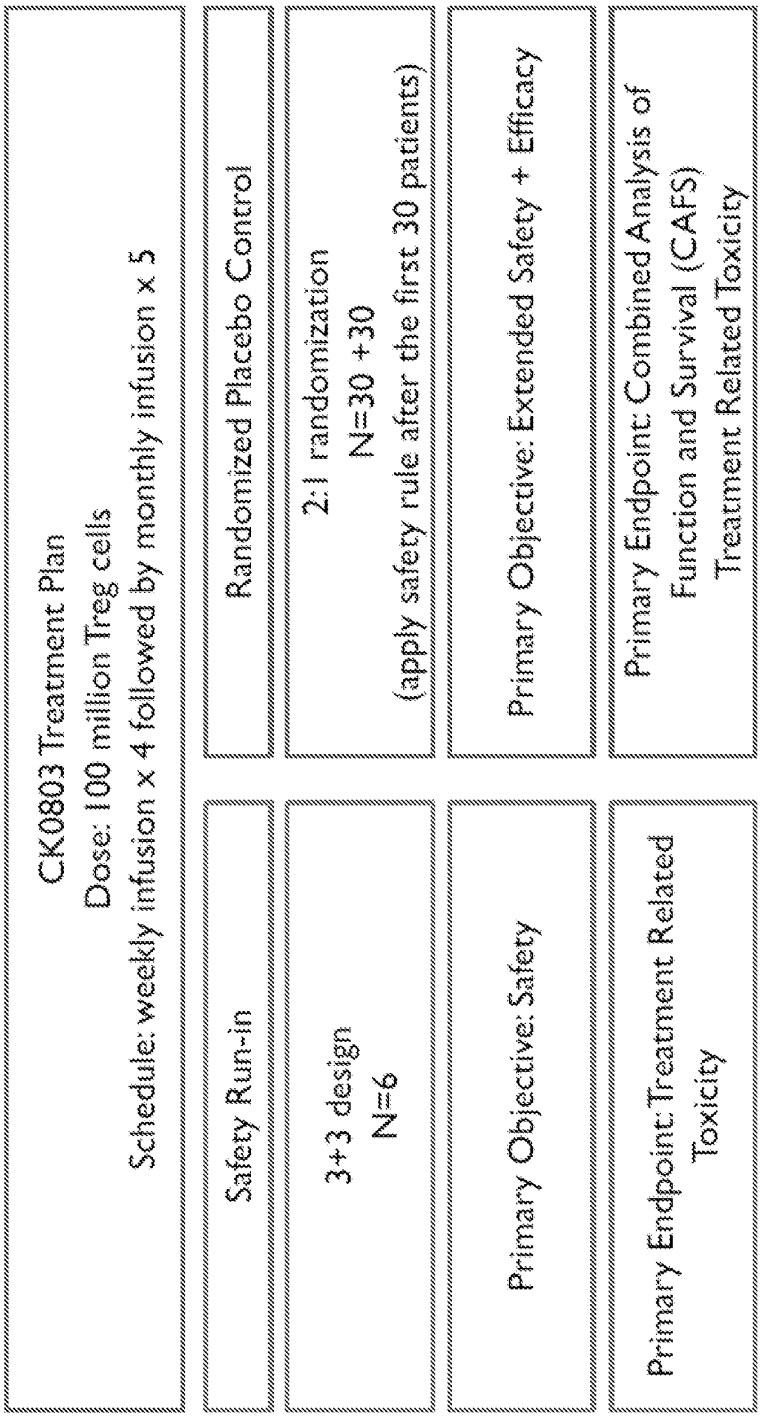
CK0803 Treatment Plan
Dose: 100 million Treg cells
Schedule: weekly infusion x 4 followed by monthly infusion x 5
Safety Run-in
3+3 design
N=6
Primary Objective: Safety
Primary Endpoint: Treatment Related Toxicity
Randomized Placebo Control
2:1 randomization
N=30 +30
(apply safety rule after the first 30 patients)
Primary Objective: Extended Safety + Efficacy
Primary Endpoint: Combined Analysis of Function and Survival (CAFS) Treatment Related Toxicity

FIG. 1

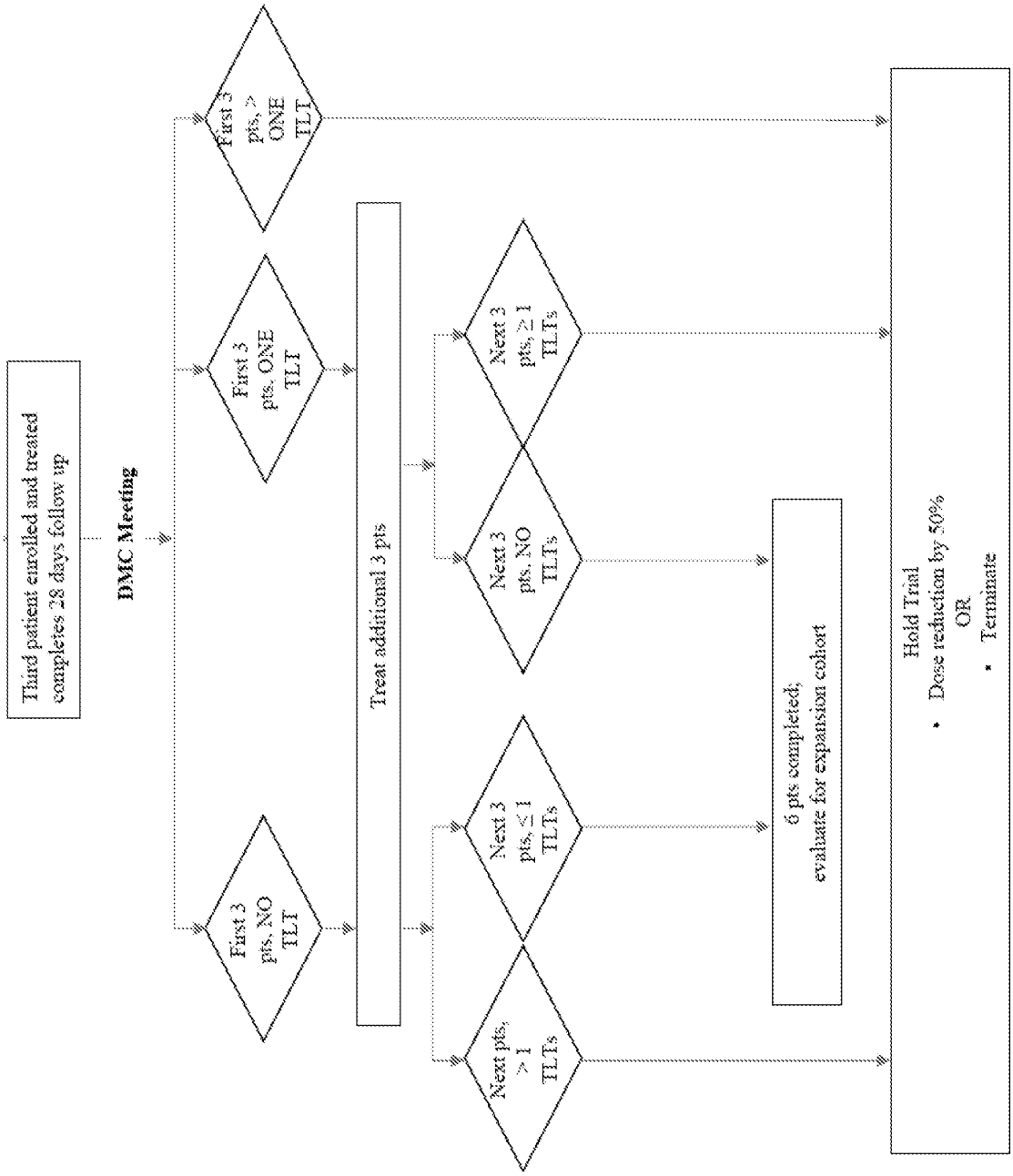
Third patient enrolled and treated completes 28 days follow up
DMC Meeting
First 3 pts, NO TLT
First 3 pts. ONE TLT
First 3 pts, > ONE TLT
Treat additional 3 pts
Next pts, > 1 TLTs
Next 3 pts, ≤ 1 TLTs
Next 3 pts, NO TLTs
Next 3 pts, ≥ 1 TLTs
6 pts completed, evaluate for expansion cohort
Hold Trial
• Dose reduction by 50%
OR
• Terminate

FIG. 2

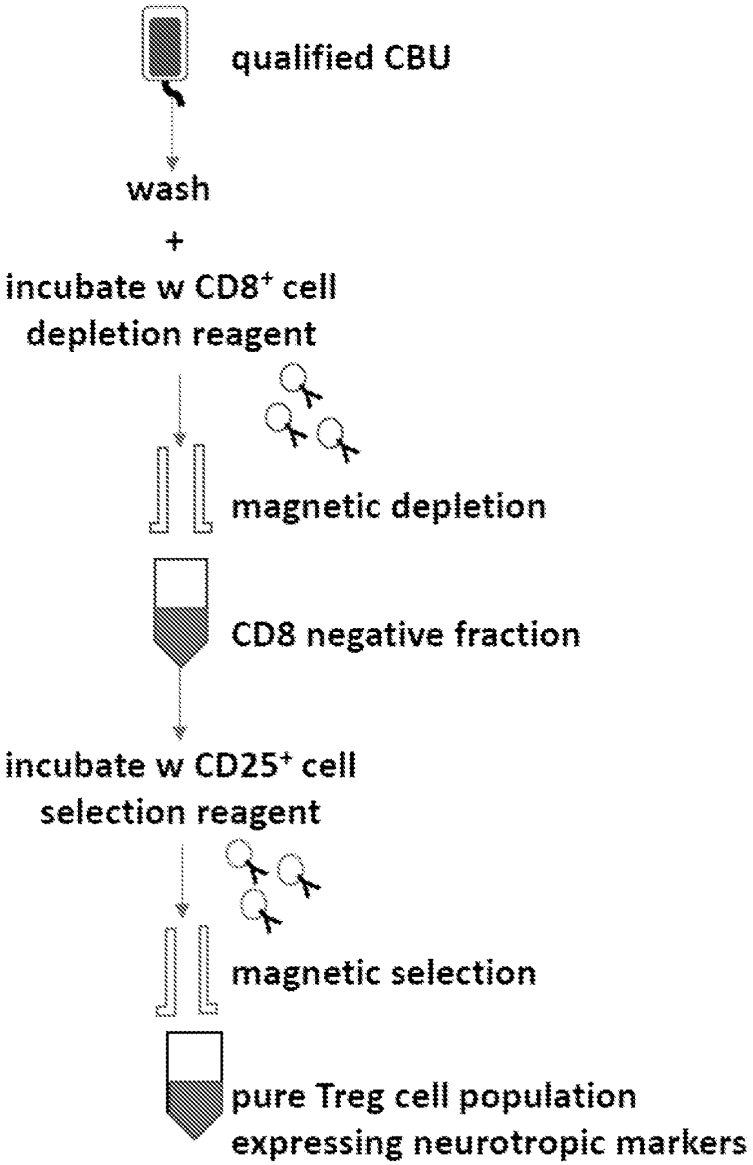
qualified CBU
wash
+
incubate w CD8+ cell depletion reagent
magnetic depletion
CD8 negative fraction
incubate w CD25+ cell selection reagent
magnetic selection
pure Treg cell population expressing neurotropic markers

FIG. 3

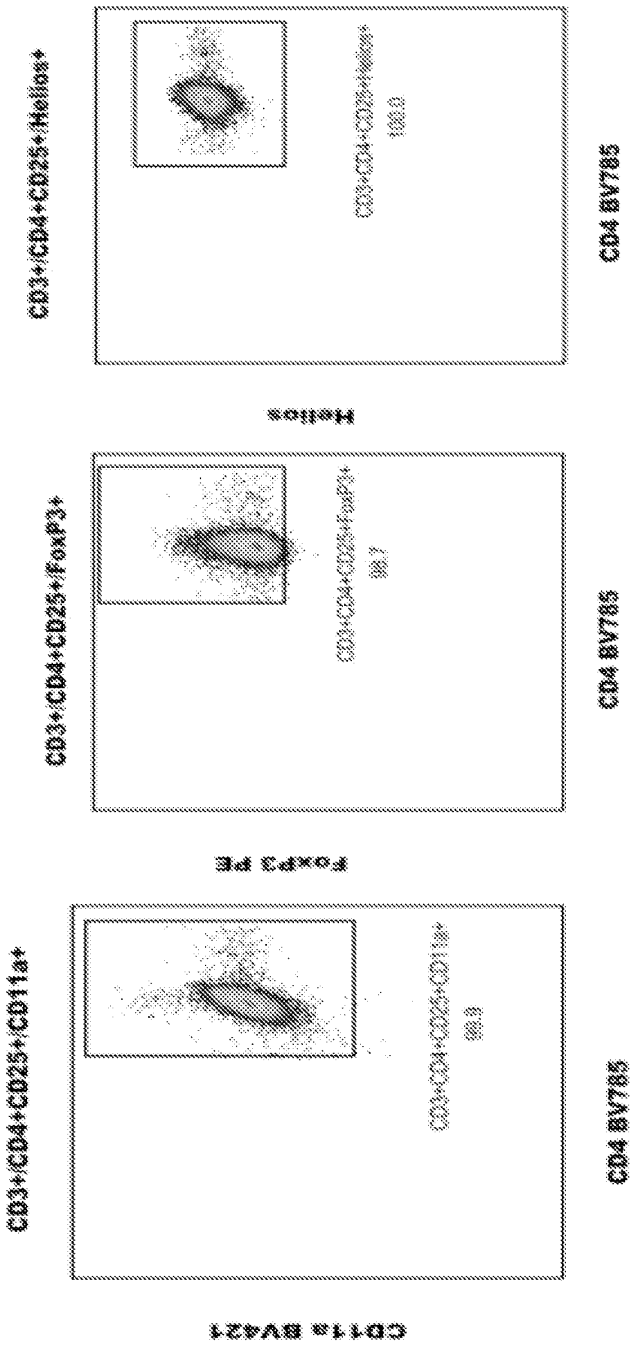
CD11a BV421
CD3+/CD4+/CD25+/CD11a+
CD4 BV785
FoxP3 PE
CD3+/CD4+/CD25+/FoxP3+
CD4 BV785
Helios
CD3+/CD4+/CD25+/Helios+
CD4 BV785

