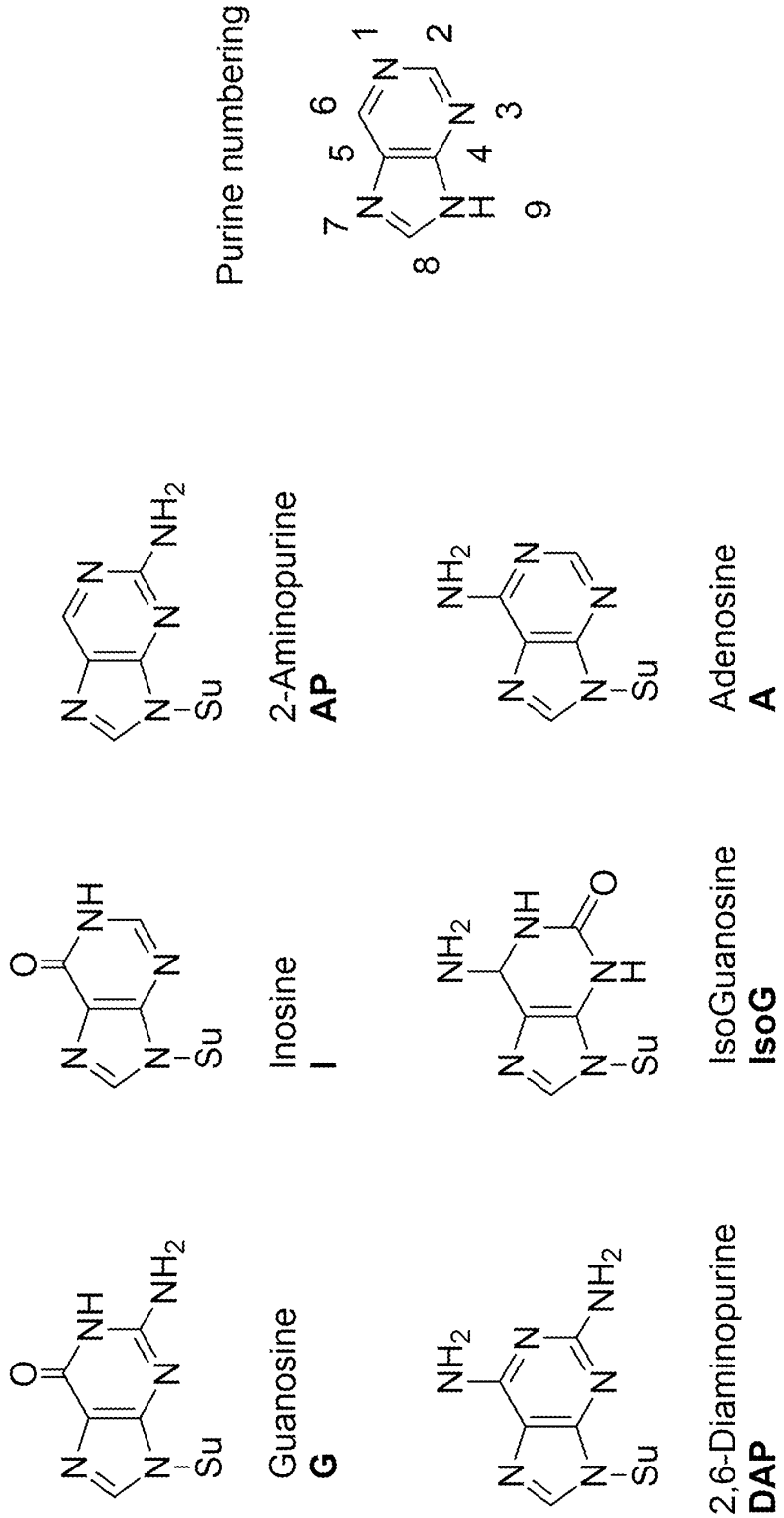

Purine numbering
1
2
3
4
5
6
7
8
9
N
H
Su
NH2
O
2-Aminopurine
AP
Adenosine
A
Inosine
I
IsoGuanosine
IsoG
Guanosine
G
2,6-Diaminopurine
DAP

FIG. 1

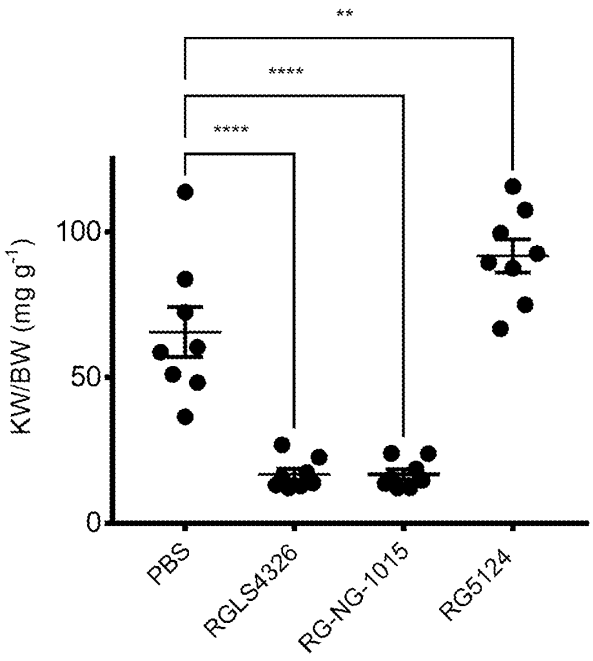

**
****
****
KW/BW (mg g-1)
100
50
0
PBS
RGLS4326
RG-NG-1015
RG5124

FIG. 2A

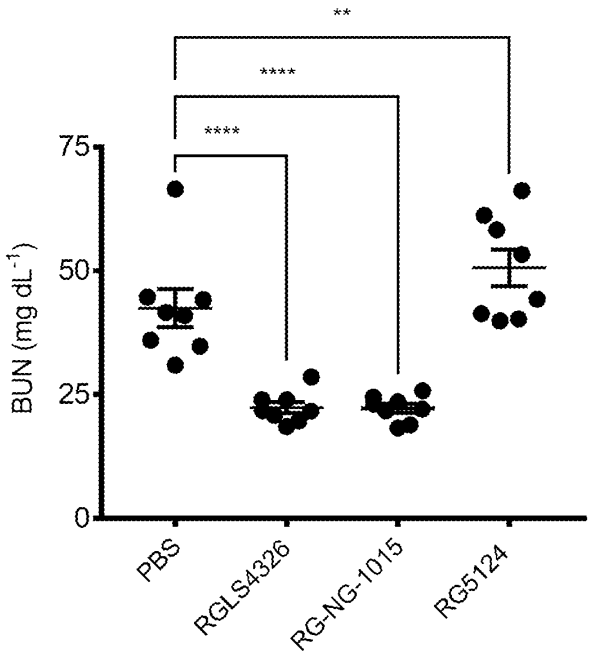

**
****
****
BUN (mg dL-1)
75
50
25
0
PBS
RGLS4326
RG-NG-1015
RG5124

FIG. 2B

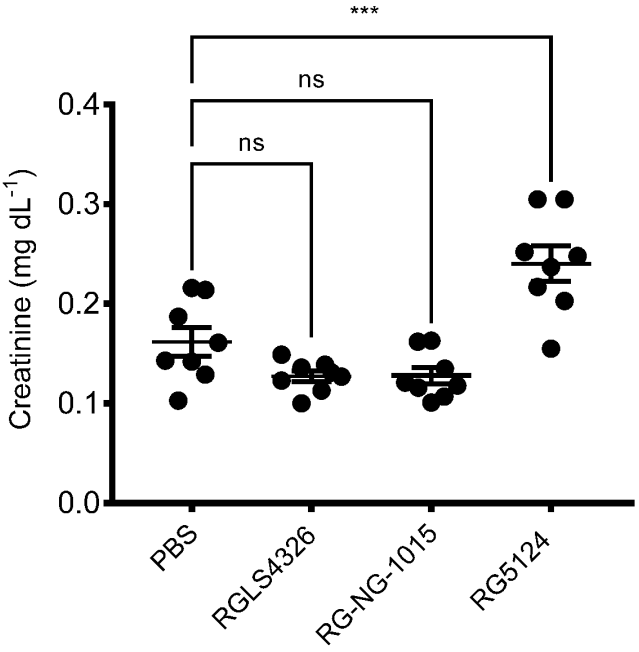
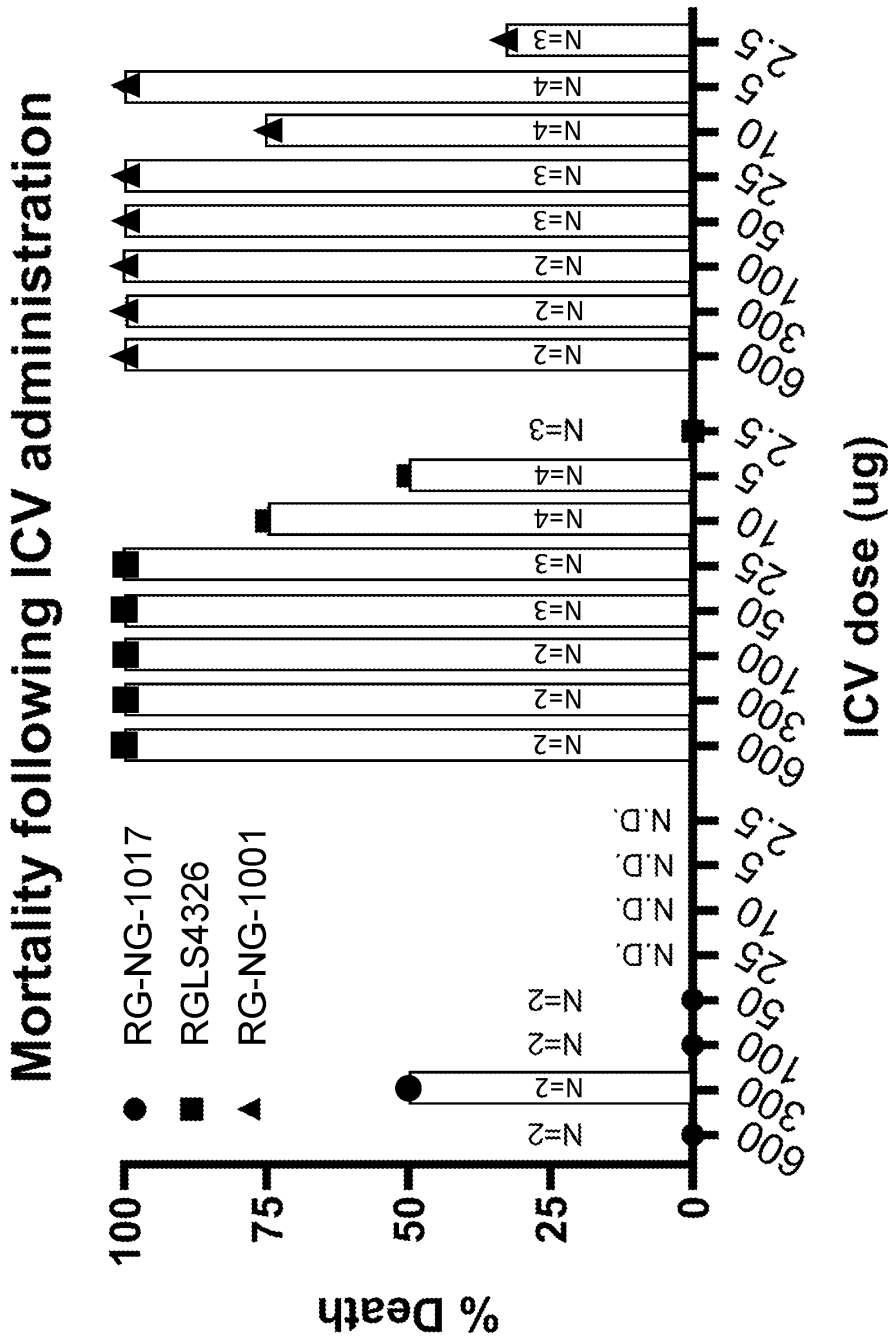

