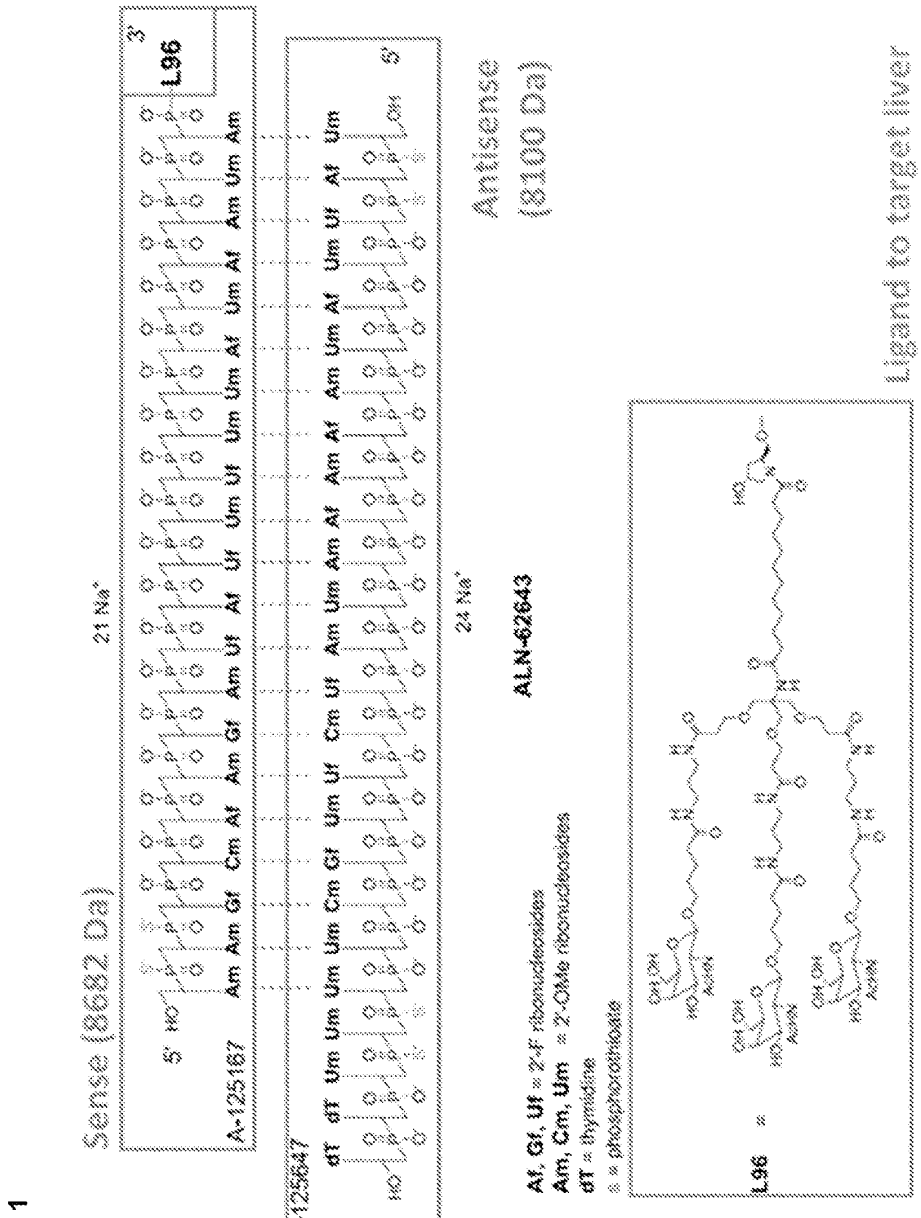
FIG. 1


Sense (8682 Da)
21 Na+
3'
L96
5'
A-125167
Am Am Gf Cm Af Am Gf Am Uf Af Uf Um Um Um Af Um Af Am Um Am
A-125647
dT dT Um Um Um Um Cm Gf Um Uf Cm Uf Am Um Am Af Am Af Am Um Af Um Uf Af Um
3'
5'
24 Na+
Antisense
(8100 Da)
Af, Gf, Uf = 2'-F ribonucleosides
Am, Cm, Um = 2'-OMe ribonucleosides
dT = thymidine
s = phosphorothioate
ALN-62643
L96 =
Ligand to target liver

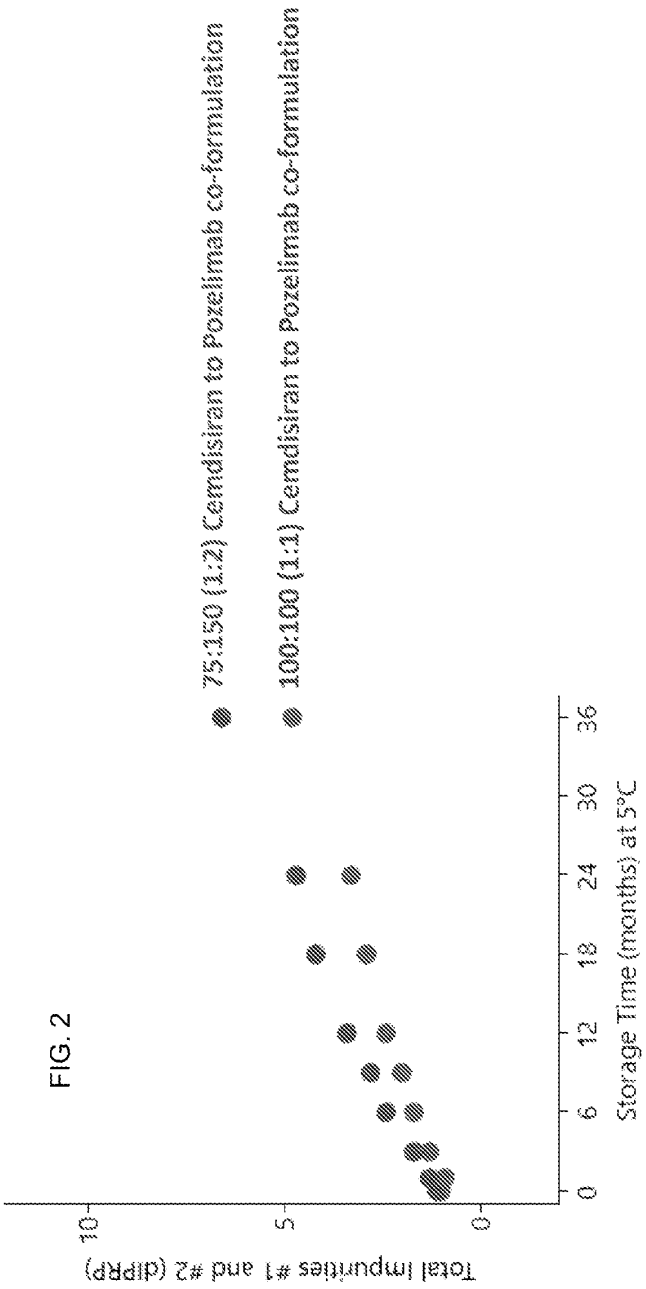

75:150 (1:2) Cemdisiran to Pozelimab co-formulation
100:100 (1:1) Cemdisiran to Pozelimab co-formulation
Total Impurities #1 and #2 (dIPRP)
0
5
10
0
6
12
18
24
30
36
Storage Time (months) at 5°C

FIG. 2

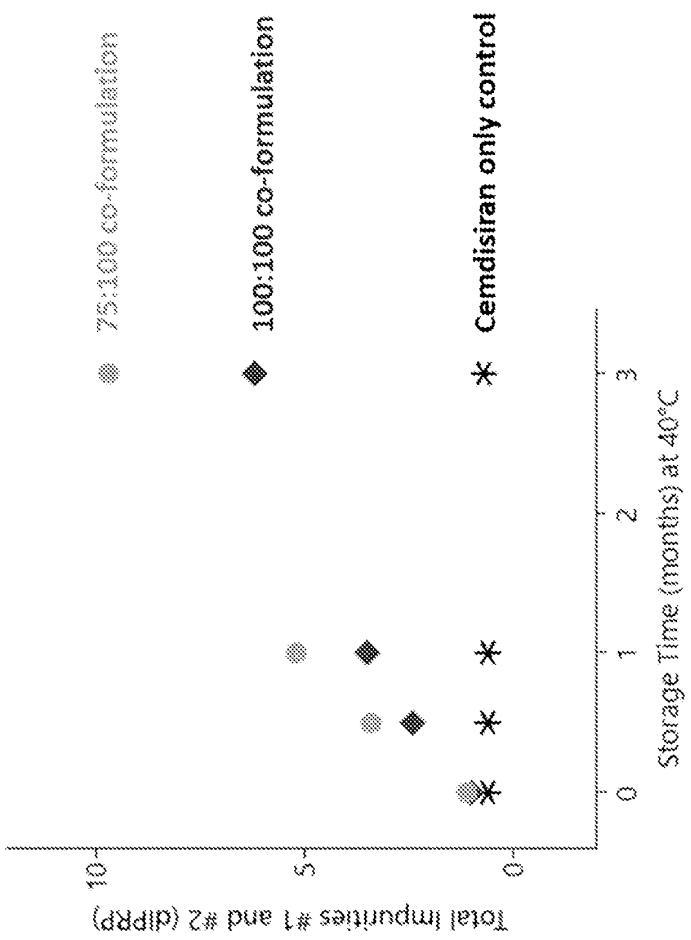

75:100 co-formulation
100:100 co-formulation
Cemdisiran only control
Total Impurities #1 and #2 (dIPRP)
10
5
0
0
1
2
3
Storage Time (months) at 40°C

FIG. 3

FIG. 4

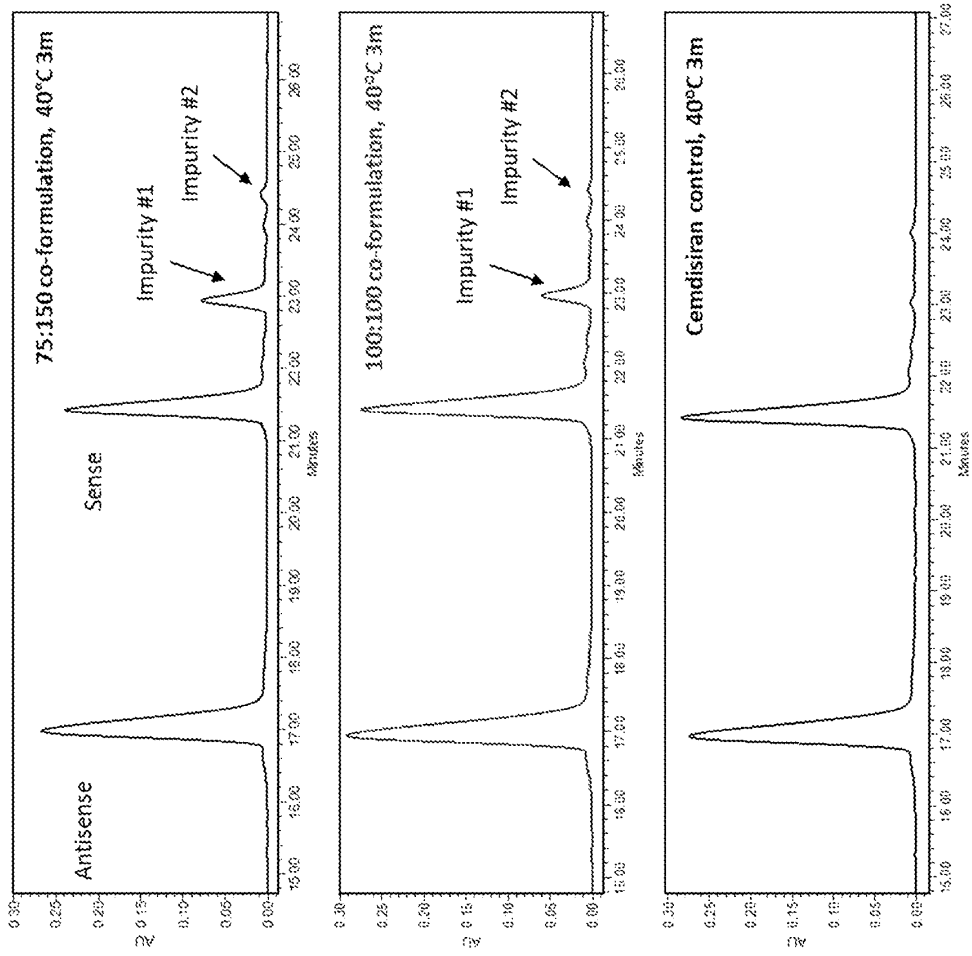

75:150 co-formulation, 40°C 3m
Antisense
Sense
Impurity #1
Impurity #2
100:100 co-formulation, 40°C 3m
Impurity #1
Impurity #2
Cemdisiran control, 40°C 3m
Minutes

FIG. 5

Cemdisiran with loss of 1 GalNAc

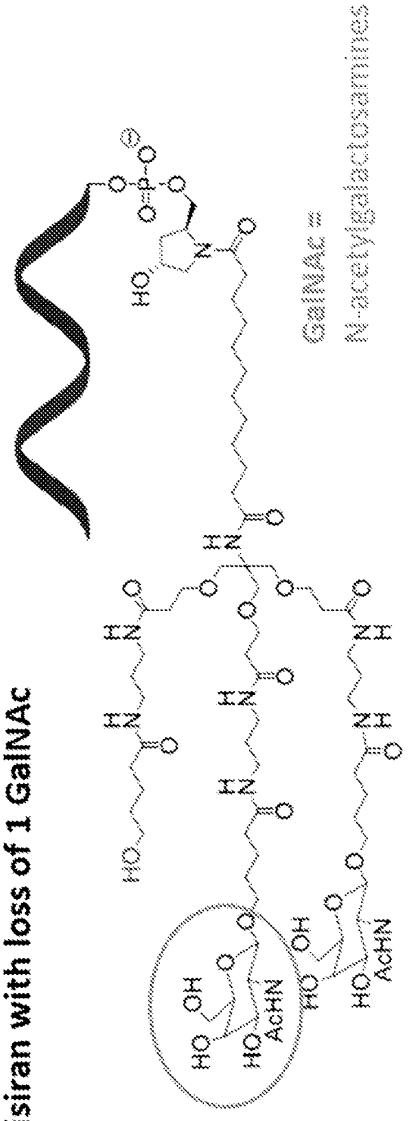


FIG. 6

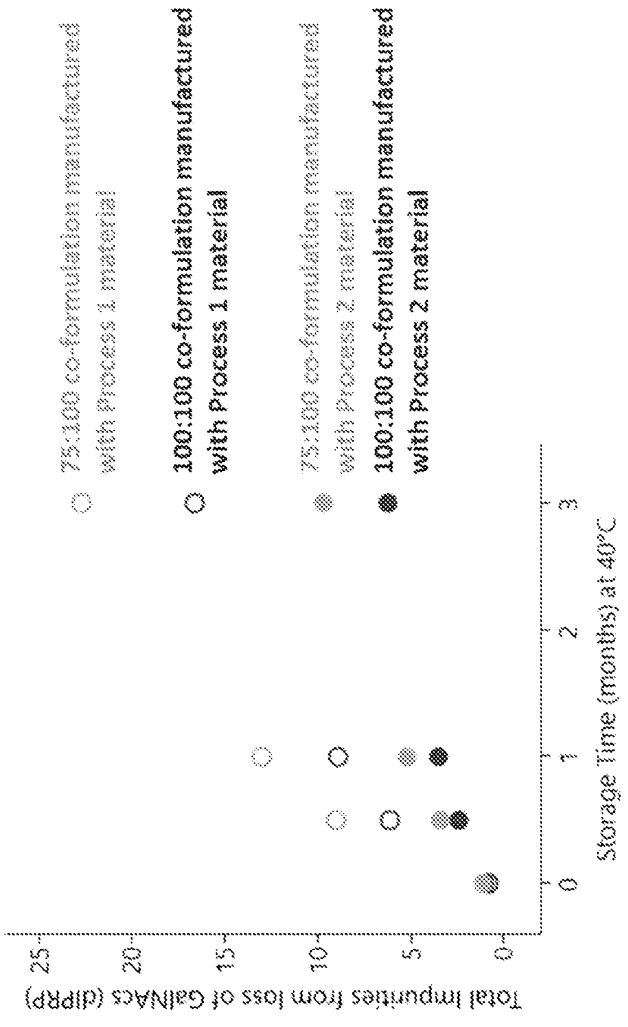

75:100 co-formulation manufactured with Process 1 material
100:100 co-formulation manufactured with Process 1 material
75:100 co-formulation manufactured with Process 2 material
100:100 co-formulation manufactured with Process 2 material
Total Impurities from loss of GalNAcs (diPRP)
25
20
15
10
5
0
0
1
2
3
Storage Time (months) at 40°C

