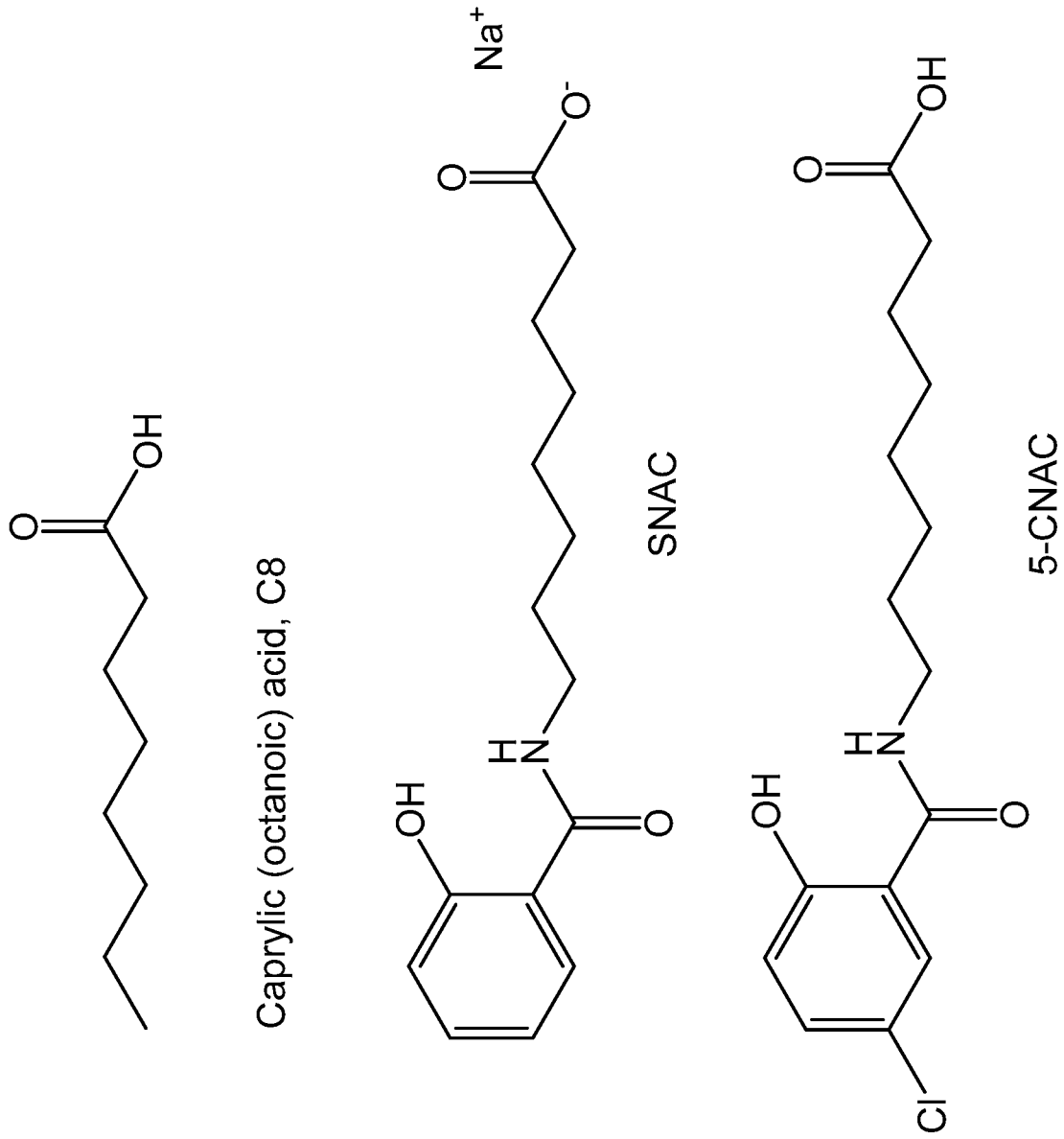
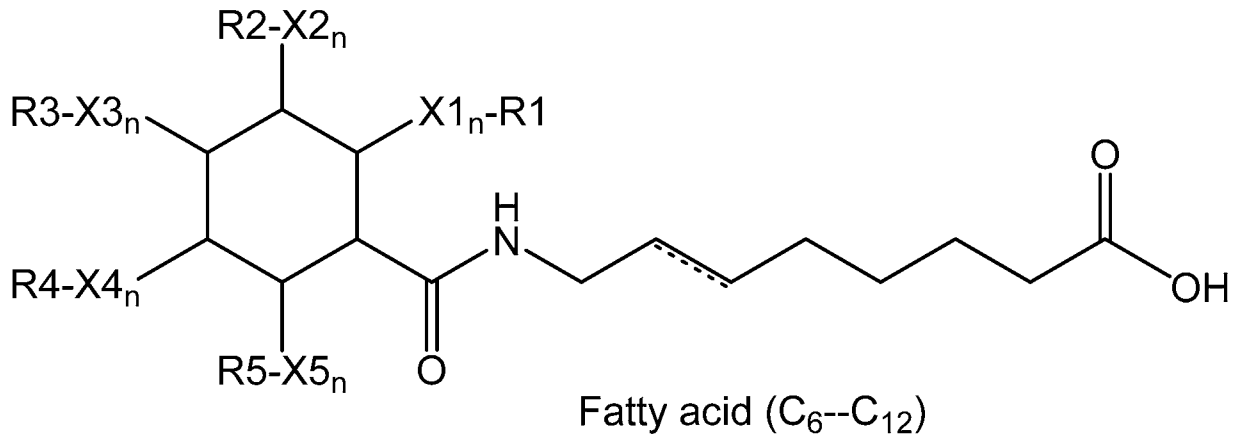
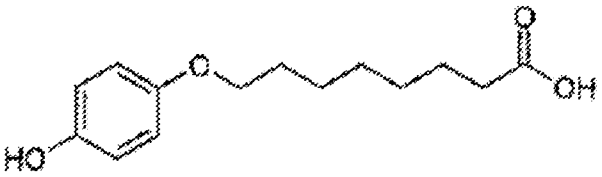