FIG. 4

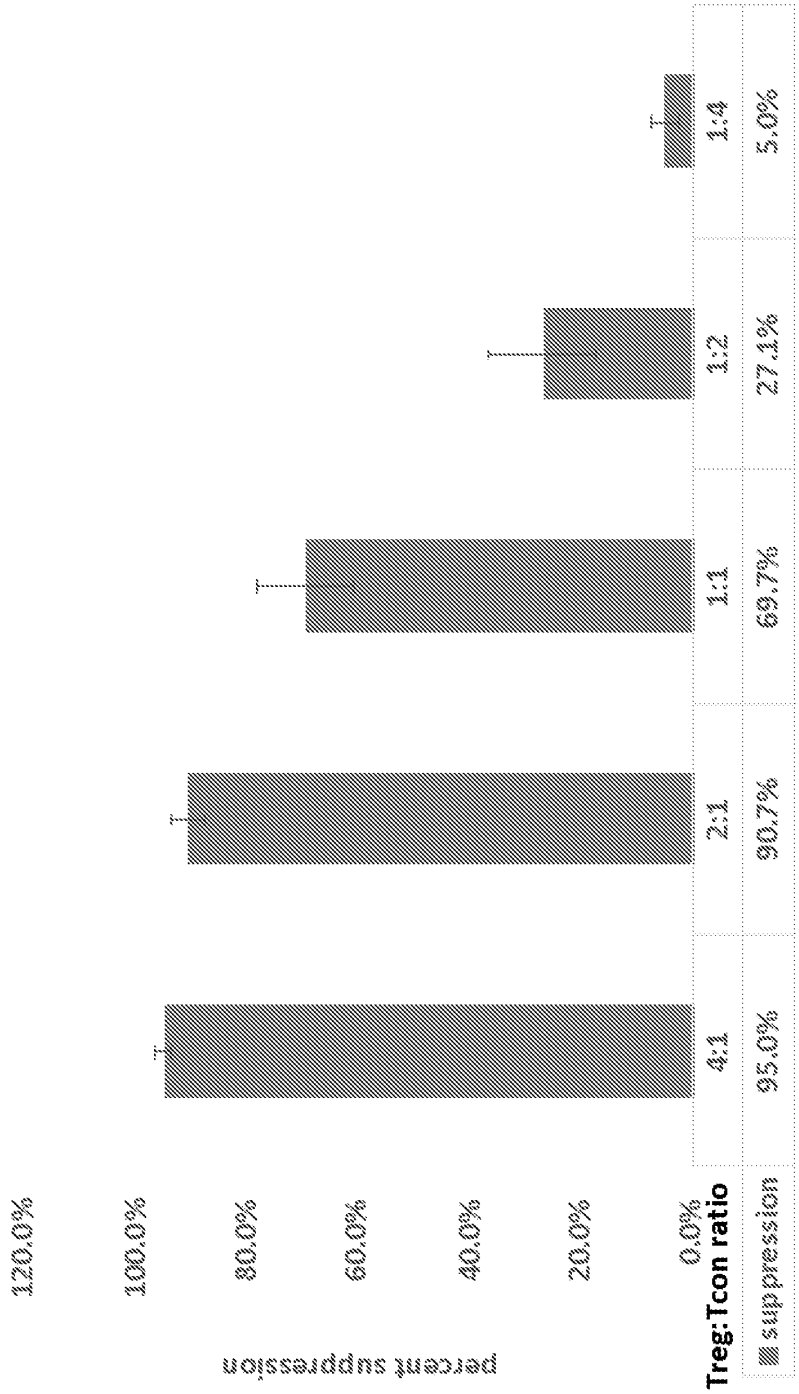
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
percent suppression
Treg:Tcon ratio
suppression
4:1
2:1
1:1
1:2
1:4
95.0%
90.7%
69.7%
27.1%
5.0%

FIG. 5

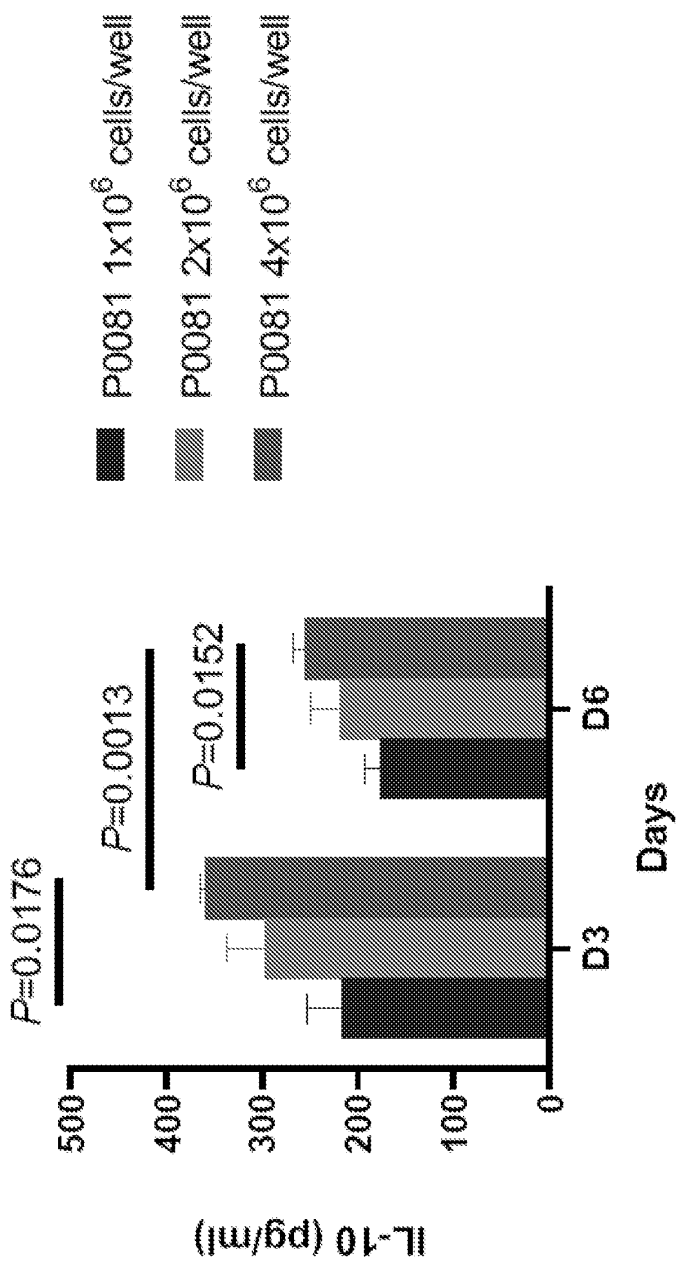
P0081 1x10^6 cells/well
P0081 2x10^6 cells/well
P0081 4x10^6 cells/well
P=0.0176
P=0.0013
P=0.0152
500
400
300
200
100
0
IL-10 (pg/ml)
D3
D6
Days

FIG. 6

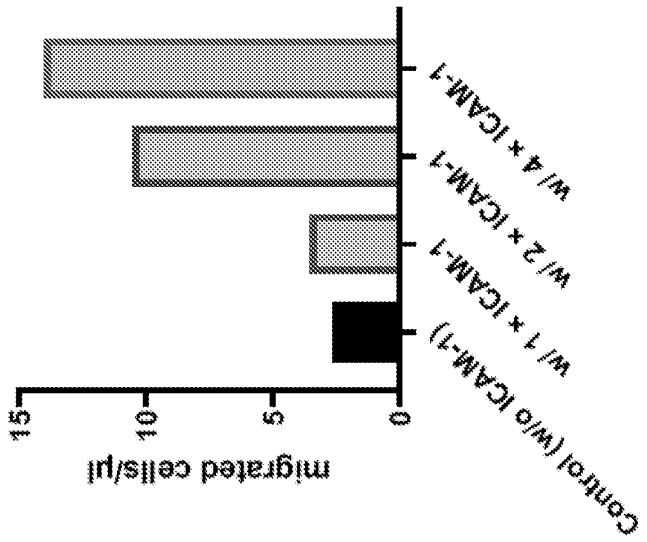
migrated cells/µl
0
5
10
15
Control (W/o ICAM-1)
W/ 1 × ICAM-1
W/ 2 × ICAM-1
W/ 4 × ICAM-1

FIG. 7B

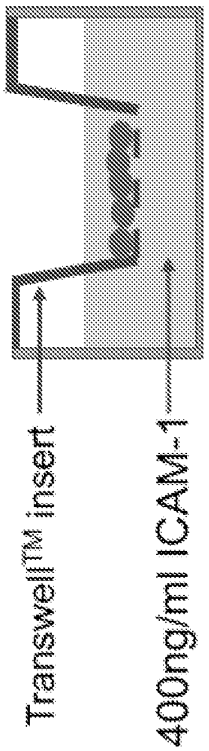
Transwell™ insert
400ng/ml ICAM-1

FIG. 7A

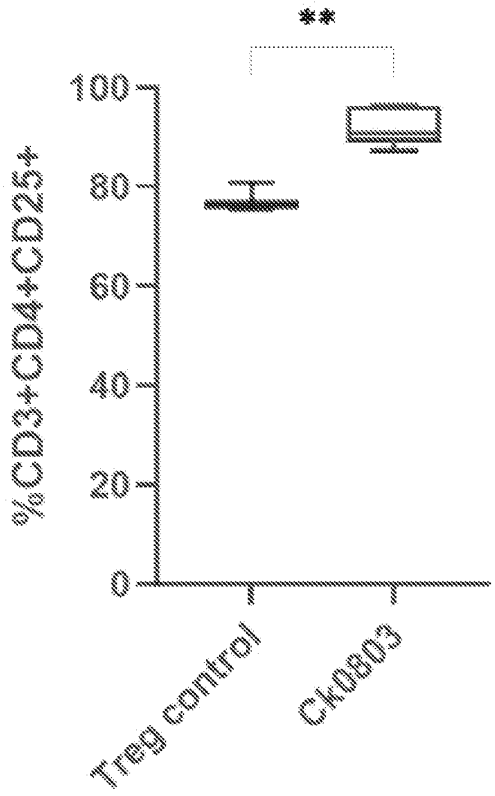

FIG. 8

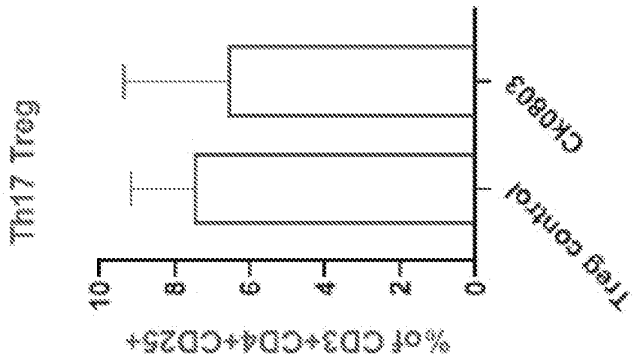

FIG. 9D

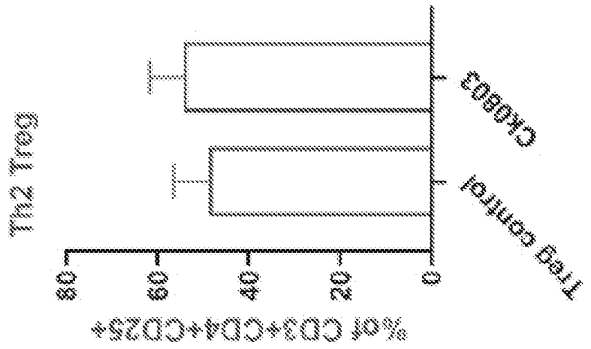

FIG. 9C

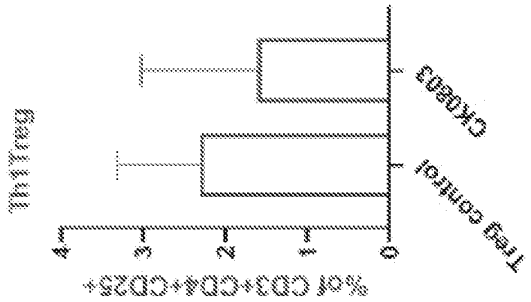

FIG. 9B

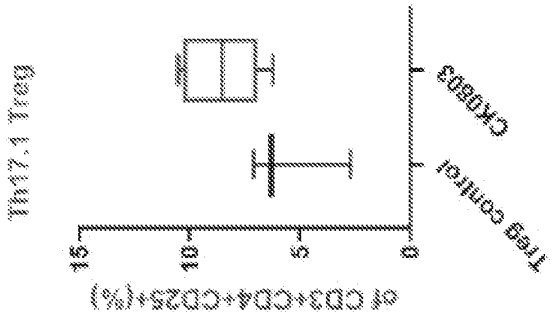

FIG. 9A

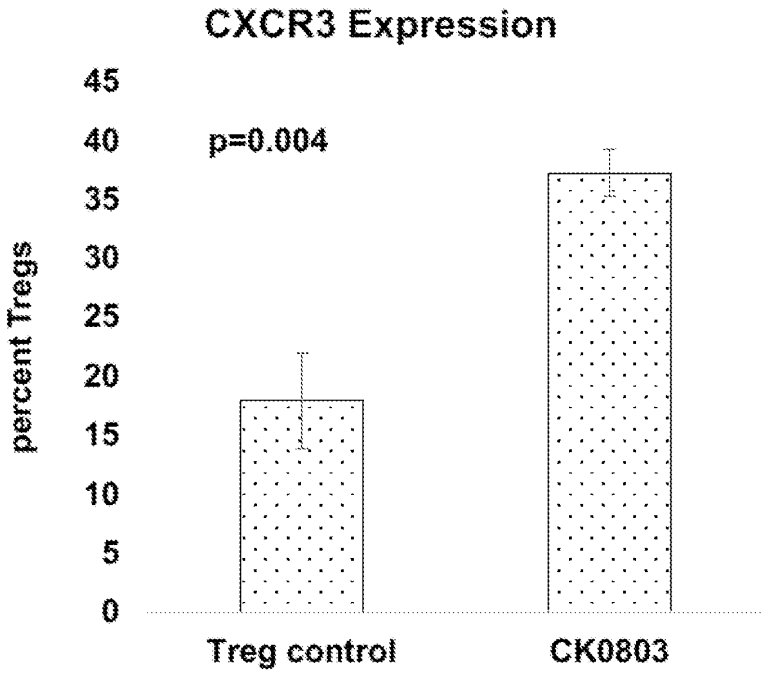
CXCR3 Expression
p=0.004
percent Tregs
45
40
35
30
25
20
15
10
5
0
Treg control
CK0803