FIG. 7

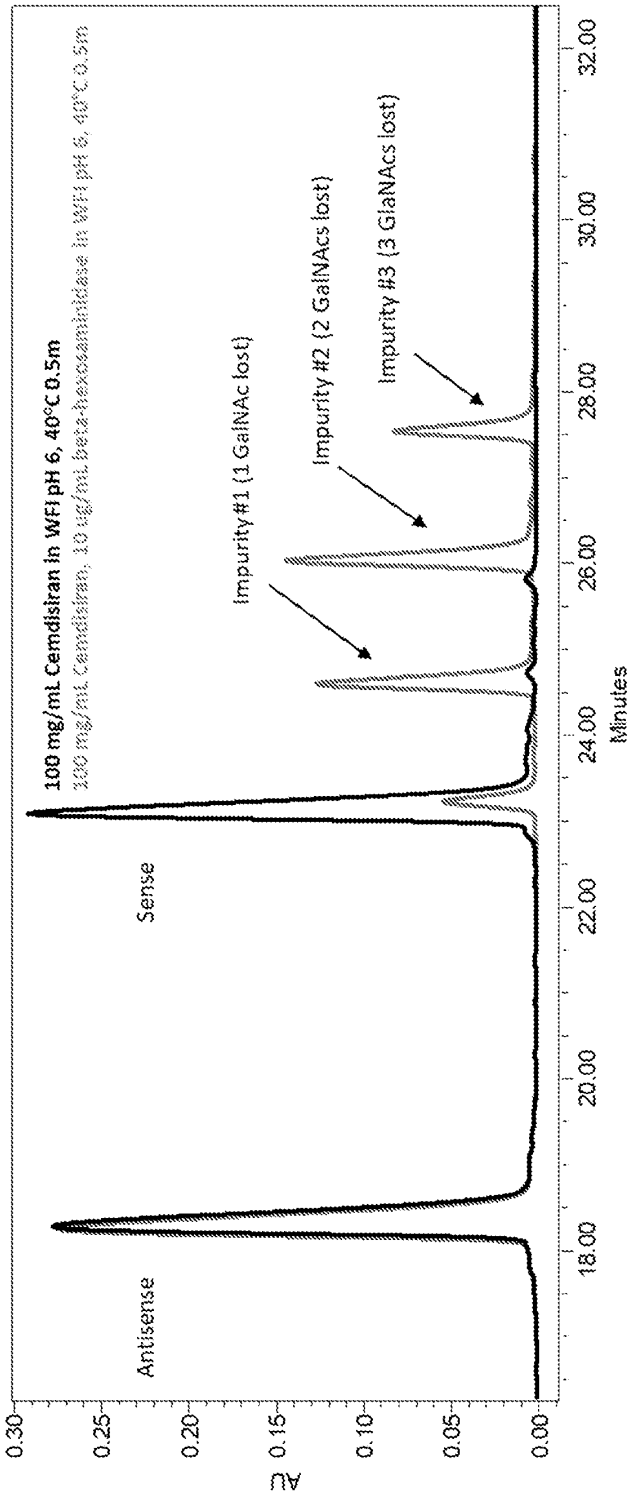

100 mg/mL Cemdisiran in WFI pH 6, 40°C 0.5m
100 mg/mL Cemdisiran, 10 ug/mL beta-hexosaminidase in WFI pH 6, 40°C 0.5m
Antisense
Sense
Impurity#1 (1 GalNAc lost)
Impurity #2 (2 GalNAcs lost)
Impurity #3 (3 GlaNAcs lost)
AU
0.30
0.25
0.20
0.15
0.10
0.05
0.00
18.00
20.00
22.00
24.00
26.00
28.00
30.00
32.00
Minutes

FIG. 8

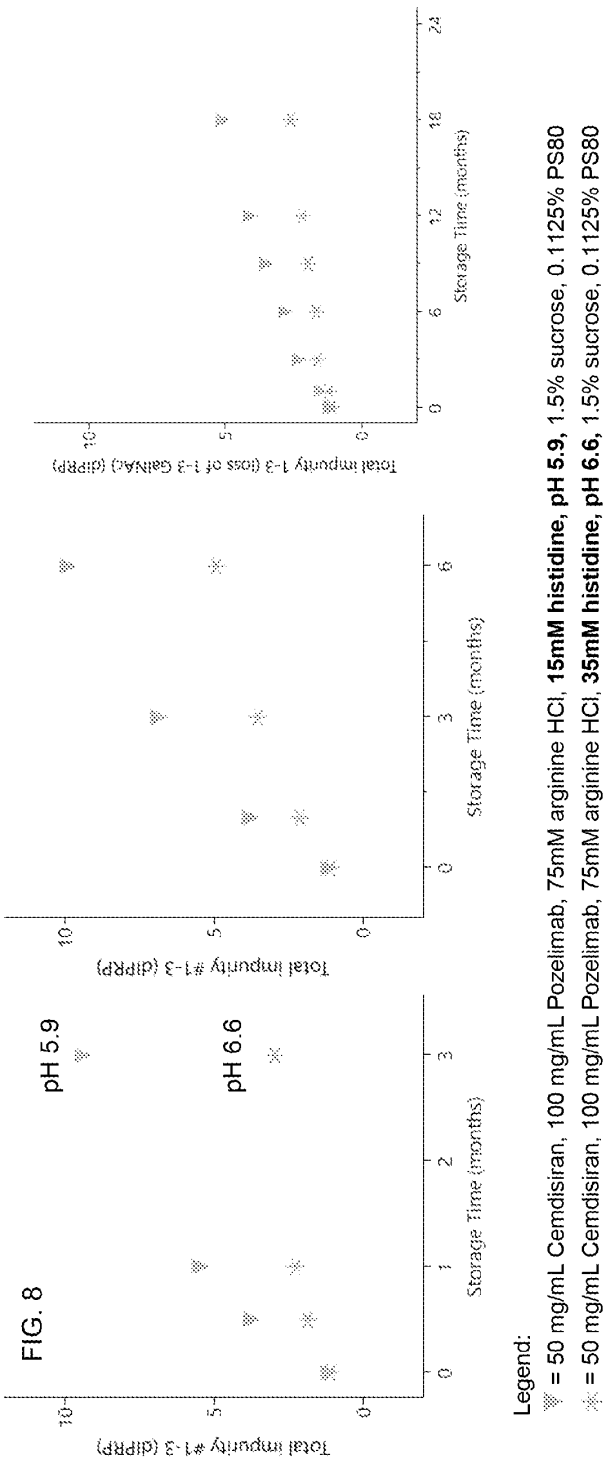
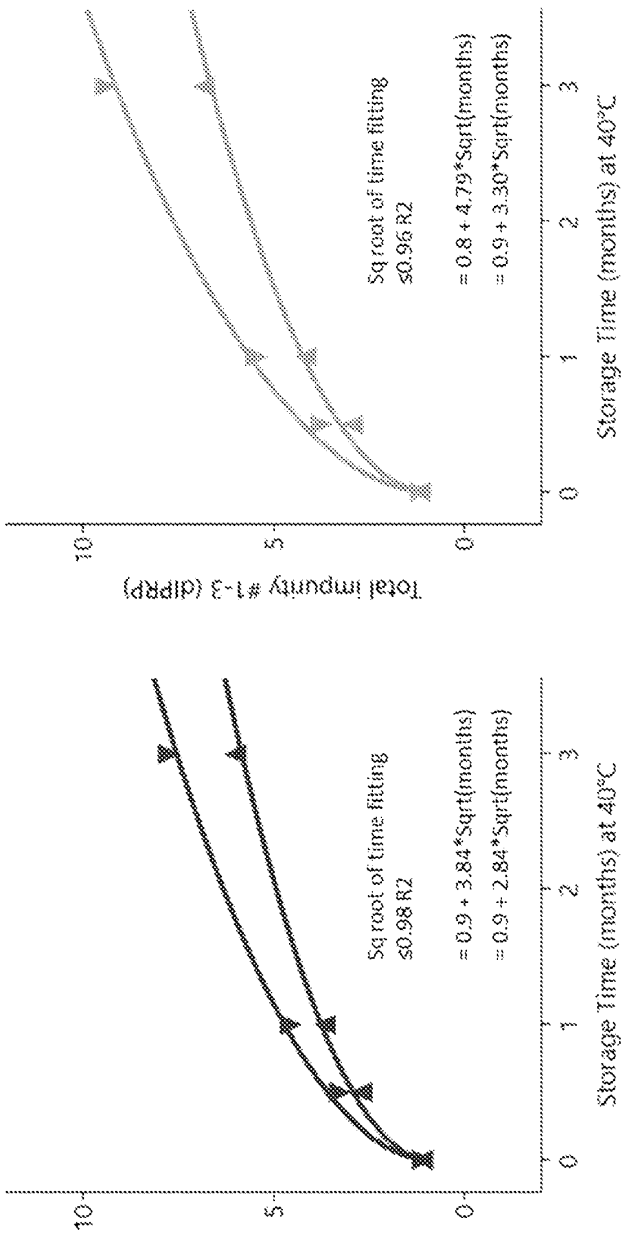

pH 5.9
pH 6.6
Total impurity #1-3 (dIPRP)
Storage Time (months)
Total impurity 1-3 (loss of 1-3 GalNAc) (dIPRP)
Storage Time (months)
Legend:
= 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 75mM arginine HCl, 15mM histidine, pH 5.9, 1.5% sucrose, 0.1125% PS80
= 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 75mM arginine HCl, 35mM histidine, pH 6.6, 1.5% sucrose, 0.1125% PS80

FIG. 9



Legend:

▼ = 100 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 50 mM Arg HCl, 10 mM His, 1.0% sucrose, 0.075% PS80, pH 6.0 (Pozelimab lot 3)

▲ = 100 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 50 mM Arg HCl, 10 mM His, 1.0% sucrose, 0.075% PS80, pH 6.0 (Pozelimab lot 4)

▽ = 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 75 mM Arg HCl, 15 mM His, 1.5% sucrose, 0.1125% PS80, pH 6.0 (Pozelimab lot 3)

△ = 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 75 mM Arg HCl, 15 mM His, 1.5% sucrose, 0.1125% PS80, pH 6.0 (Pozelimab lot 4)

FIG. 10

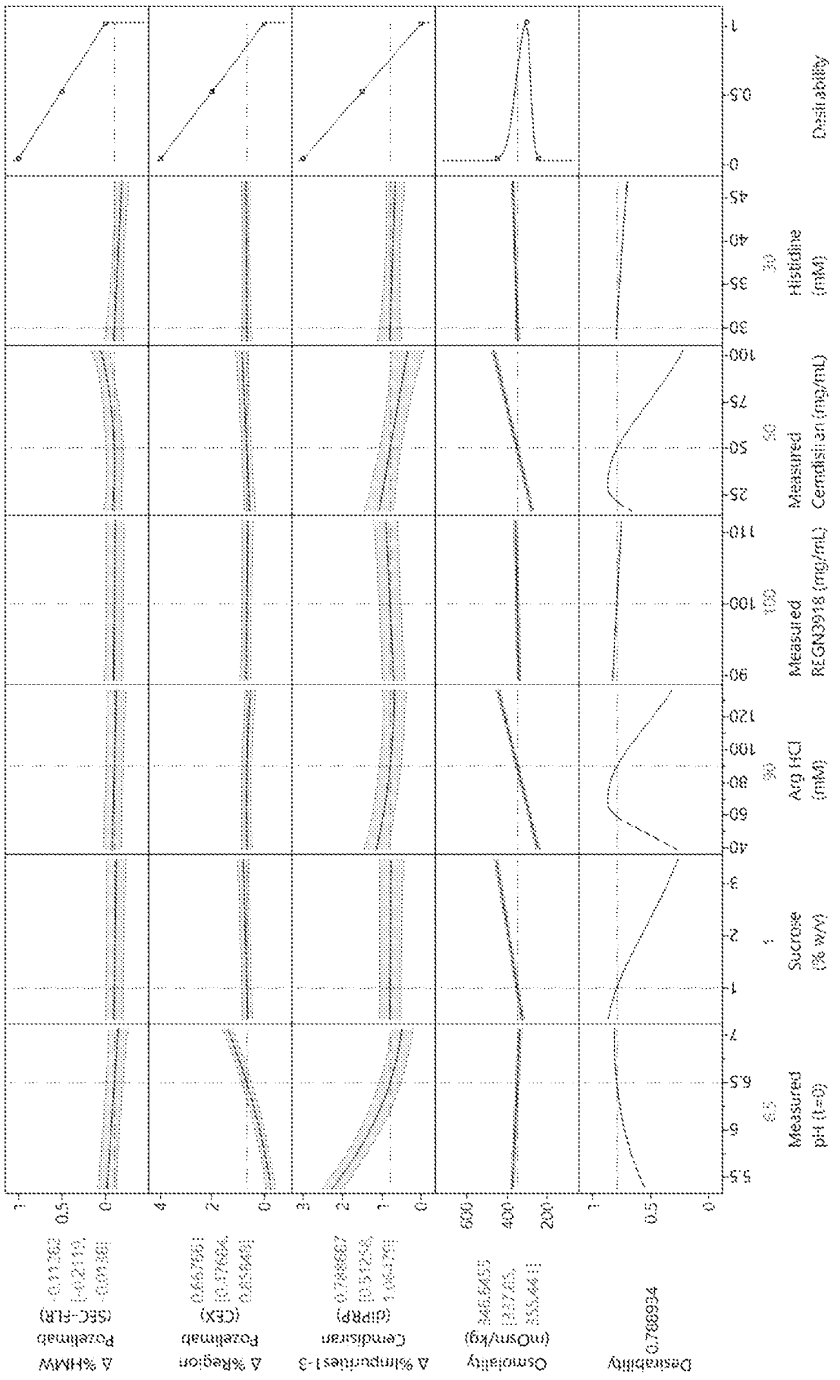

Δ %HMW Rozelimab (SEC-HLR)
Δ %Region Rozelimab (CEX)
Δ %Impurities 1-3 Cemdisiran (GPRP)
Osmolality (mOsm/kg)
Desirability
Measured pH (t=0)
Sucrose (% w/v)
Arg HCl (mM)
Measured REGN3918 (mg/mL)
Measured Cemdisiran (mg/mL)
Histidine (mM)
Desirability

FIG. 11

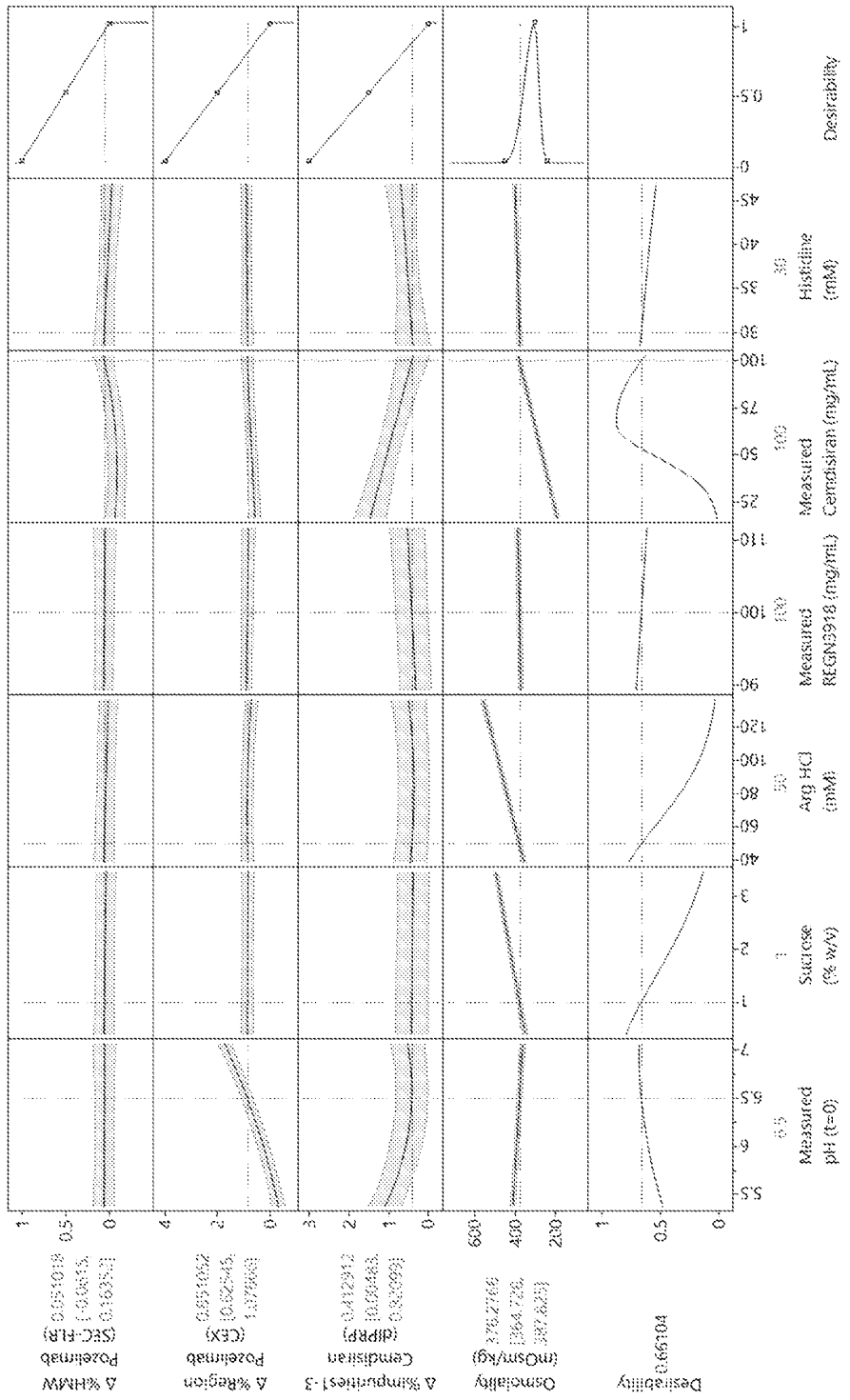
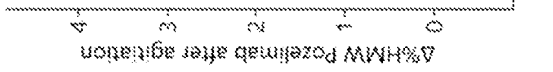

Δ %HMW Pozelimab (SEC-FLR)
Δ %Region Pozelimab (CEX)
Δ %Impurities1-3 Cemdisiran (dIPRP)
Osmolality (mOsm/kg)
Desirability
Measured pH (t=0)
Sucrose (% w/v)
Arg HCl (mM)
Measured REGN3918 (mg/mL)
Measured Cemdisiran (mg/mL)
Histidine (mM)
Desirability

FIG. 12



Legend:

Δ = 100 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 50 mM arginine HCl, 30 mM histidine, 1% sucrose, X% PS80, pH 6.5

X = 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 90 mM Arg HCl, 30 mM histidine, 1% sucrose, X% PS80, pH 6.5

