10
1
0
8
16
24
32
40
48
Time (hr)

FIG. 4

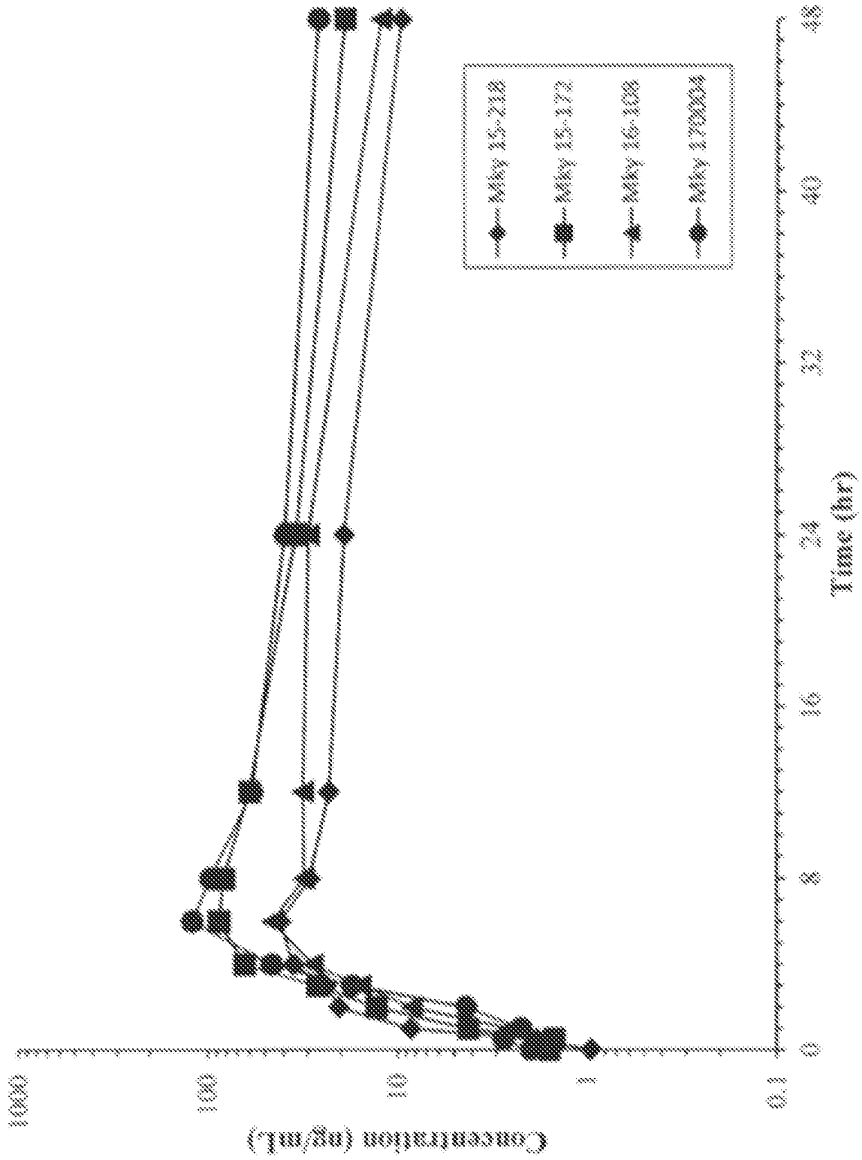

Concentration (ng/mL)
1000
100
10
1
0.1
0
8
16
24
32
40
48
Time (hr)
MKy 15-218
MKy 15-172
MKy 16-108
MKy 170034