FIG. 10

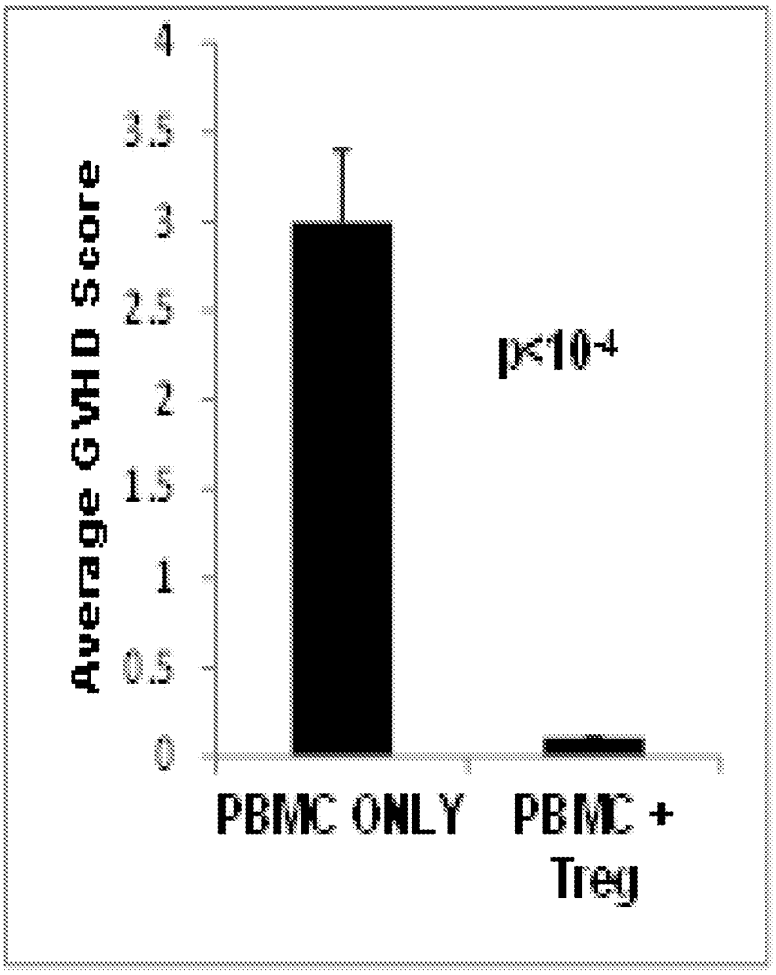

FIG. 11A

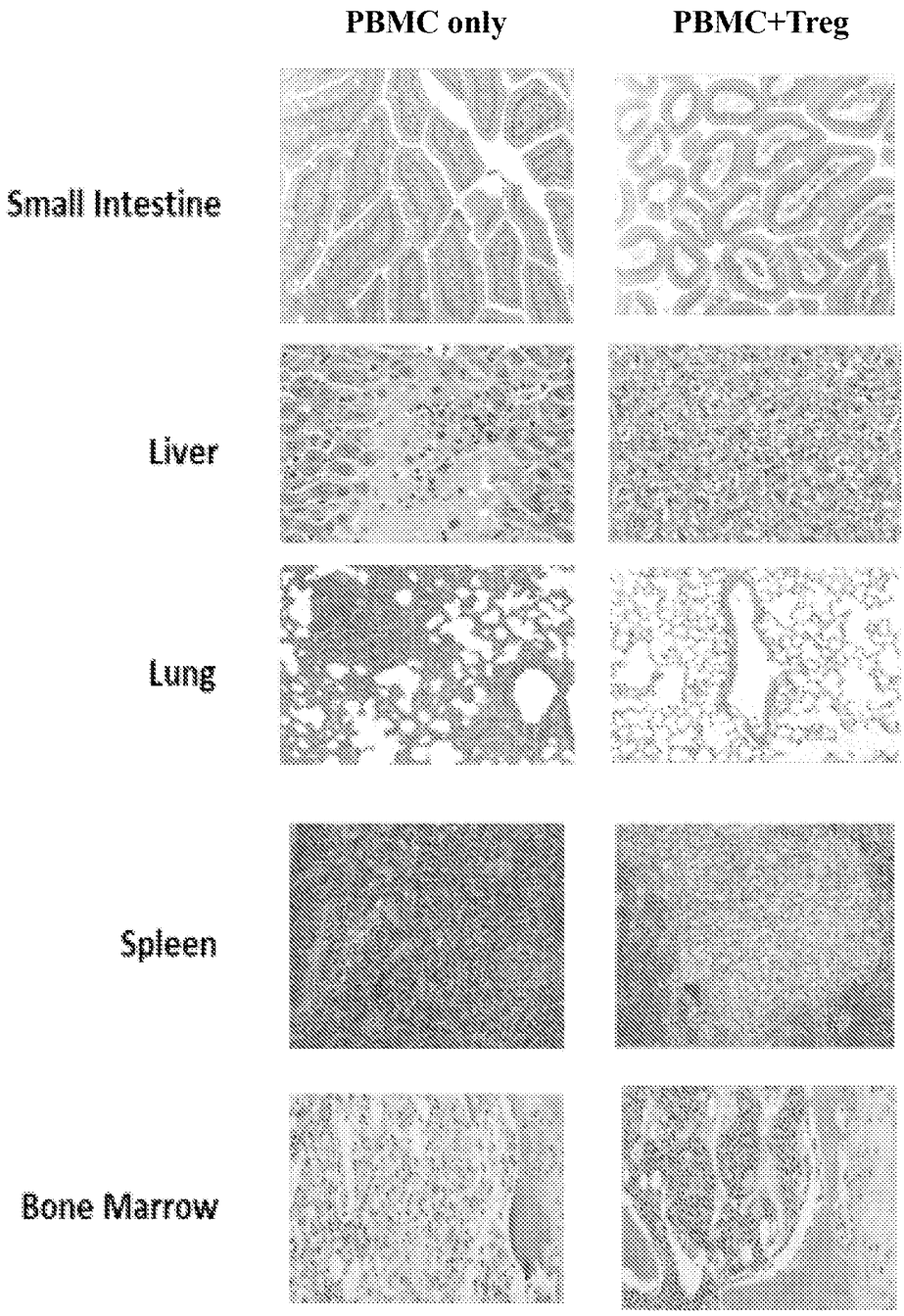
PBMC only
PBMC+Treg
Small Intestine
Liver
Lung
Spleen
Bone Marrow

FIG. 11B

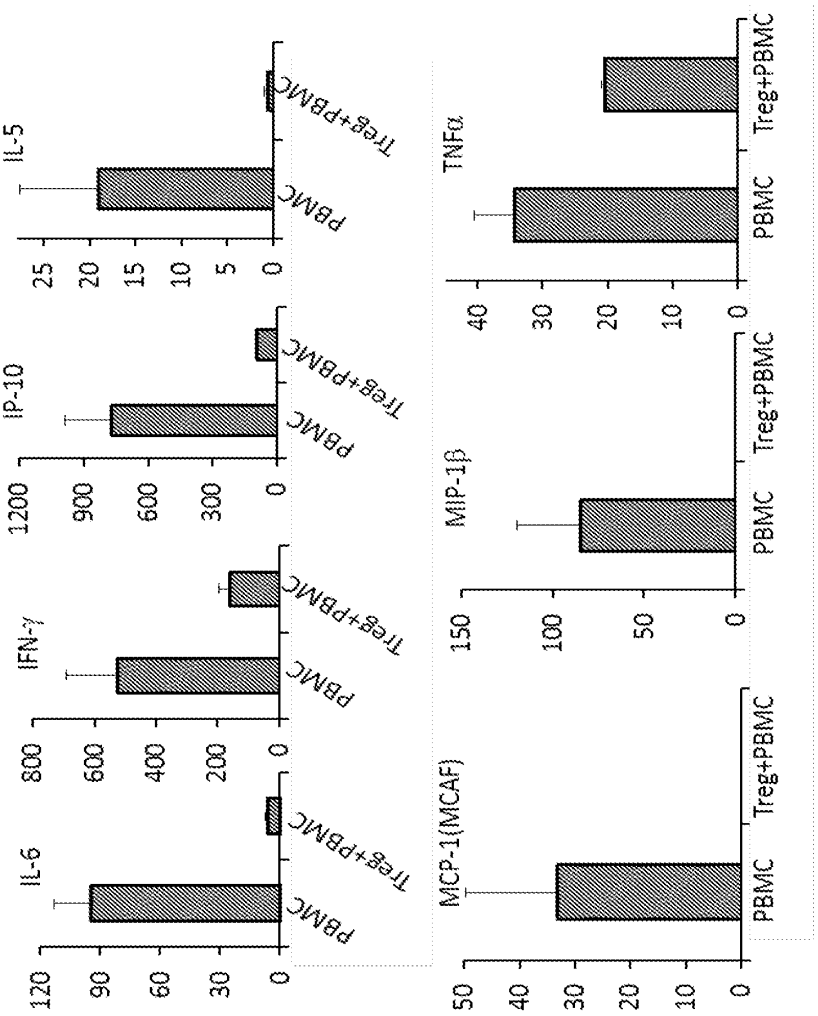

FIG. 11C

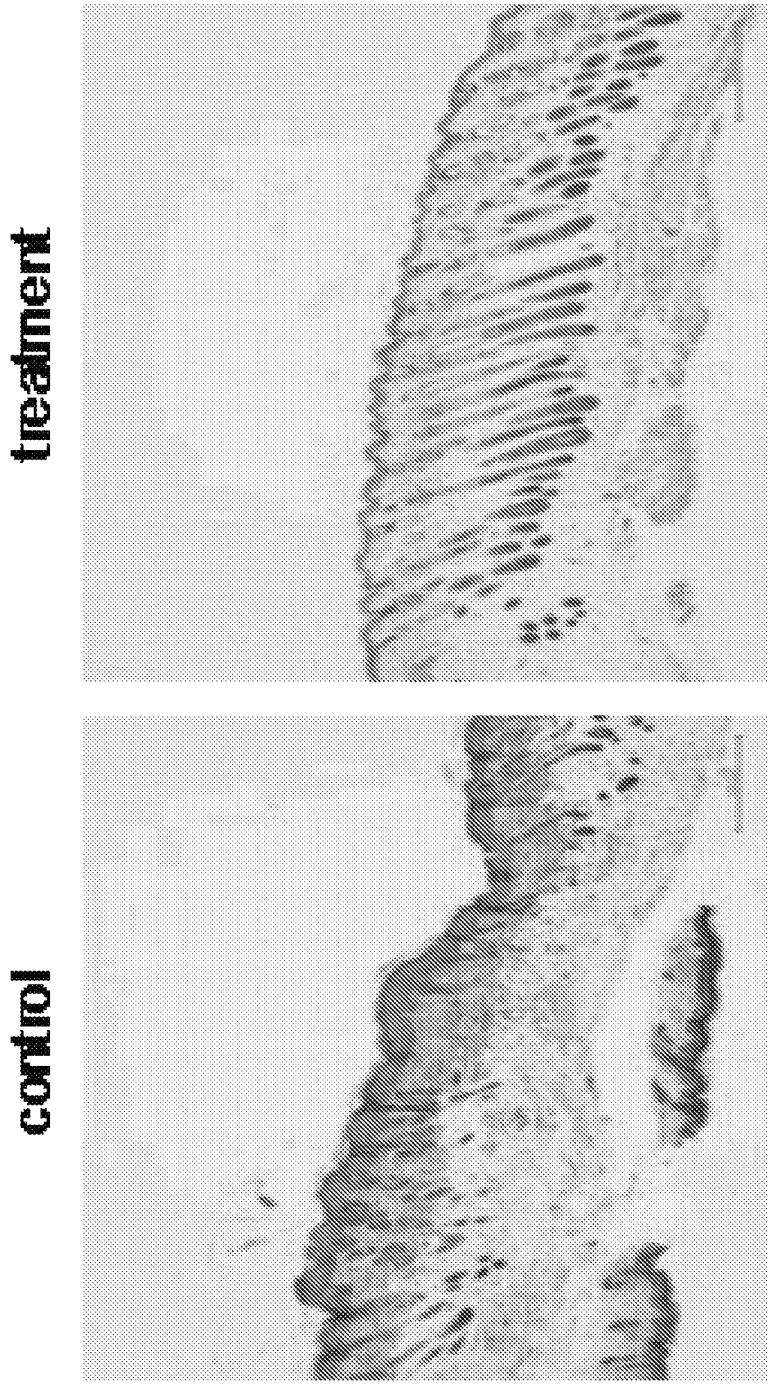

FIG. 12A

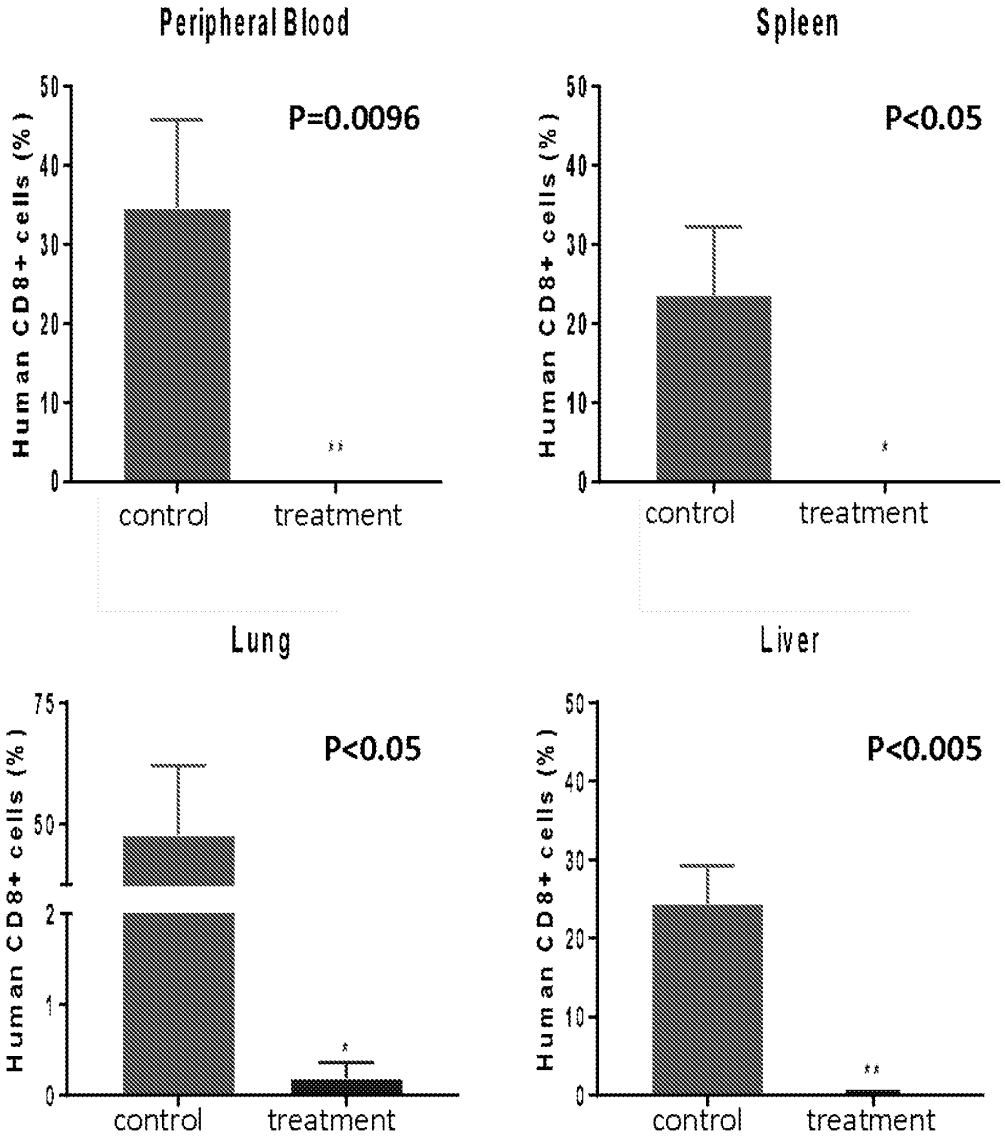
Peripheral Blood
P=0.0096
Human CD8+ cells (%)
50
40
30
20
10
0
control
treatment
Spleen
P<0.05
Human CD8+ cells (%)
50
40
30
20
10
0
control
treatment
Lung
P<0.05
Human CD8+ cells (%)
75
50
2
1
0
control
treatment
Liver
P<0.005
Human CD8+ cells (%)
50
40
30
20
10
0
control
treatment