OH
O
Caprylic (octanoic) acid, C8
Na+
O-
O
HN
OH
O
SNAC
OH
O
HN
OH
O
Cl
5-CNAC

FIG. 1A

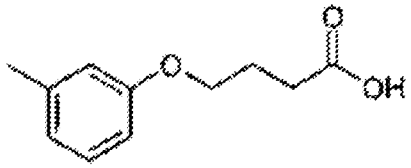


- The ring comprises at least one fatty acid substituent between C_6 and C_{12}, e.g., C_8, and at least two polar group substituents, wherein:
  - At least one of R1..R5 comprises or consists of a halogen group (e.g., F, Cl, or Br)
  - At least one of R1..R5 comprises or consists of an OH group
- At least two of R1..R5 are not H
- X1 to X5 are alkyl spacers, e.g., CH_2, wherein n is independently between 0 and 5

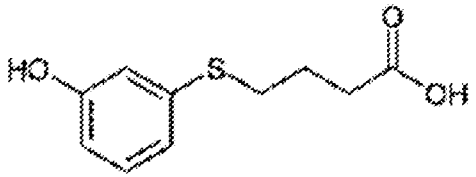
FIG. 1B



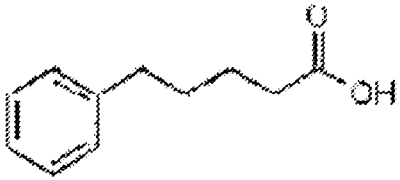
4-HPO
8-(4-hydroxyphenoxy) octanoic acid



3-TBA
4-m-tolyloxybutyric acid



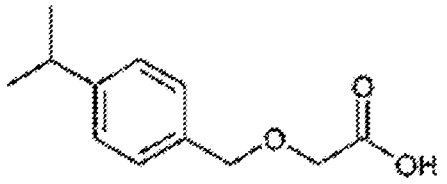
3-HPSB
4-(3-hydroxyphenylsulfanyl)butyric acid



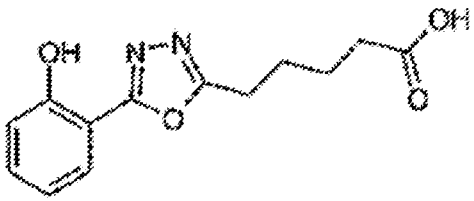
5-PPA
5-phenylpentanoic acid



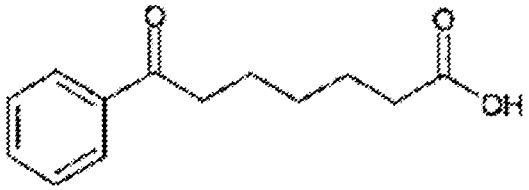
2-HPOD
8-(2-hydroxyphenoxy)octyldiethanolamine



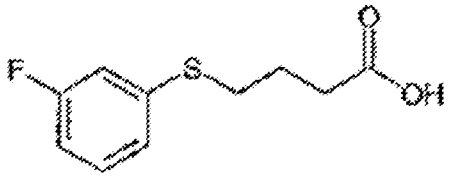
4-IBOA
(4-isopropylbenzyloxy)acetic acid