FIG. 5

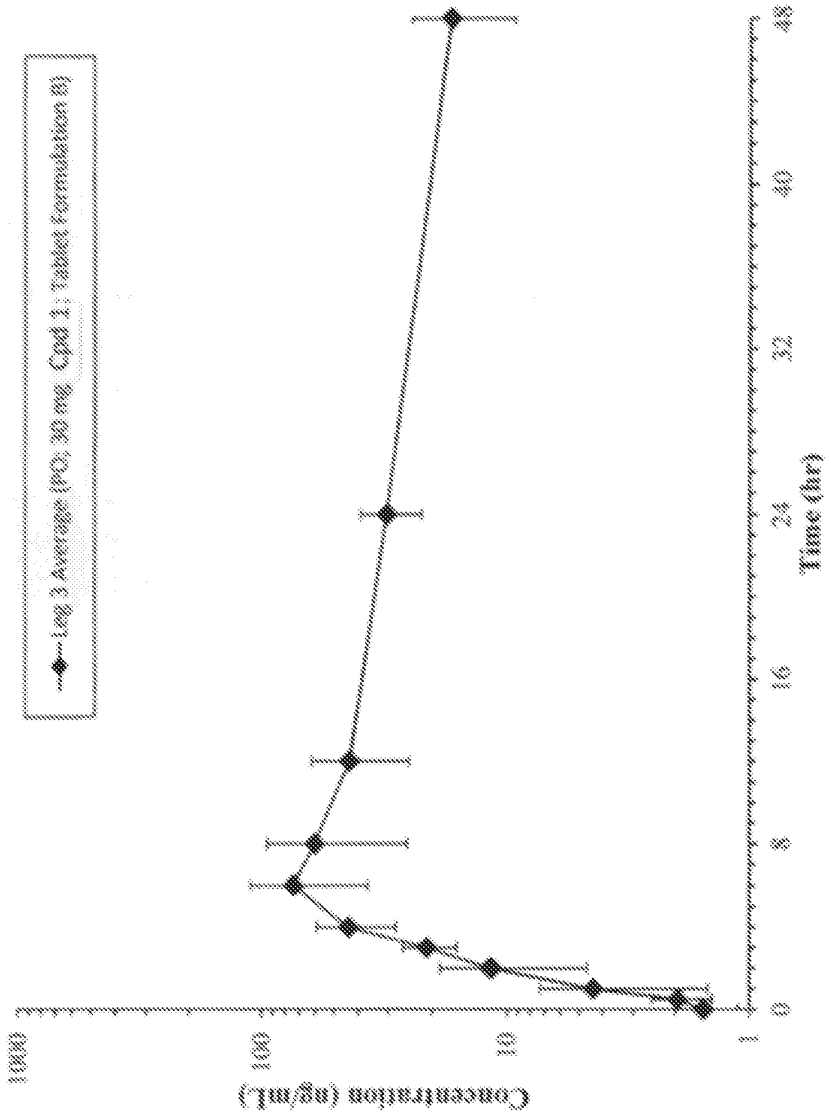

Concentration (ng/mL)
1000
100
10
1
0
8
16
24
32
40
48
Time (hr)
Lng 3 Average (PO, 30 mg, Cpd 1, Tablet Formulation B)

FIG. 6

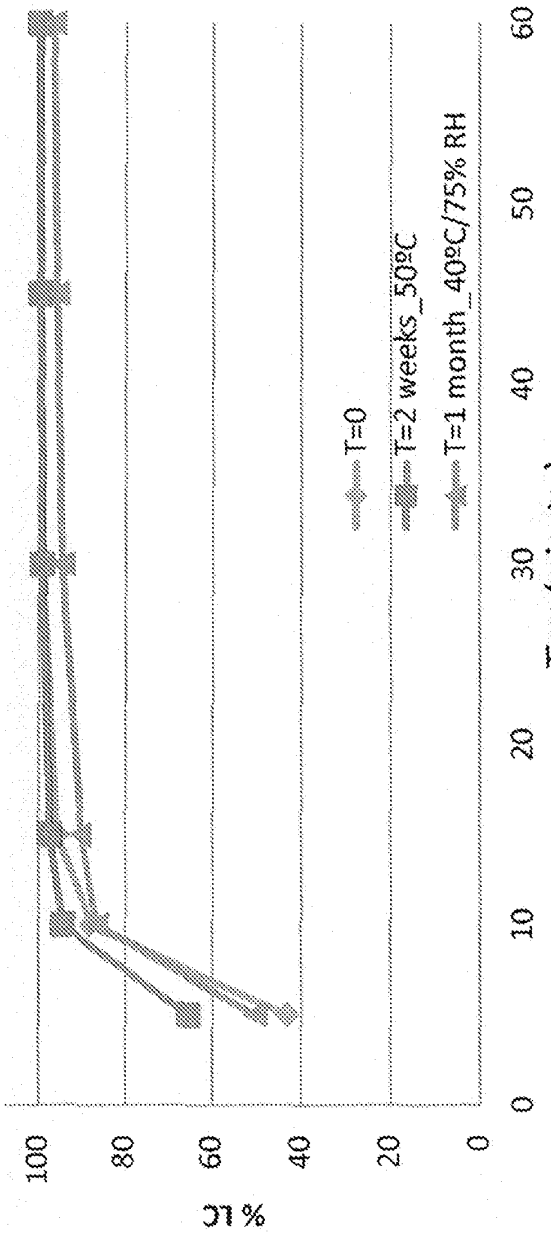

100
80
60
40
20
0
% IC
0
10
20
30
40
50
60
Time (minutes)
T=0
T=2 weeks_50ºC
T=1 month_40ºC/75% RH