FIG. 12B

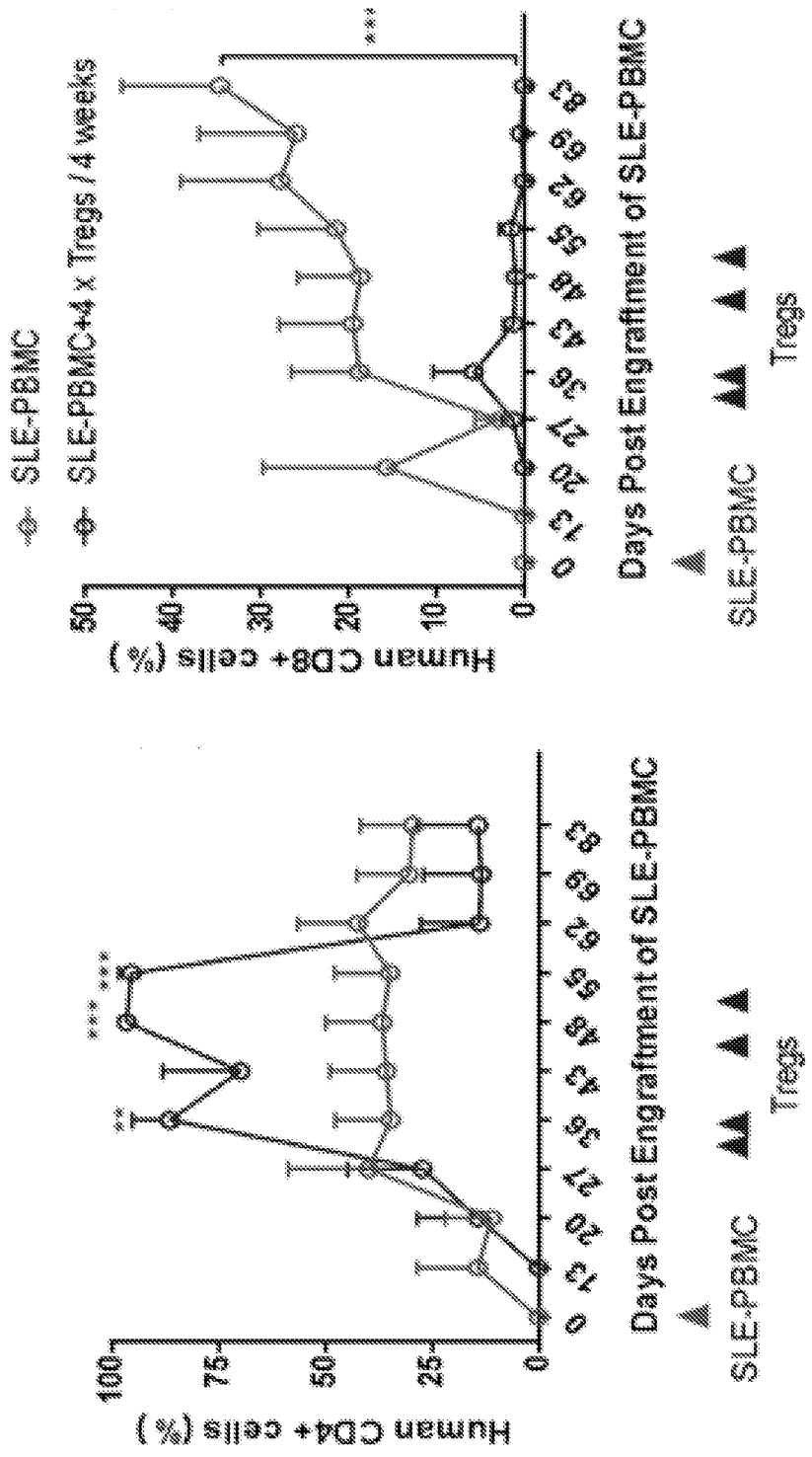
SLE-PBMC
SLE-PBMC+4 x Tregs / 4 weeks
Human CD8+ cells (%)
Days Post Engraftment of SLE-PBMC
SLE-PBMC
Tregs
Human CD4+ cells (%)
Days Post Engraftment of SLE-PBMC
SLE-PBMC
Tregs

FIG. 12C

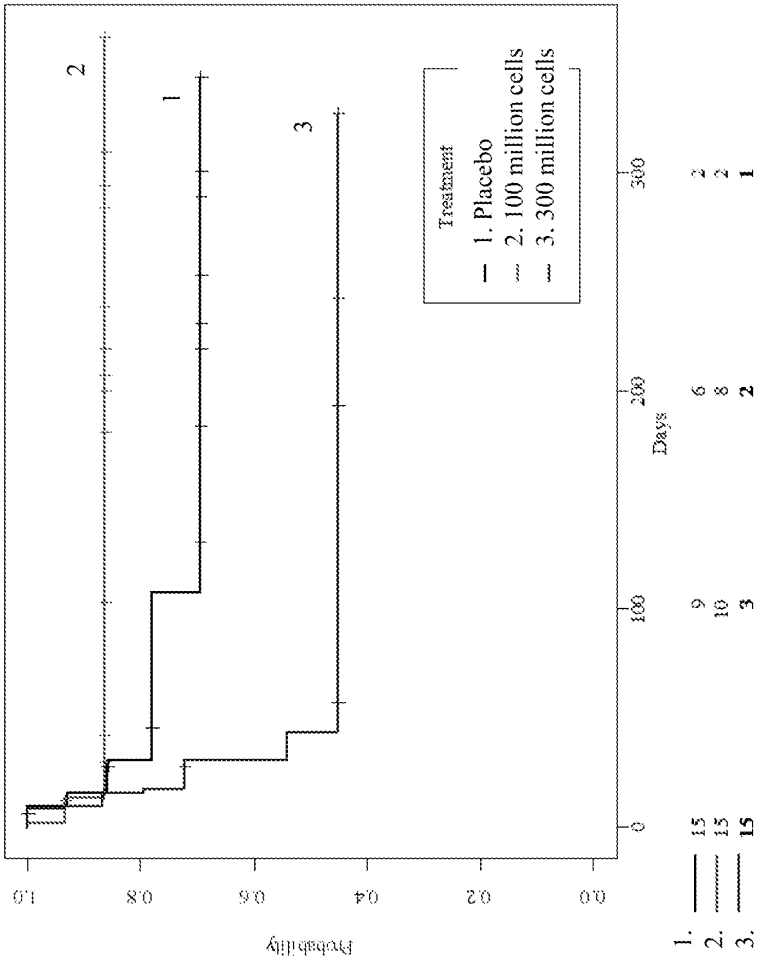
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
100
200
300
Days
Treatment
1. Placebo
2. 100 million cells
3. 300 million cells
1
2
3
1. 15 9 6 2
2. 15 10 8 2
3. 15 3 2 1