FIG. 13

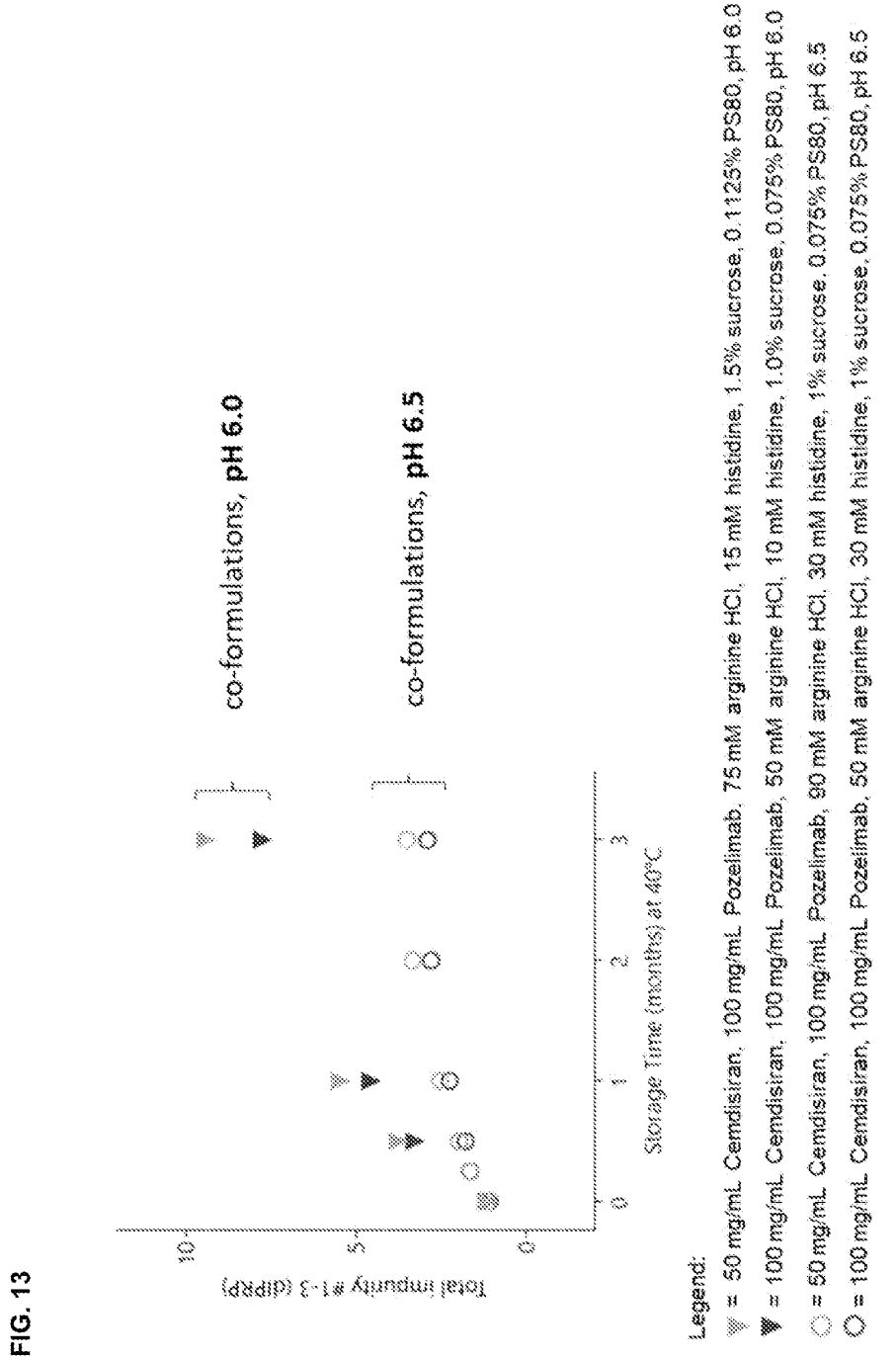
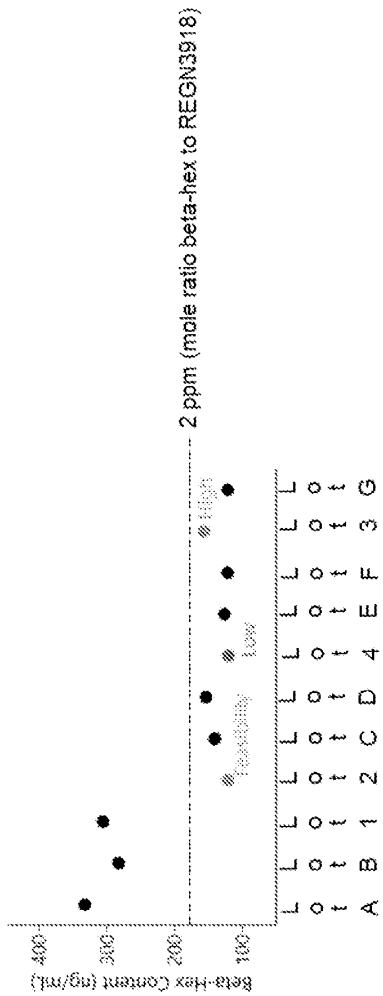

co-formulations, pH 6.0
co-formulations, pH 6.5
Total impurity #1-3 (dIPRP)
10
5
0
0
1
2
3
Storage Time (months) at 40°C
Legend:
= 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 75 mM arginine HCl, 15 mM histidine, 1.5% sucrose, 0.1125% PS80, pH 6.0
= 100 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 50 mM arginine HCl, 10 mM histidine, 1.0% sucrose, 0.075% PS80, pH 6.0
= 50 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 90 mM arginine HCl, 30 mM histidine, 1% sucrose, 0.075% PS80, pH 6.5
= 100 mg/mL Cemdisiran, 100 mg/mL Pozelimab, 50 mM arginine HCl, 30 mM histidine, 1% sucrose, 0.075% PS80, pH 6.5

FIG. 14



Pozelimab Lot	Beta-Hex (ng/mL)
Lot A	332
Lot B	282
Lot 1	305
Lot 2	121
Lot C	140
Lot D	153
Lot 4	120
Lot E	126
Lot F	121
Lot 3	156
Lot G	121

FIG. 15

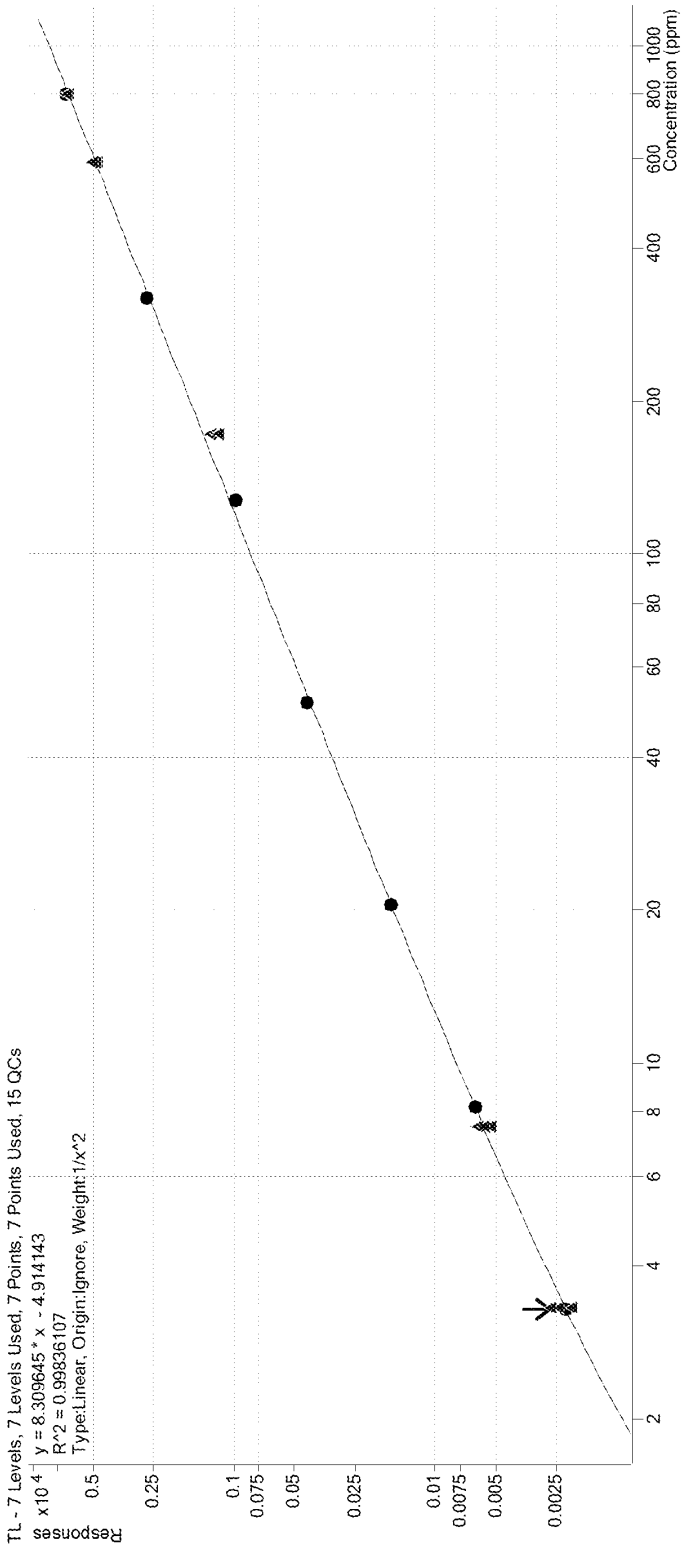

TL - 7 Levels, 7 Levels Used, 7 Points, 7 Points Used, 15 QCs
y = 8.309645 * x - 4.914143
R^2 = 0.99836107
Type:Linear, Origin:Ignore, Weight:1/x^2
x10 4
Responses
0.5
0.25
0.1
0.075
0.05
0.025
0.01
0.0075
0.005
0.0025
2
4
6
8
10
20
40
60
80
100
200
400
600
800
1000
Concentration (ppm)

FIG. 16

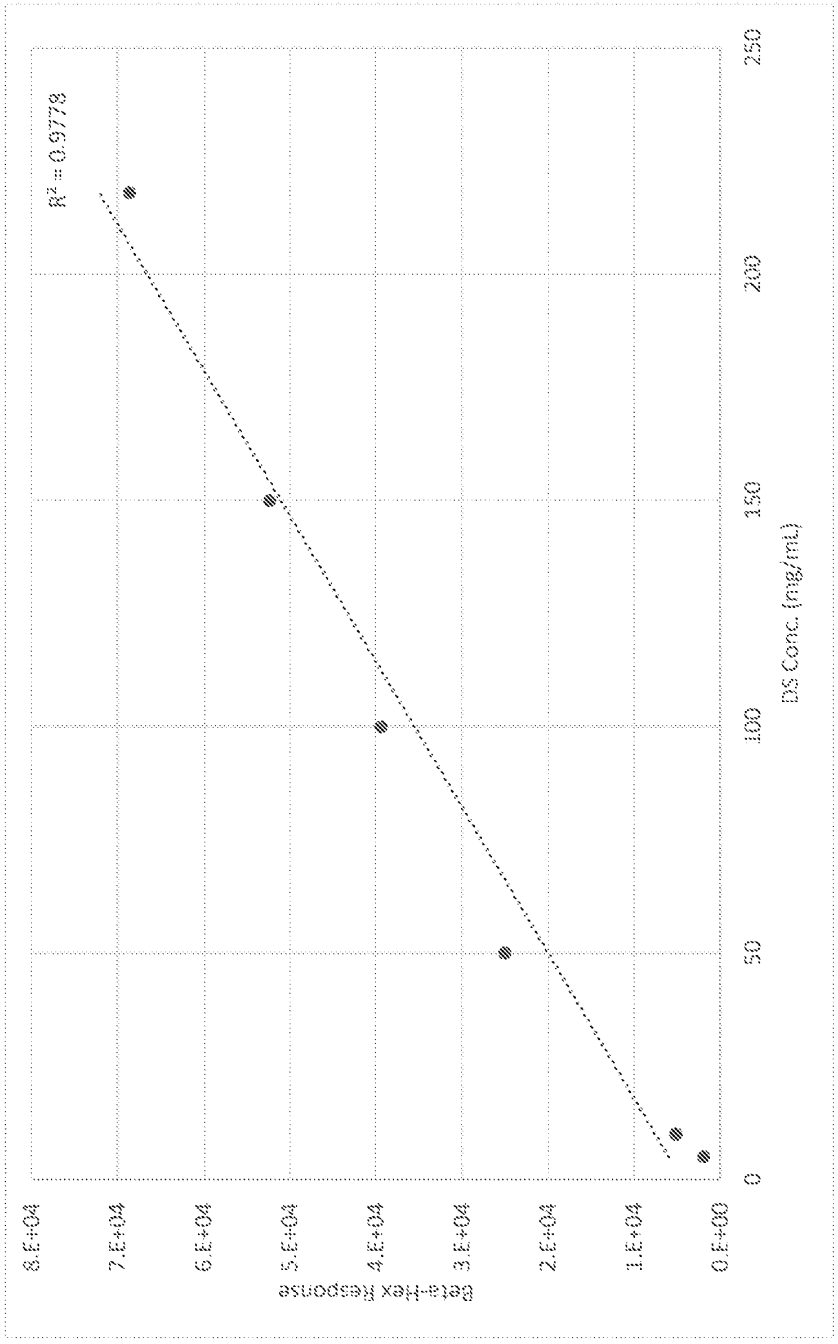
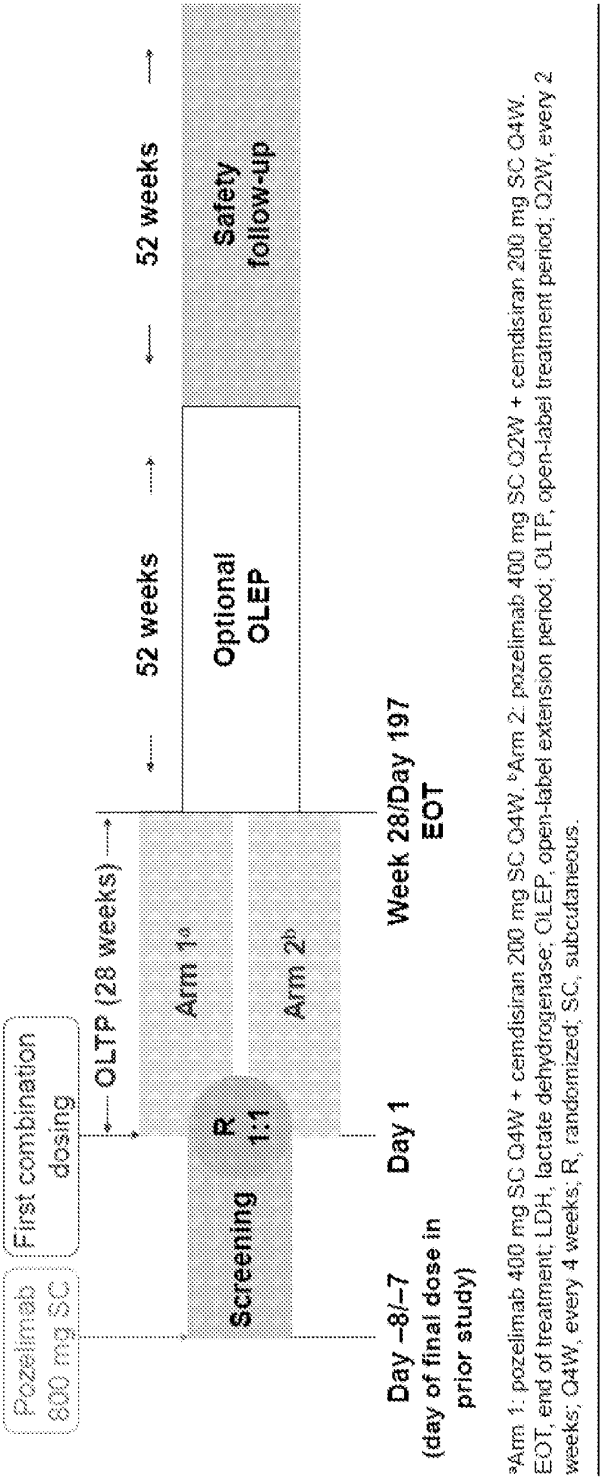
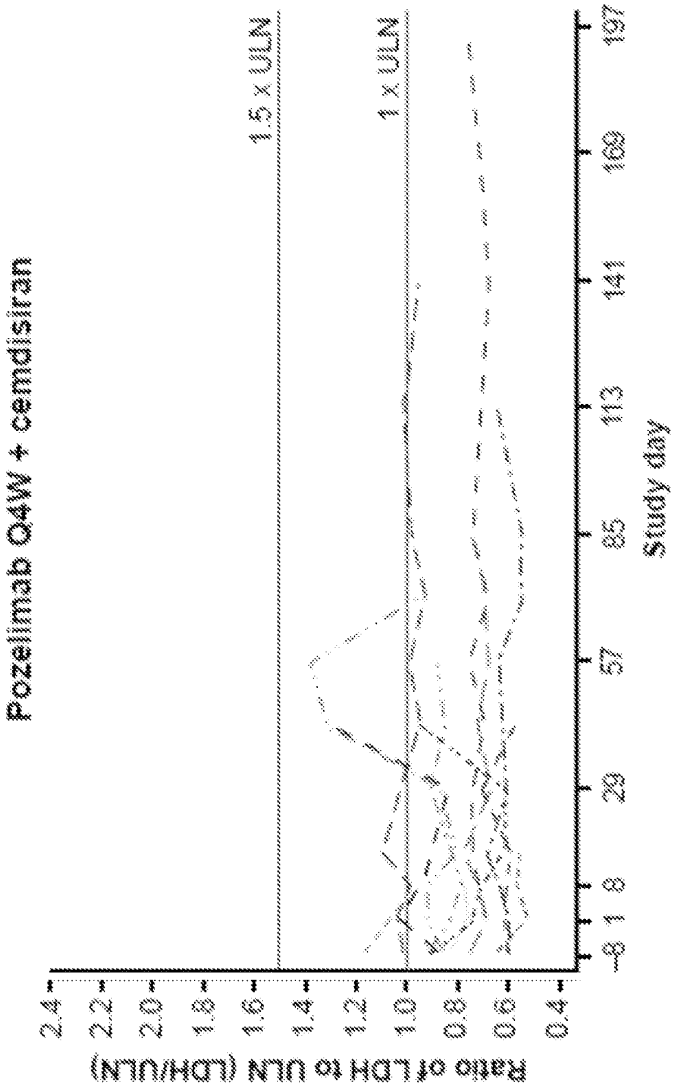

$R^2 = 0.9778$
Beta-Hex Response
8.E+04
7.E+04
6.E+04
5.E+04
4.E+04
3.E+04
2.E+04
1.E+04
0.E+00
0
50
100
150
200
250
DS Conc. (mg/mL)

FIG. 17



[a]Arm 1: pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W. [b]Arm 2: pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W. EOT, end of treatment; LDH, lactate dehydrogenase; OLEP, open-label extension period; OLTP, open-label treatment period; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomized; SC, subcutaneous.