FIG. 7

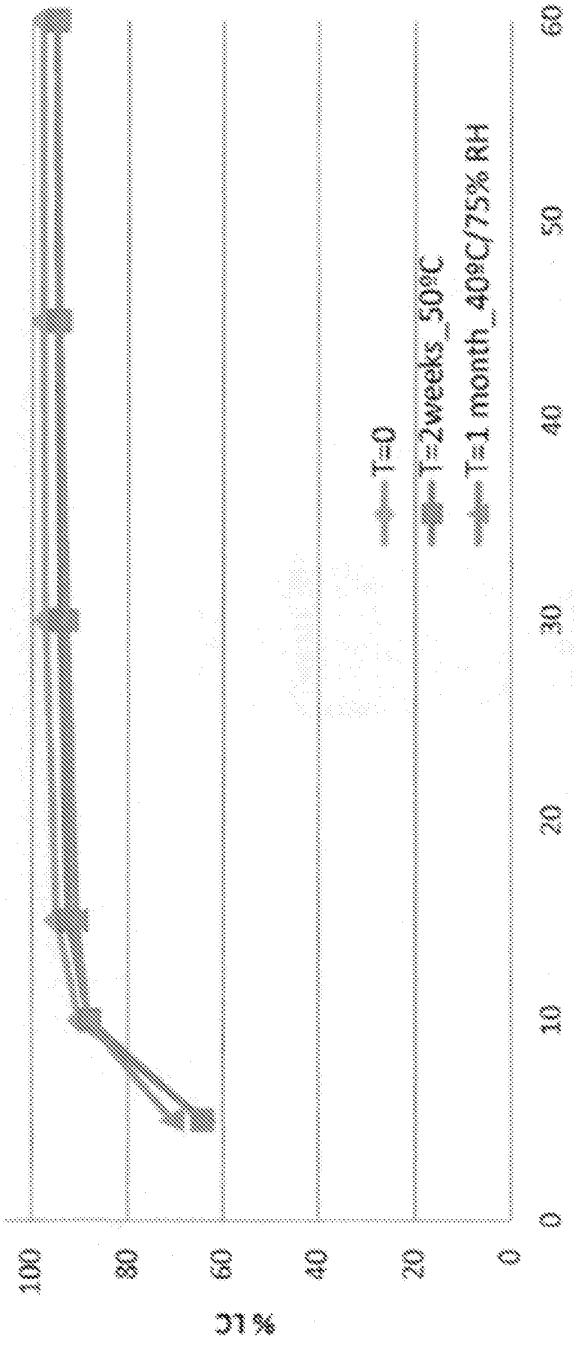

100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)
T=0
T=2weeks_50°C
T=1 month_40°C/75% RH

FIG. 8

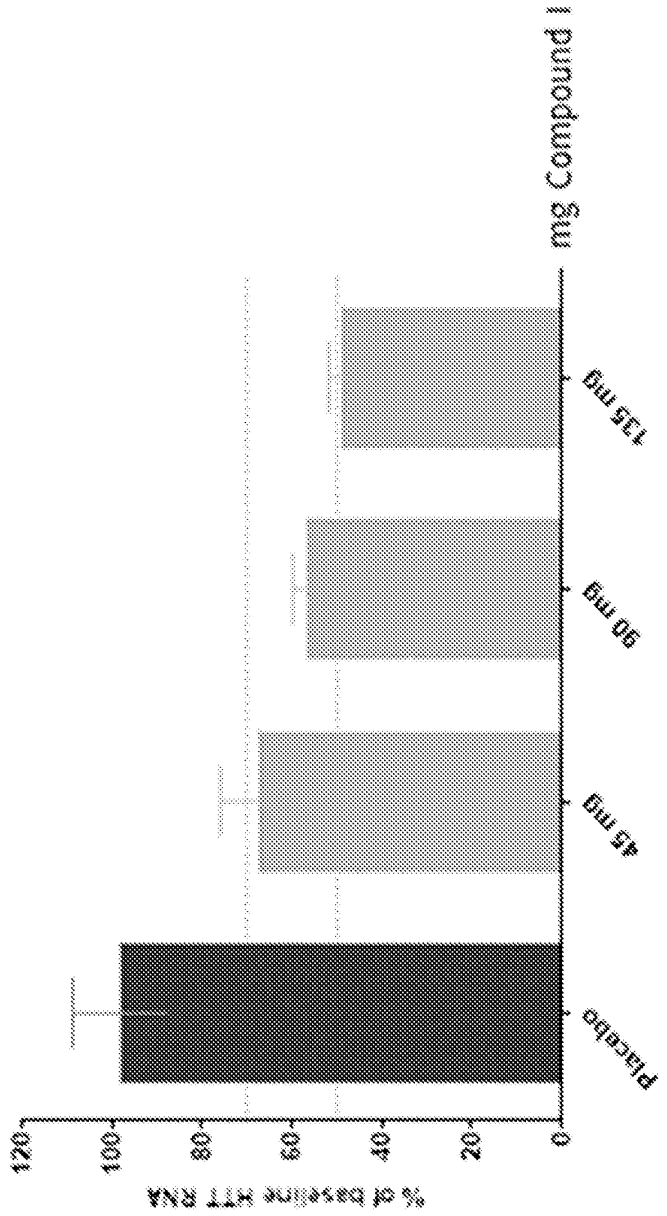

mg Compound I
135 mg
90 mg
45 mg
Placebo
% of baseline HTT RNA
120
100
80
60
40
20
0