***
ns
ns
0.4
0.3
0.2
0.1
0.0
Creatinine (mg dL-1)
PBS
RGLS4326
RG-NG-1015
RG5124

FIG. 2C



N.D. = Not Determined

FIG. 3

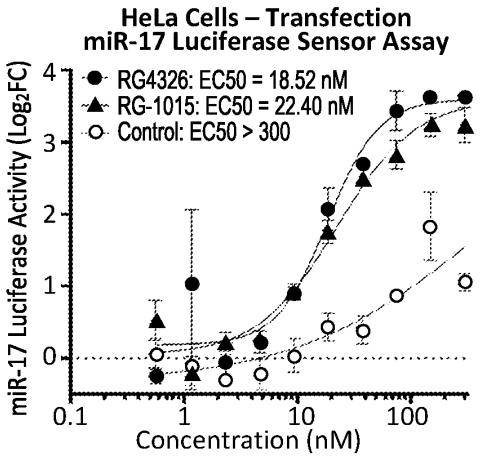


FIG. 4A

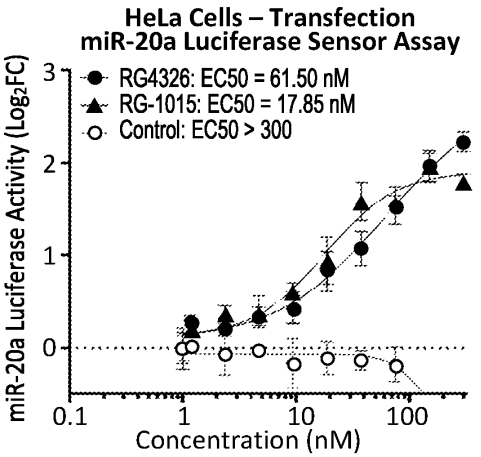


FIG. 4B

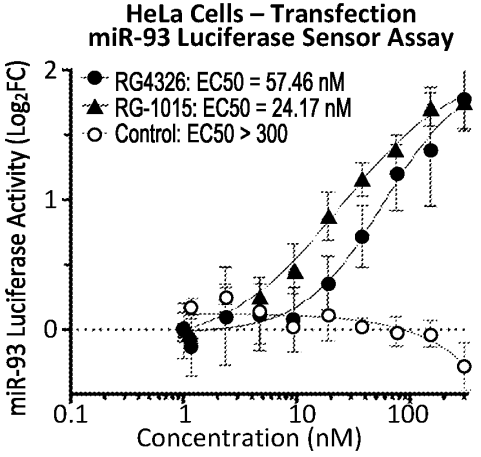


FIG. 4C

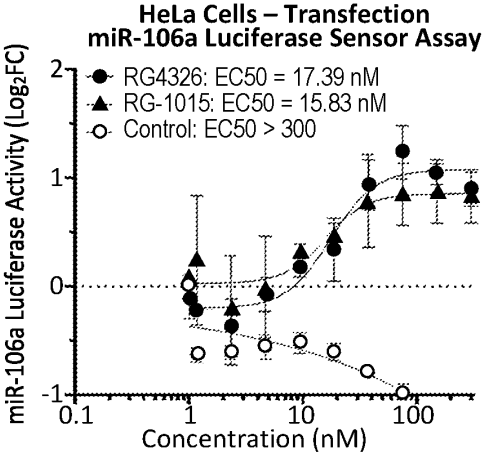


FIG. 4D

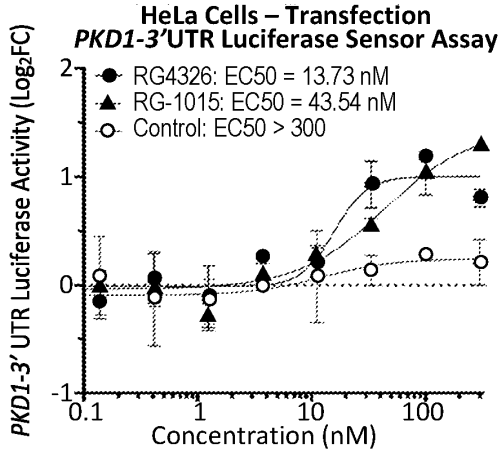


FIG. 4E

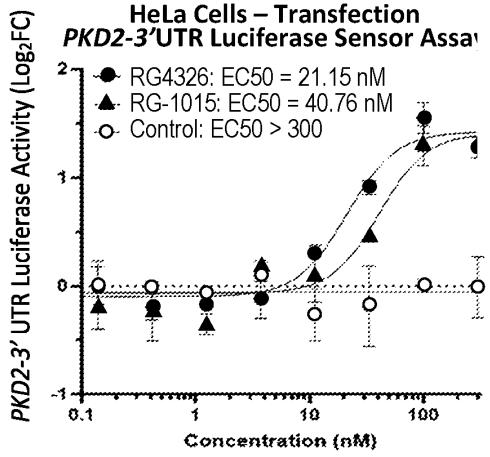


FIG. 4F

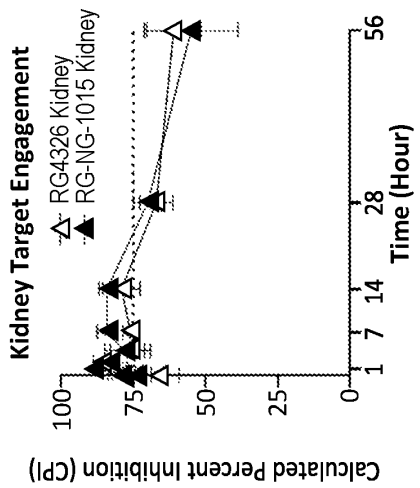


FIG. 5C

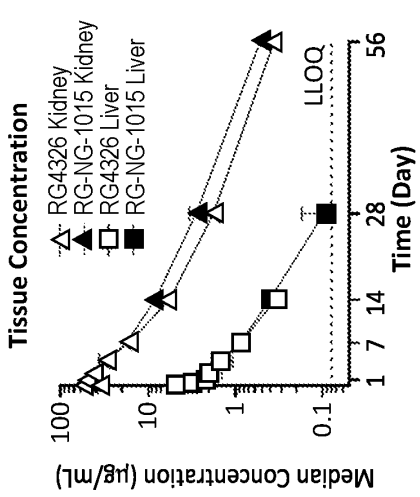


FIG. 5B

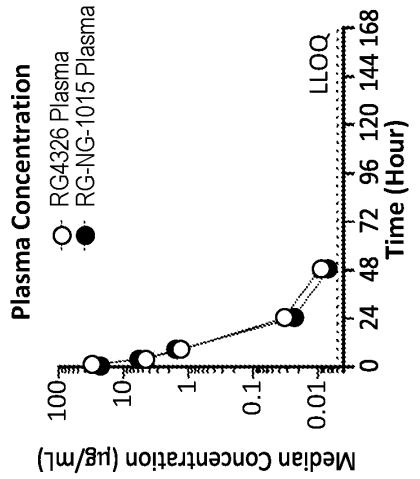


FIG. 5A

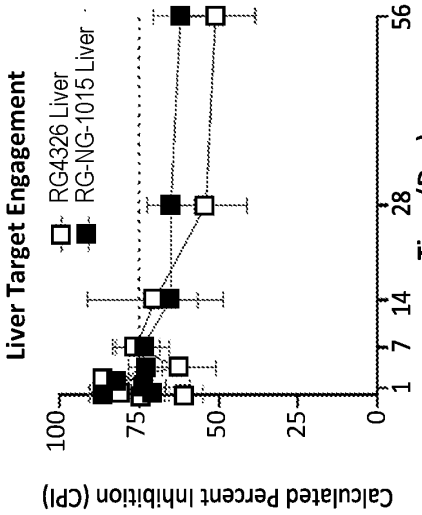


FIG. 5D

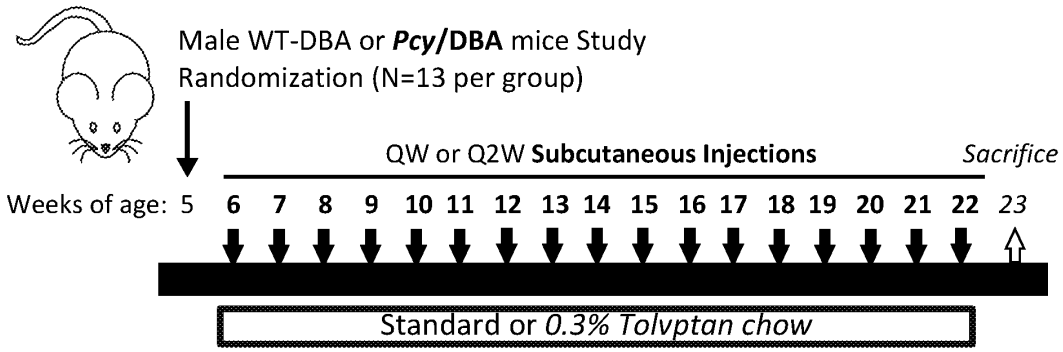


FIG. 6A

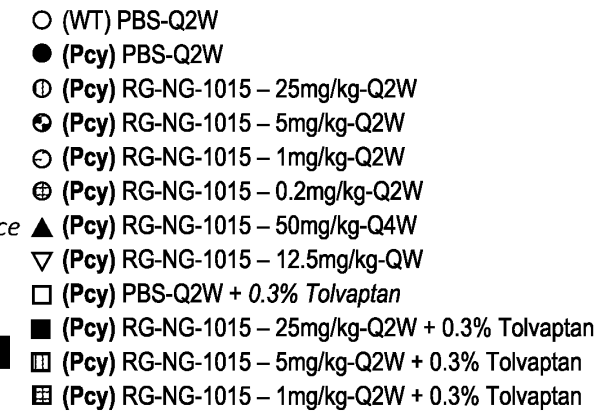


FIG. 6B

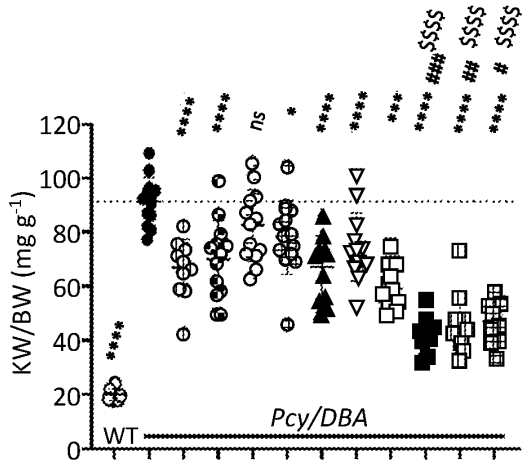


FIG. 6C

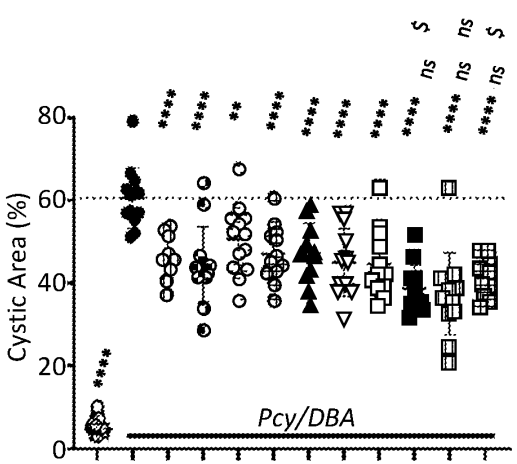


FIG. 6D

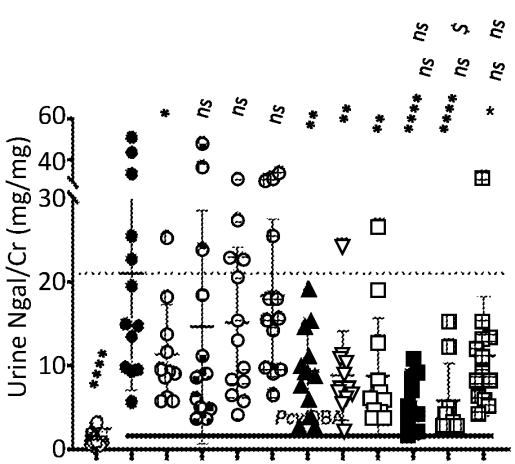


FIG. 6E

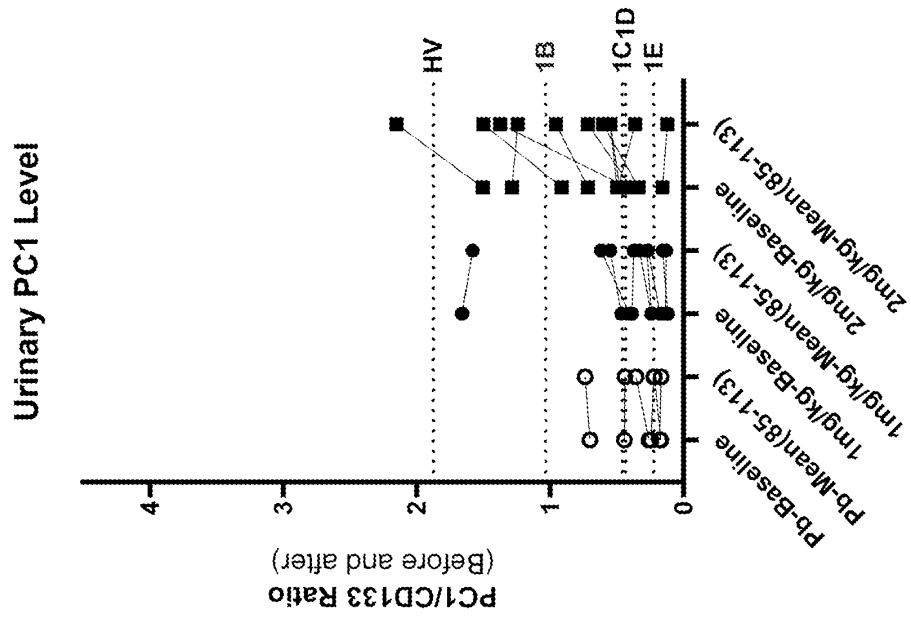

Urinary PC1 Level
PC1/CD133 Ratio
(Before and after)
0
1
2
3
4
HV
1B
1C1D
1E
Pb-Baseline
Pb-Mean(B5-113)
1mg/kg-Baseline
1mg/kg-Mean(B5-113)
2mg/kg-Baseline
2mg/kg-Mean(B5-113)

FIG. 7B

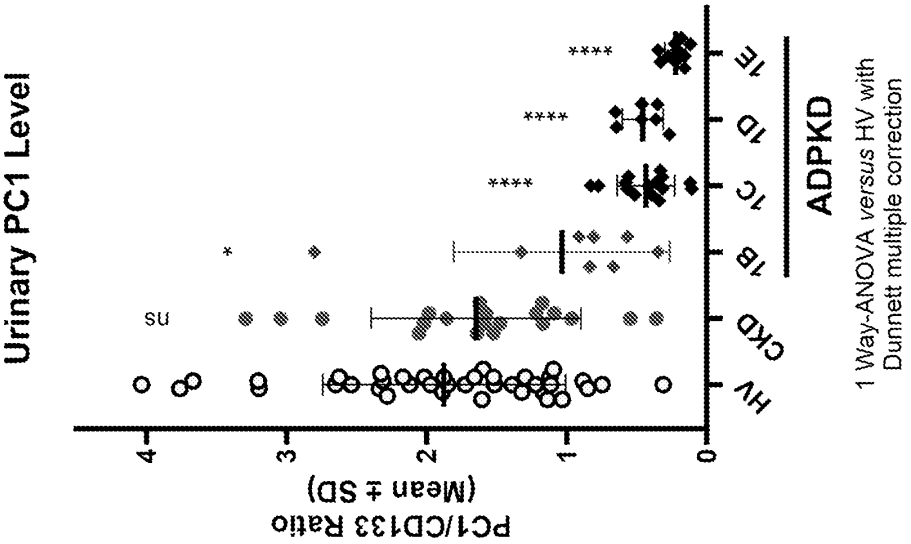

Urinary PC1 Level
PC1/CD133 Ratio
(Mean ± SD)
0
1
2
3
4
HV
CKD
1B
1C
1D
1E
ADPKD
ns
*
****
****
****
1 Way-ANOVA versus HV with
Dunnett multiple correction

FIG. 7A

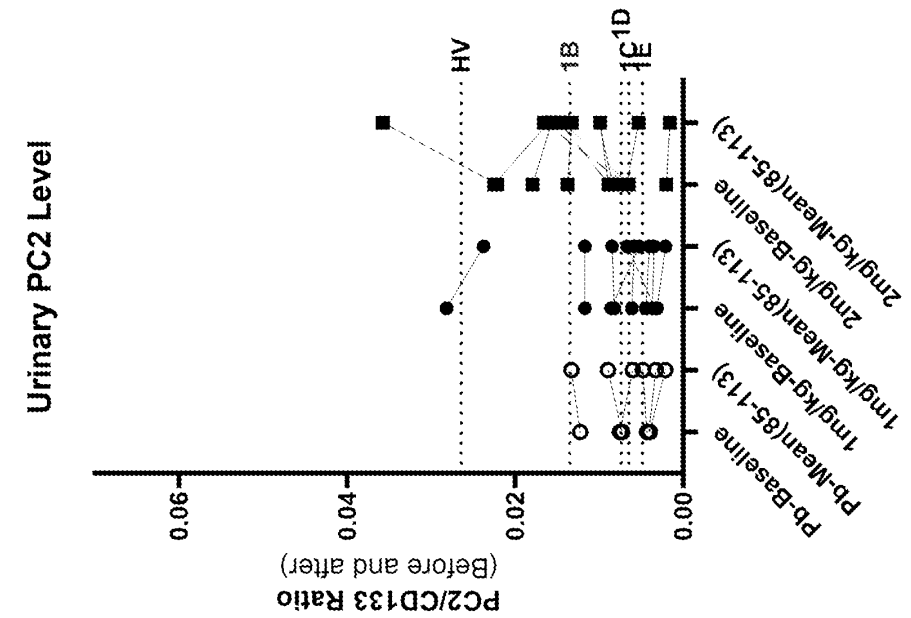

Urinary PC2 Level
PC2/CD133 Ratio
(Before and after)
0.06
0.04
0.02
0.00
HV
1B
1C
1D
1E
Pb-Baseline
Pb-Mean(85-113)
1mg/kg-Baseline
1mg/kg-Mean(85-113)
2mg/kg-Baseline
2mg/kg-Mean(85-113)

FIG. 7D

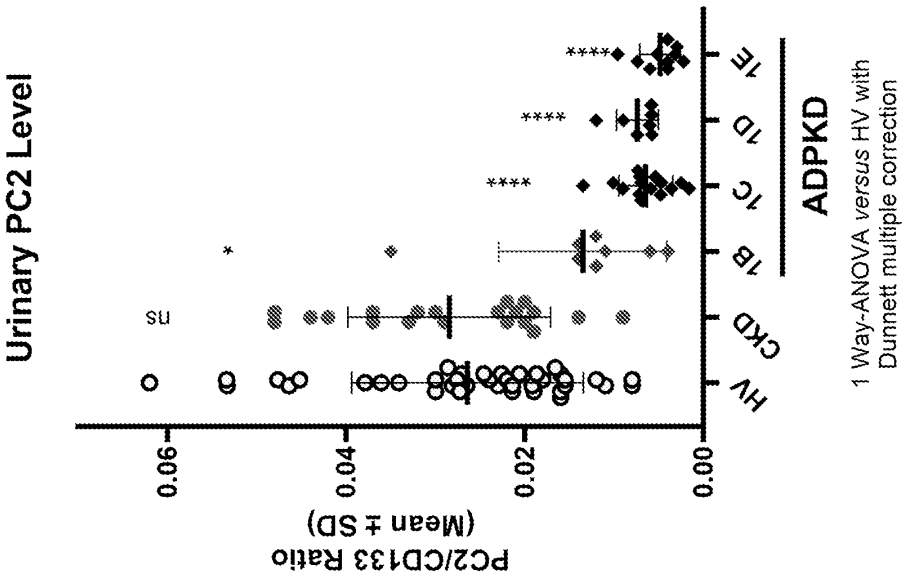

Urinary PC2 Level
PC2/CD133 Ratio
(Mean ± SD)
0.06
0.04
0.02
0.00
HV
CKD
1B
1C
1D
1E
ADPKD
ns
*
****
****
****
1 Way-ANOVA versus HV with
Dunnett multiple correction

FIG. 7C

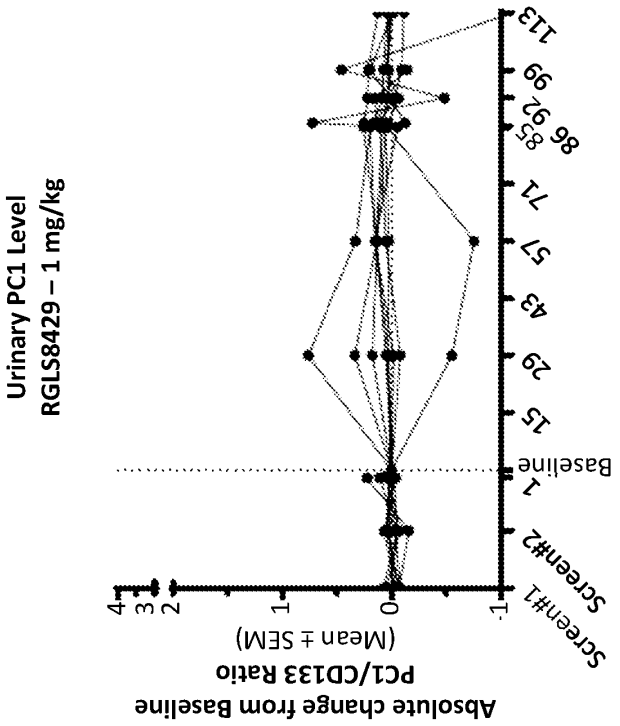

Urinary PC1 Level
RGLS8429 – 1 mg/kg
Absolute change from Baseline
PC1/CD133 Ratio
(Mean ± SEM)
4
3
2
1
0
-1
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
92
99
113
Days