FIG. 18


Pozelimab Q4W + cemdisiran
1.5 x ULN
1 x ULN
Ratio of LDH to ULN (LDH/ULN)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
-9
1
8
29
57
85
113
141
169
197
Study day

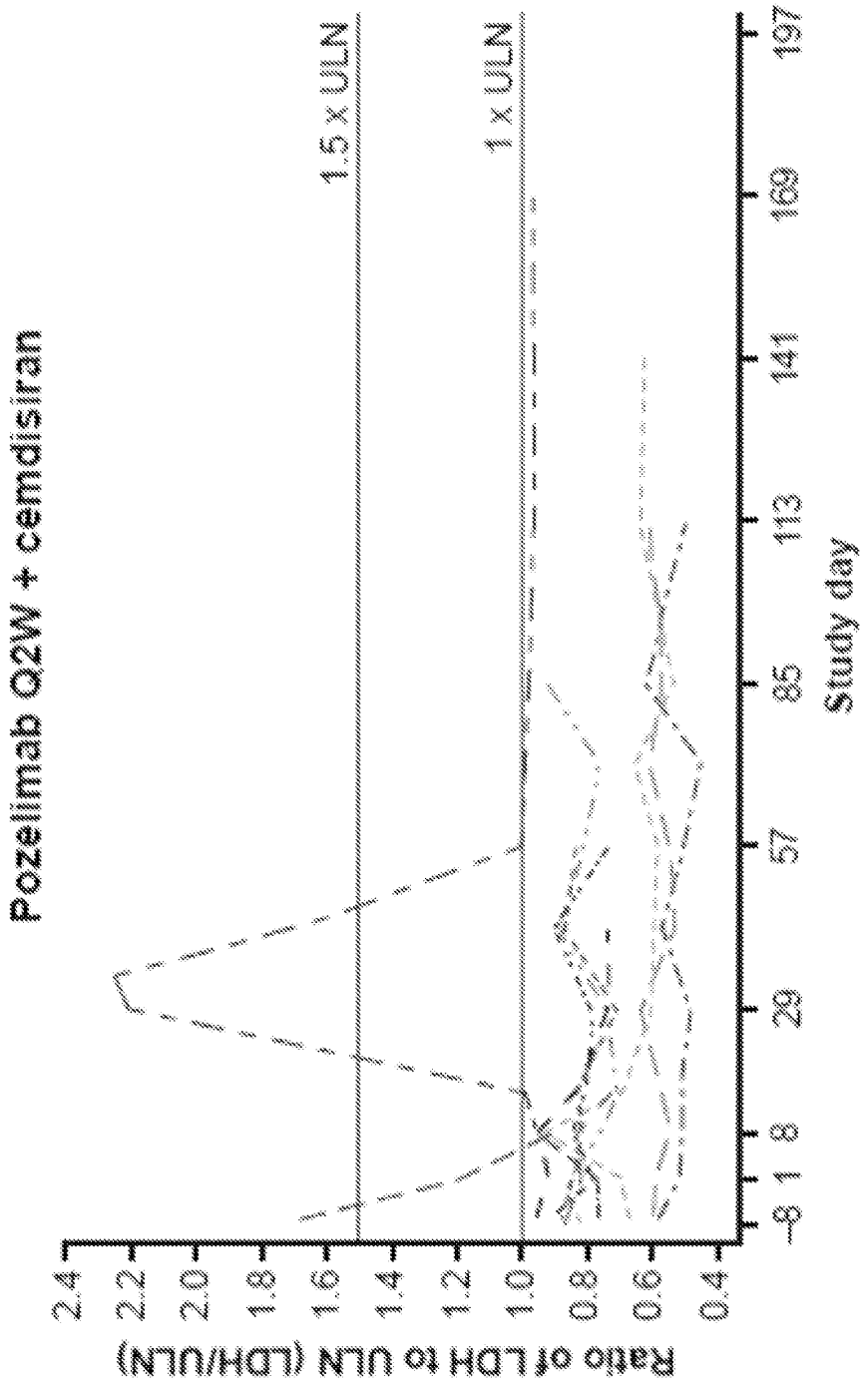
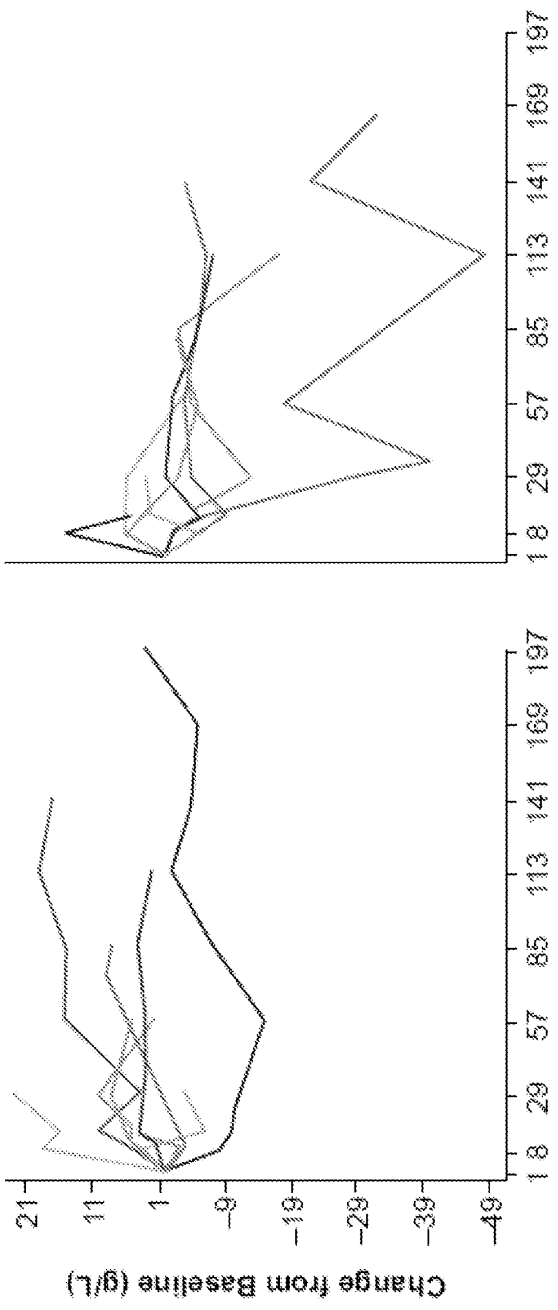

Pozelimab Q2W + cemdisiran
1.5 x ULN
1 x ULN
Ratio of LDH to ULN (LDH/ULN)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
-8
1
8
29
57
85
113
141
169
197
Study day

FIG. 19

FIG. 20



Arm 1: pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W. Arm 2: pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W. SC, subcutaneous; Q2W, every 2 weeks; Q4W, every 4 weeks.

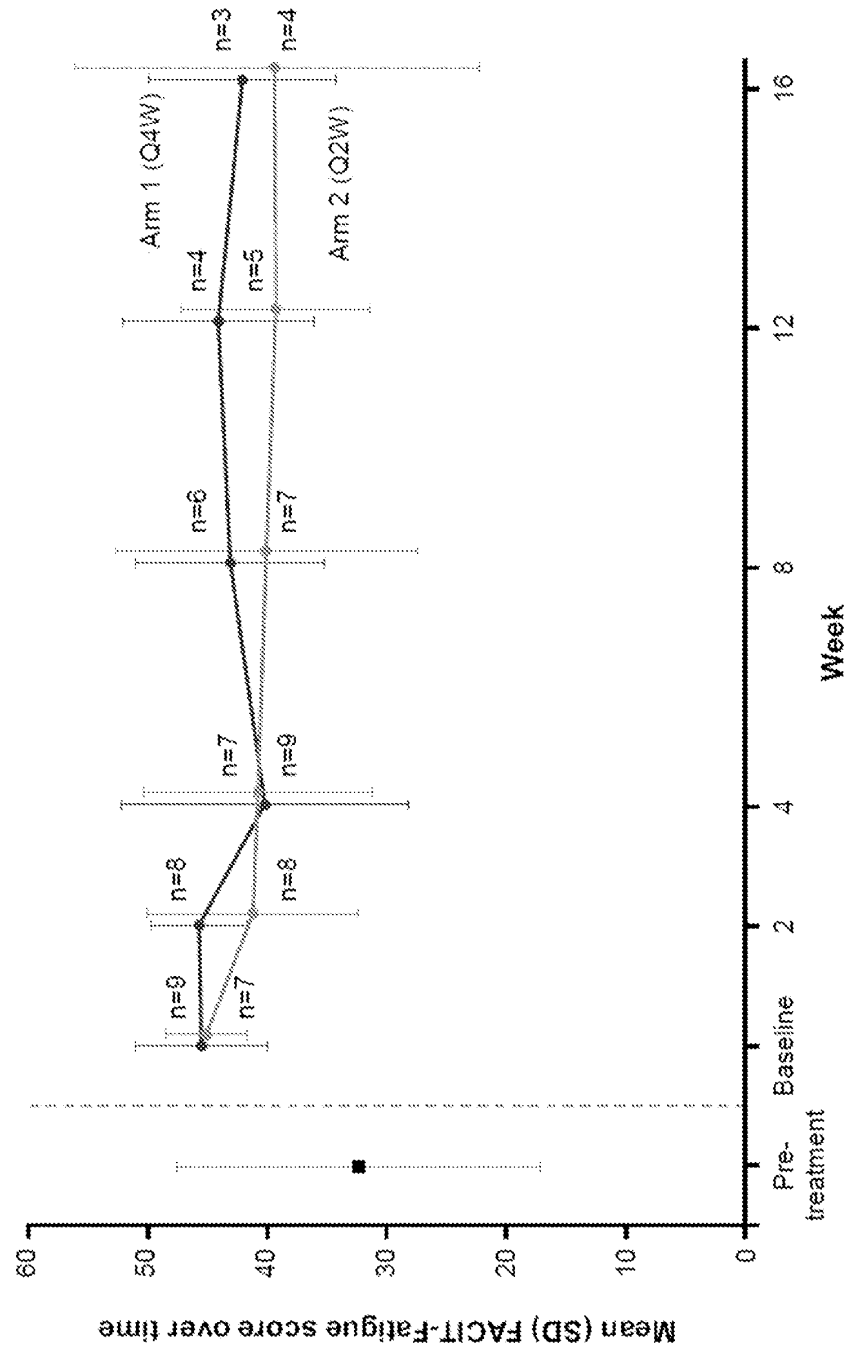

Mean (SD) FACIT-Fatigue score over time
60
50
40
30
20
10
0
Pre-treatment
Baseline
2
4
8
12
16
Week
Arm 1 (Q4W)
Arm 2 (Q2W)
n=9
n=7
n=8
n=8
n=7
n=9
n=6
n=7
n=4
n=5
n=3
n=4

FIG. 21A

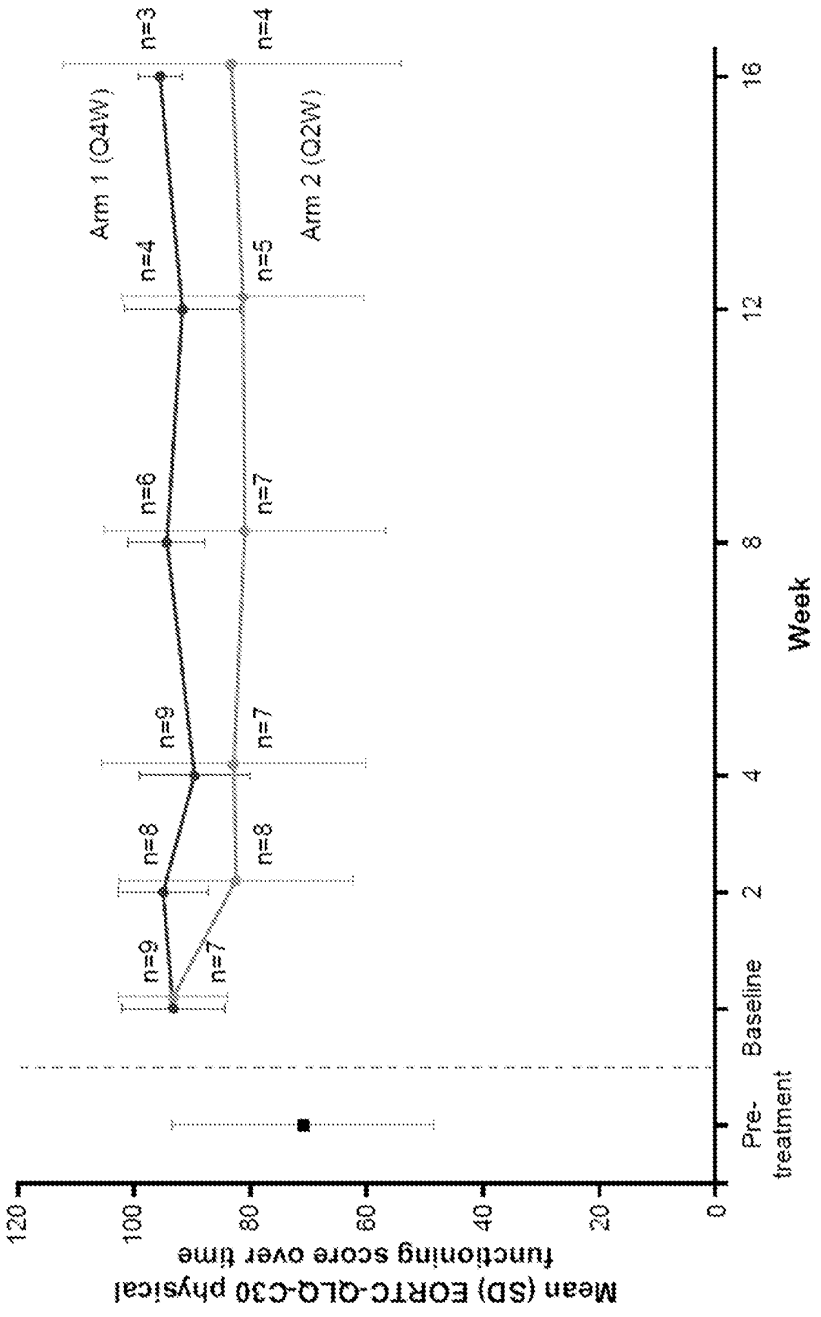

Mean (SD) EORTC-QLQ-C30 physical functioning score over time
120
100
80
60
40
20
0
Pre-treatment
Baseline
2
4
8
12
16
Week
Arm 1 (Q4W)
Arm 2 (Q2W)
n=9
n=7
n=8
n=8
n=9
n=7
n=6
n=7
n=4
n=5
n=3
n=4

FIG. 21B

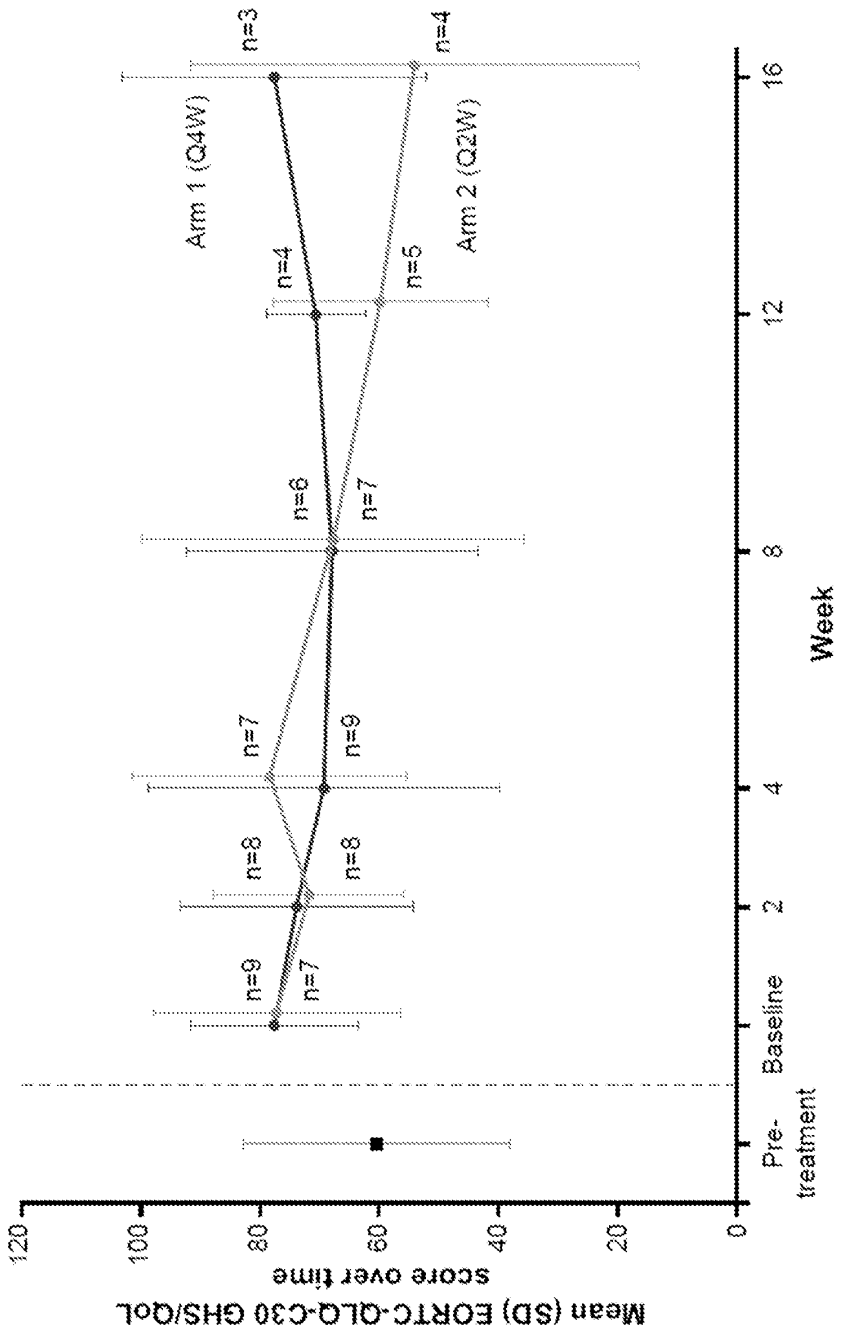

Mean (SD) EORTC-QLQ-C30 GHS/QoL score over time
120
100
80
60
40
20
0
Pre-treatment
Baseline
2
4
8
12
16
Week
Arm 1 (Q4W)
Arm 2 (Q2W)
n=9
n=7
n=8
n=8
n=7
n=9
n=6
n=7
n=4
n=5
n=3
n=4