FIG. 9A

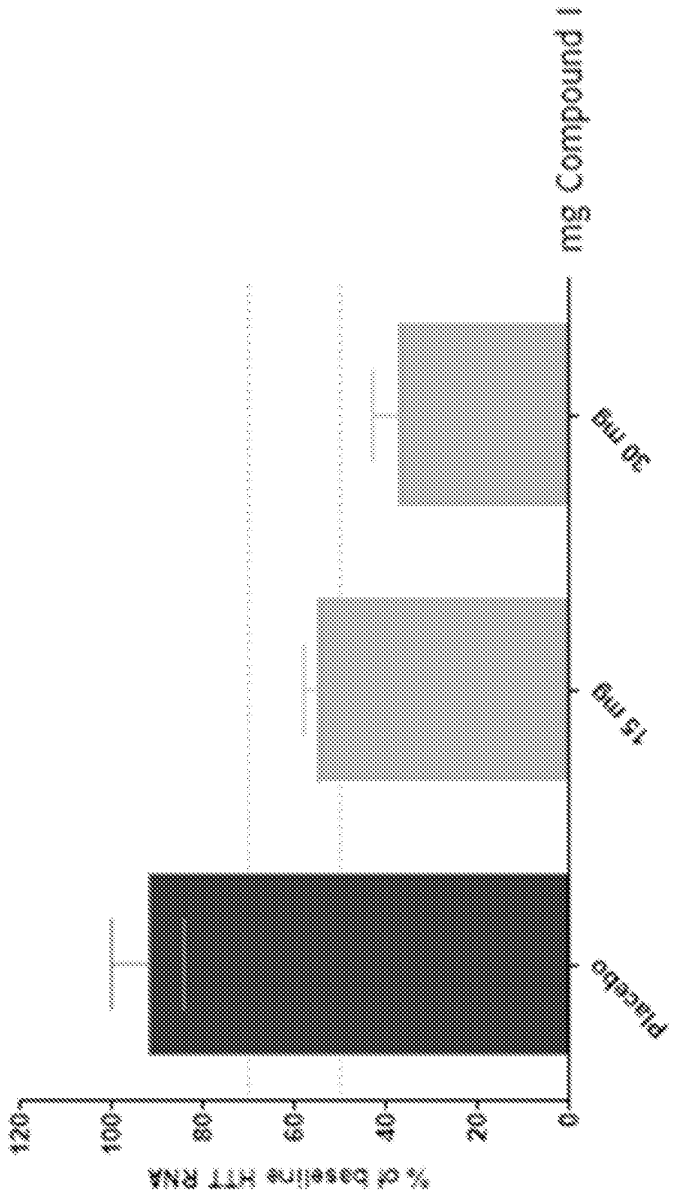

mg Compound 1
Placebo
15 mg
30 mg
0
20
40
60
80
100
120
% of baseline HTT RNA

FIG. 9B

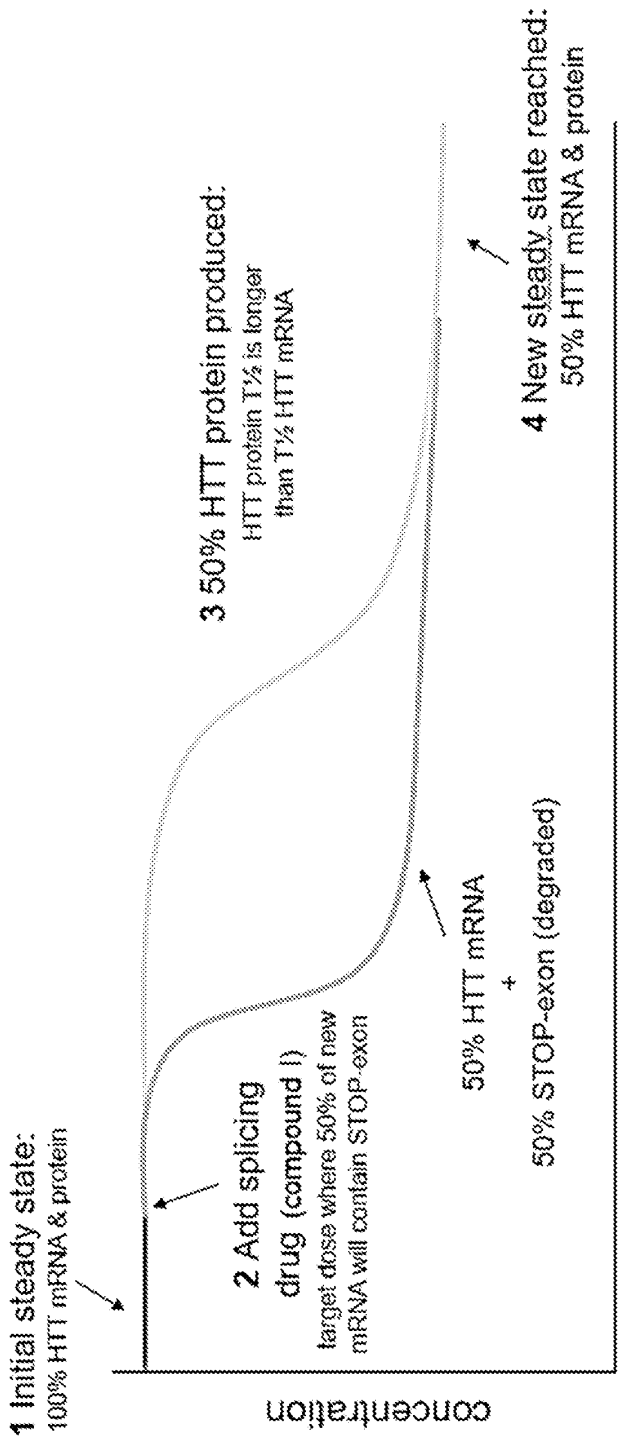

1 Initial steady state:
100% HTT mRNA & protein
2 Add splicing drug (compound I)
target dose where 50% of new mRNA will contain STOP-exon
3 50% HTT protein produced:
HTT protein T½ is longer than T½ HTT mRNA
4 New steady state reached:
50% HTT mRNA & protein
50% HTT mRNA
+
50% STOP-exon (degraded)
concentration
time