FIG. 13

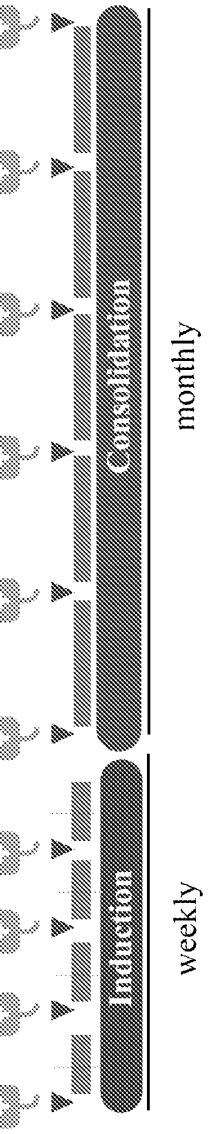

FIG. 14A

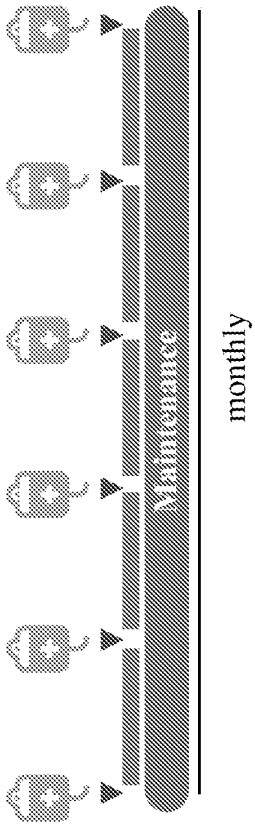

FIG. 14B

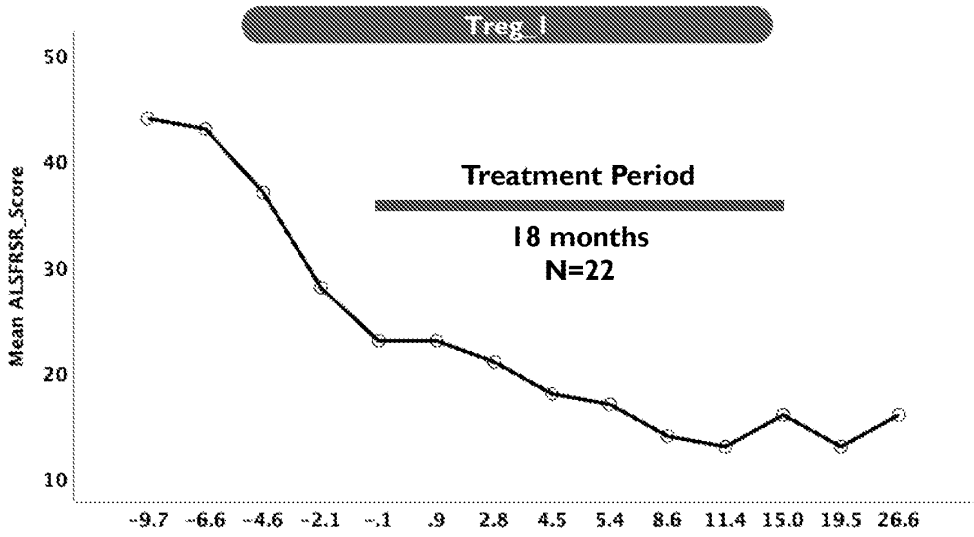

FIG. 15A

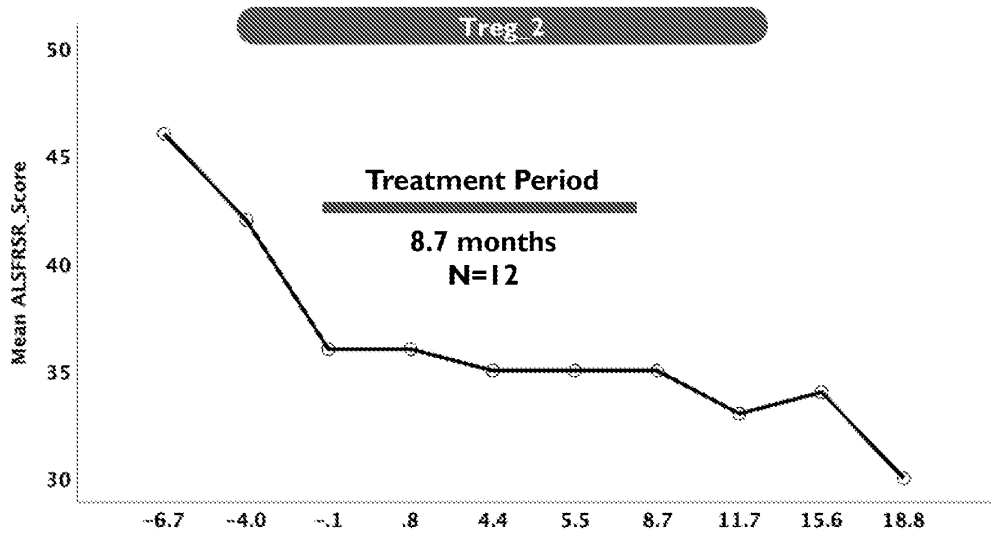

FIG. 15B

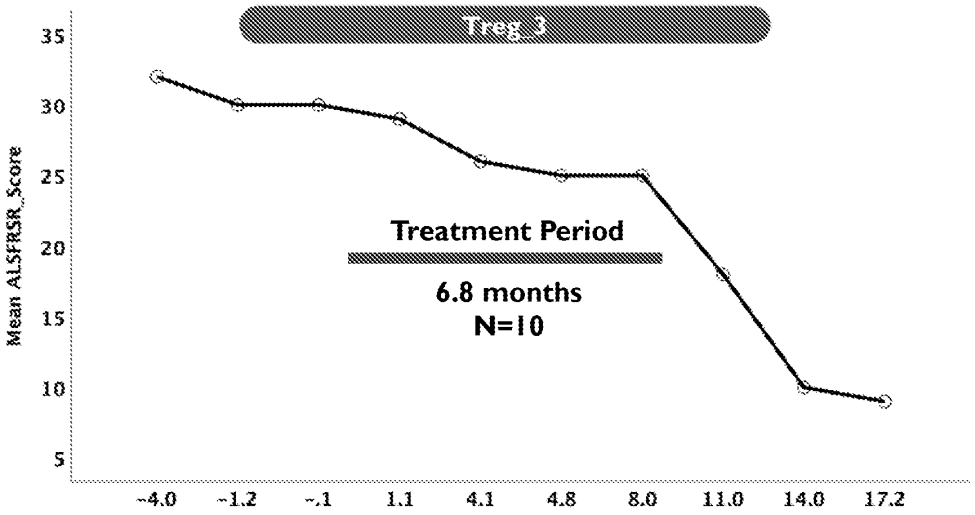

FIG. 15C

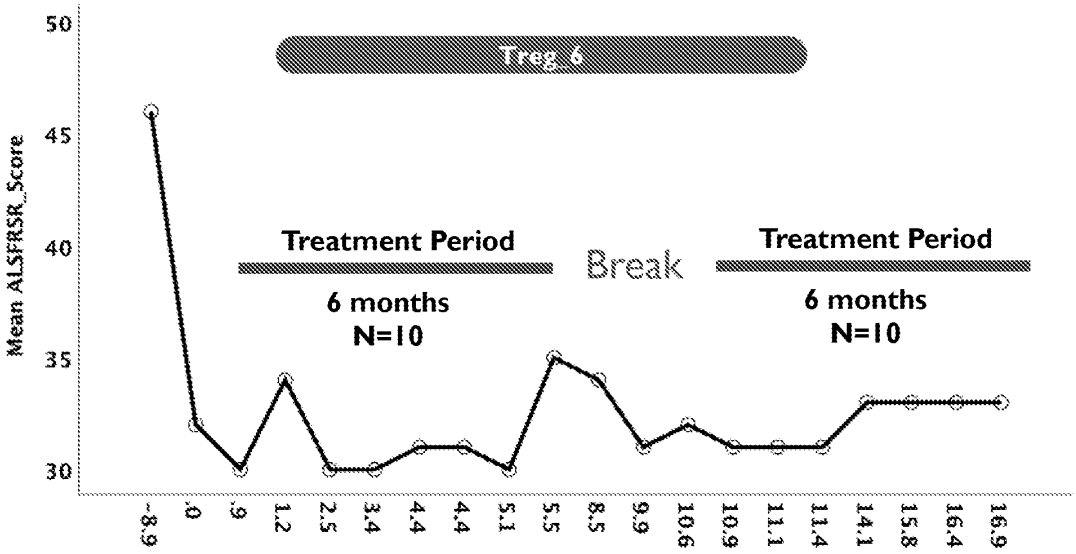

FIG. 15D

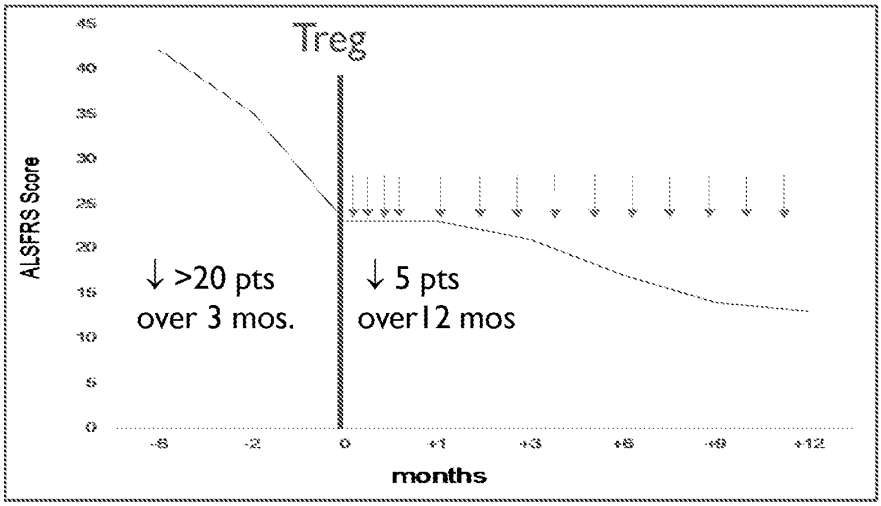

FIG. 16A

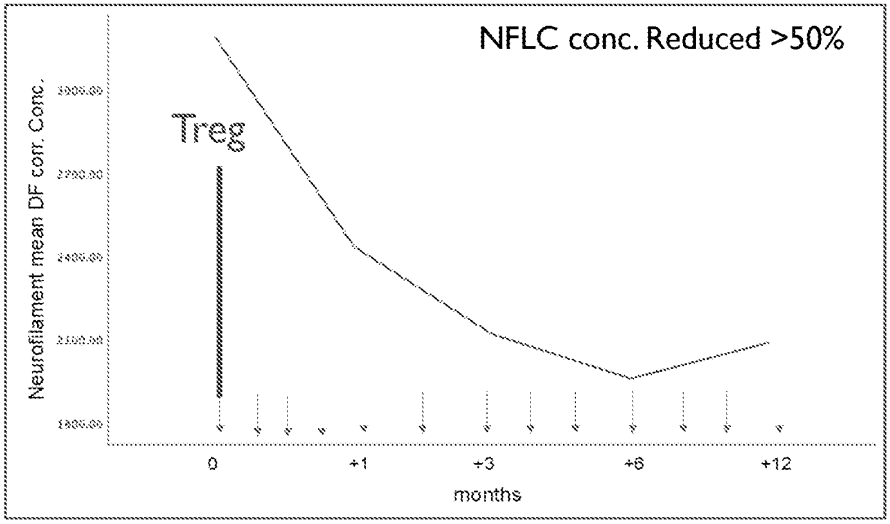

FIG. 16B

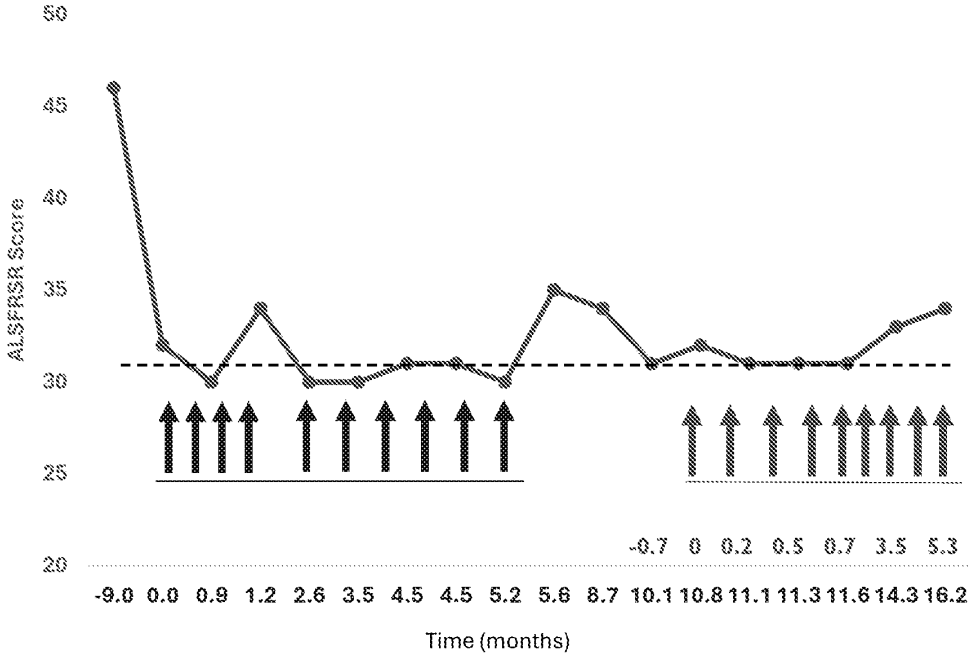

FIG. 17A

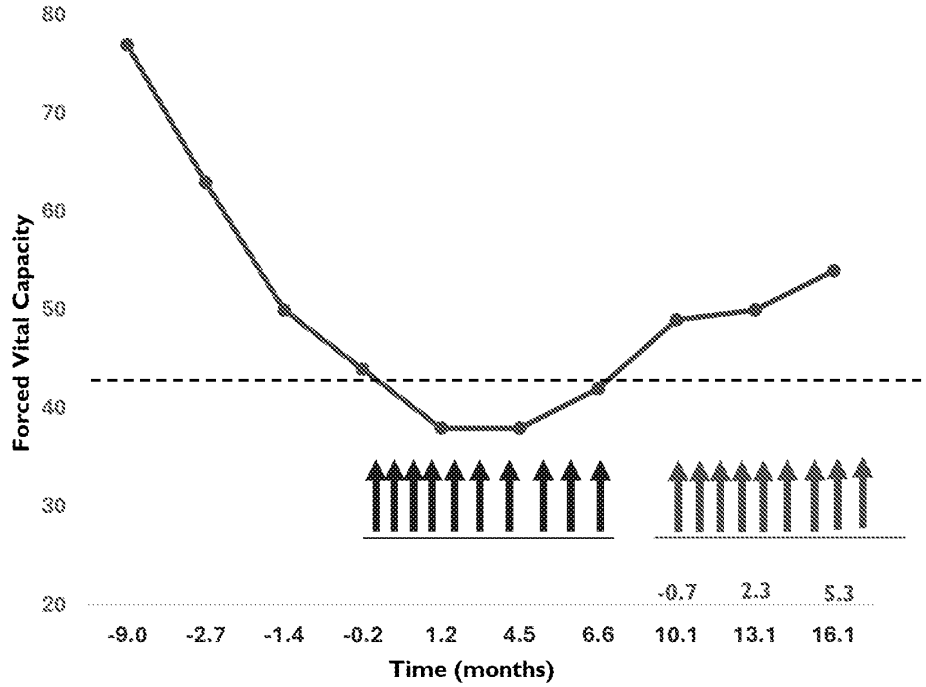

FIG. 17B

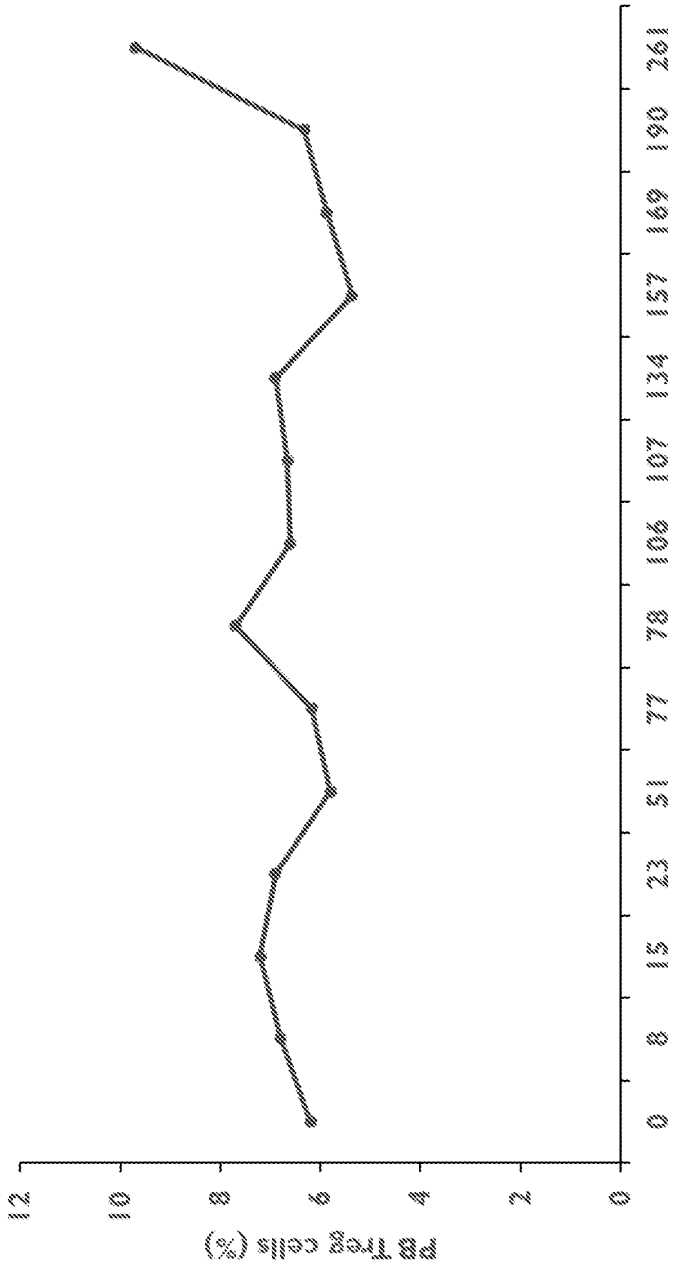
PB Treg cells (%)
0
2
4
6
8
10
12
Days
0
8
15
23
51
77
78
106
107
134
157
169
190
261