FIG. 21C

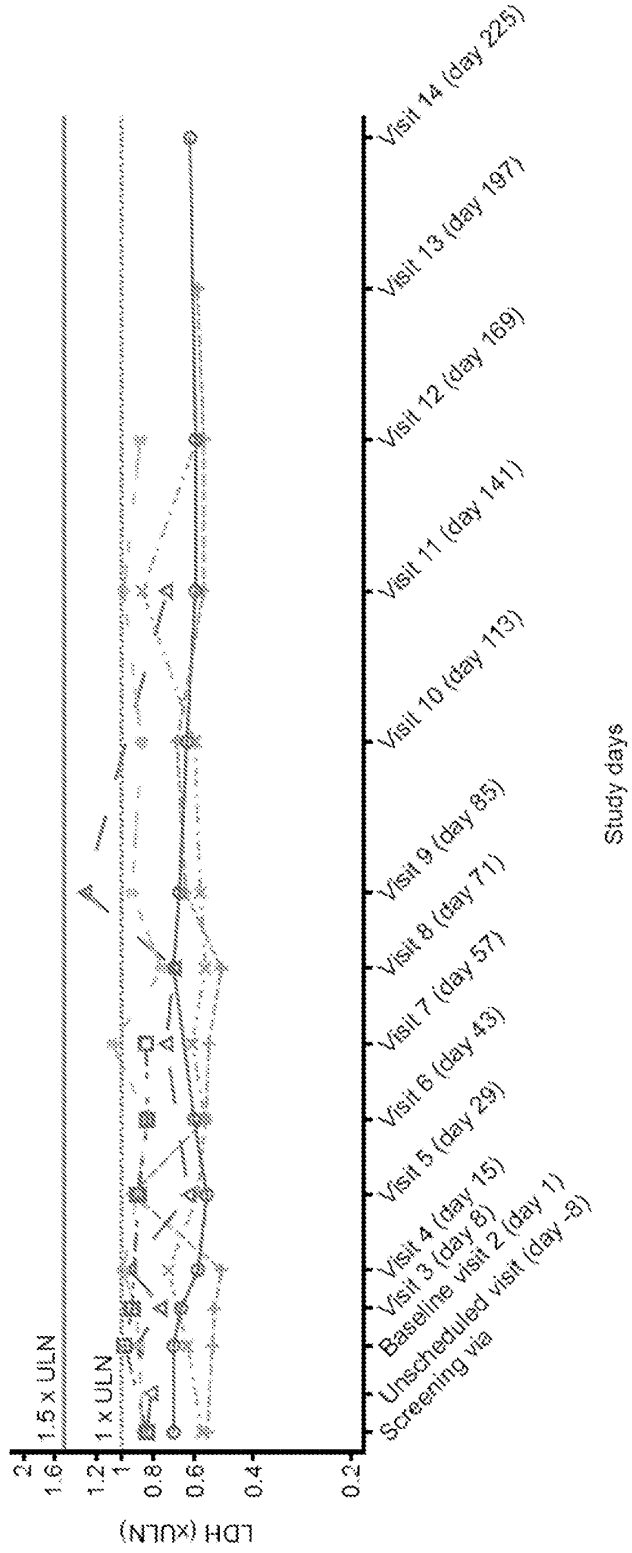
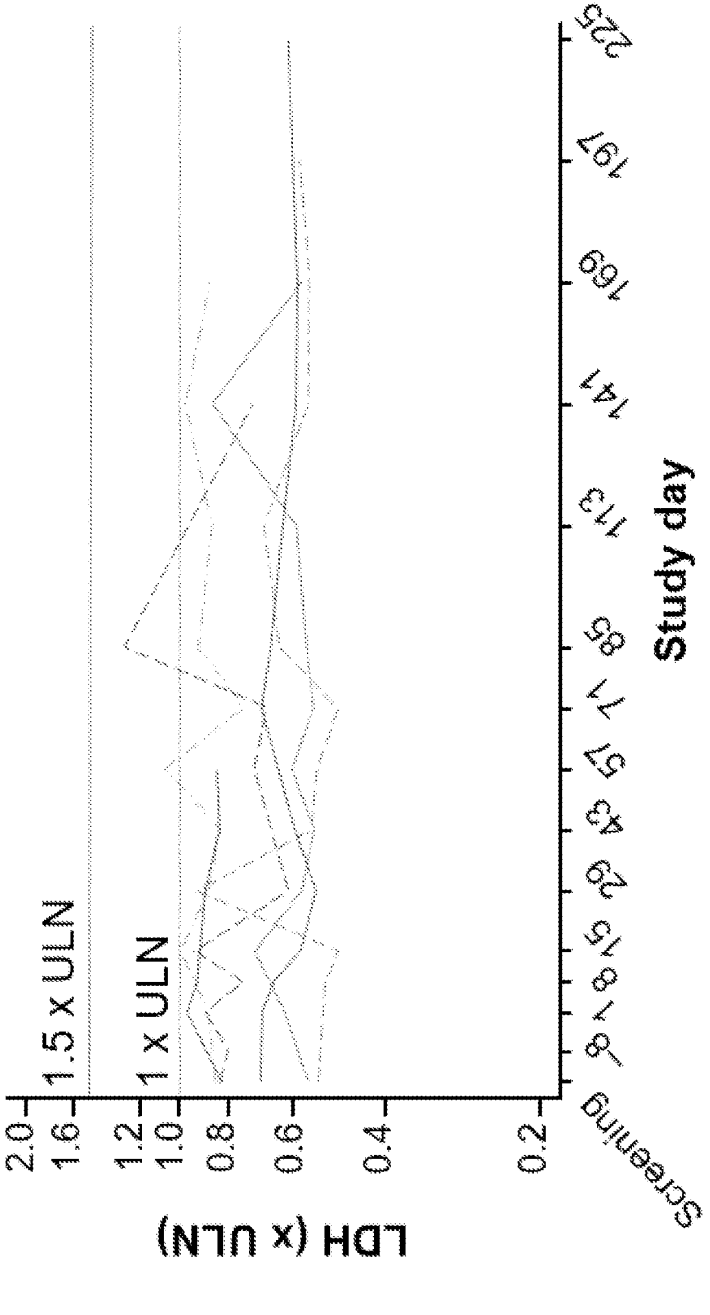

LDH (xULN)
2
1.6
1.2
1
0.8
0.6
0.4
0.2
1.5 x ULN
1 x ULN
Visit 14 (day 225)
Visit 13 (day 197)
Visit 12 (day 169)
Visit 11 (day 141)
Visit 10 (day 113)
Visit 9 (day 85)
Visit 8 (day 71)
Visit 7 (day 57)
Visit 6 (day 43)
Visit 5 (day 29)
Visit 4 (day 15)
Visit 3 (day 8)
Baseline visit 2 (day 1)
Unscheduled visit (day -8)
Screening via
Study days

FIG. 22

FIG. 23



Each line represents an individual patient. LDH, lactate dehydrogenase; ULN, upper limit of normal.

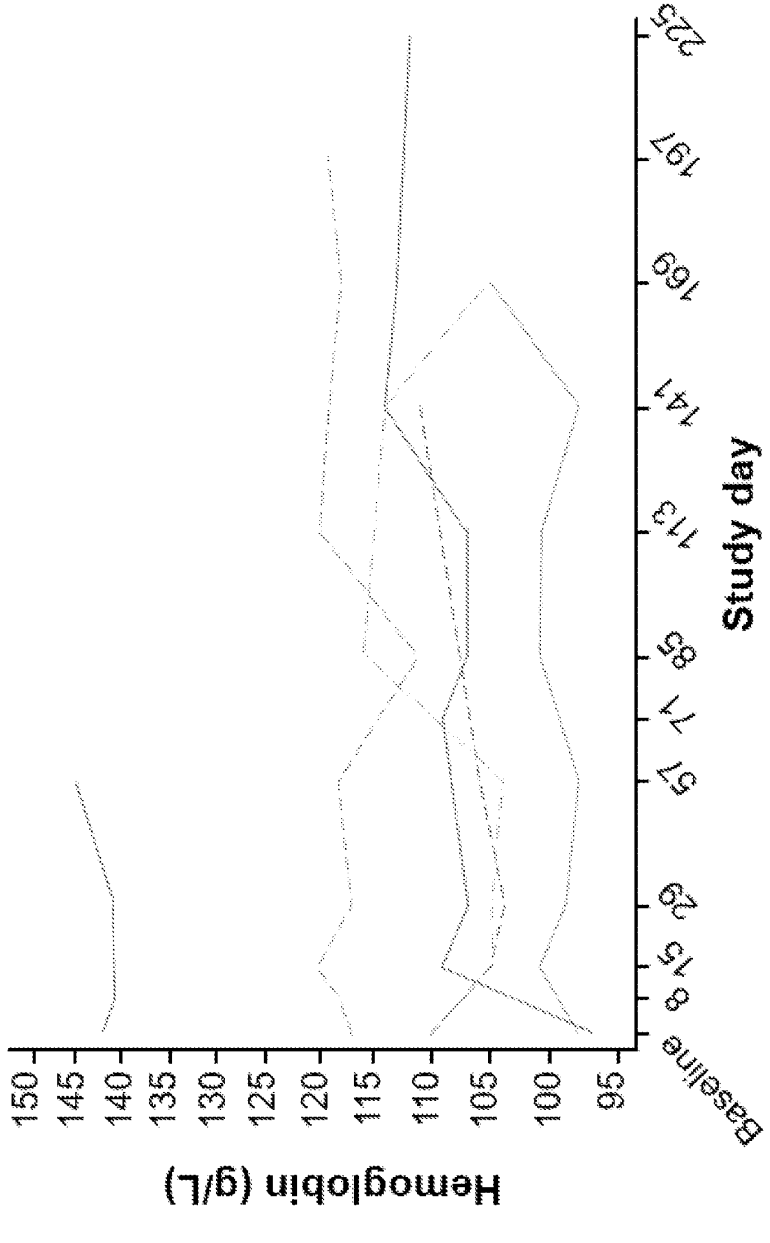
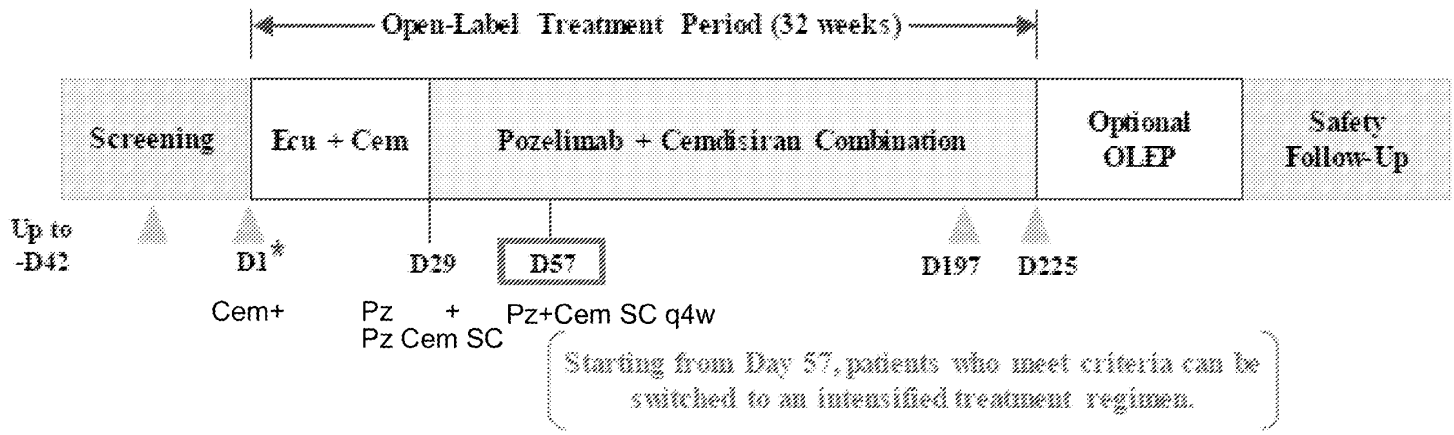

Hemoglobin (g/L)
150
145
140
135
130
125
120
115
110
105
100
95
Baseline
8
15
29
57
71
85
113
141
169
197
225
Study day
Each line represents an individual patient.

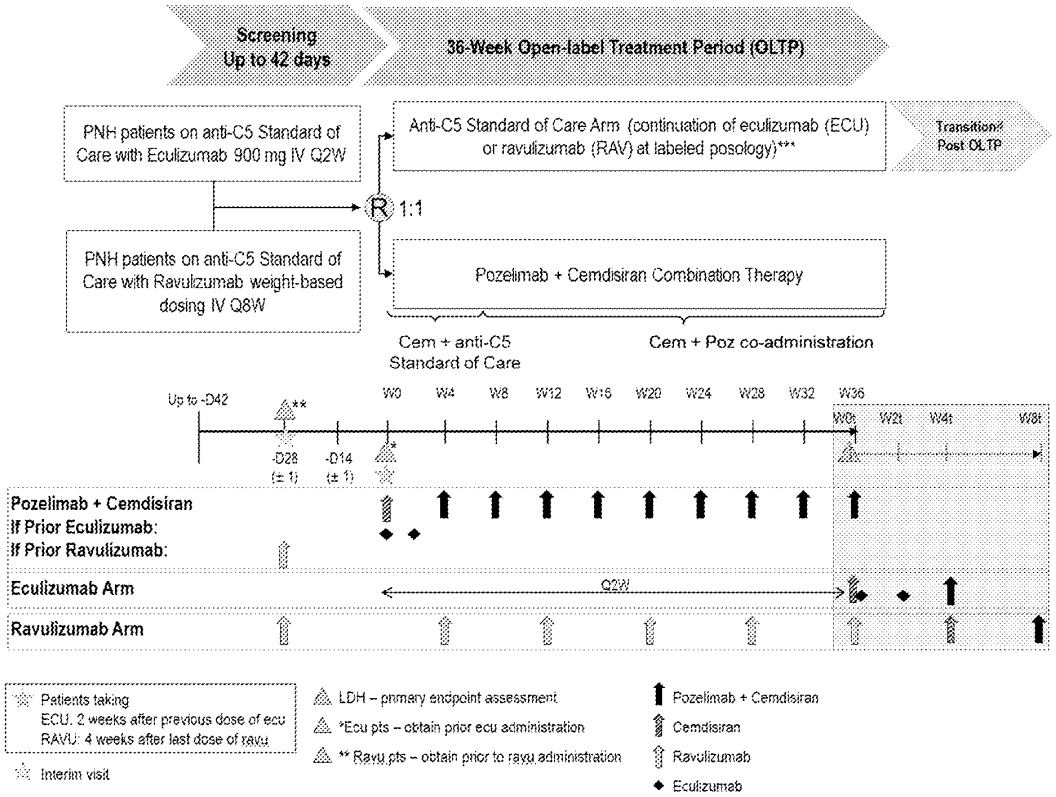
FIG. 24

FIG. 25



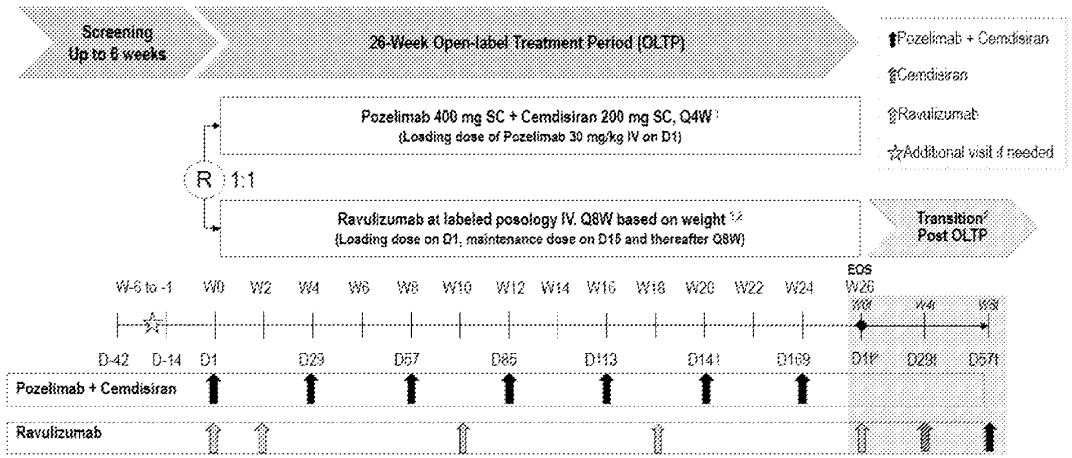
Cem, cemdisiran; Ecu, eculizumab; LDH, lactate dehydrogenase; optional OLEP, open-label extension period
In lieu of the safety follow-up period, patients who complete the optional OLEP may be able to continue study treatment in a post-trial access program.