FIG. 10

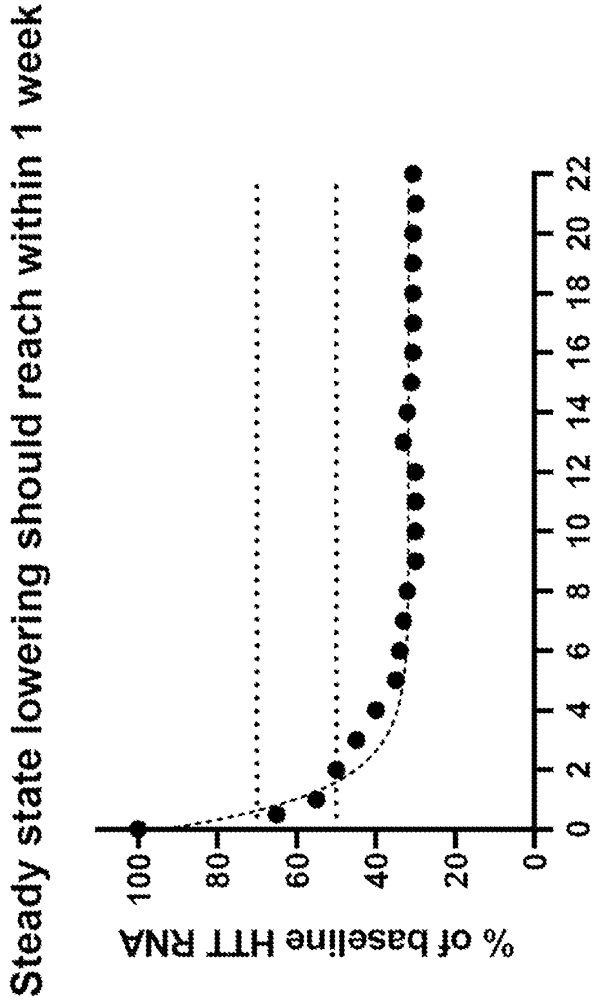

HTT mRNA abundance
Steady state lowering should reach within 1 week
% of baseline HTT RNA
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
22
Days

FIG. 11A

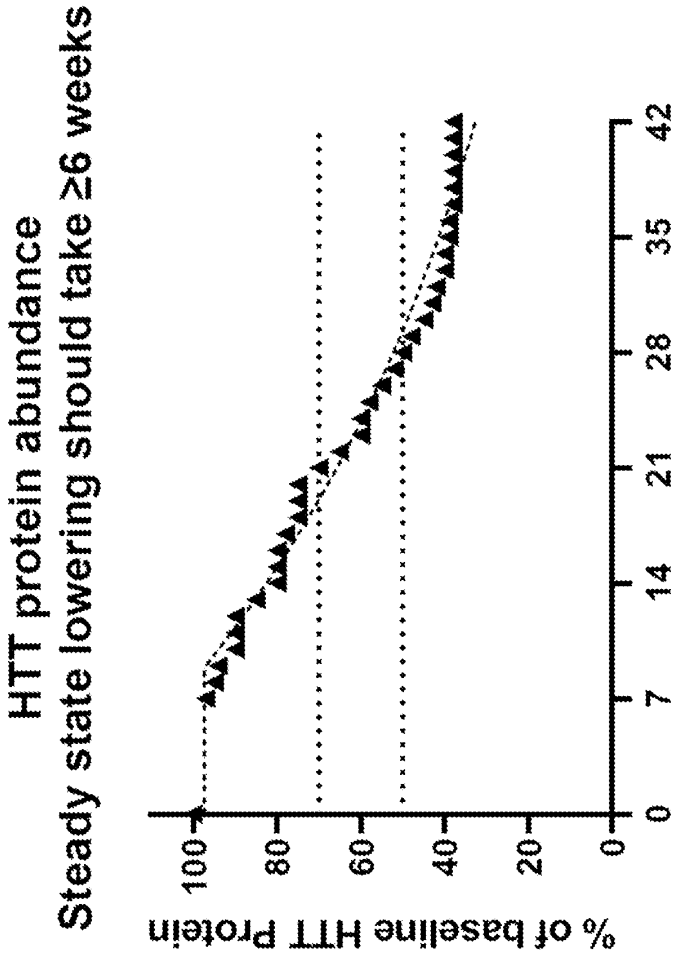

HTT protein abundance
Steady state lowering should take ≥6 weeks
% of baseline HTT Protein
100
80
60
40
20
0
0
7
14
21
28
35
42
Days