FIG. 8B

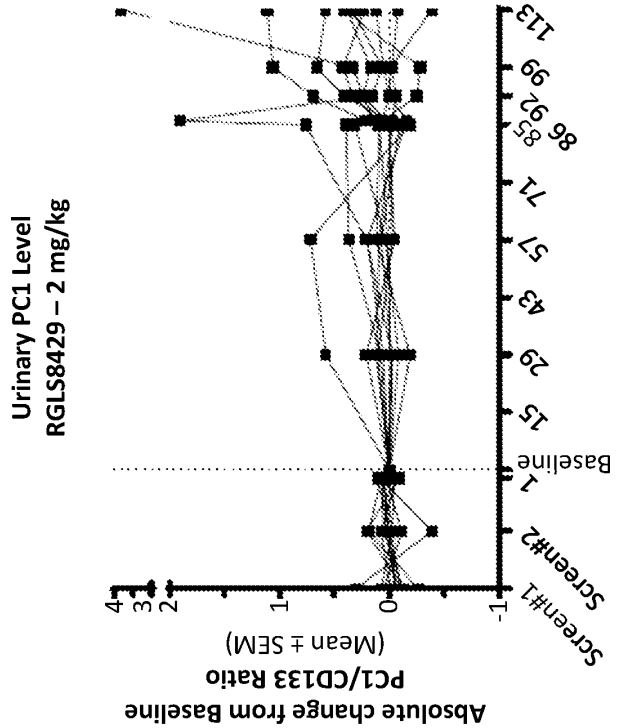

Urinary PC1 Level
RGLS8429 – 2 mg/kg
Absolute change from Baseline
PC1/CD133 Ratio
(Mean ± SEM)
4
3
2
1
0
-1
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
92
99
113
Days

FIG. 8A

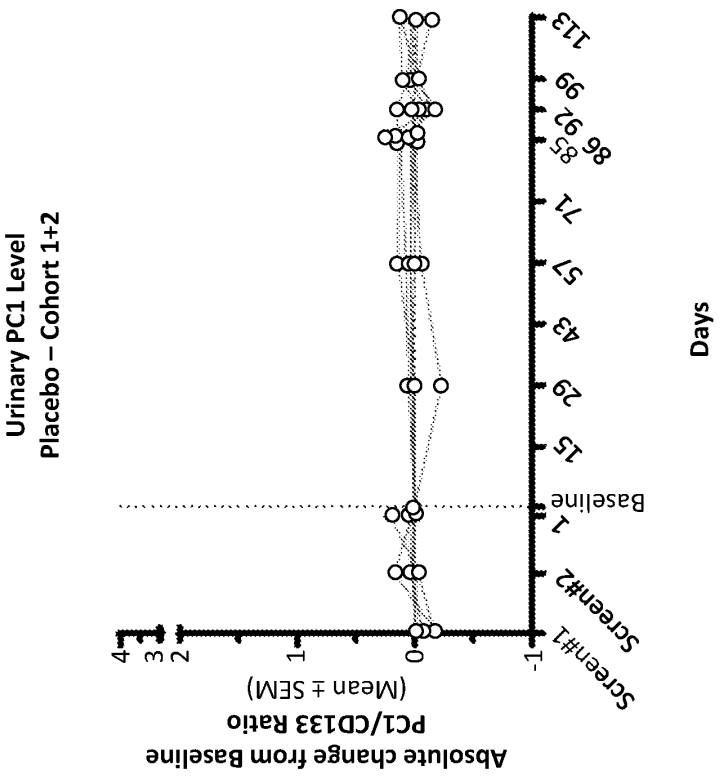

Urinary PC1 Level
Placebo – Cohort 1+2
Absolute change from Baseline
PC1/CD133 Ratio
(Mean ± SEM)
4
3
2
1
0
-1
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
86
92
99
113
Days

FIG. 8C

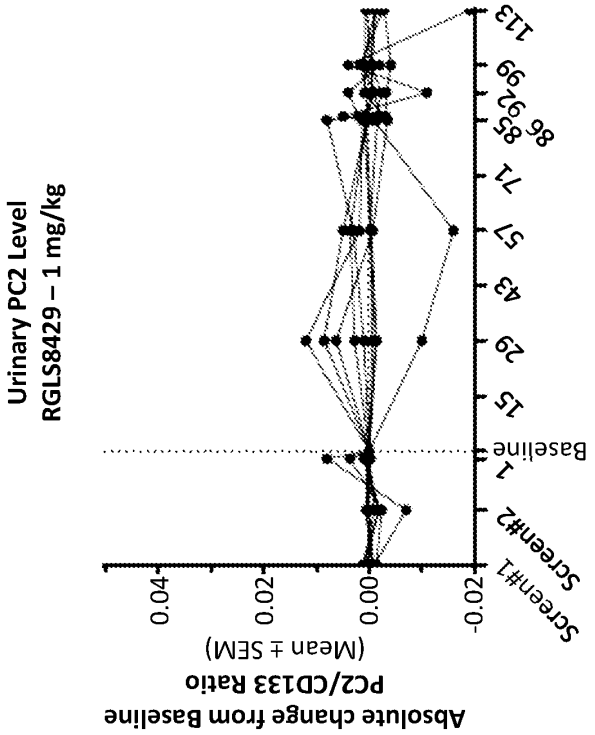

Urinary PC2 Level
RGLS8429 – 1 mg/kg
Absolute change from Baseline
PC2/CD133 Ratio
(Mean ± SEM)
0.04
0.02
0.00
-0.02
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
92
99
113
Days

FIG. 9B

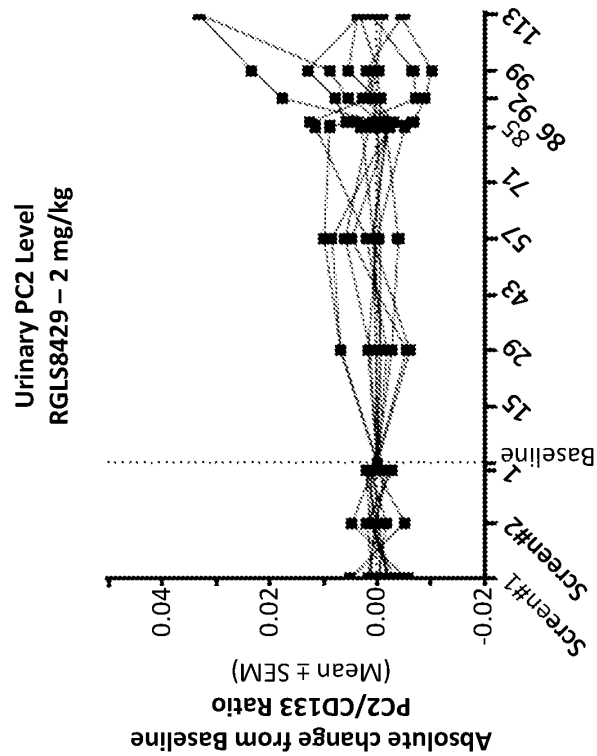

Urinary PC2 Level
RGLS8429 – 2 mg/kg
Absolute change from Baseline
PC2/CD133 Ratio
(Mean ± SEM)
0.04
0.02
0.00
-0.02
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
92
99
113
Days

FIG. 9A

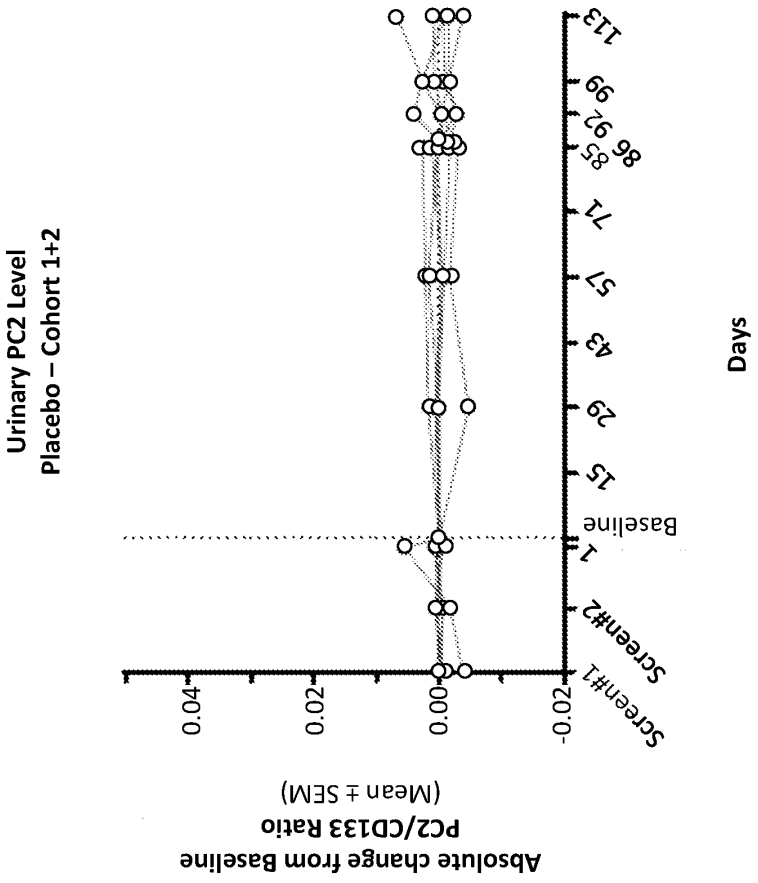

Urinary PC2 Level
Placebo – Cohort 1+2
Absolute change from Baseline
PC2/CD133 Ratio
(Mean ± SEM)
0.04
0.02
0.00
-0.02
Screen#1
Screen#2
1
Baseline
15
29
43
57
71
85
86
92
99
113
Days