FIG. 17C

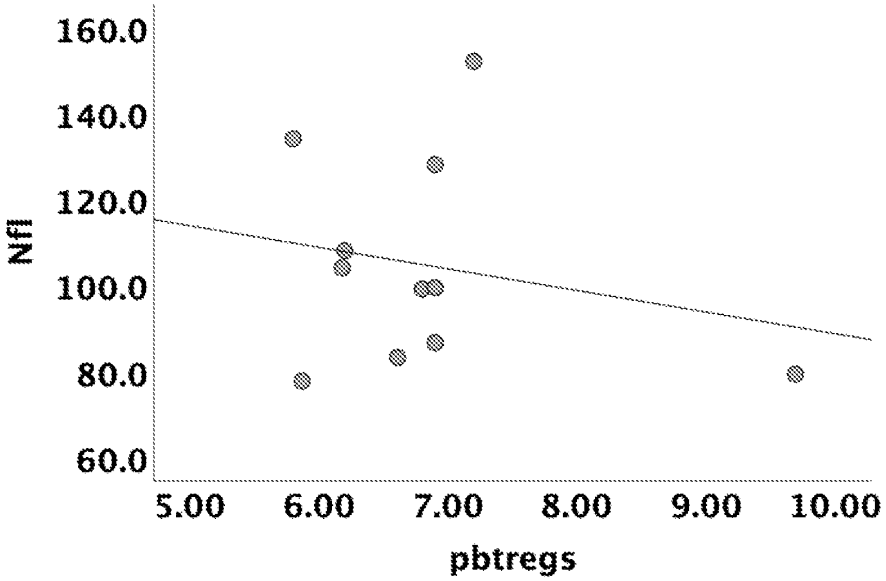

FIG. 17D

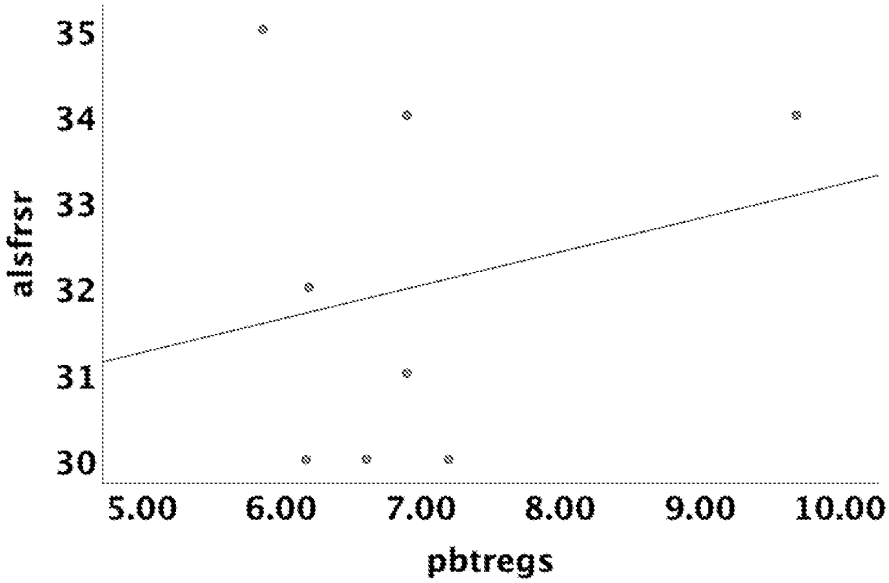

FIG. 17E

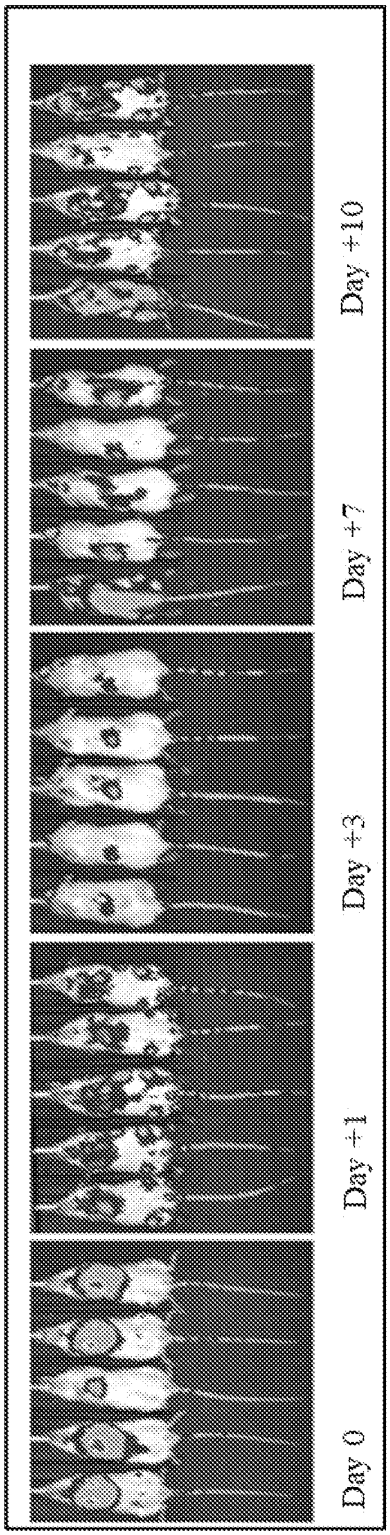

FIG. 18

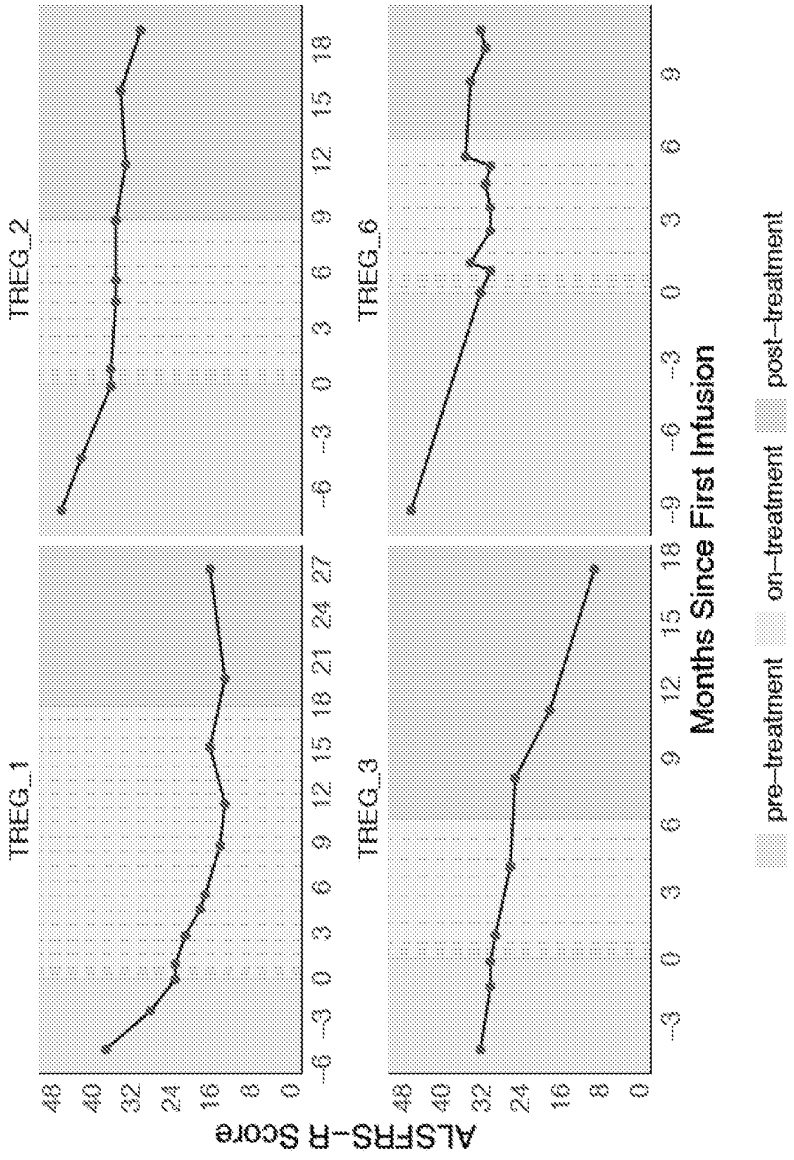
TREG_1
TREG_2
TREG_3
TREG_6
ALSFRS-R Score
Months Since First Infusion
pre-treatment
on-treatment
post-treatment

FIG. 19A

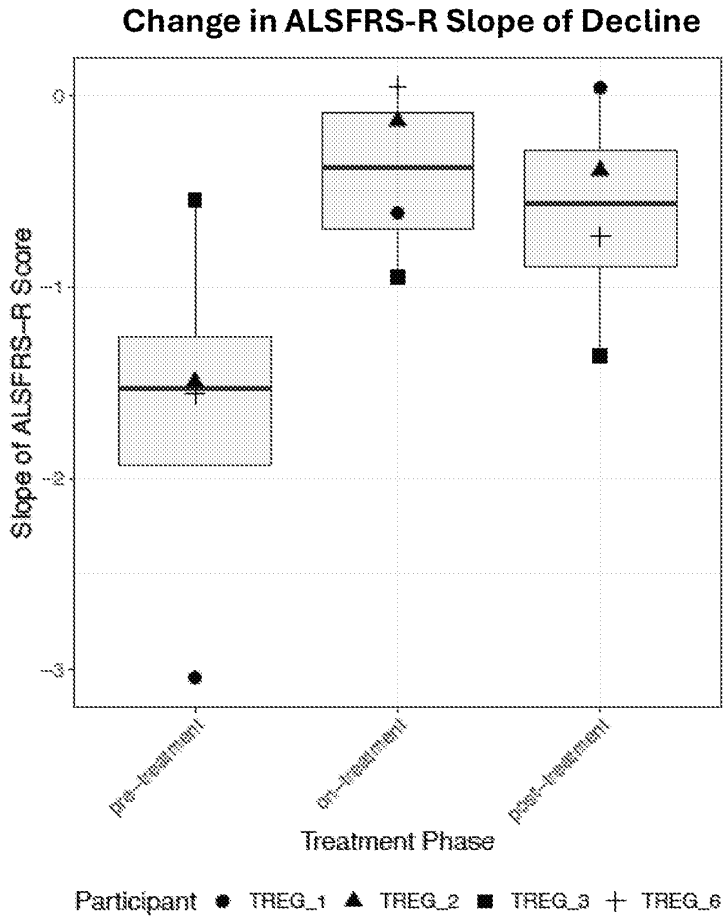
Change in ALSFRS-R Slope of Decline
Slope of ALSFRS-R Score
0
-1
-2
-3
pre-treatment
on-treatment
post-treatment
Treatment Phase
Participant
TREG_1
TREG_2
TREG_3
TREG_6

FIG. 19B

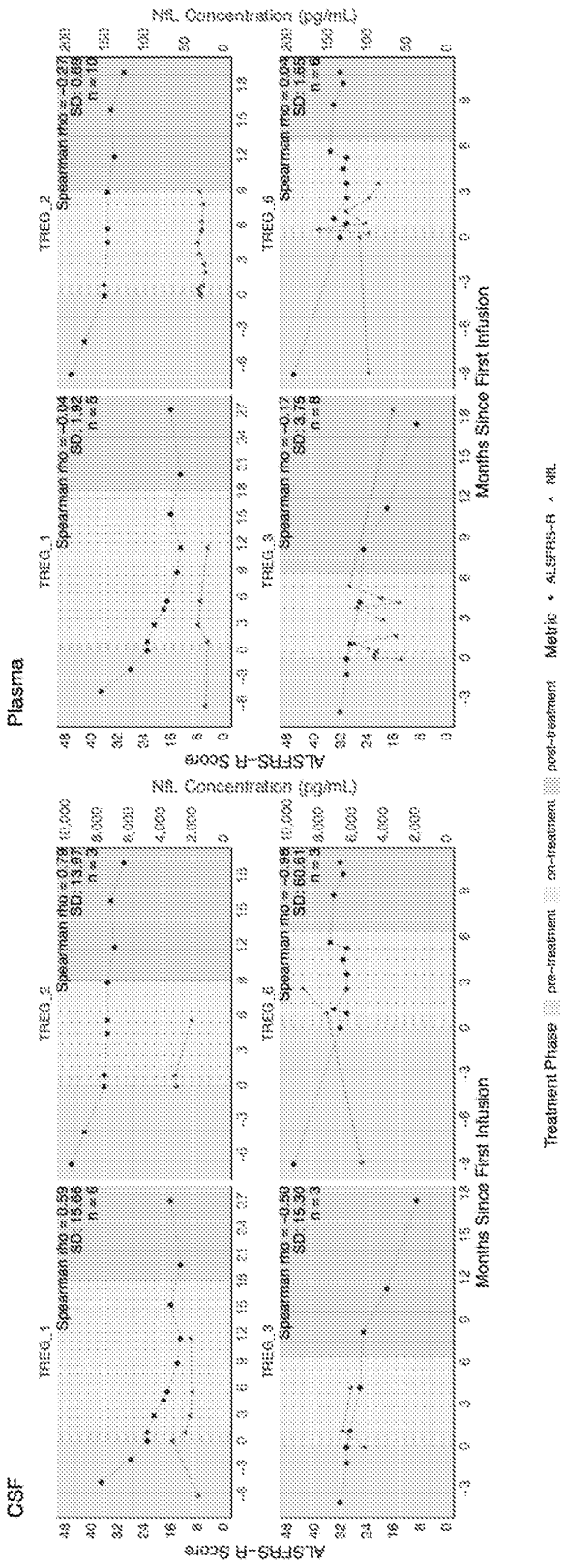
Plasma
CSF
NfL Concentration (pg/mL)
ALSFRS-R Score
Months Since First Infusion
TREG_1
TREG_2
TREG_3
TREG_6
Spearman rho = -0.04
SD: 1.92
n = 5
Spearman rho = -0.27
SD: 0.69
n = 10
Spearman rho = -0.12
SD: 3.75
n = 8
Spearman rho = 0.04
SD: 1.55
n = 6
Spearman rho = 0.59
SD: 15.66
n = 6
Spearman rho = 0.78
SD: 13.87
n = 3
Spearman rho = -0.50
SD: 15.30
n = 3
Spearman rho = -0.98
SD: 60.61
n = 3
Treatment Phase pre-treatment on-treatment post-treatment Metric ALSFRS-R NfL

FIG. 19C

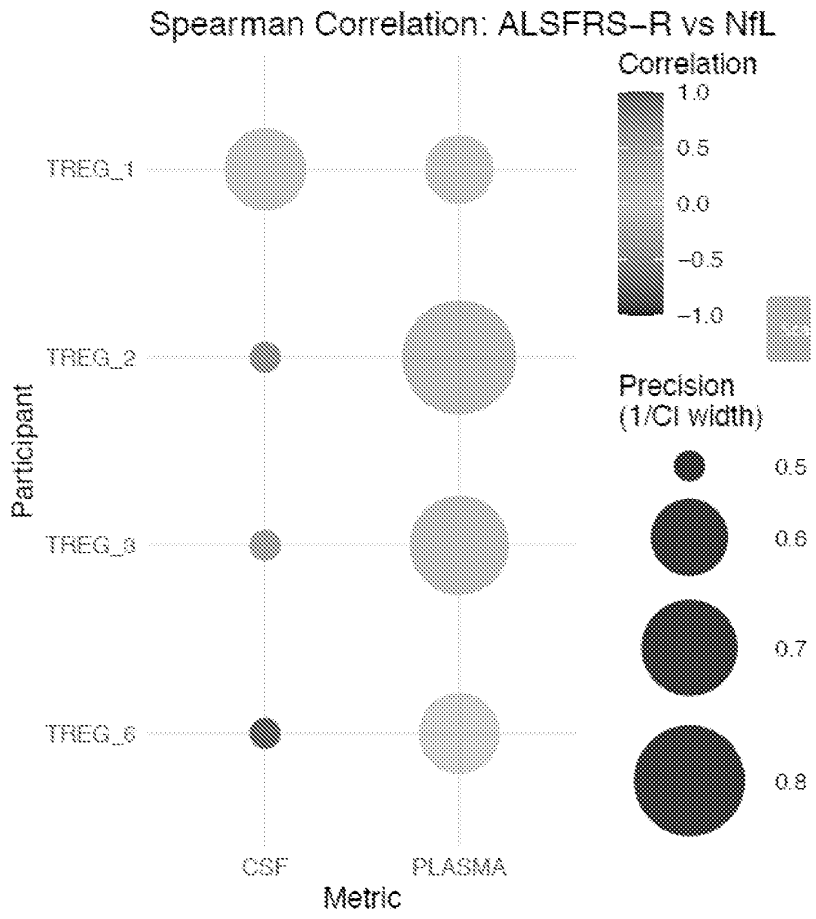
Spearman Correlation: ALSFRS−R vs NfL
Correlation
1.0
0.5
0.0
−0.5
−1.0
Precision
(1/CI width)
0.5
0.6
0.7
0.8
Participant
TREG_1
TREG_2
TREG_3
TREG_6
CSF
PLASMA
Metric