FIG. 11B

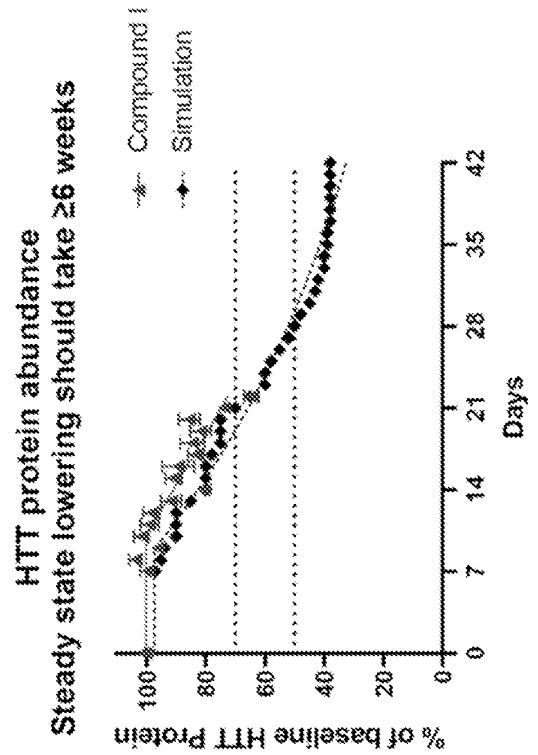


FIG. 12B

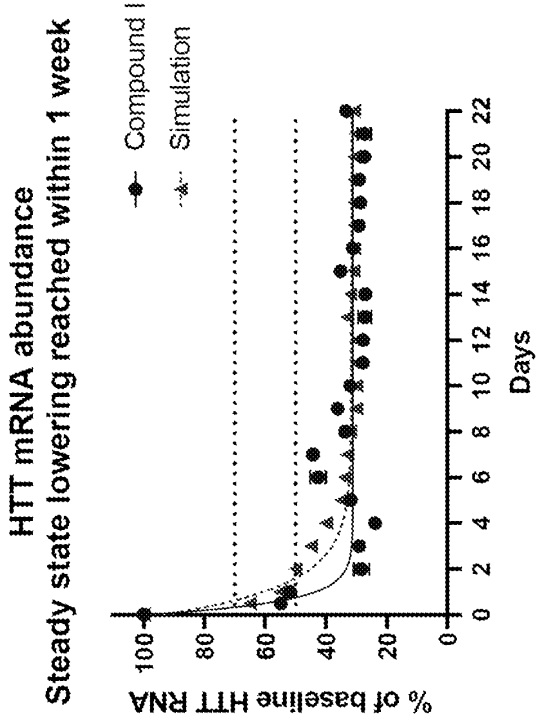


FIG. 12A

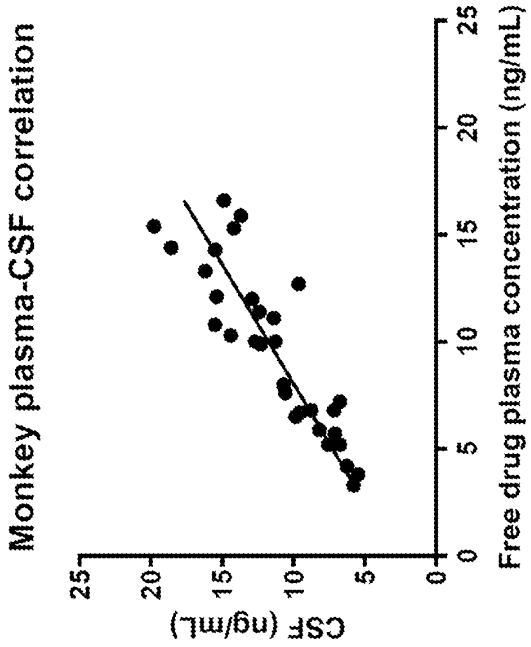


FIG. 13B