FIG. 26



Patients who complete anti-C5 Standard of Care arm and plan to enroll into the open-label extension with pozelimab and cemdisiran combination will undergo a transition period to phase in combination treatment

FIG. 27



1. Patients randomized to pozelimab/cemdisiran will receive a 30 mg/kg IV loading dose of pozelimab on day 1 prior to start of subcutaneous (SC) combination treatment; Those randomized to ravulizumab will start on ravulizumab as per prescribing information as follows: if ≥40 kg to <60 kg, 2400 mg IV loading dose with 3000 mg IV maintenance dose; if ≥60 kg to <100 kg, 2700 mg IV loading dose with 3300 mg IV maintenance dose; if ≥100 kg, 3000 mg IV loading dose with 3600 mg IV maintenance dose; the loading dose will be administered on day 1 (+ 2 days) with the maintenance dose administered 2 weeks after the loading dose, and thereafter at every 8 weeks; Patients who discontinue the combination or ravulizumab treatment as well as patients who decline enrollment into the follow on studies (R3918-PNH-2022, R3918-PNH-2050) will undergo a safety off-treatment follow-up period of up to 52 weeks.

2. Patients who complete ravulizumab treatment arm (last dose at OLTP week 18) and plan to enroll into the open label extension with pozelimab and cemdisiran combination will receive an additional ravulizumab dose at OLTP week 26 (also D1t) and undergo a transition period to phase in combination treatment. During the transition period, patients will receive cemdisiran at 29 days after the last dose of ravulizumab (D29t), and pozelimab-cemdisiran combination at 57 days after the last dose of ravulizumab (D57t).

Patients who complete ravulizumab treatment arm and plan to enroll into the R3918-PNH-2022 study will also receive ravulizumab at OLTP week 26 (end of study) before enrolling into the next study.

FIG. 28

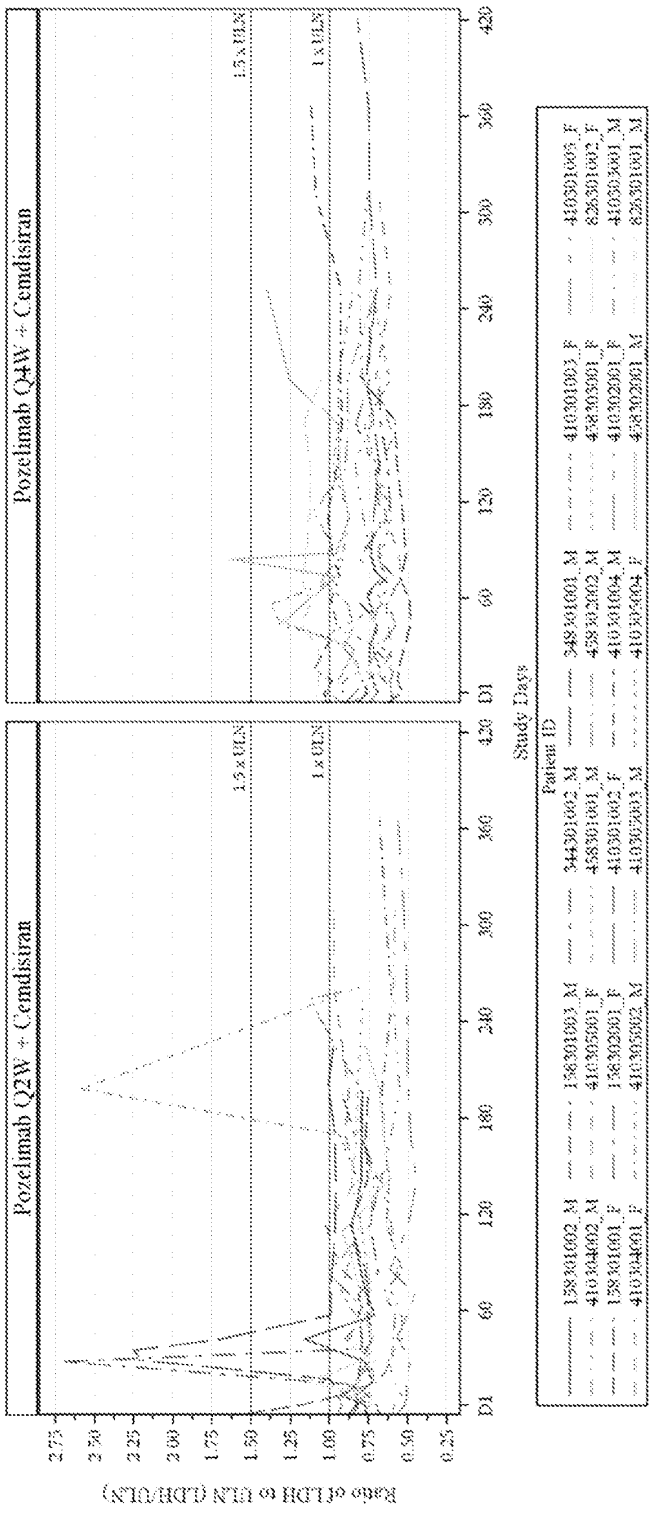

Pozelimab Q2W + Cemdisiran
Pozelimab Q4W + Cemdisiran
1.5 x ULN
1 x ULN
Ratio of LDH to ULN (LDH/ULN)
Study Days
Patient ID

FIG. 29

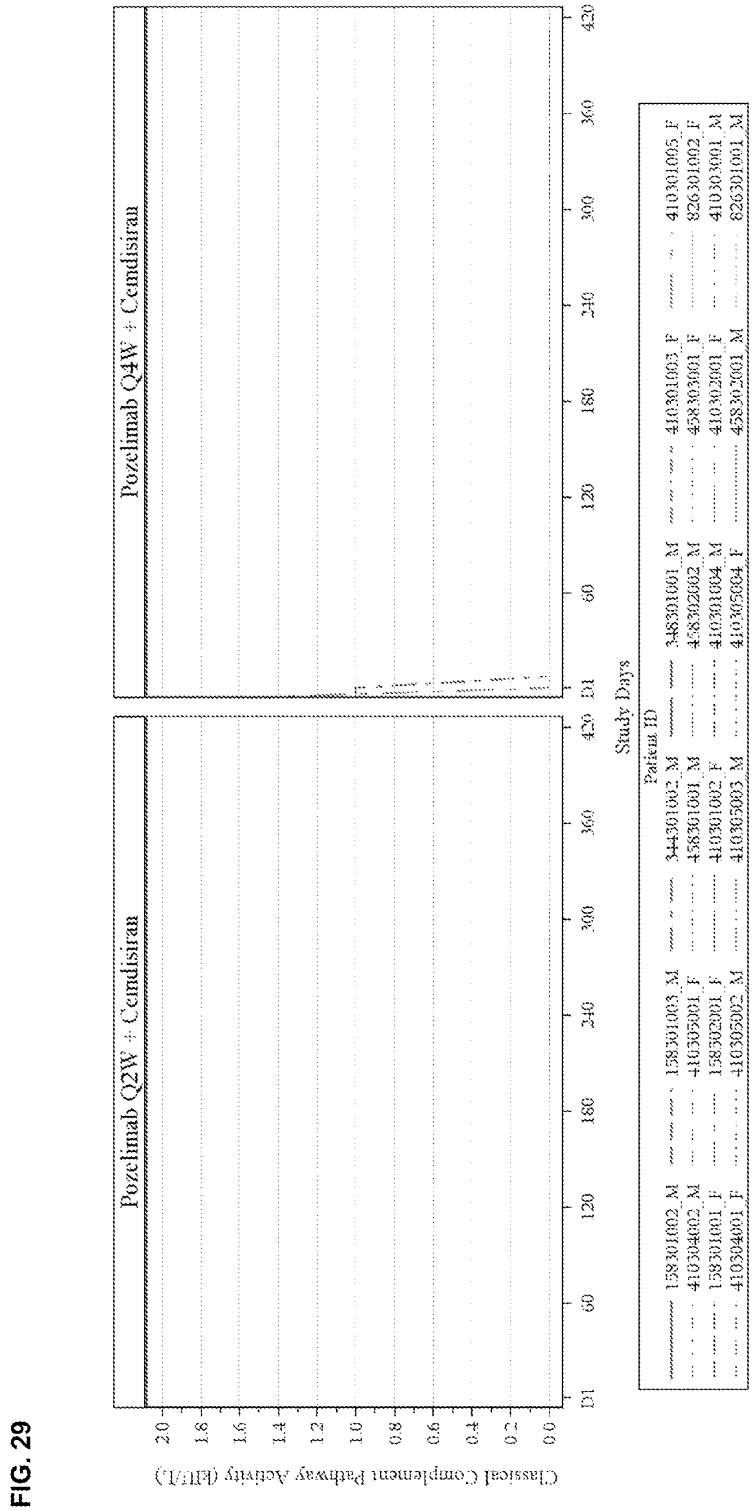

Pozelimab Q2W + Cemdisiran
Pozelimab Q4W + Cemdisiran
Classical Complement Pathway Activity (dilU/L)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
D1
60
120
180
240
300
360
420
Study Days
Patient ID
158301002_M
410304002_M
158301001_F
410304001_F
158301003_M
410305001_F
158302001_F
410305002_M
344301002_M
458301001_M
410301002_F
410305003_M
348301001_M
458302002_M
410301004_M
410305004_F
410301003_F
458302001_F
410302001_F
458302001_M
410301005_F
826301002_F
410302001_M
826301001_M

FIG. 30

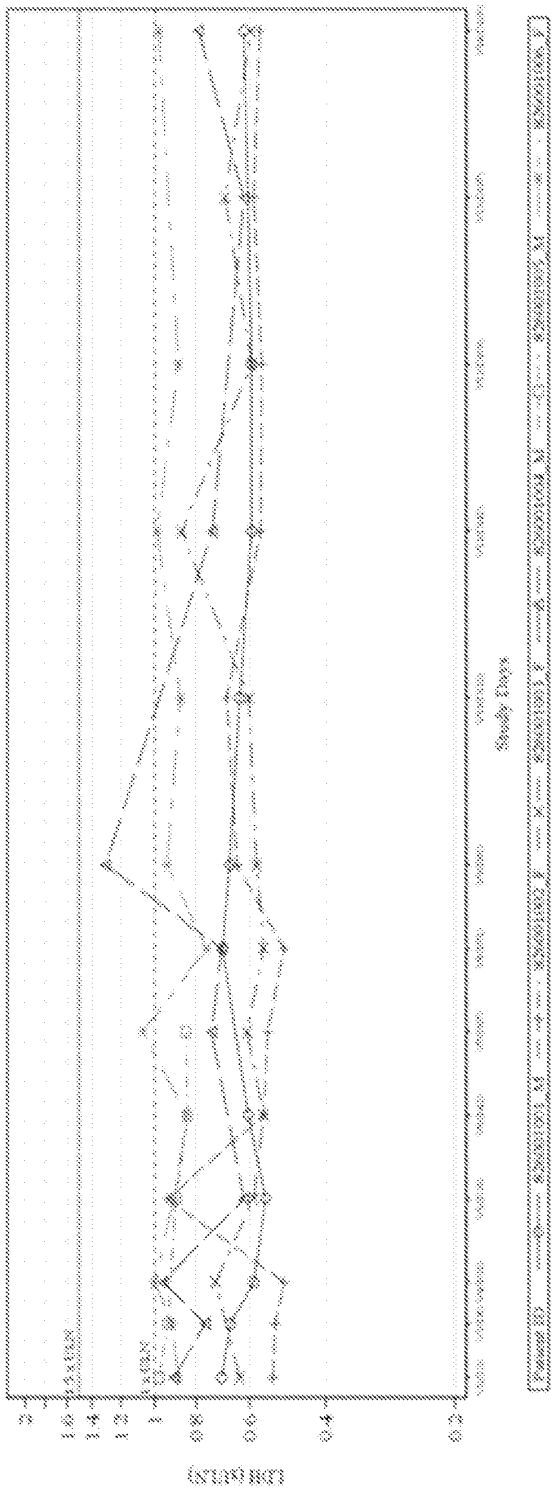
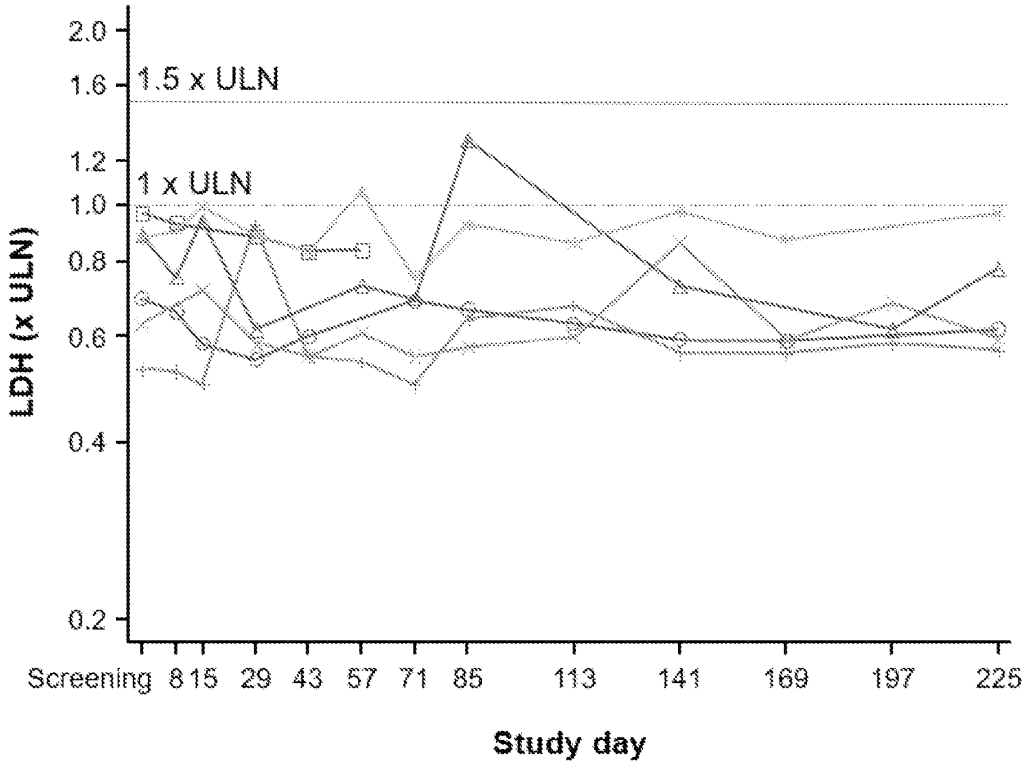
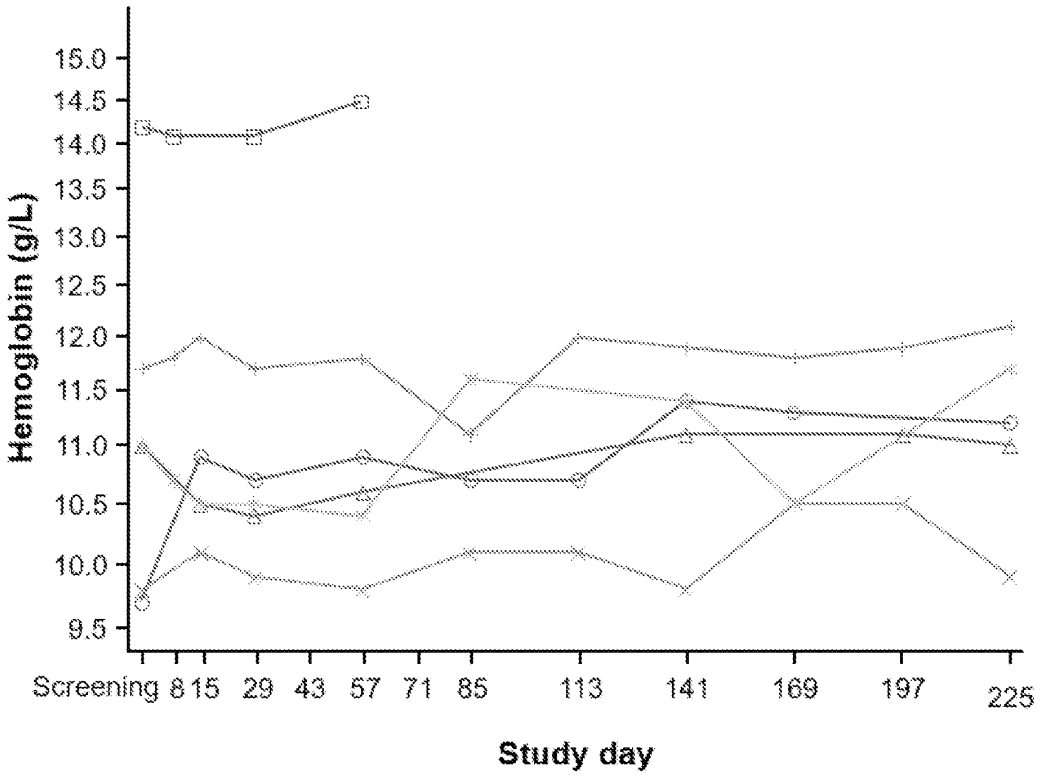


FIG. 31



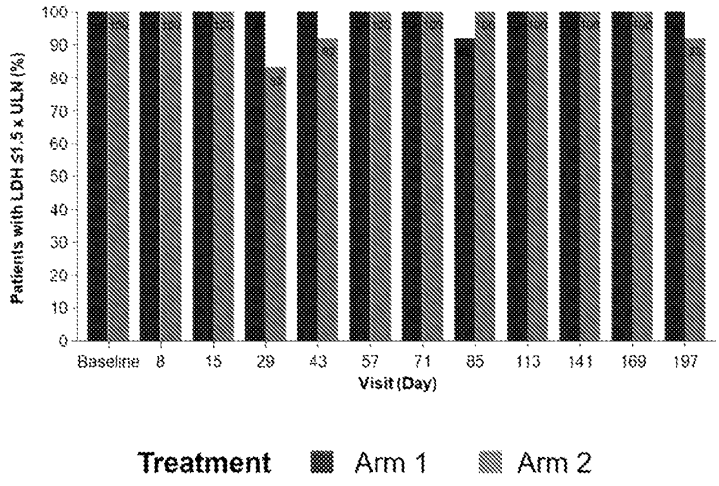
Each line represents an individual patient. LDH, lactate dehydrogenase; ULN, upper limit of normal.