FIG. 9C

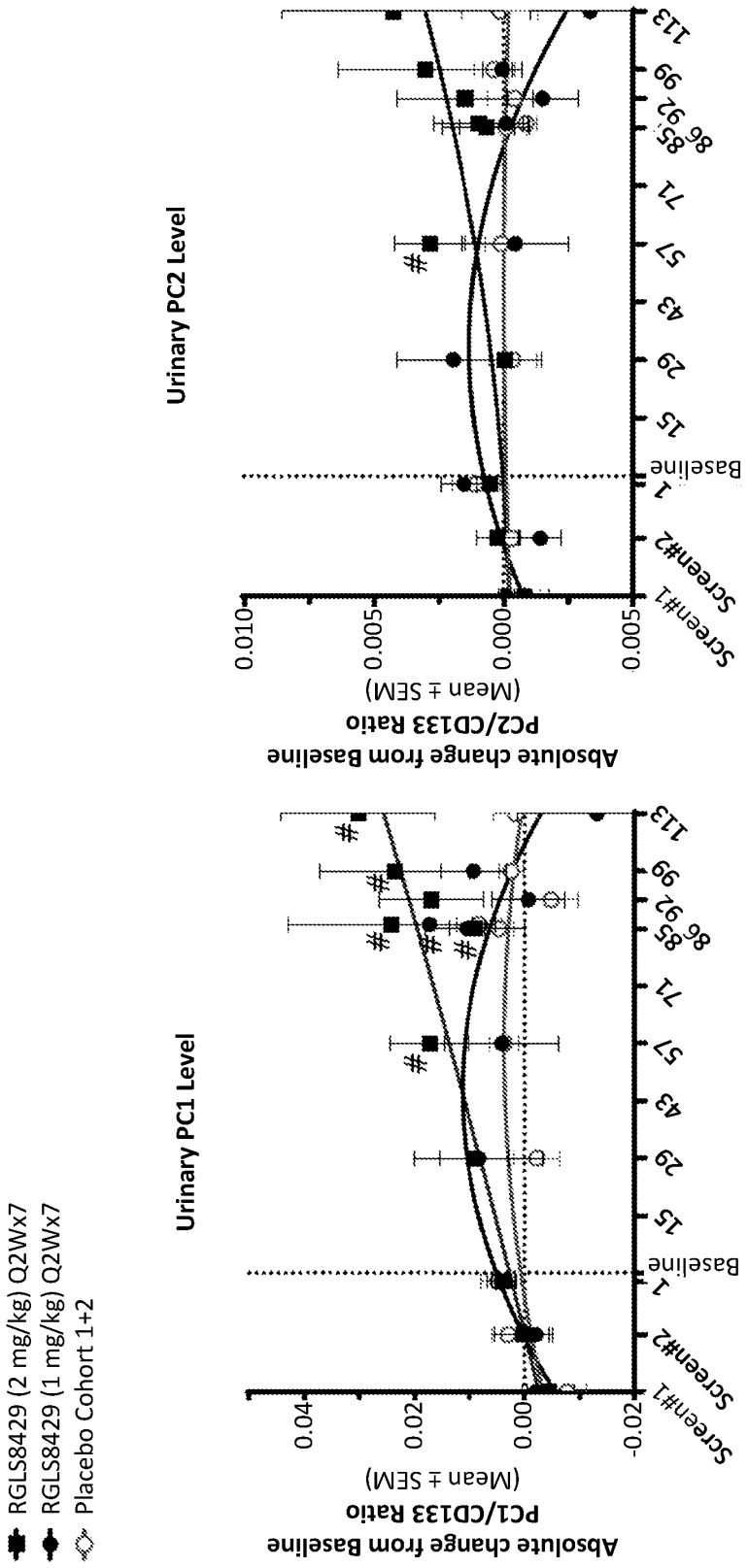


FIG. 10A

FIG. 10B

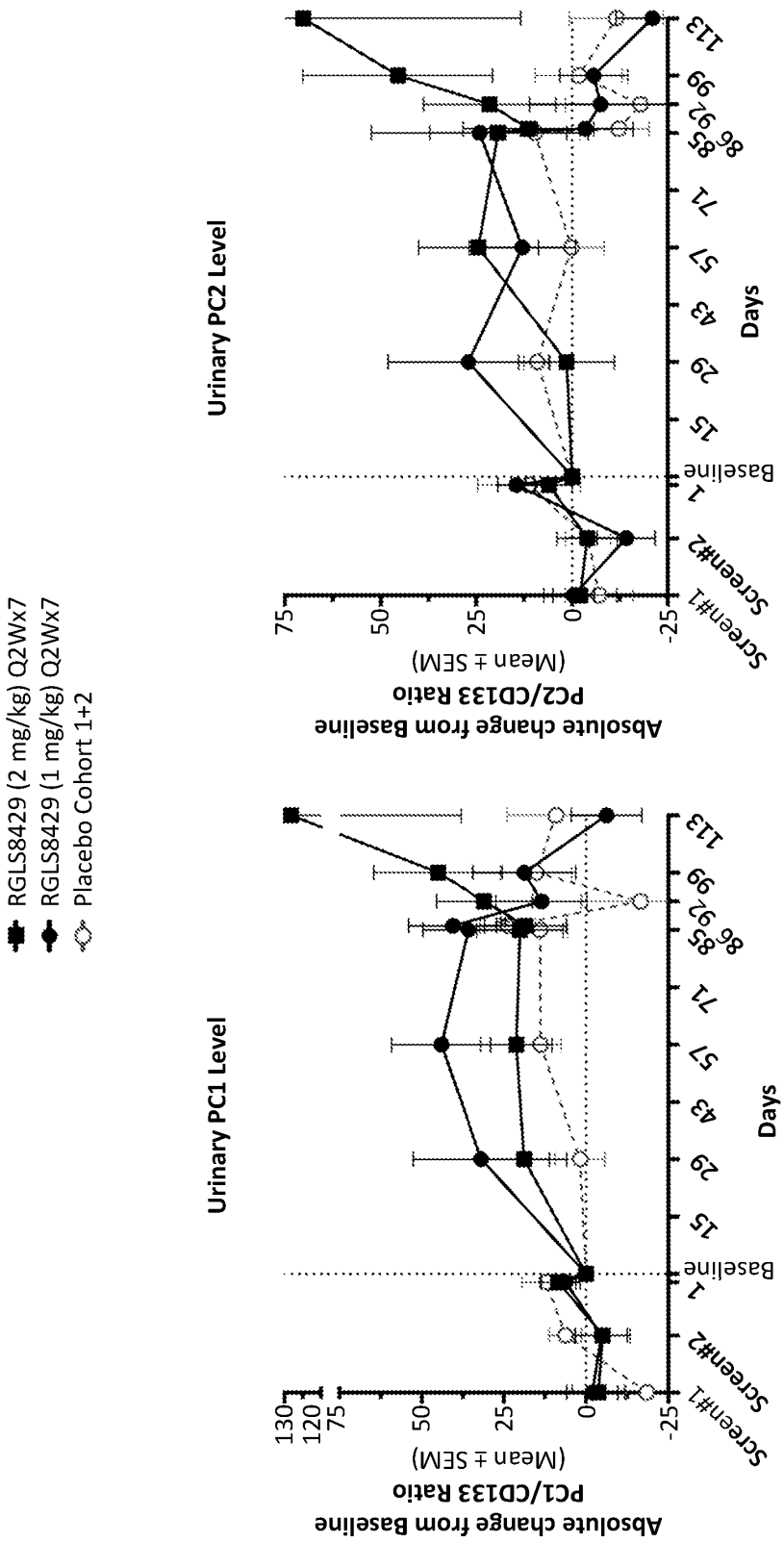


FIG. 11A

FIG. 11B

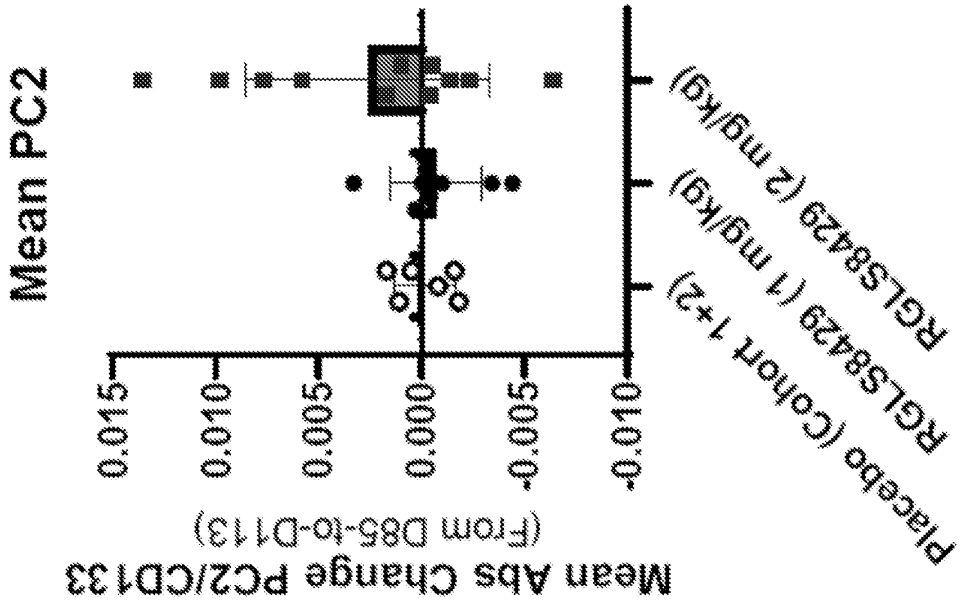


FIG. 12B

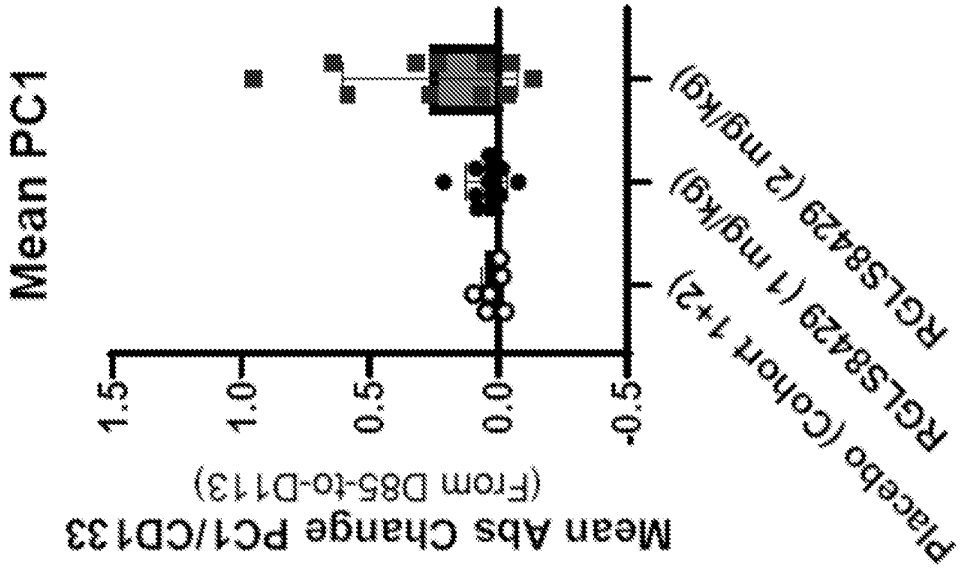


FIG. 12A

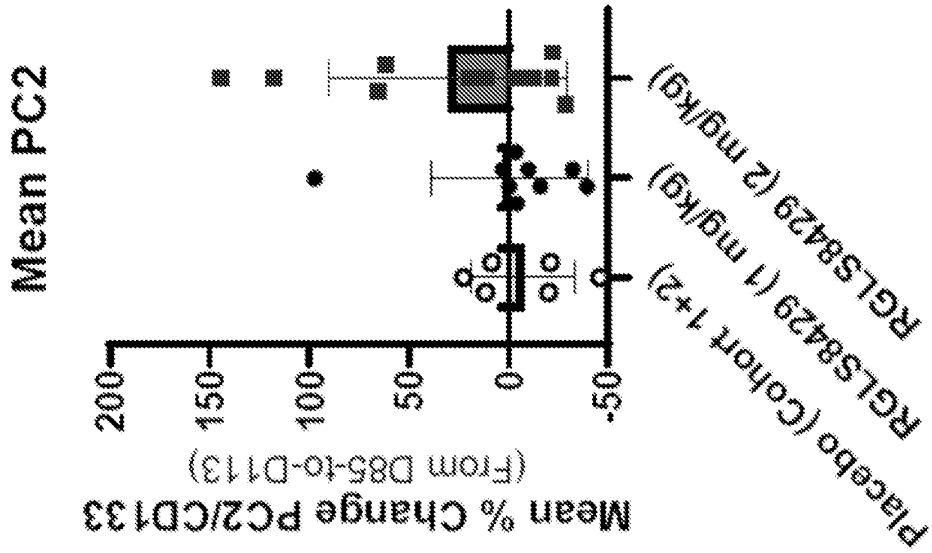


FIG. 13B

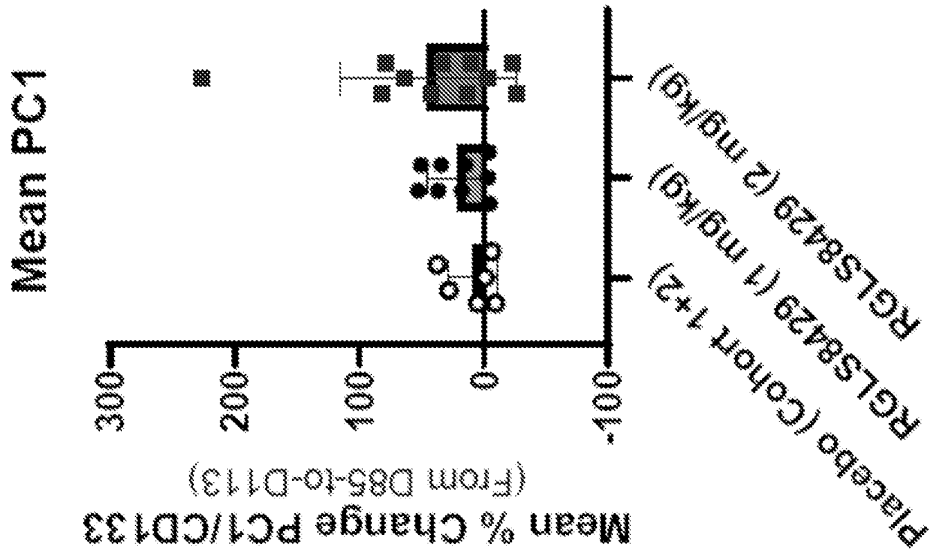


FIG. 13A

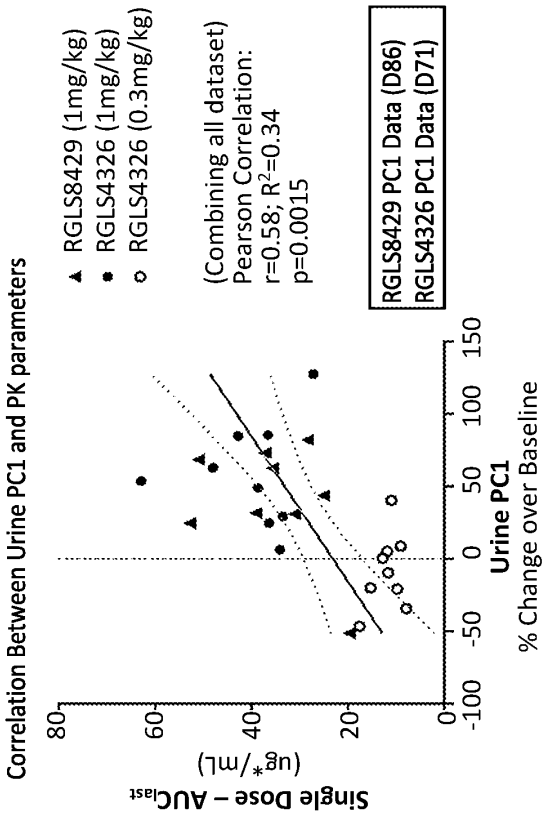


FIG. 14B

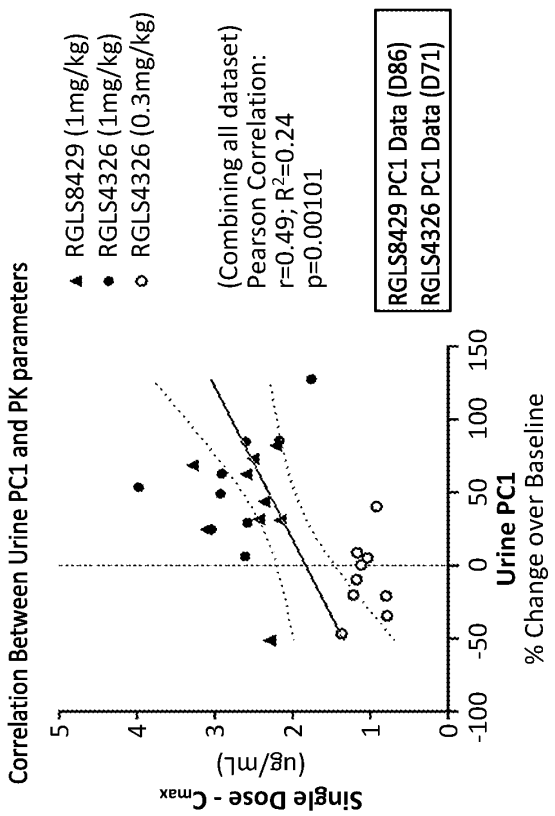


FIG. 14A

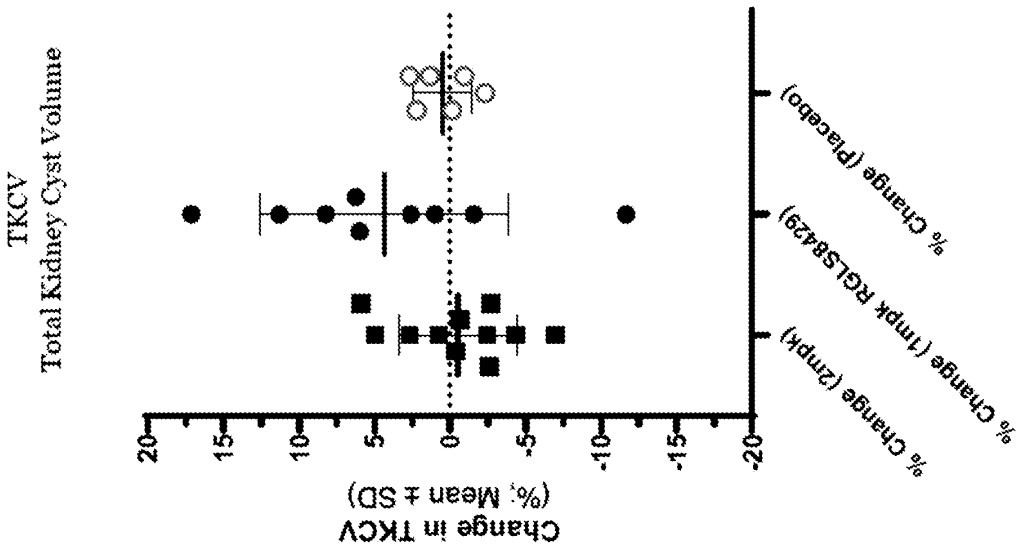


FIG. 15B

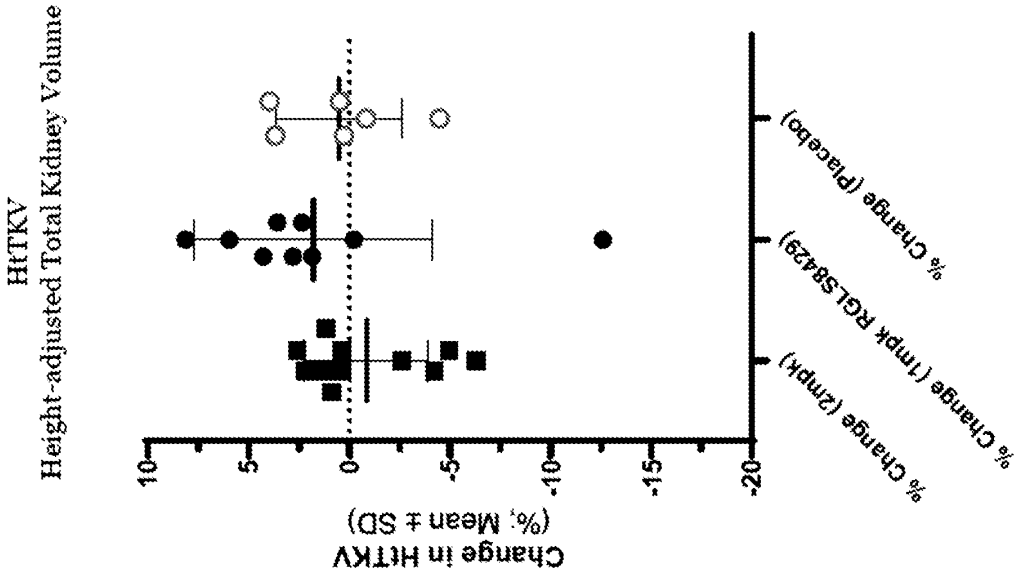


FIG. 15A

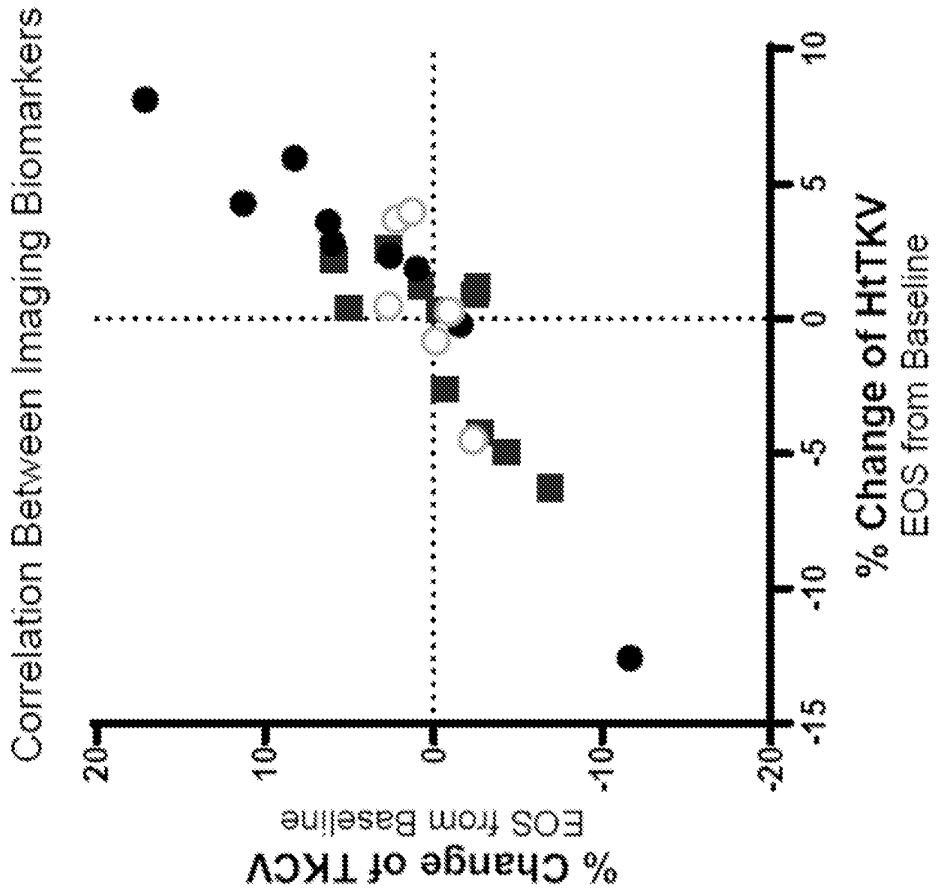

Correlation Between Imaging Biomarkers
% Change of HtTKV
EOS from Baseline
10
5
0
-5
-10
-15
% Change of TKCV
EOS from Baseline
20
10
0
-10
-20