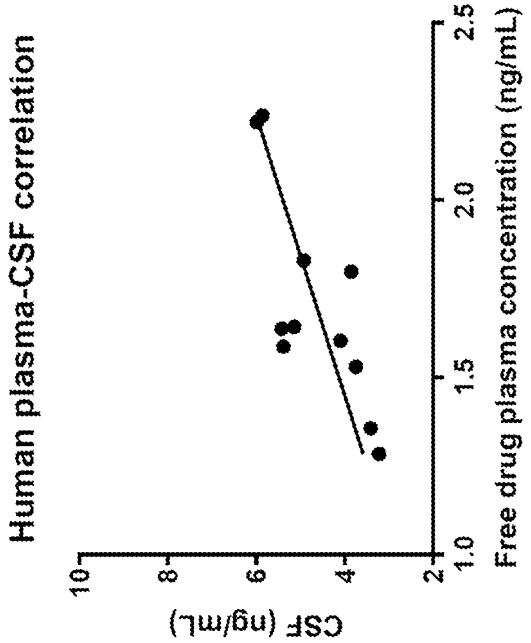


FIG. 13A

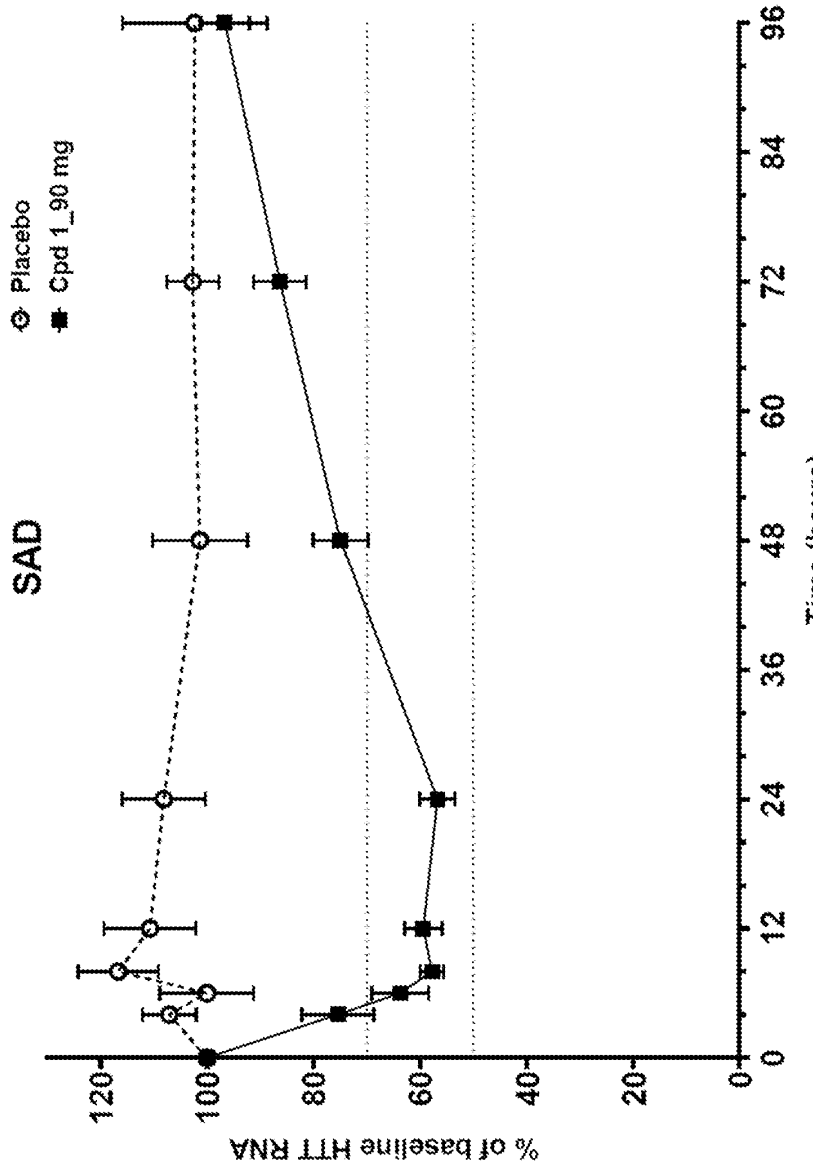

SAD
Placebo
Cpd 1_90 mg
% of baseline HTT RNA
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
Time (hours)