FIG. 32



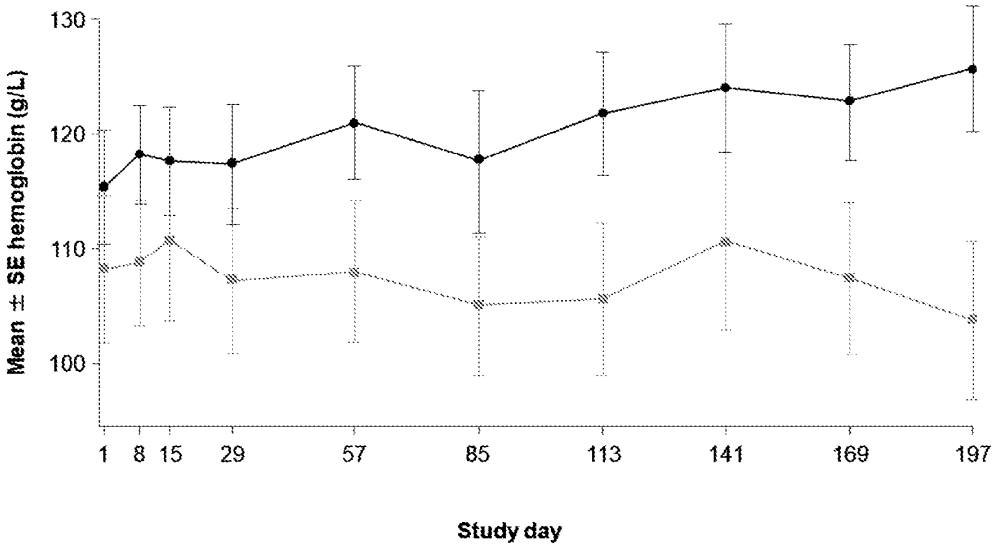
Each line represents an individual patient.

FIG. 33



Arm 1: Pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W. Arm 2: Pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W. LDH, lactate dehydrogenase; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; ULN, upper limit of normal.

FIG. 34



Number of patients:

Arm 1	12	12	11	10	11	12	12	12	12	12
Arm 2	11	11	10	12	12	12	12	12	12	12

Arm 1: Pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W. Arm 2: Pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W. SC, subcutaneous; SE, standard error; Q2W, every 2 weeks; Q4W, every 4 weeks.

FIG. 35

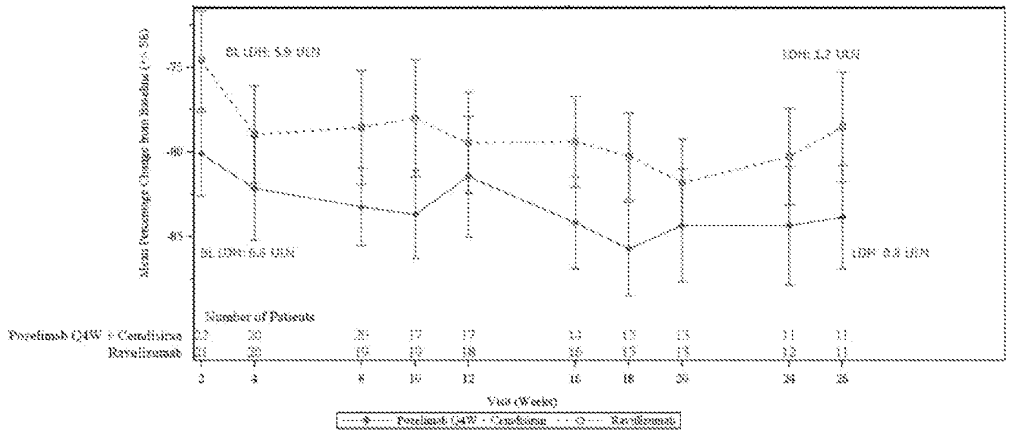

Mean Percentage Change from Baseline (+/- SE)
Number of Patients
Visit (Weeks)

FIG. 36

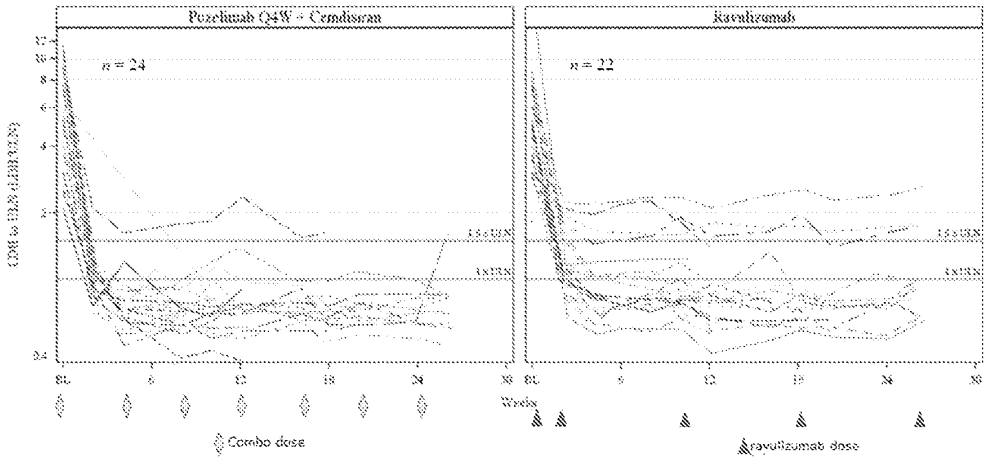

Pozelimab Q4W + Cemdisiran
Ravulizumab
n = 24
n = 22
Weeks
Combo dose
Ravulizumab dose

FIG. 37

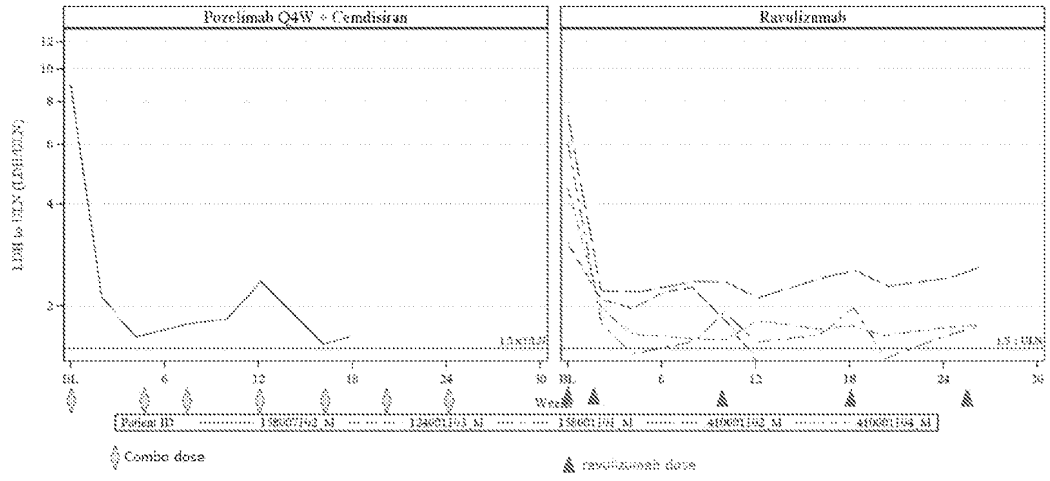

Pozelimab Q4W + Cemdisiran
Ravulizumab
LDH to HEN (LDH/HEN)
Weeks
Patient ID
Combo dose
ravulizumab dose

FIG. 38

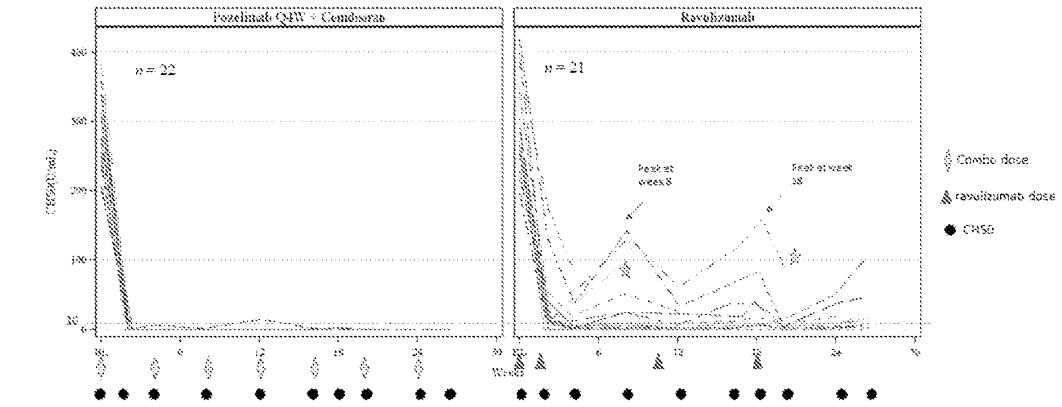

Pozelimab Q4W + Cemdisiran
Revohzumab
n = 22
n = 21
Peak at week 8
Peak at week 38
Cemdi dose
revolizumab dose
CH50
Reference Range: 176-382 U/mL

FIG. 39

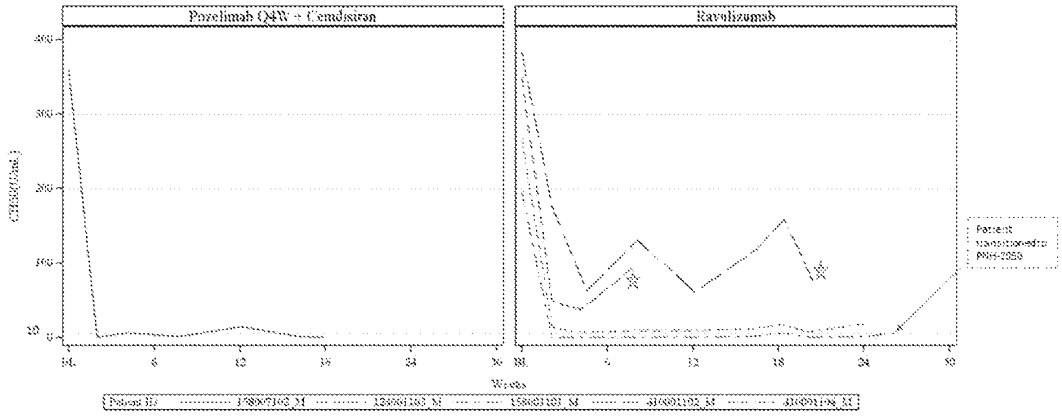


FIG. 40

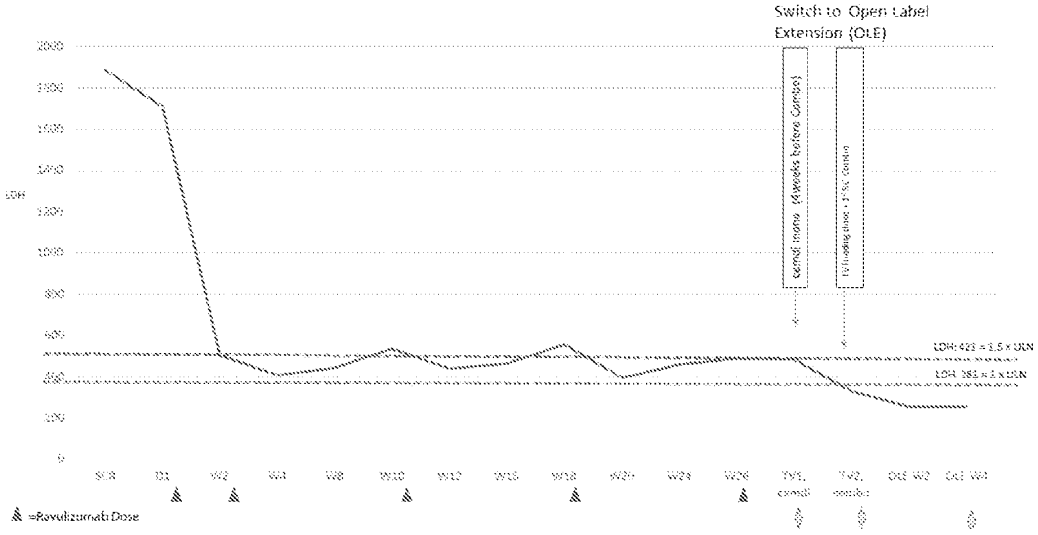

Switch to Open Label Extension (OLE)
LDH
2000
1800
1600
1400
1200
1000
800
600
400
200
0
SCR
D1
W2
W4
W8
W10
W12
W16
W18
W20
W24
W26
TV1, cemdi
TV2, nonibu
OLE W2
OLE W4
=Revulizumab Dose

FIG. 41

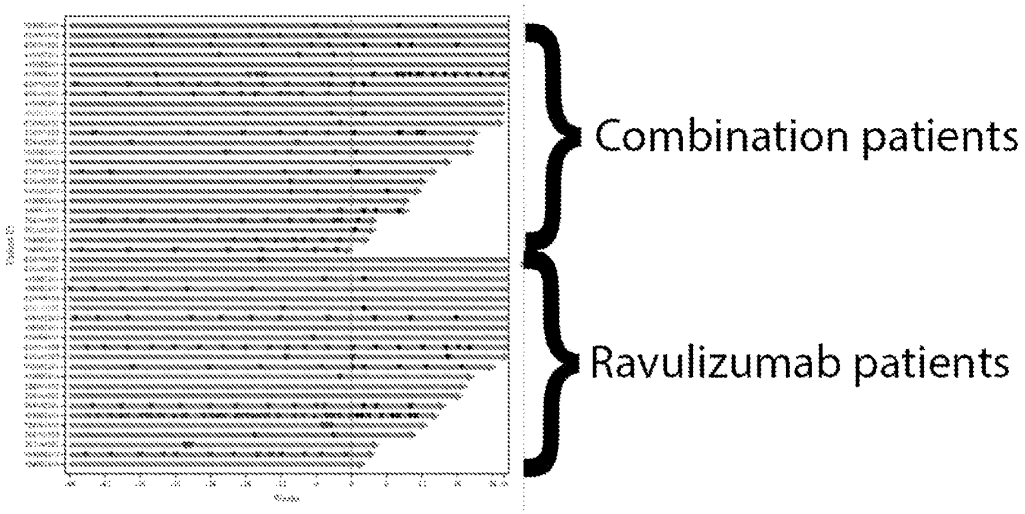


FIG. 42

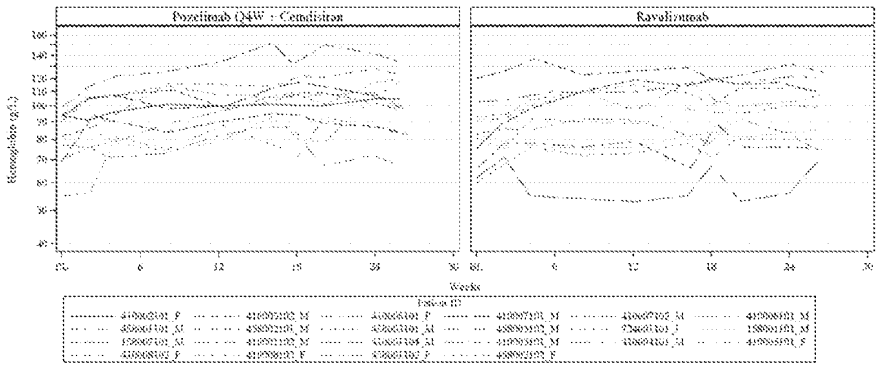


FIG. 43

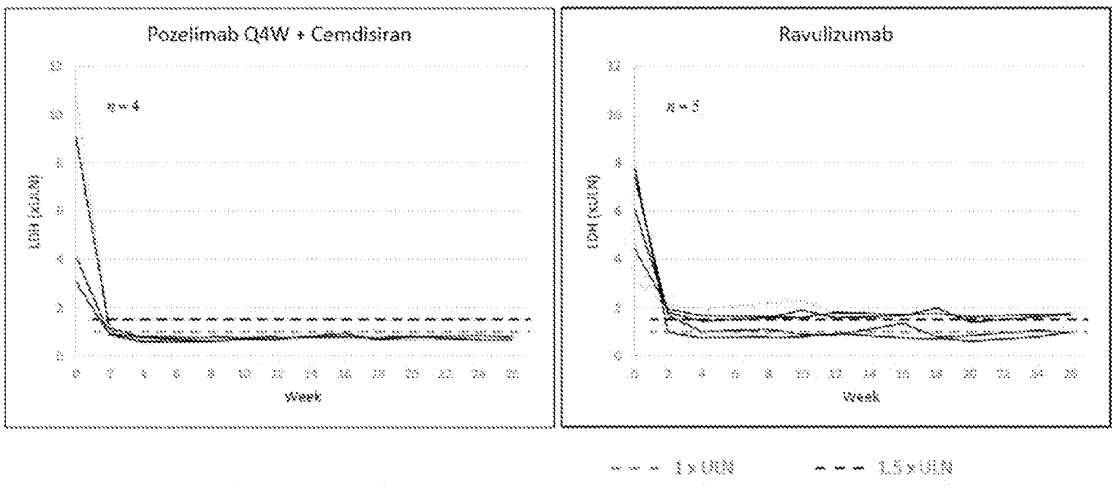
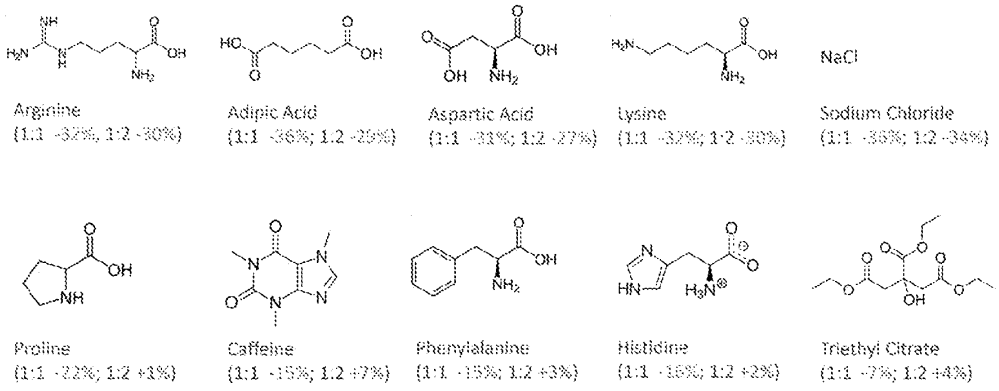