2-PHOD
2-(5-pentanoic acid)-5-(2-hydroxyphenyl)-l ,3,4-oxadiazole



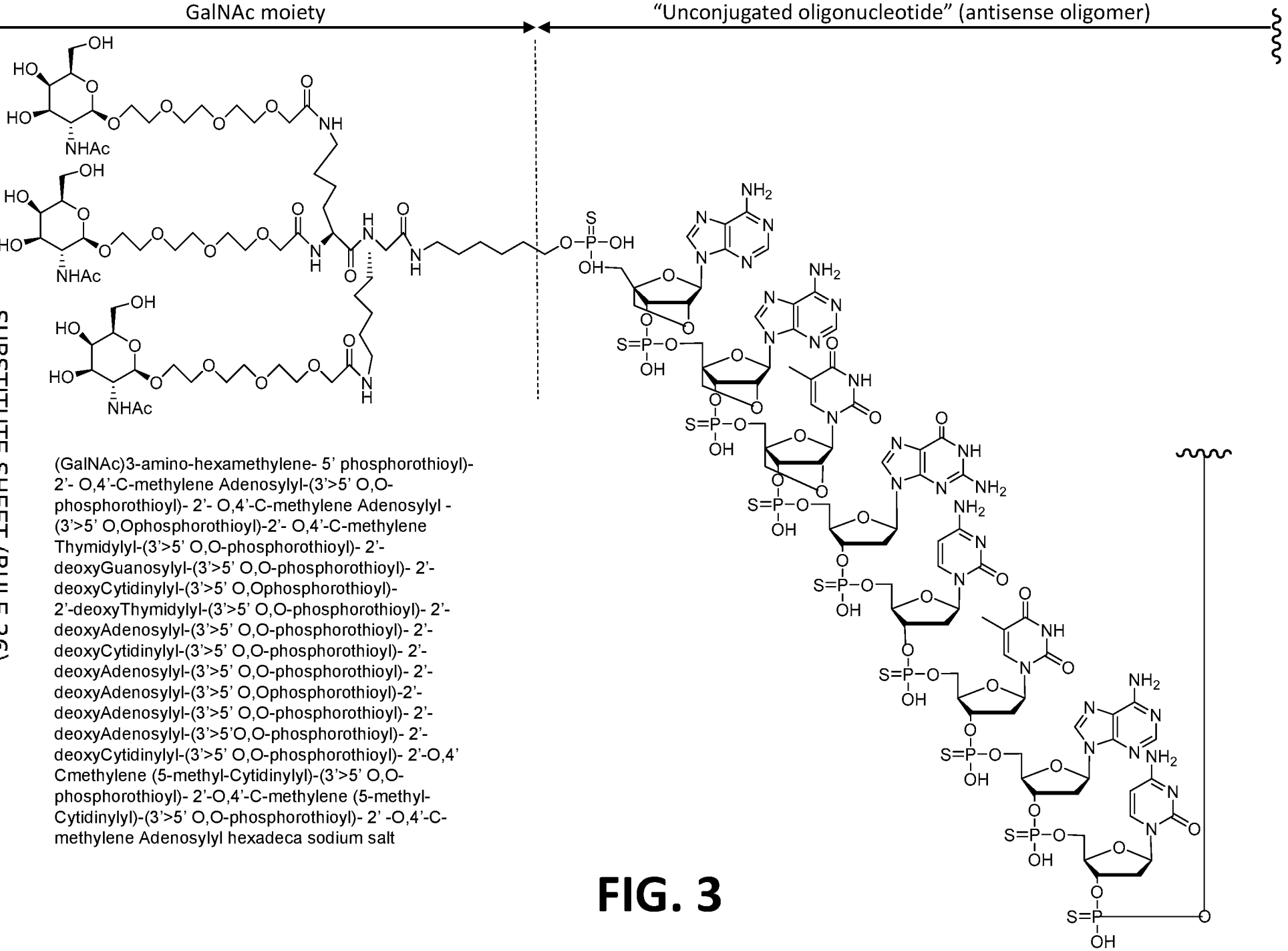
7-OPHA
7-oxo-7-phenylheptanoic acid



3-FPSB
4-(3-fluorophenylsulfanyl)butyric acid

SUBSTITUTE SHEET (RULE 26)