FIG. 14

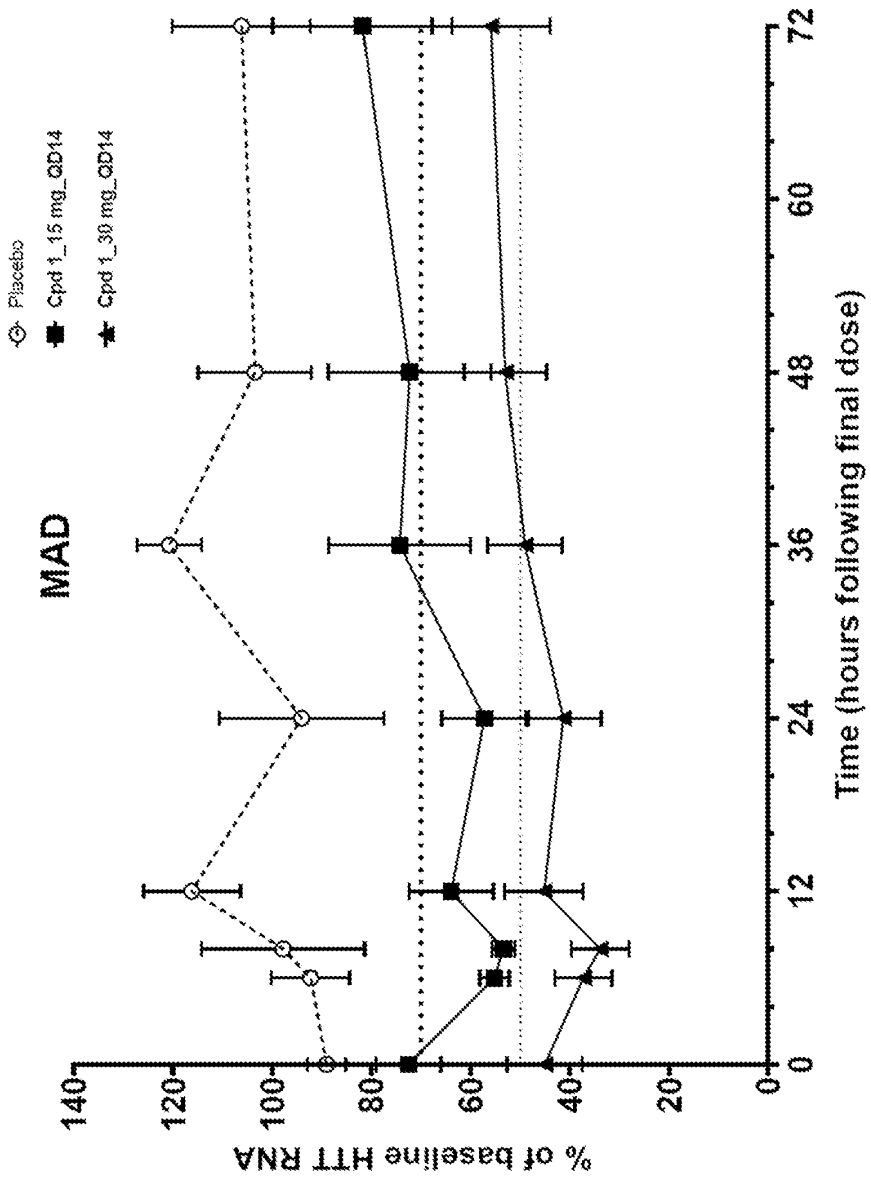

MAD
Placebo
Cpd 1_15 mg_QD14
Cpd 1_30 mg_QD14
% of baseline HTT RNA
140
120
100
80
60
40
20
0
0
12
24
36
48
60
72
Time (hours following final dose)

FIG. 15

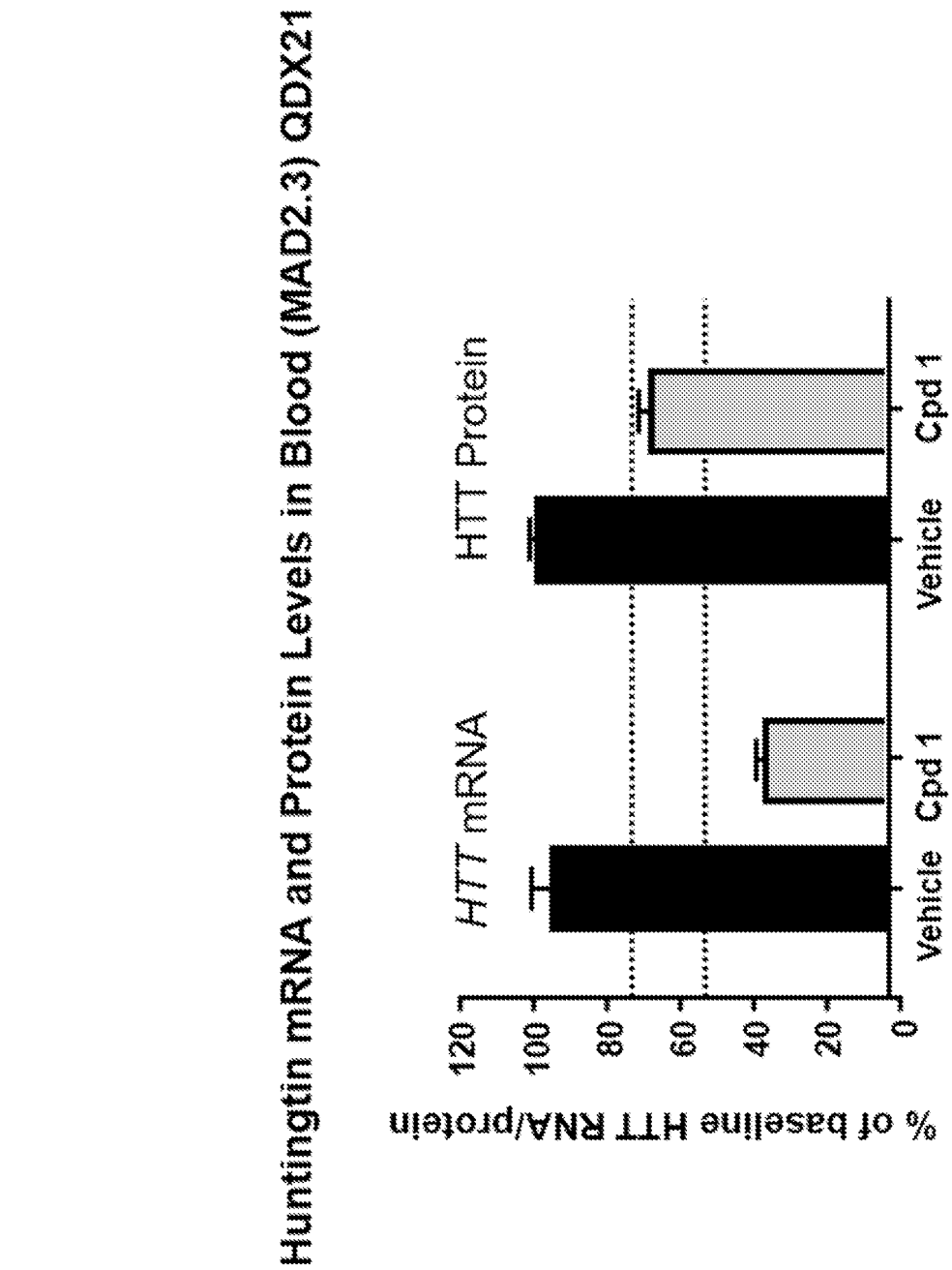

Huntingtin mRNA and Protein Levels in Blood (MAD2.3) QDX21
% of baseline HTT RNA/protein
120
100
80
60
40
20
0
HTT mRNA
HTT Protein
Vehicle
Cpd 1
Vehicle
Cpd 1

FIG. 16