Pozelimab Q4W + Cemdisiran
n = 4
Week
Ravulizumab
n = 5
Week
1 x ULN
1.5 x ULN

FIG. 44


Arginine
(1:1 -32%; 1:2 -30%)
Adipic Acid
(1:1 -36%; 1:2 -29%)
Aspartic Acid
(1:1 -31%; 1:2 -27%)
Lysine
(1:1 -32%; 1:2 -30%)
NaCl
Sodium Chloride
(1:1 -36%; 1:2 -34%)
Proline
(1:1 -22%; 1:2 +1%)
Caffeine
(1:1 -15%; 1:2 +7%)
Phenylalanine
(1:1 -15%; 1:2 +3%)
Histidine
(1:1 -16%; 1:2 +2%)
Triethyl Citrate
(1:1 -7%; 1:2 +4%)

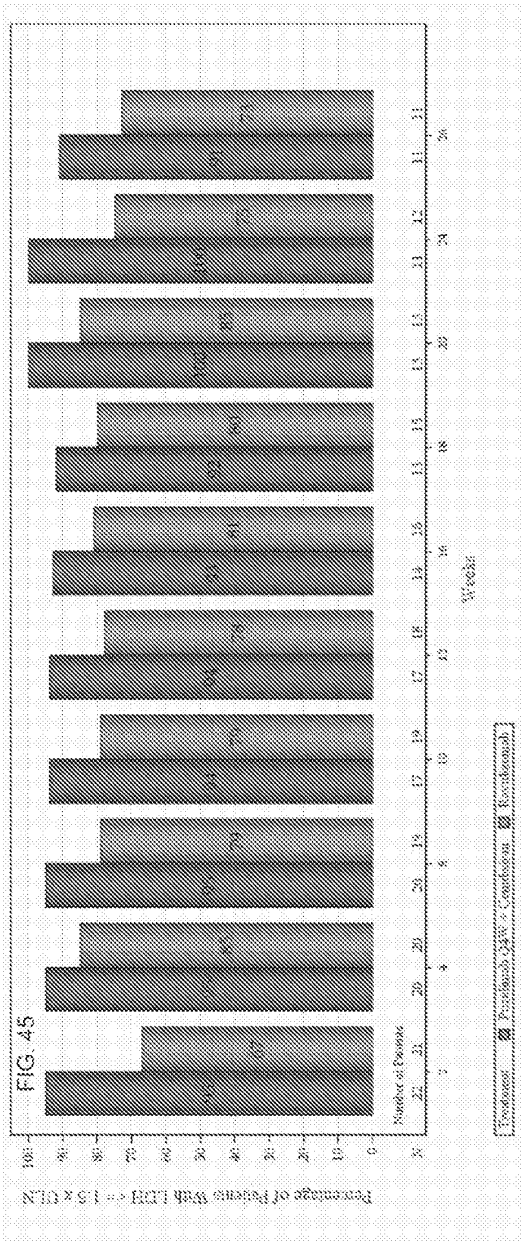

Percentage of Patients With LDH <= 1.5 x ULN
Number of Patients
Week

FIG. 45

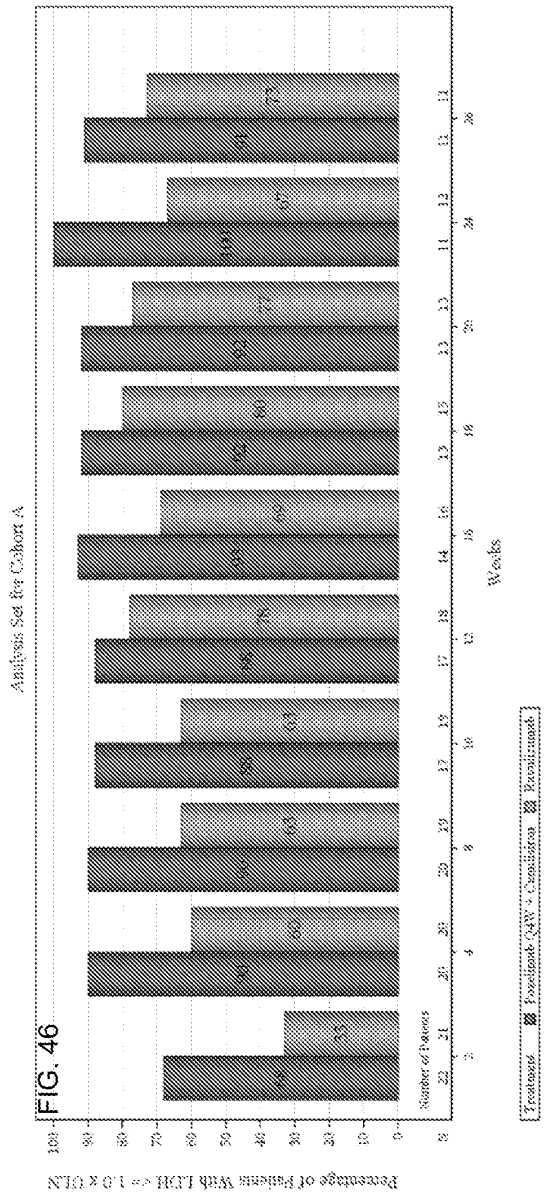
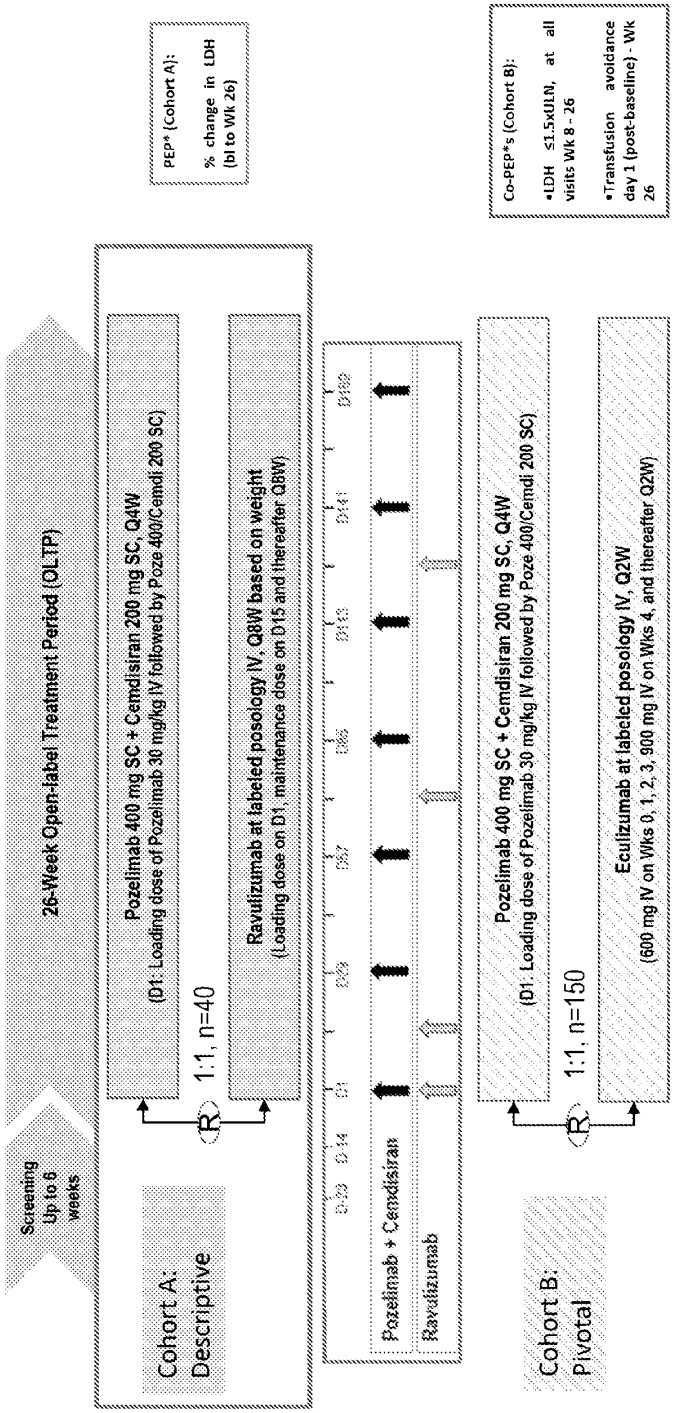

Analysis Set for Cohort A
Percentage of Patients With LDH <= 1.0 x ULN
Weeks
Number of Patients
Treatment
Pembrolizumab + Chemotherapy
Recruitment

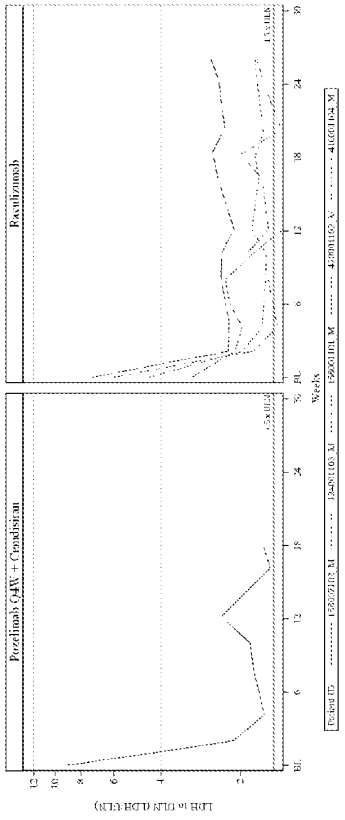
FIG. 46

FIG. 47


Screening
Up to 8 weeks
26-Week Open-label Treatment Period (OLTP)
Cohort A: Descriptive
Pozelimab 400 mg SC + Cemdisiran 200 mg SC, Q4W
(D1: Loading dose of Pozelimab 30 mg/kg IV followed by Poze 400/Cemdi 200 SC)
R
1:1, n=40
Ravulizumab at labeled posology IV, Q8W based on weight
(Loading dose on D1, maintenance dose on D15 and thereafter Q8W)
Pozelimab + Cemdisiran
Ravulizumab
D1
D8
D15
D57
D85
D113
D141
D169
D-28
D-14
PEP* (Cohort A):
% change in LDH (bl to Wk 26)
Co-PEP*s (Cohort B):
•LDH ≤1.5xULN, at all visits Wk 8 - 26
•Transfusion avoidance day 1 (post-baseline) - Wk 26
Cohort B: Pivotal
Pozelimab 400 mg SC + Cemdisiran 200 mg SC, Q4W
(D1: Loading dose of Pozelimab 30 mg/kg IV followed by Poze 400/Cemdi 200 SC)
R
1:1, n=150
Eculizumab at labeled posology IV, Q2W
(600 mg IV on Wks 0, 1, 2, 3, 900 mg IV on Wks 4, and thereafter Q2W)
*PEP = primary endpoint
PA3 = protocol amendment 3

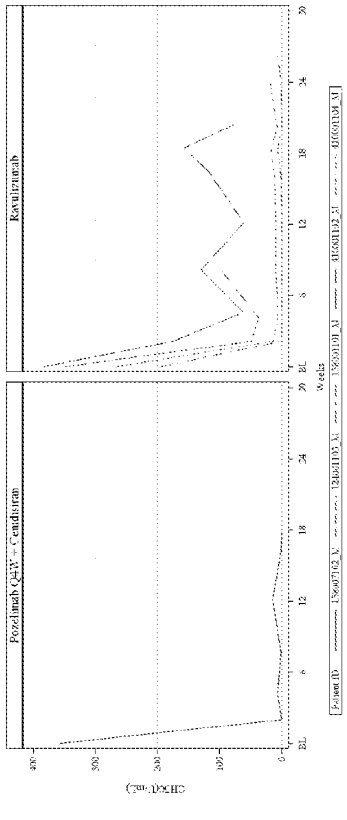

Pexelizumab Q4W + Canakinumab
Ravulizumab
Hemoglobin (g/L)
Weeks
Patient ID

FIG. 48



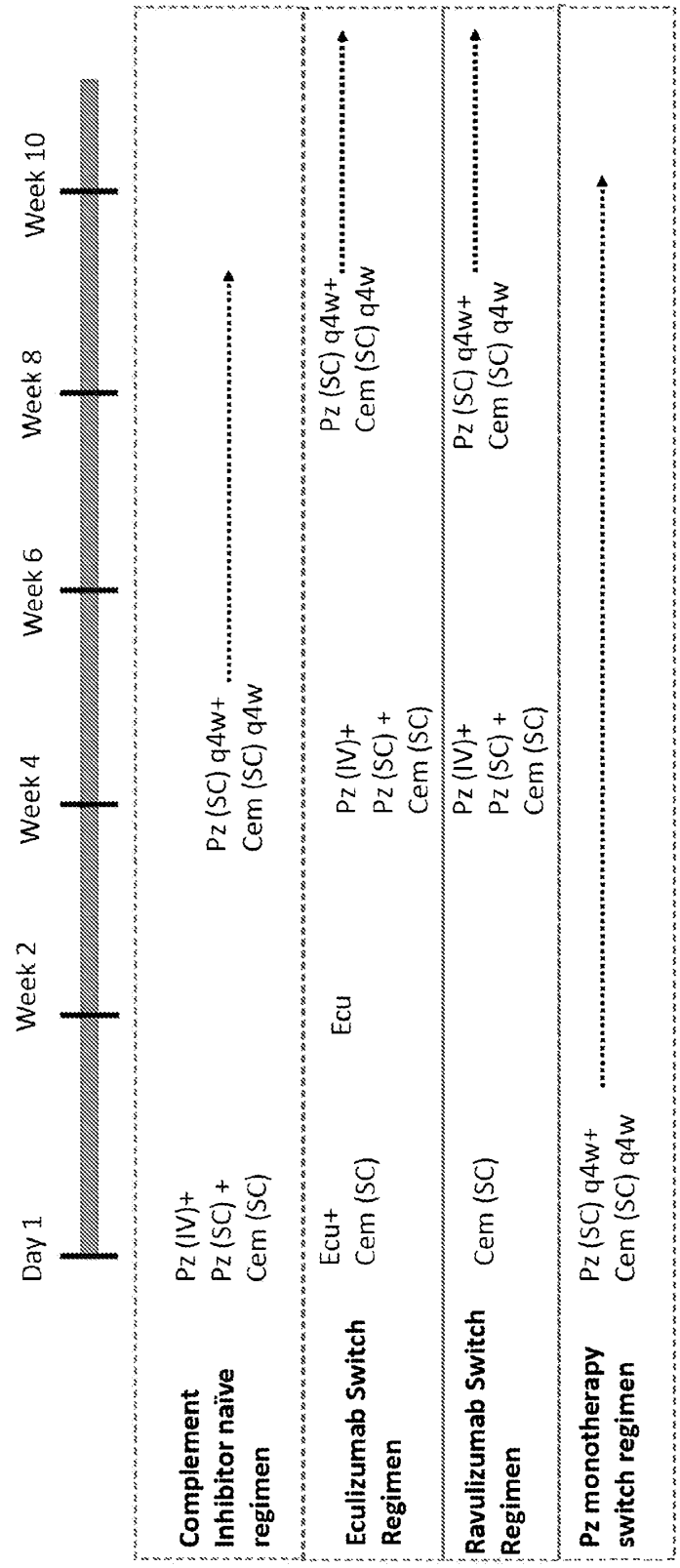
LDH

FIG. 49



CH50

FIG. 50


Day 1
Week 2
Week 4
Week 6
Week 8
Week 10
Complement Inhibitor naïve regimen
Pz (IV)+ Pz (SC) + Cem (SC)
Pz (SC) q4w+ Cem (SC) q4w
Eculizumab Switch Regimen
Ecu+ Cem (SC)
Ecu
Pz (IV)+ Pz (SC) + Cem (SC)
Pz (SC) q4w+ Cem (SC) q4w
Ravulizumab Switch Regimen
Cem (SC)
Pz (IV)+ Pz (SC) + Cem (SC)
Pz (SC) q4w+ Cem (SC) q4w
Pz monotherapy switch regimen
Pz (SC) q4w+ Cem (SC) q4w