FIG. 15C

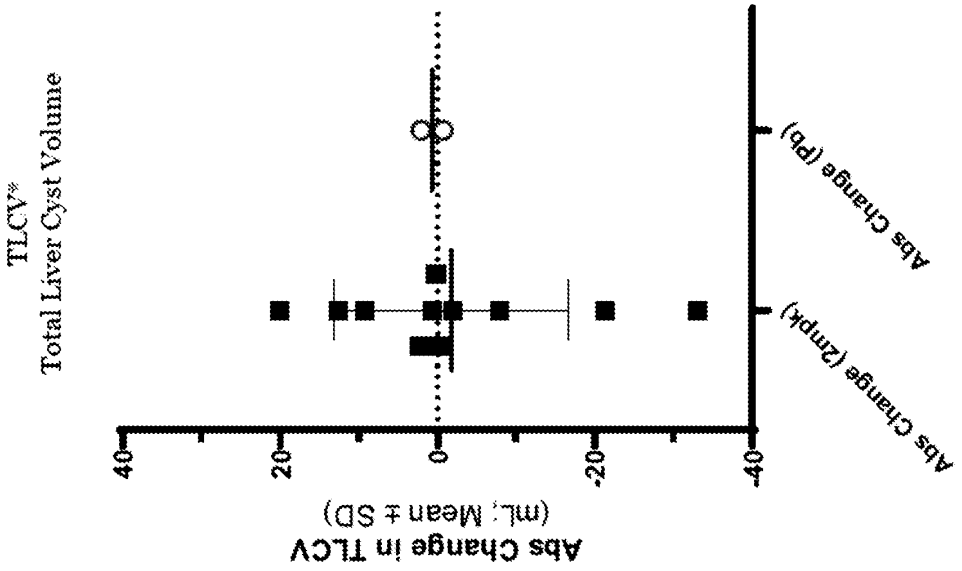


FIG. 16B

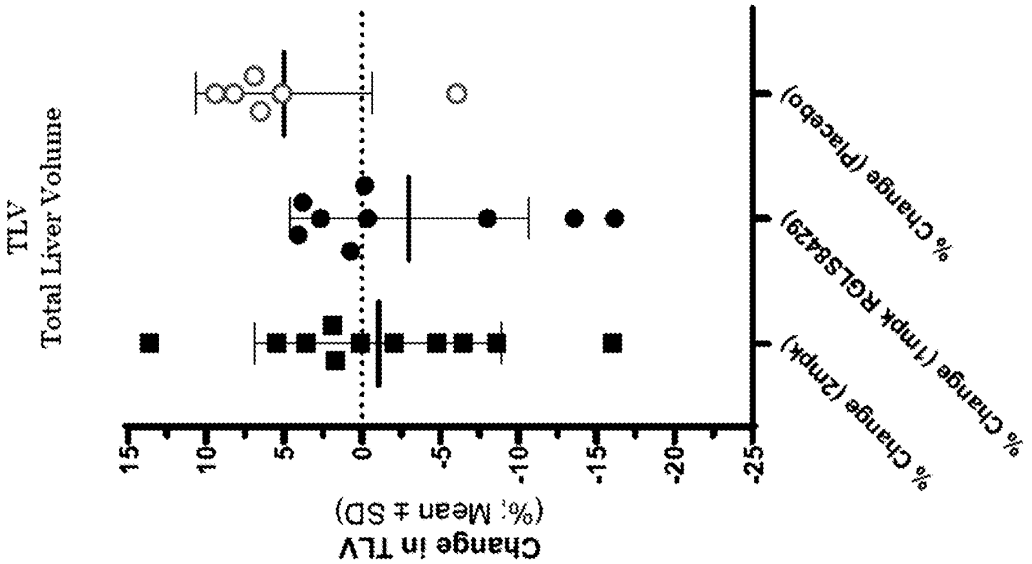


FIG. 16A

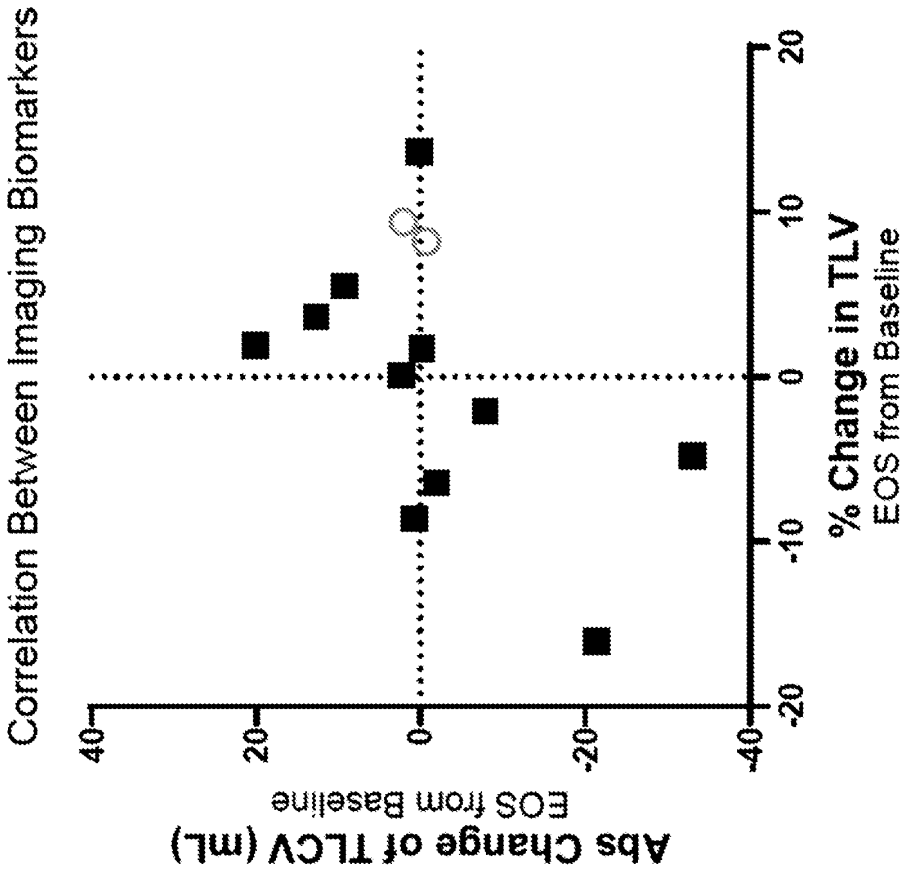

Correlation Between Imaging Biomarkers
Abs Change of TLCV (mL)
EOS from Baseline
40
20
0
-20
-40
% Change in TLV
EOS from Baseline
20
10
0
-10
-20