FIG. 19D

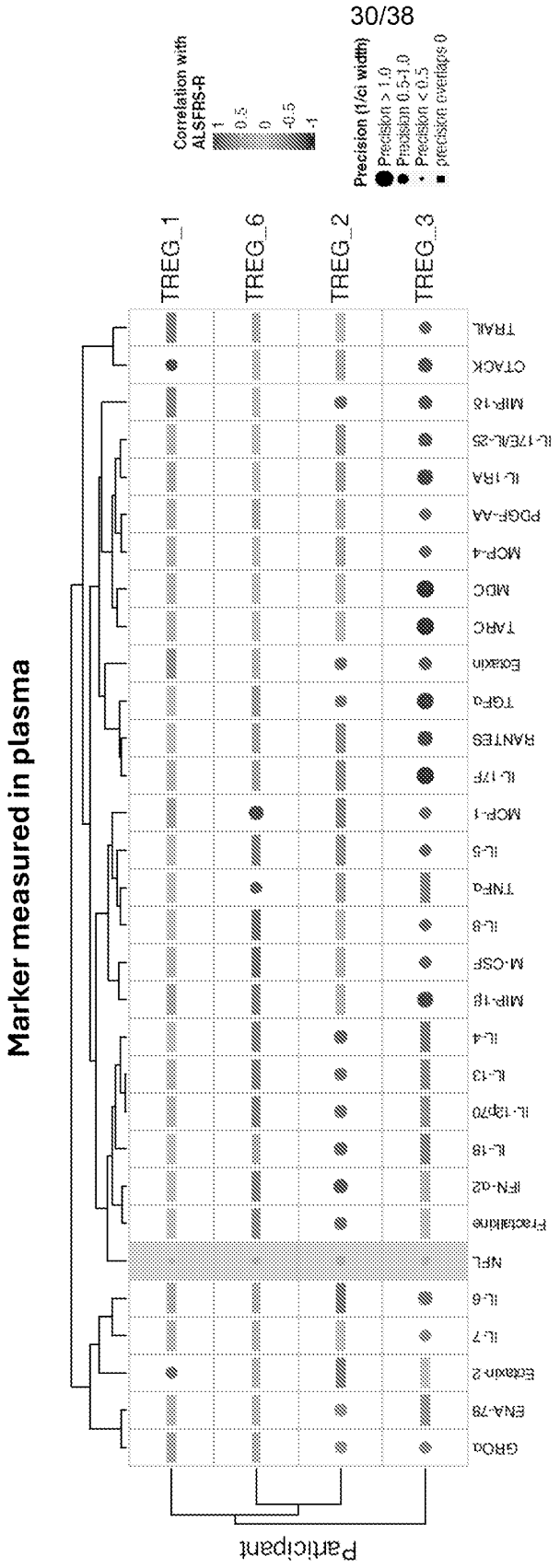
Correlation with ALSFRS-R
1
0.5
0
-0.5
-1
Precision (1/ci width)
Precision > 1.0
Precision 0.5-1.0
Precision < 0.5
precision overlaps 0
TREG_1
TREG_6
TREG_2
TREG_3
Marker measured in plasma
Participant
TRAIL
CTACK
MIP-1δ
IL-17E/IL-25
IL-1RA
PDGF-AA
MCP-4
MDC
TARC
Eotaxin
TGFα
RANTES
IL-17F
MCP-1
IL-5
TNFα
IL-9
M-CSF
MIP-1β
IL-4
IL-13
IL-12p70
IL-1β
IFN-α2
Fractalkine
NFL
IL-6
IL-7
Eotaxin-2
ENA-78
GROα

FIG. 20A

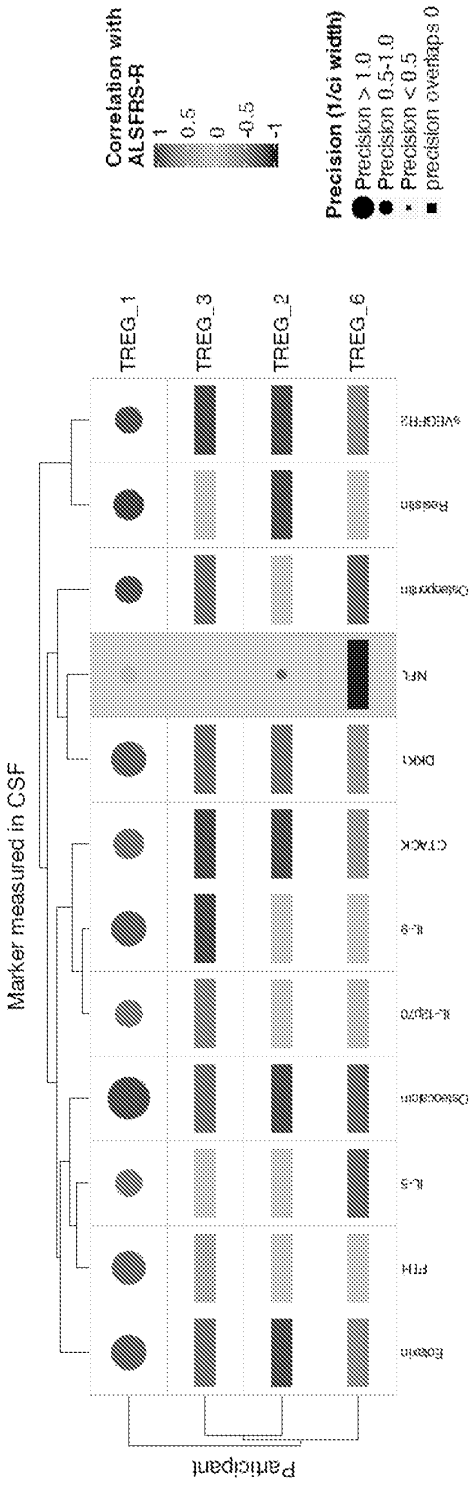
Correlation with ALSFRS-R
1
0.5
0
-0.5
-1
Precision (1/ci width)
Precision > 1.0
Precision 0.5-1.0
Precision < 0.5
precision overlaps 0
TREG_1
TREG_3
TREG_2
TREG_6
Marker measured in CSF
Participant

FIG. 20B

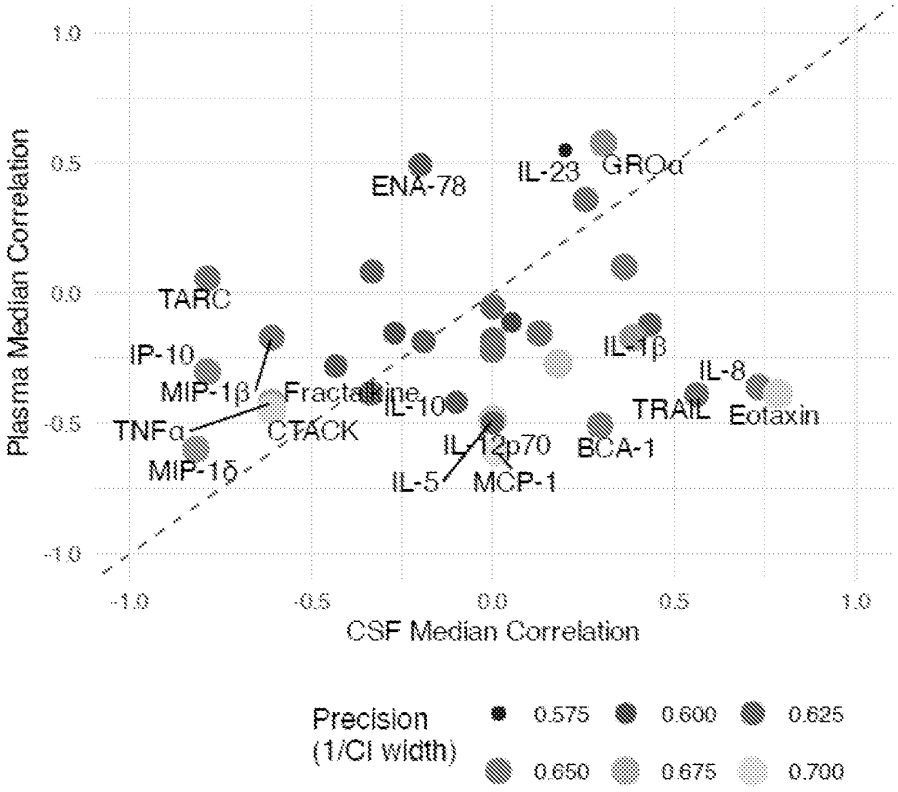
Plasma Median Correlation
CSF Median Correlation
1.0
0.5
0.0
-0.5
-1.0
ENA-78
IL-23
GROα
TARC
IP-10
MIP-1β
Fractalkine
IL-10
IL-1β
IL-8
TRAIL
Eotaxin
TNFα
CTACK
IL-12p70
BCA-1
MIP-1δ
IL-5
MCP-1
Precision
(1/CI width)
0.575
0.600
0.625
0.650
0.675
0.700

FIG. 21A

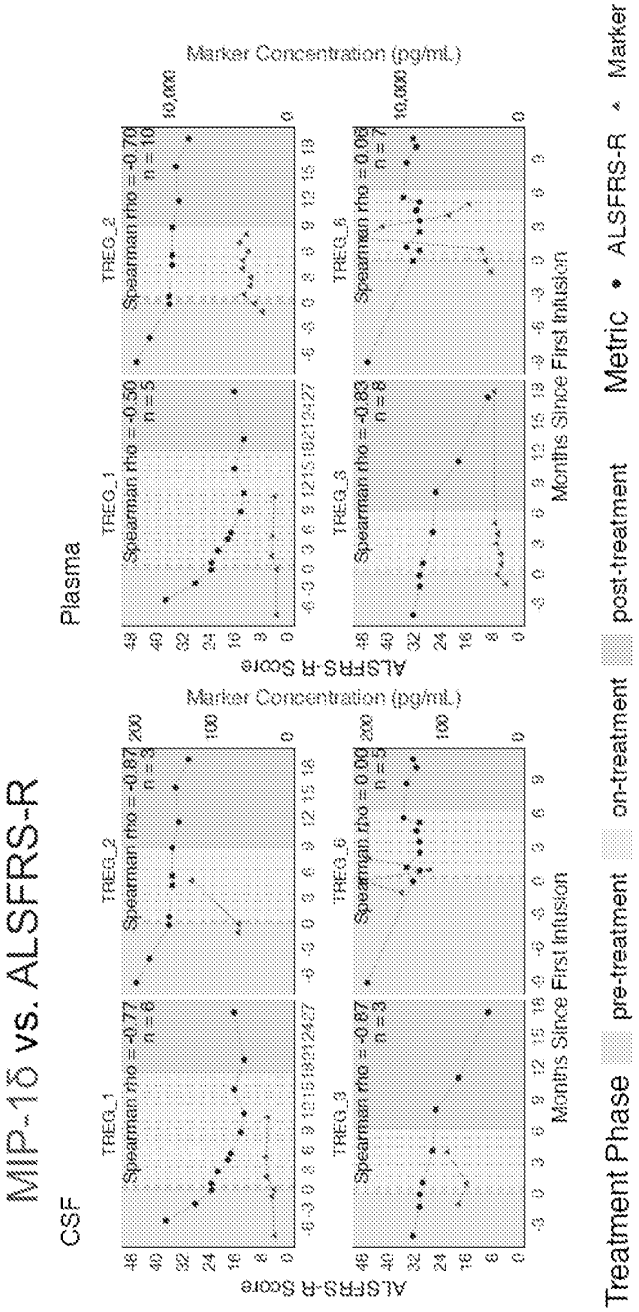
MIP-1δ vs. ALSFRS-R
CSF
Plasma
TREG_1
TREG_2
TREG_3
TREG_6
Spearman rho = +0.77
n = 8
Spearman rho = +0.87
n = 3
Spearman rho = -0.87
n = 3
Spearman rho = 0.00
n = 5
Spearman rho = -0.50
n = 5
Spearman rho = +0.70
n = 10
Spearman rho = -0.83
n = 8
Spearman rho = 0.06
n = 7
ALSFRS-R Score
Marker Concentration (pg/mL)
Months Since First Infusion
Treatment Phase
pre-treatment
on-treatment
post-treatment
Metric
ALSFRS-R
Marker