FIG. 16C

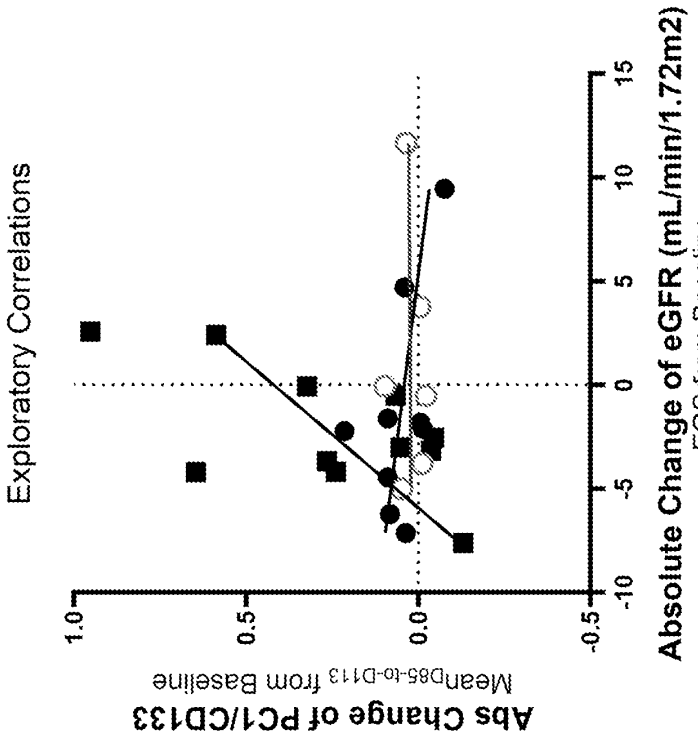


FIG. 17B

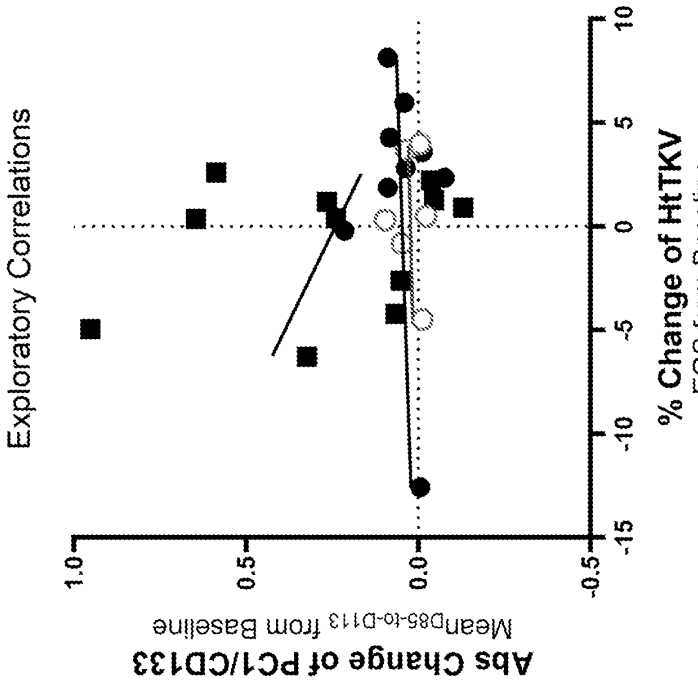


FIG. 17A

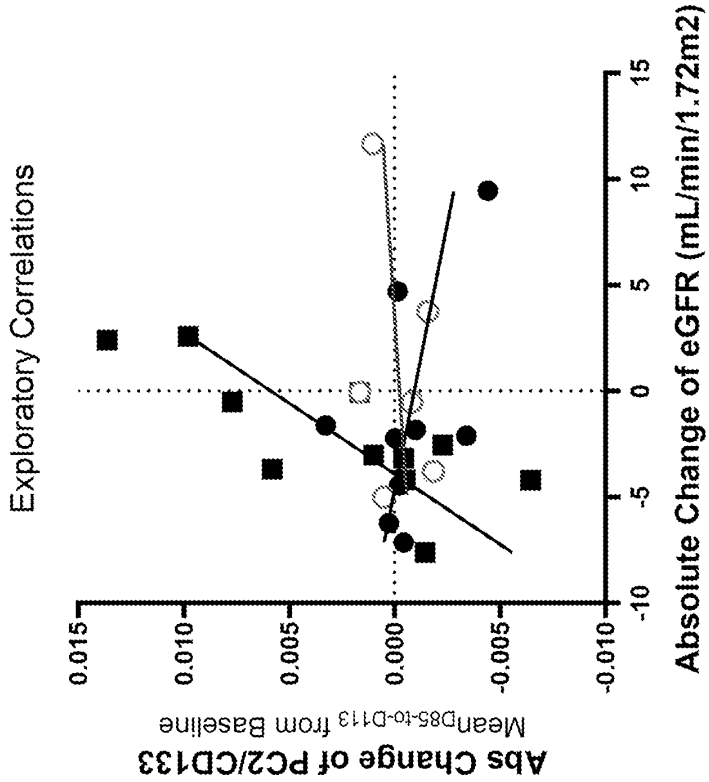


FIG. 17D

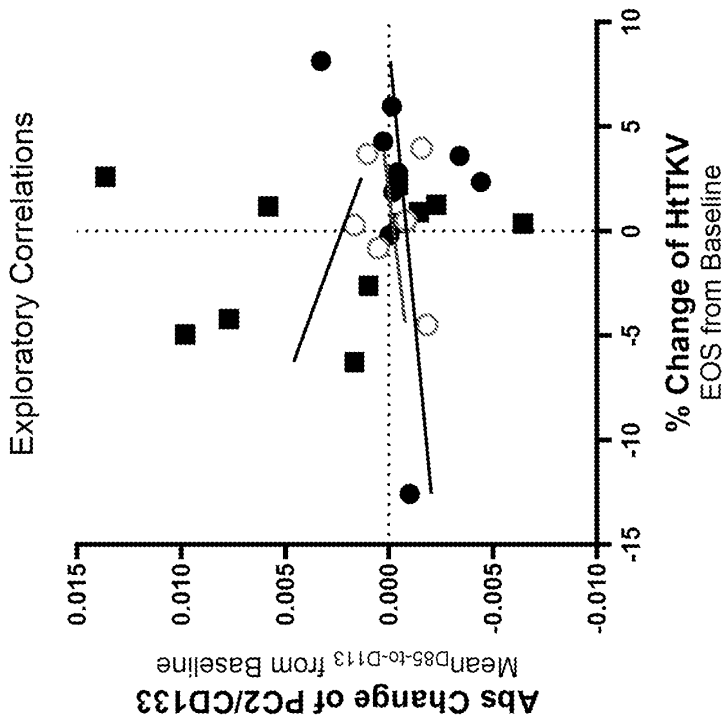


FIG. 17C

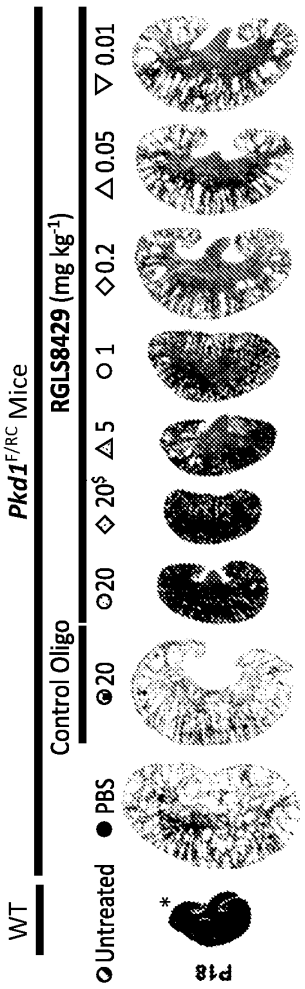


FIG. 18A

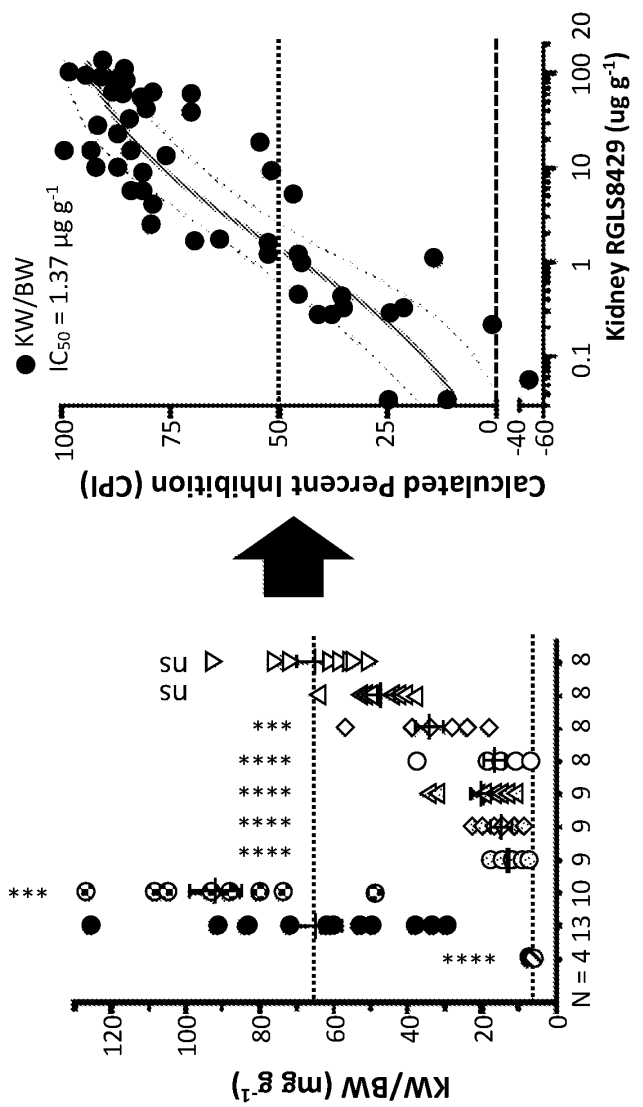


FIG. 18B

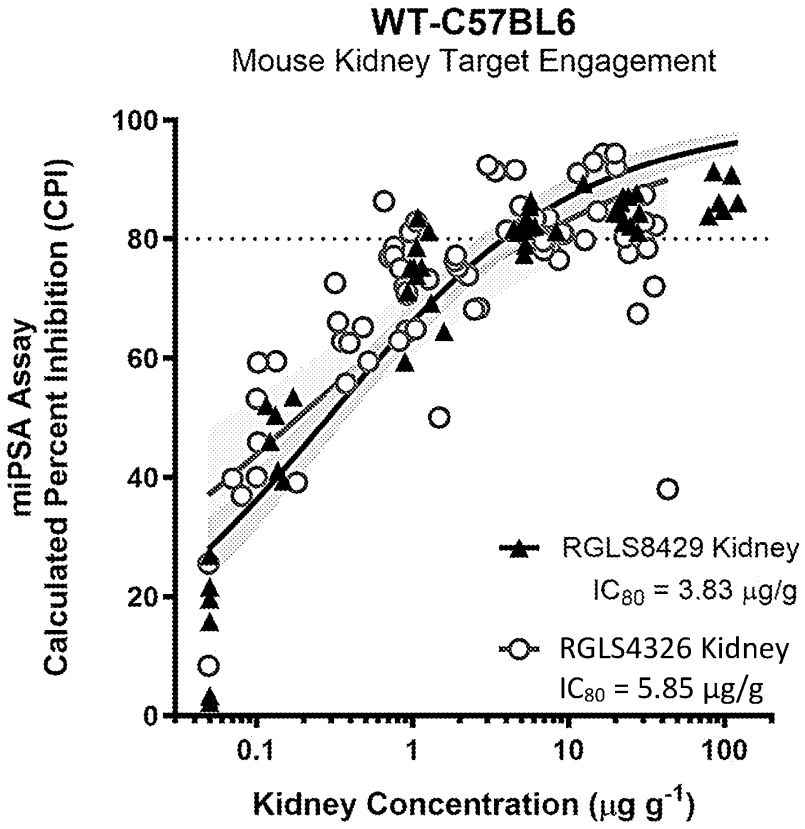

WT-C57BL6
Mouse Kidney Target Engagement
miPSA Assay
Calculated Percent Inhibition (CPI)
100
80
60
40
20
0
0.1
1
10
100
Kidney Concentration (μg g-1)
RGLS8429 Kidney
IC80 = 3.83 μg/g
RGLS4326 Kidney
IC80 = 5.85 μg/g

FIG. 18C

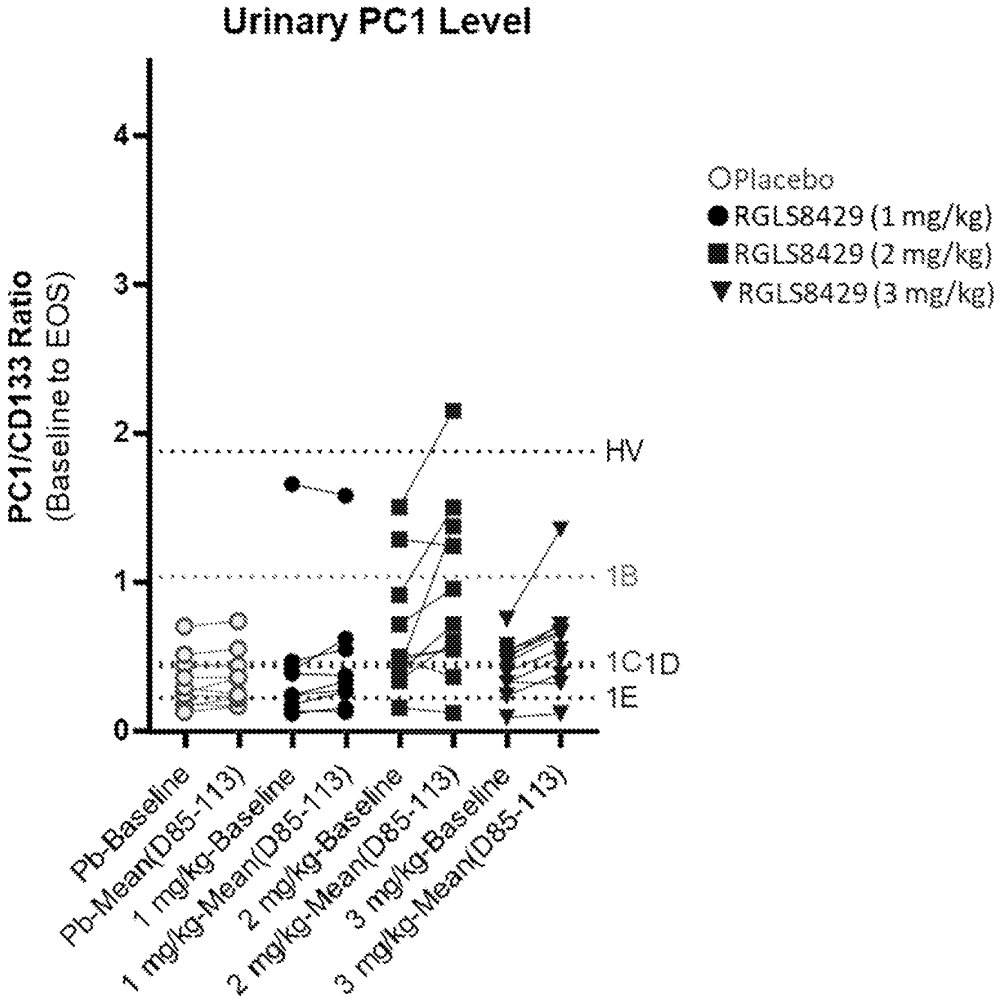

Urinary PC1 Level
PC1/CD133 Ratio
(Baseline to EOS)
4
3
2
1
0
HV
1B
1C1D
1E
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
Pb-Baseline
Pb-Mean(D85-113)
1 mg/kg-Baseline
1 mg/kg-Mean(D85-113)
2 mg/kg-Baseline
2 mg/kg-Mean(D85-113)
3 mg/kg-Baseline
3 mg/kg-Mean(D85-113)

FIG. 19A

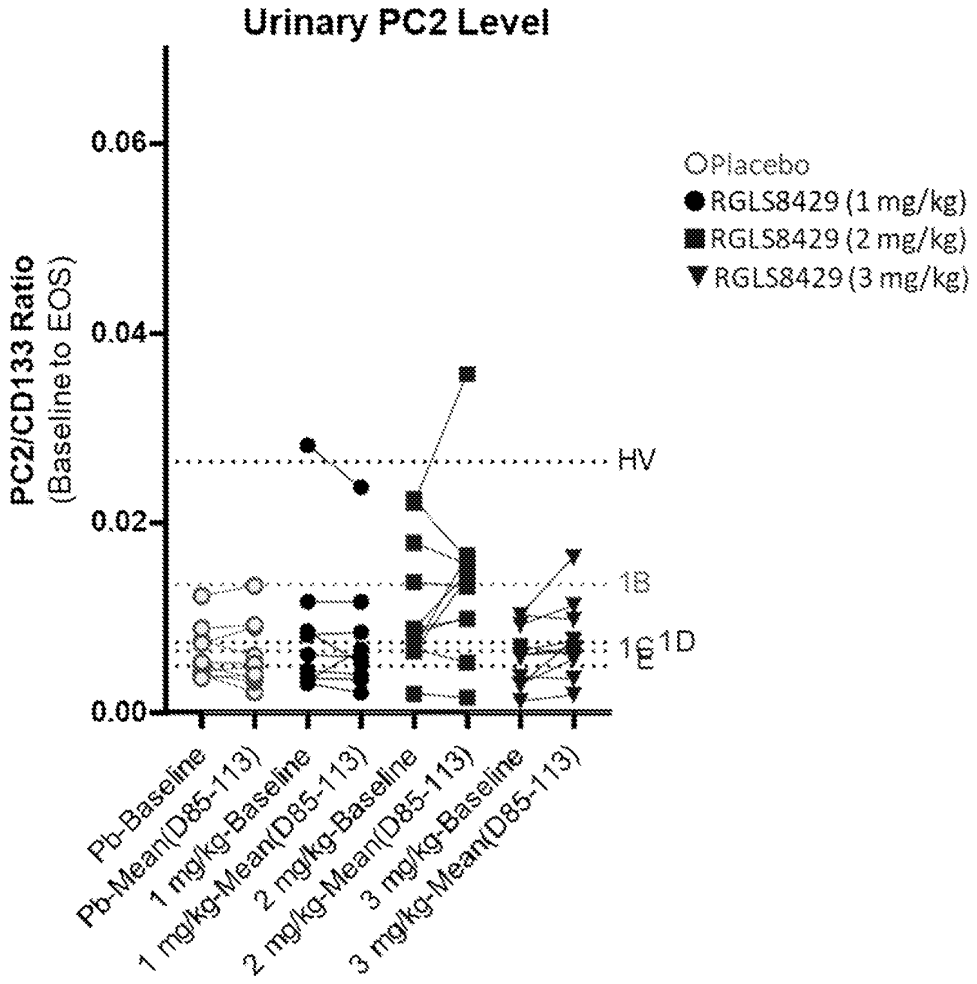

Urinary PC2 Level
PC2/CD133 Ratio
(Baseline to EOS)
0.06
0.04
0.02
0.00
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
HV
1B
1C
1D
Pb-Baseline
Pb-Mean(D85-113)
1 mg/kg-Baseline
1 mg/kg-Mean(D85-113)
2 mg/kg-Baseline
2 mg/kg-Mean(D85-113)
3 mg/kg-Baseline
3 mg/kg-Mean(D85-113)

FIG. 19B

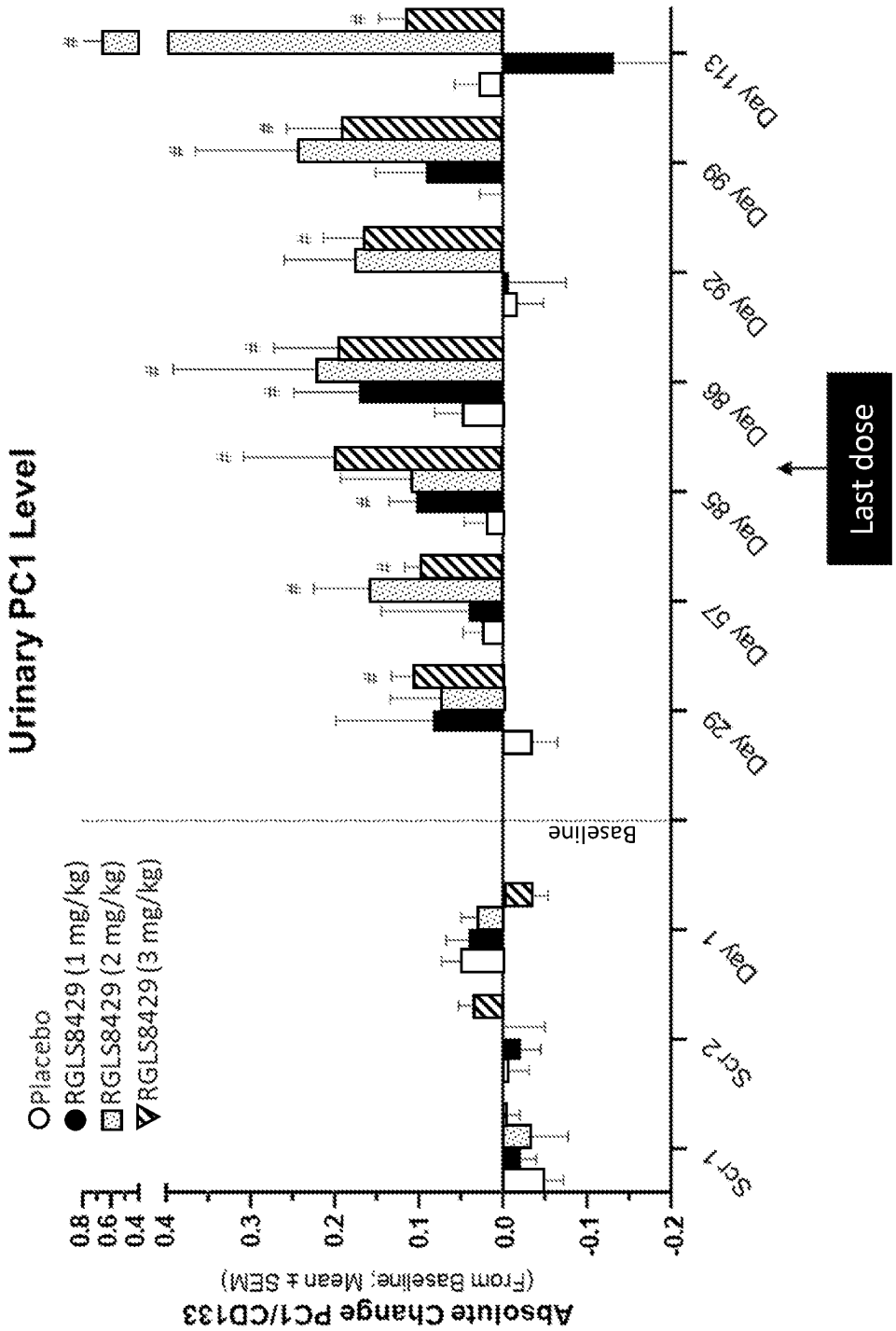

Urinary PC1 Level
Absolute Change PC1/CD133
(From Baseline; Mean ± SEM)
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
Baseline
Last dose
Scr 1
Scr 2
Day 1
Day 29
Day 57
Day 85
Day 86
Day 92
Day 99
Day 113
0.8
0.6
0.4
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2

FIG. 20A

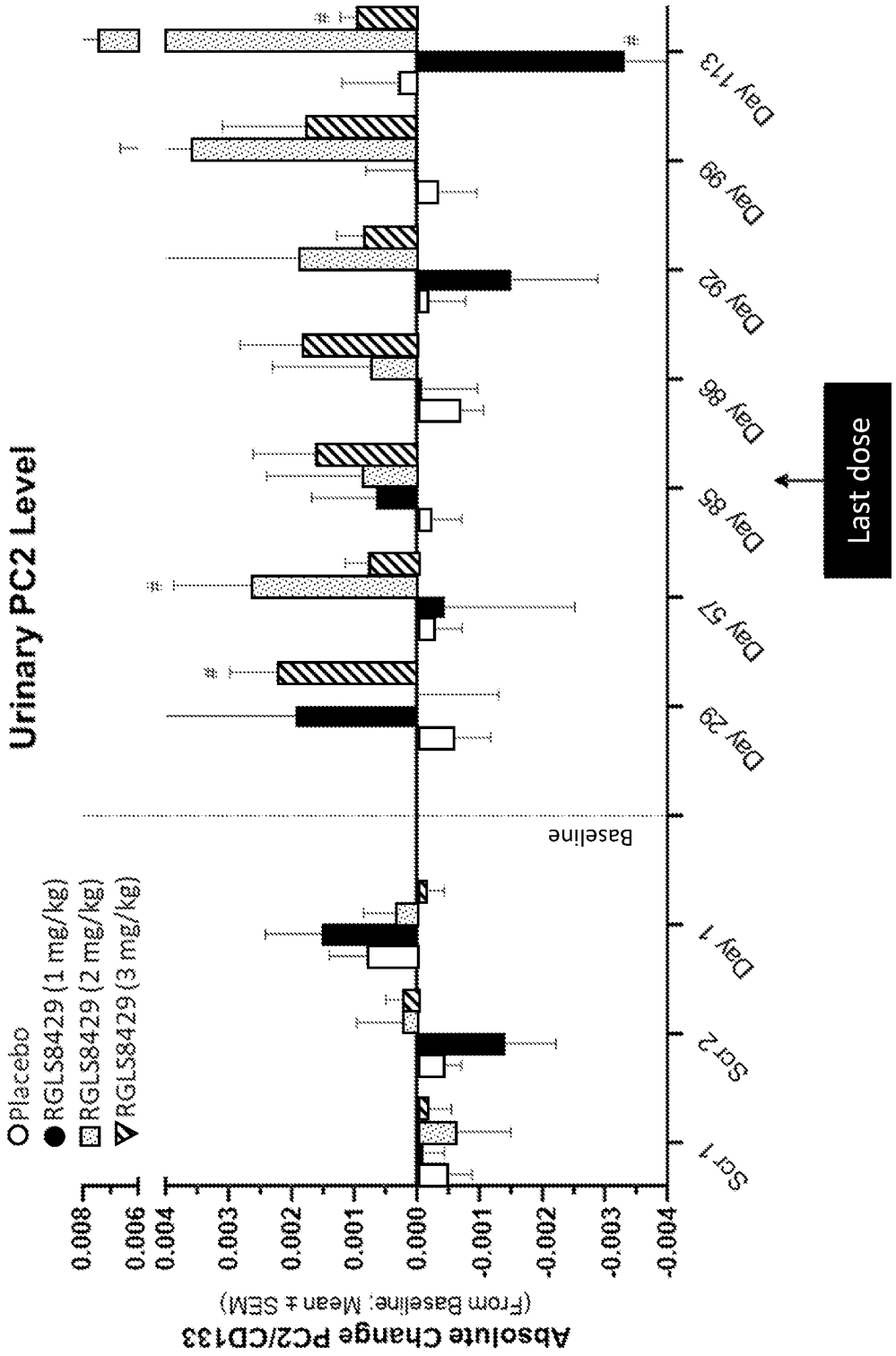

Urinary PC2 Level
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
Absolute Change PC2/CD133
(From Baseline: Mean ± SEM)
0.008
0.006
0.004
0.003
0.002
0.001
0.000
-0.001
-0.002
-0.003
-0.004
Scr 1
Scr 2
Day 1
Baseline
Day 29
Day 57
Day 85
Day 86
Day 92
Day 99
Day 113
Last dose

FIG. 20B

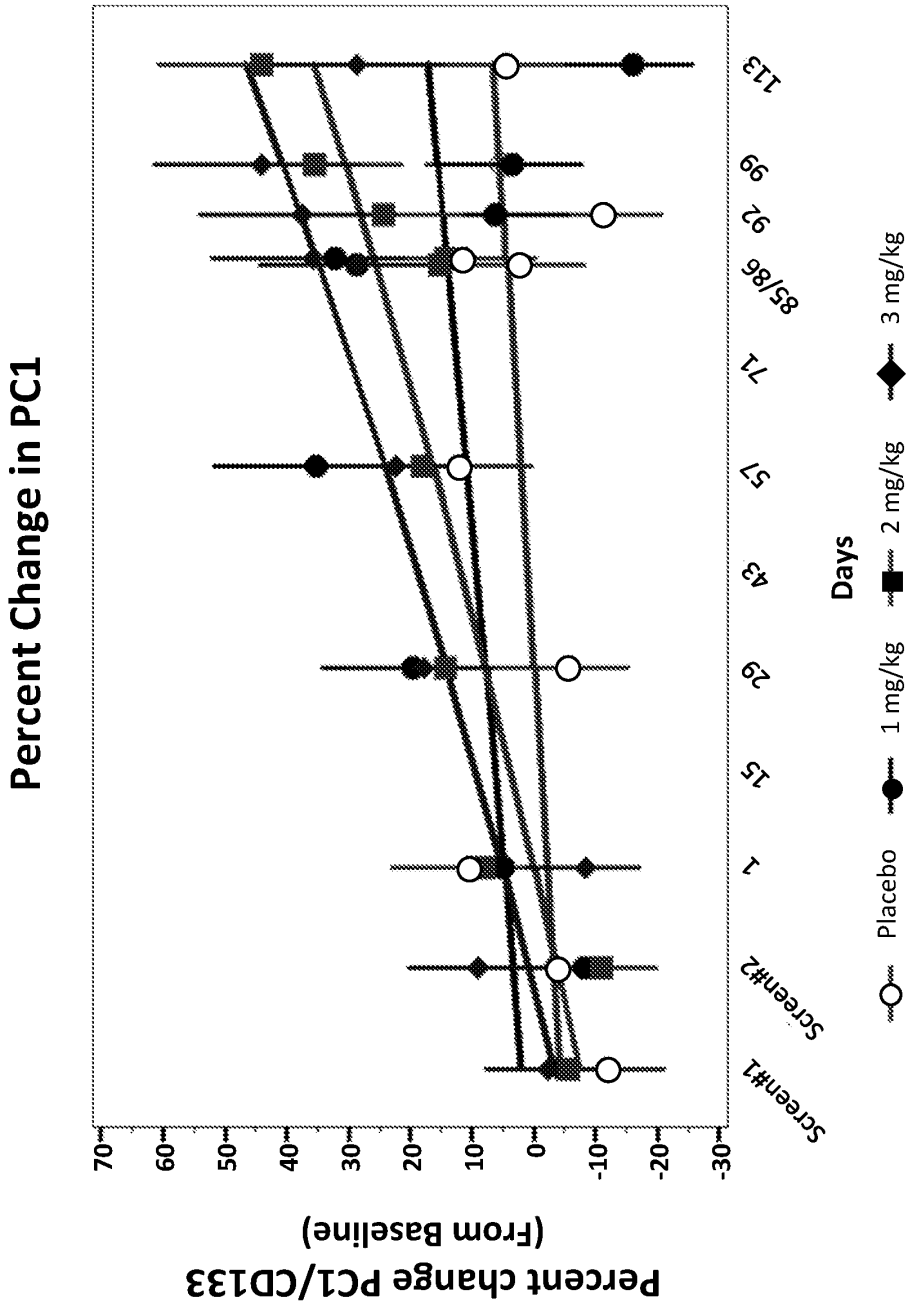

Percent Change in PC1
Percent change PC1/CD133
(From Baseline)
70
60
50
40
30
20
10
0
-10
-20
-30
Screen#1
Screen#2
1
15
29
43
57
71
85/86
92
99
113
Days
Placebo
1 mg/kg
2 mg/kg
3 mg/kg

FIG. 21A

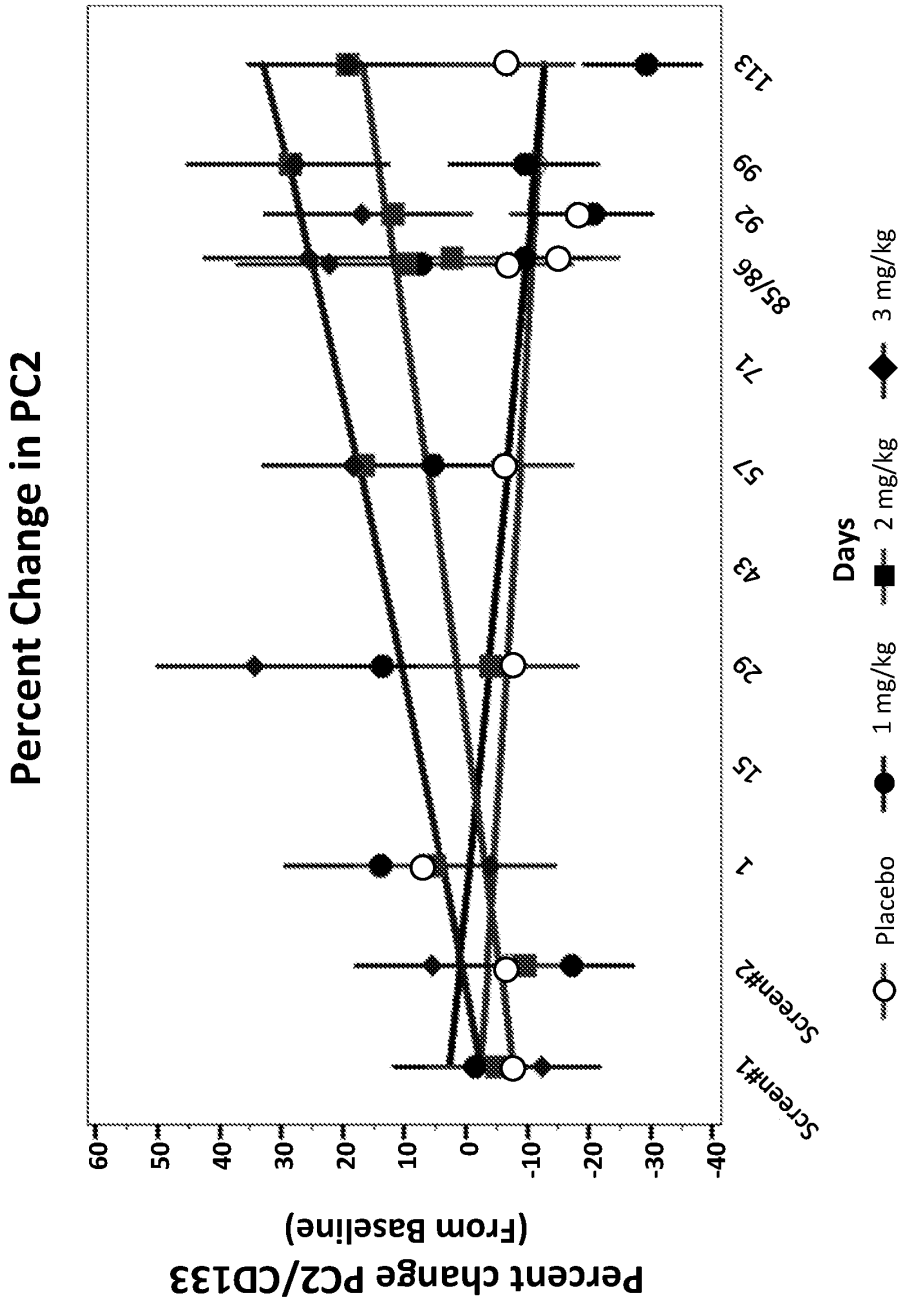

Percent Change in PC2
Percent change PC2/CD133
(From Baseline)
60
50
40
30
20
10
0
-10
-20
-30
-40
Screen#1
Screen#2
1
15
29
43
57
71
85/86
92
99
113
Days
Placebo
1 mg/kg
2 mg/kg
3 mg/kg

FIG. 21B

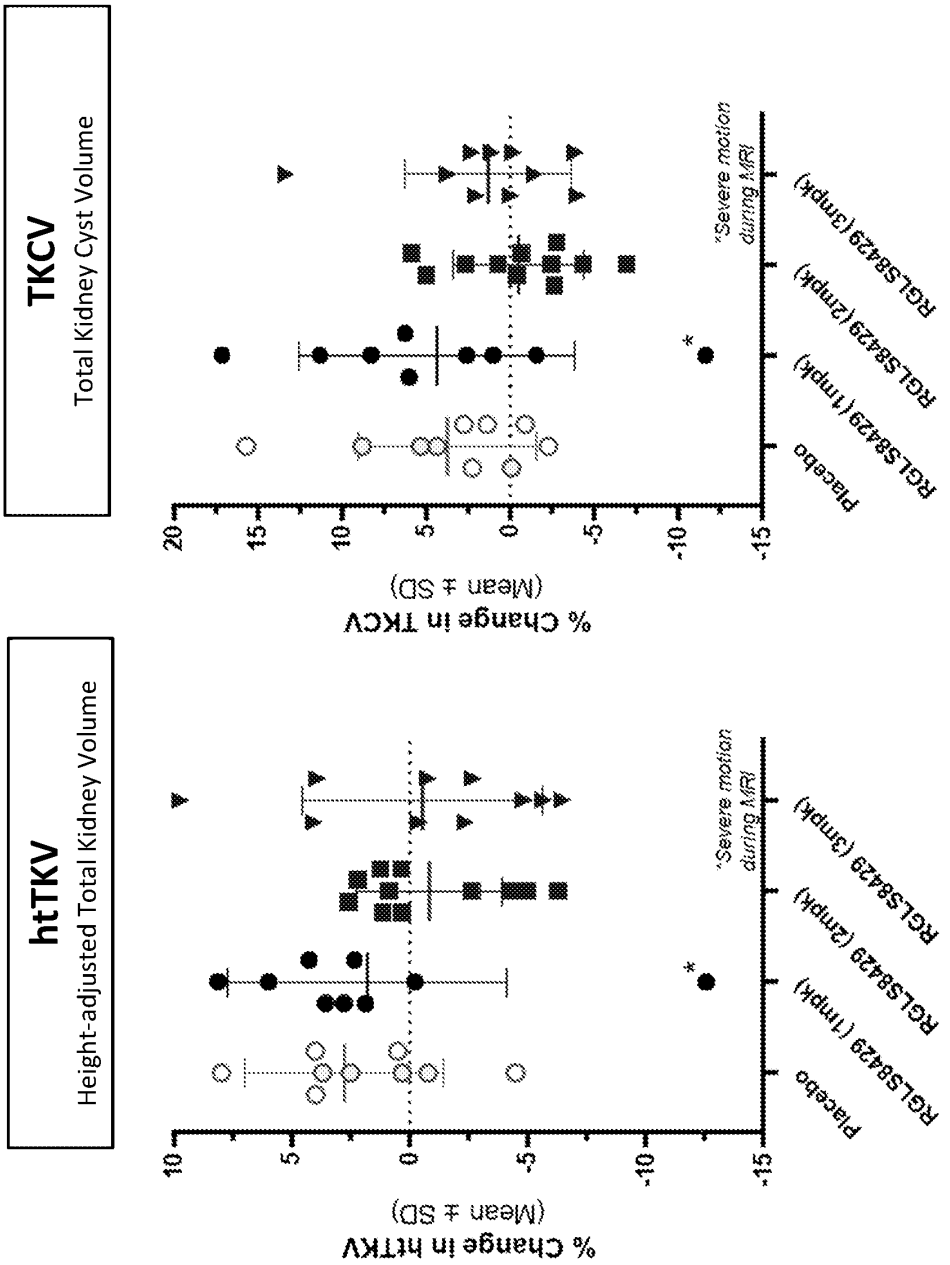


FIG. 22B

FIG. 22A

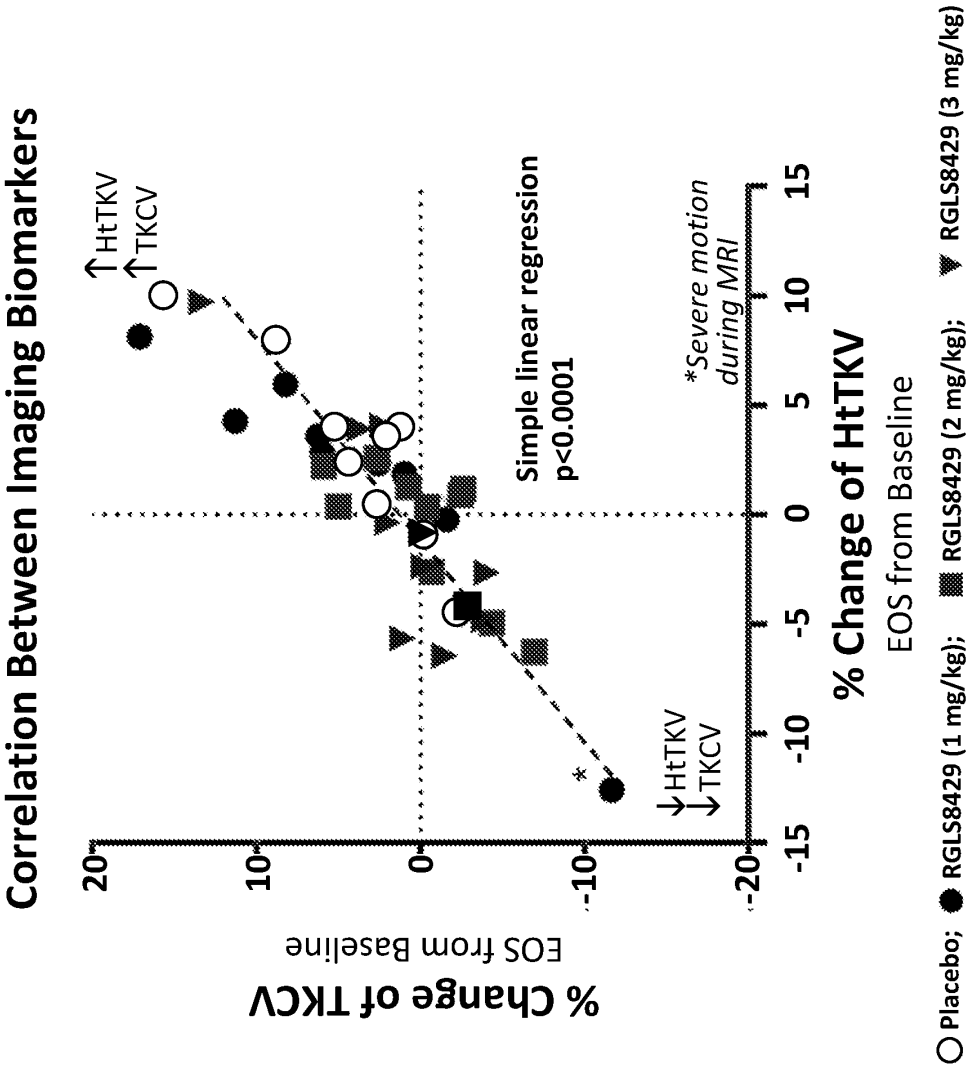

Correlation Between Imaging Biomarkers
↑HtTKV
↑TKCV
Simple linear regression
p<0.0001
*Severe motion during MRI
↓HtTKV
↓TKCV
% Change of TKCV
EOS from Baseline
% Change of HtTKV
EOS from Baseline
20
10
0
-10
-20
-15
-10
-5
0
5
10
15
Placebo; RGLS8429 (1 mg/kg); RGLS8429 (2 mg/kg); RGLS8429 (3 mg/kg)