FIG. 21B

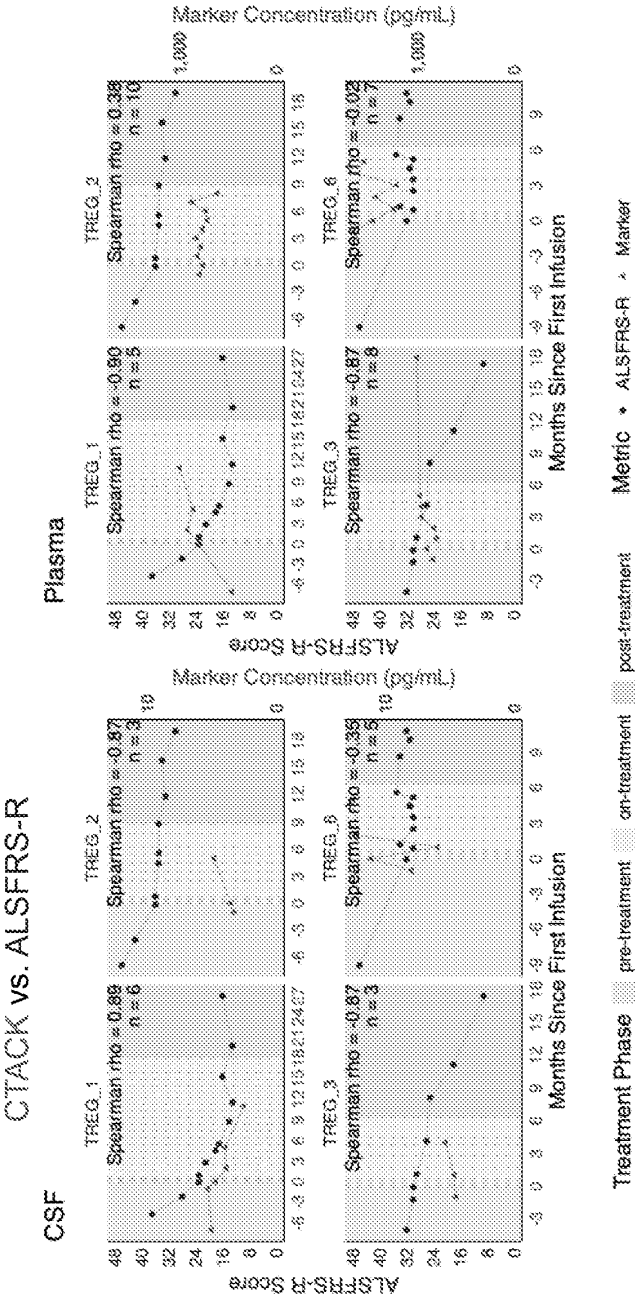
CTACK vs. ALSFRS-R
CSF
Plasma
TREG_1
TREG_2
TREG_3
TREG_6
Spearman rho = -0.88
n = 6
Spearman rho = -0.87
n = 3
Spearman rho = -0.99
n = 6
Spearman rho = -0.39
n = 10
Spearman rho = -0.87
n = 3
Spearman rho = -0.39
n = 5
Spearman rho = -0.87
n = 8
Spearman rho = -0.02
n = 7
ALSFRS-R Score
Marker Concentration (pg/mL)
Months Since First Infusion
Treatment Phase
pre-treatment
on-treatment
post-treatment
Metric
ALSFRS-R
Marker

FIG. 21C

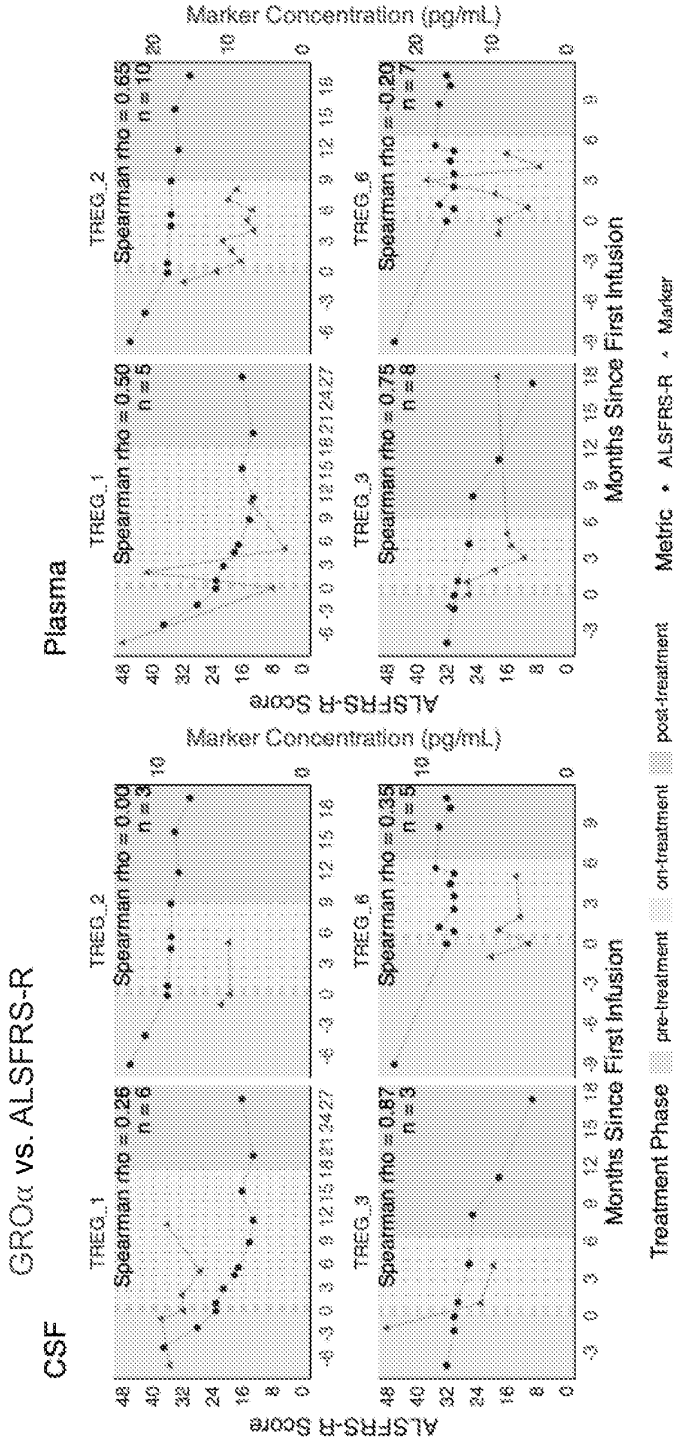
GROα vs. ALSFRS-R
CSF
Plasma
Marker Concentration (pg/mL)
ALSFRS-R Score
Months Since First Infusion
TREG_1
TREG_2
TREG_3
TREG_6
Spearman rho = 0.26
n = 6
Spearman rho = 0.00
n = 3
Spearman rho = 0.87
n = 3
Spearman rho = 0.35
n = 5
Spearman rho = 0.50
n = 5
Spearman rho = 0.65
n = 10
Spearman rho = 0.75
n = 8
Spearman rho = -0.20
n = 7
Treatment Phase
pre-treatment
on-treatment
post-treatment
Metric
ALSFRS-R
Marker

FIG. 21D

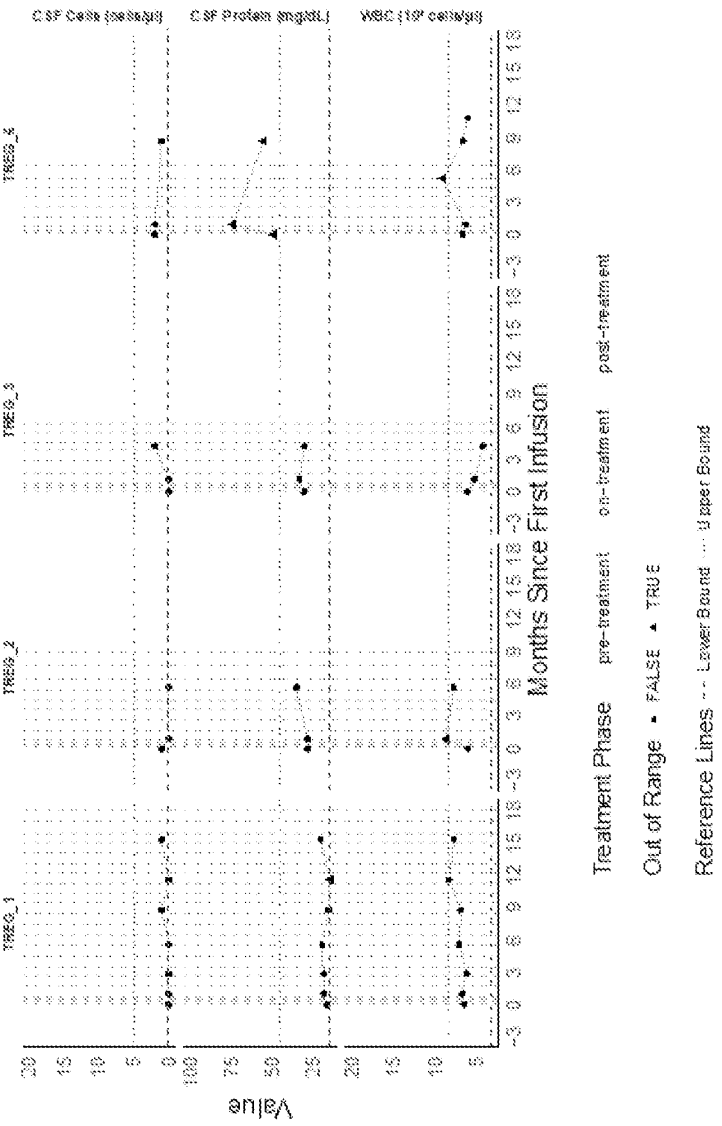
CSF Cells (cells/µL)
CSF Protein (mg/dL)
WBC (10³ cells/µL)
TREG_1
TREG_2
TREG_3
TREG_4
Value
Months Since First Infusion
Treatment Phase pre-treatment on-treatment post-treatment
Out of Range FALSE TRUE
Reference Lines Lower Bound Upper Bound

FIG. 22

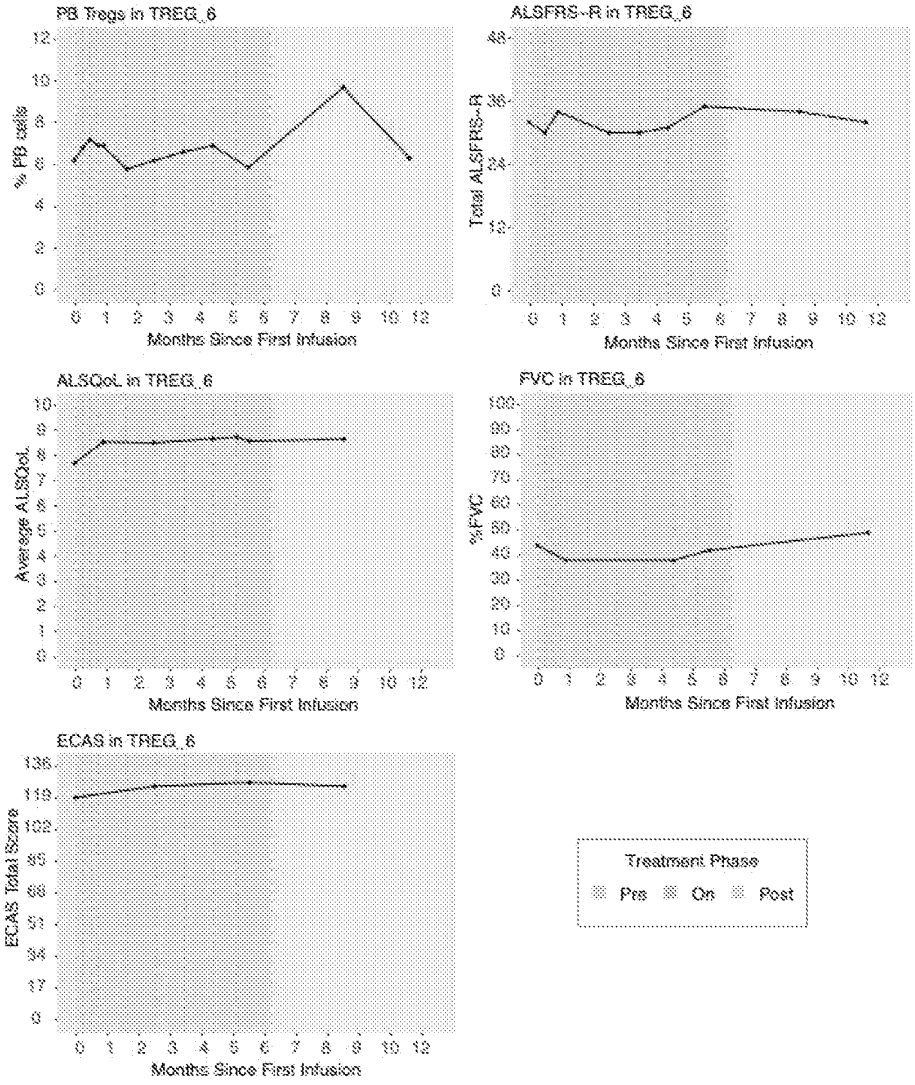
PB Tregs in TREG_6
% PB cells
Months Since First Infusion
ALSFRS-R in TREG_6
Total ALSFRS-R
Months Since First Infusion
ALSQoL in TREG_6
Average ALSQoL
Months Since First Infusion
FVC in TREG_6
%FVC
Months Since First Infusion
ECAS in TREG_6
ECAS Total Score
Months Since First Infusion
Treatment Phase
Pre
On
Post

FIG. 23

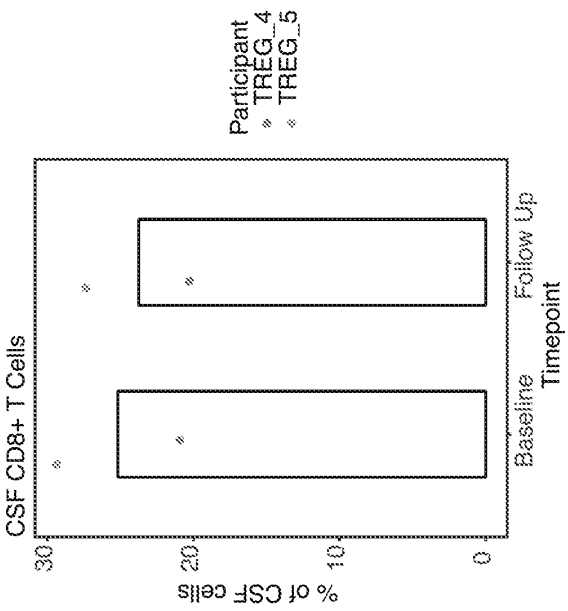

FIG. 24B

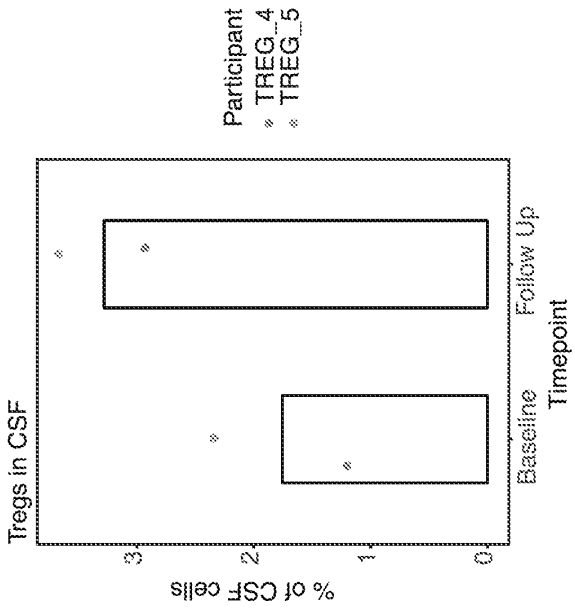

FIG. 24A