FIG. 22C

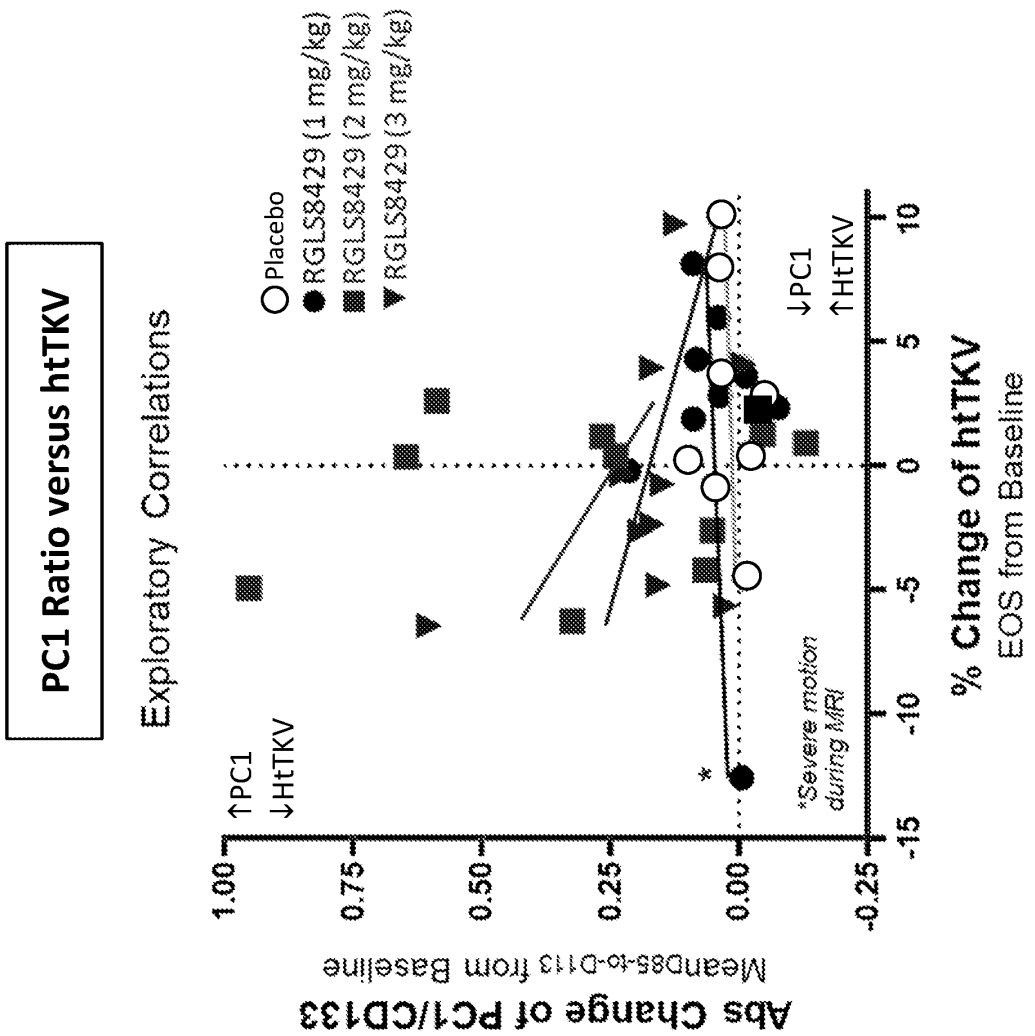

PC1 Ratio versus htTKV
Exploratory Correlations
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
↑PC1
↓HtTKV
↓PC1
↑HtTKV
*Severe motion during MRI
Abs Change of PC1/CD133
MeanD85-to-D113 from Baseline
% Change of htTKV
EOS from Baseline
1.00
0.75
0.50
0.25
0.00
-0.25
-15
-10
-5
0
5
10

FIG. 23A

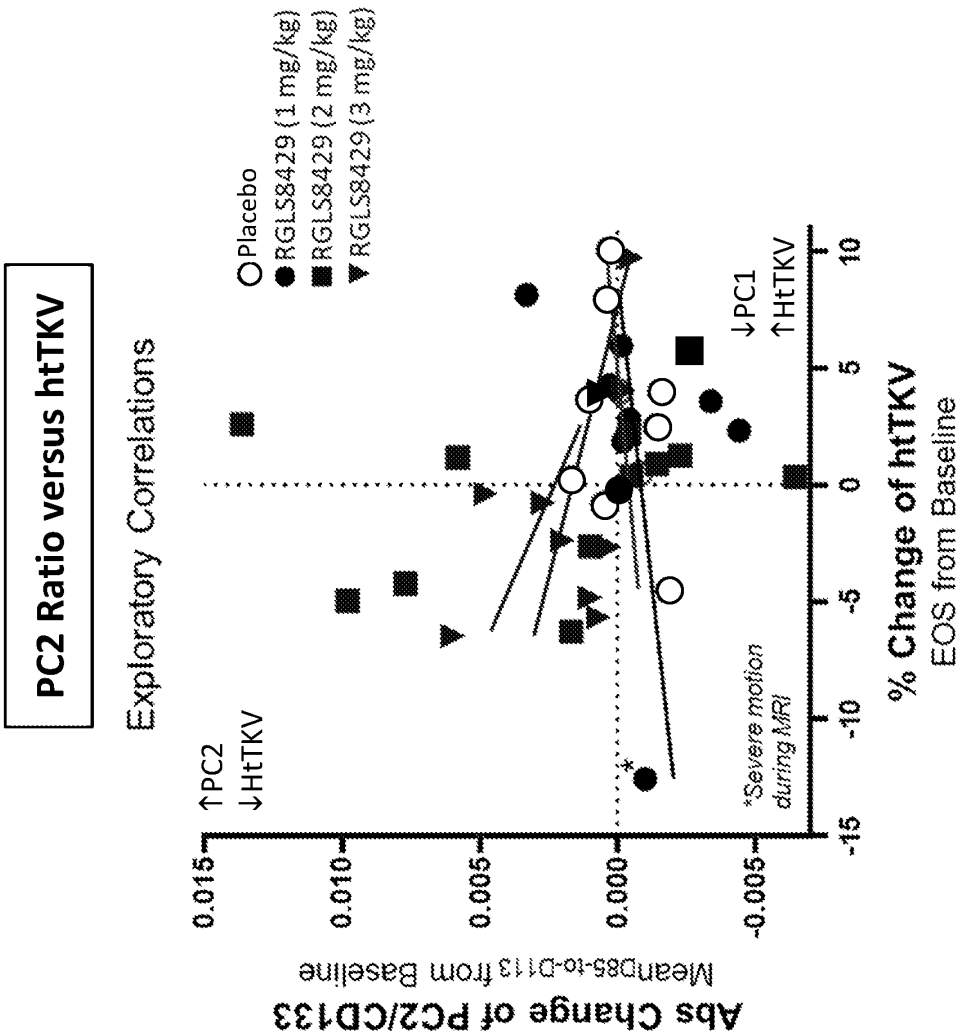

PC2 Ratio versus htTKV
Exploratory Correlations
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
↑PC2
↓HtTKV
↓PC1
↑HtTKV
*Severe motion during MRI
Abs Change of PC2/CD133
MeanD85-to-D113 from Baseline
% Change of htTKV
EOS from Baseline
0.015
0.010
0.005
0.000
-0.005
-15
-10
-5
0
5
10

FIG. 23B

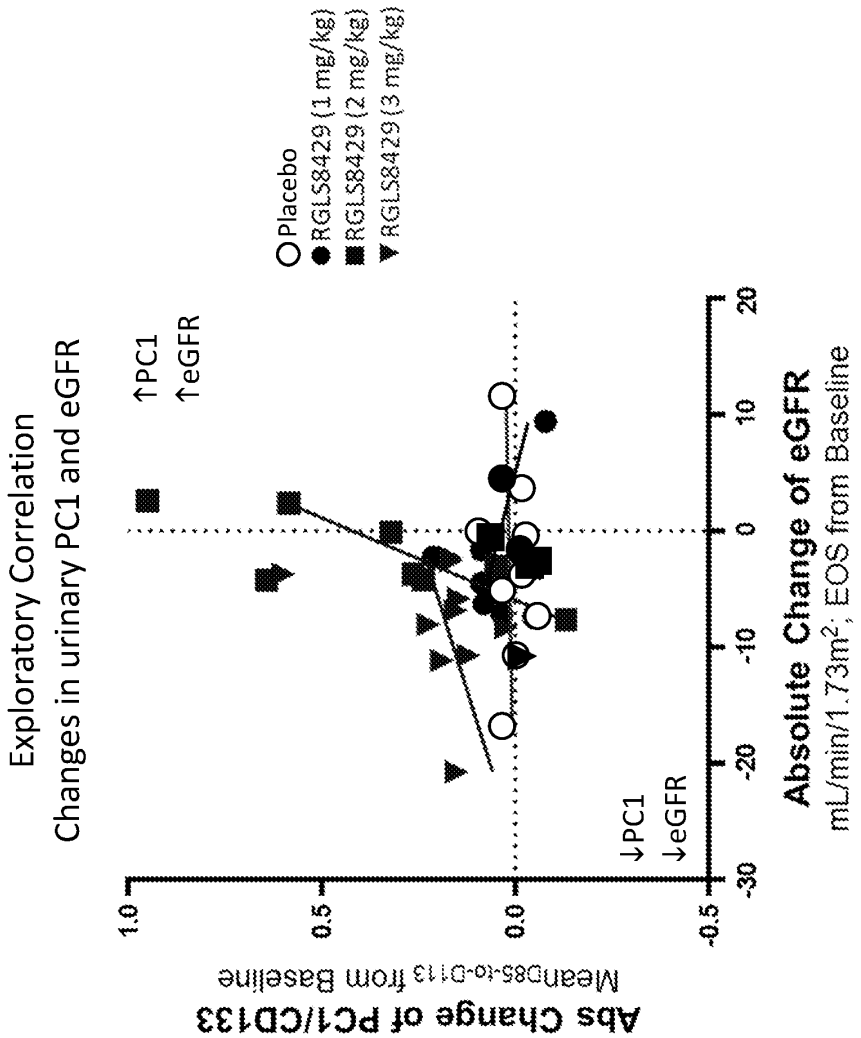

Exploratory Correlation
Changes in urinary PC1 and eGFR
↑PC1
↑eGFR
Placebo
RGLS8429 (1 mg/kg)
RGLS8429 (2 mg/kg)
RGLS8429 (3 mg/kg)
Abs Change of PC1/CD133
MeanD85-to-D113 from Baseline
1.0
0.5
0.0
-0.5
↓PC1
↓eGFR
-30
-20
-10
0
10
20
Absolute Change of eGFR
mL/min/1.73m2; EOS from Baseline

FIG. 24

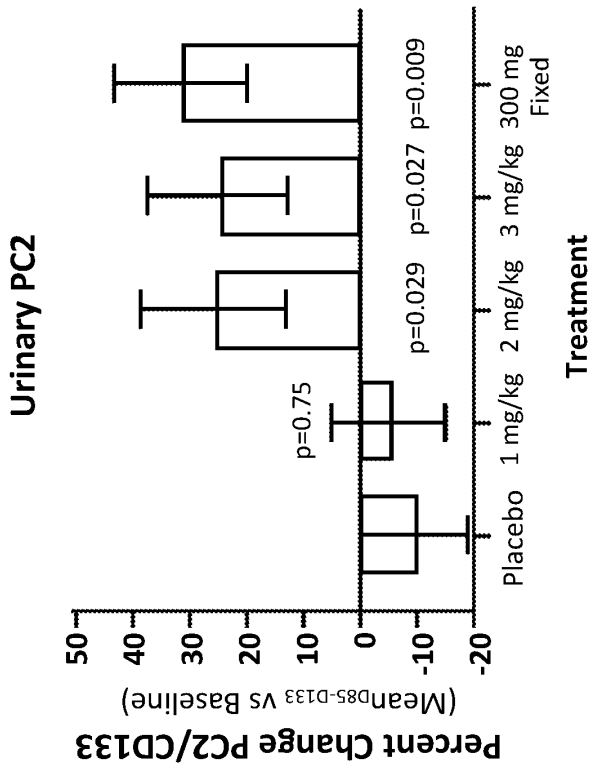


FIG. 25B

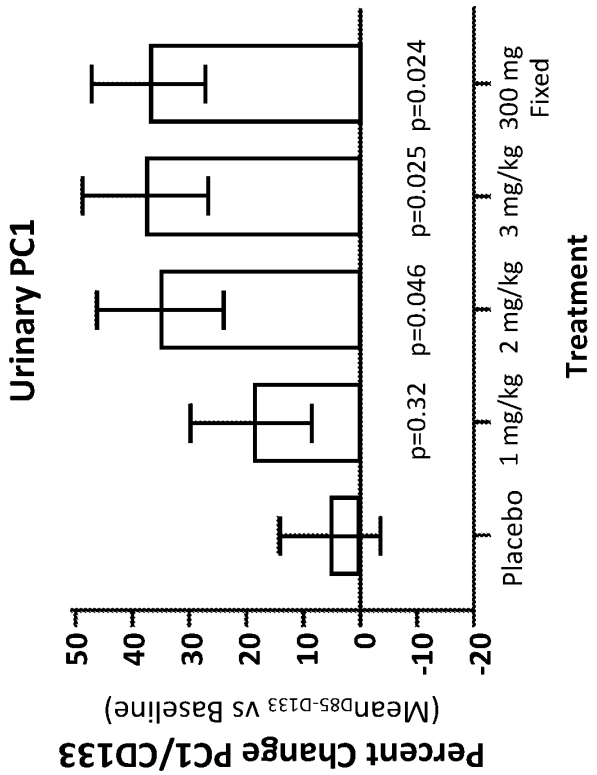


FIG. 25A

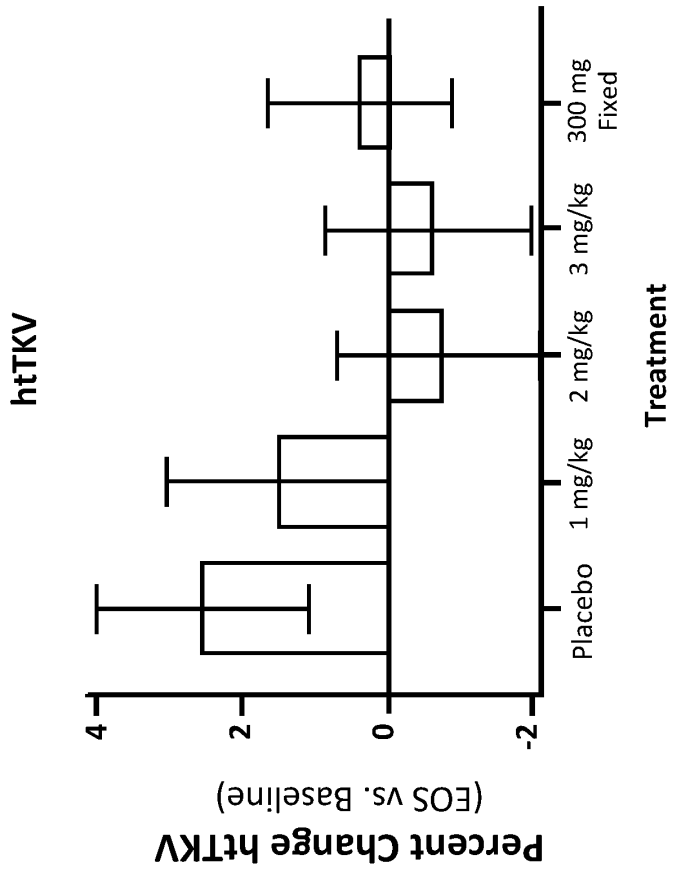

htTKV
Percent Change htTKV
(EOS vs. Baseline)
4
2
0
-2
Placebo
1 mg/kg
2 mg/kg
3 mg/kg
300 mg Fixed
Treatment

FIG. 26