FIG. 2



(GalNAc)3-amino-hexamethylene- 5' phosphorothioyl)-2'- O,4'-C-methylene Adenosylyl-(3'>5' O,O-phosphorothioyl)- 2'- O,4'-C-methylene Adenosylyl -(3'>5' O,Ophosphorothioyl)-2'- O,4'-C-methylene Thymidylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyGuanosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,Ophosphorothioyl)-2'-deoxyThymidylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5' O,Ophosphorothioyl)-2'-deoxyAdenosylyl-(3'>5' O,O-phosphorothioyl)- 2'-deoxyAdenosylyl-(3'>5'O,O-phosphorothioyl)- 2'-deoxyCytidinylyl-(3'>5' O,O-phosphorothioyl)- 2'-O,4' Cmethylene (5-methyl-Cytidinylyl)-(3'>5' O,O-phosphorothioyl)- 2'-O,4'-C-methylene (5-methyl-Cytidinylyl)-(3'>5' O,O-phosphorothioyl)- 2' -O,4'-C-methylene Adenosylyl hexadeca sodium salt

FIG. 3

SUBSTITUTE SHEET (RULE 26)

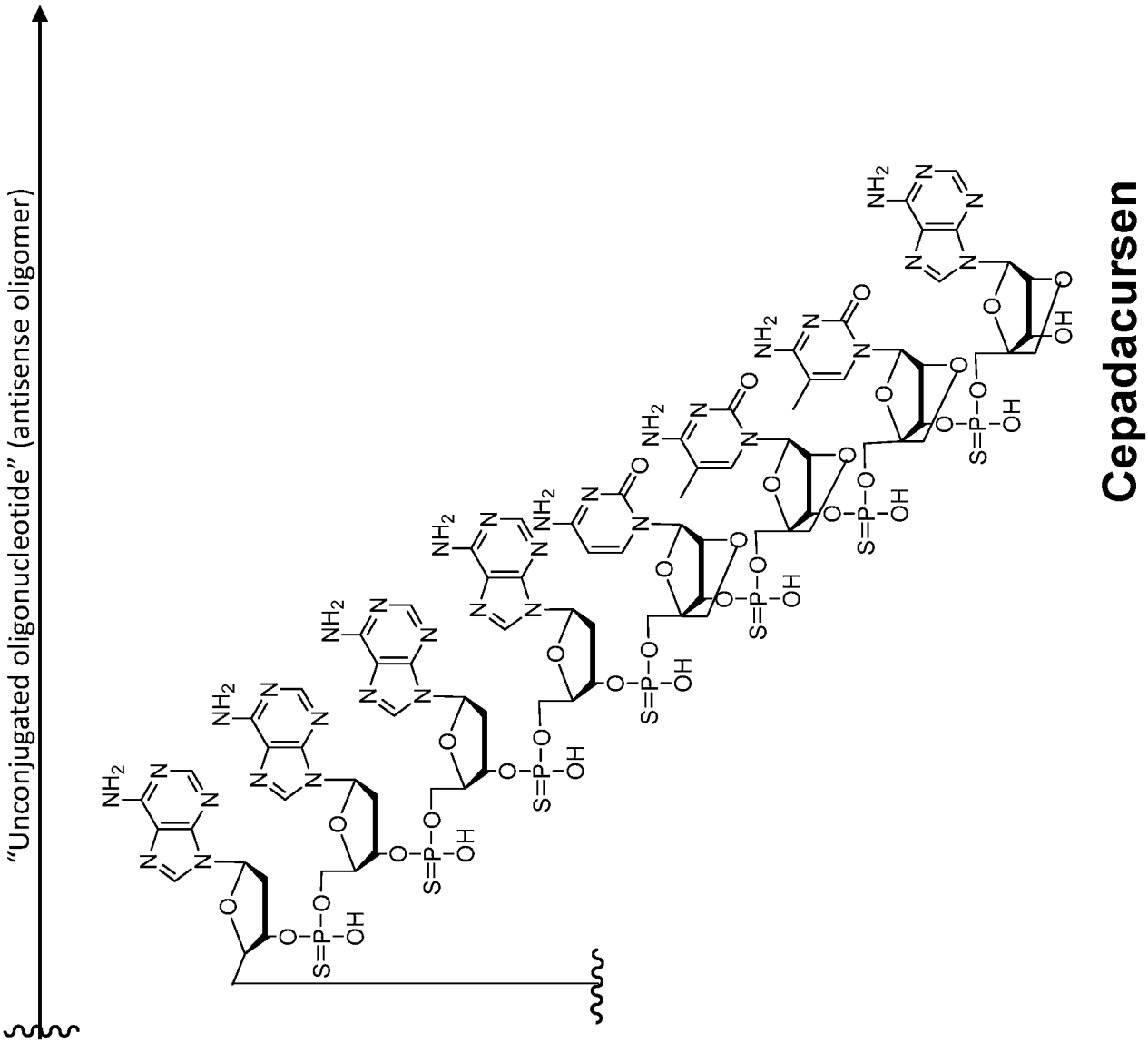
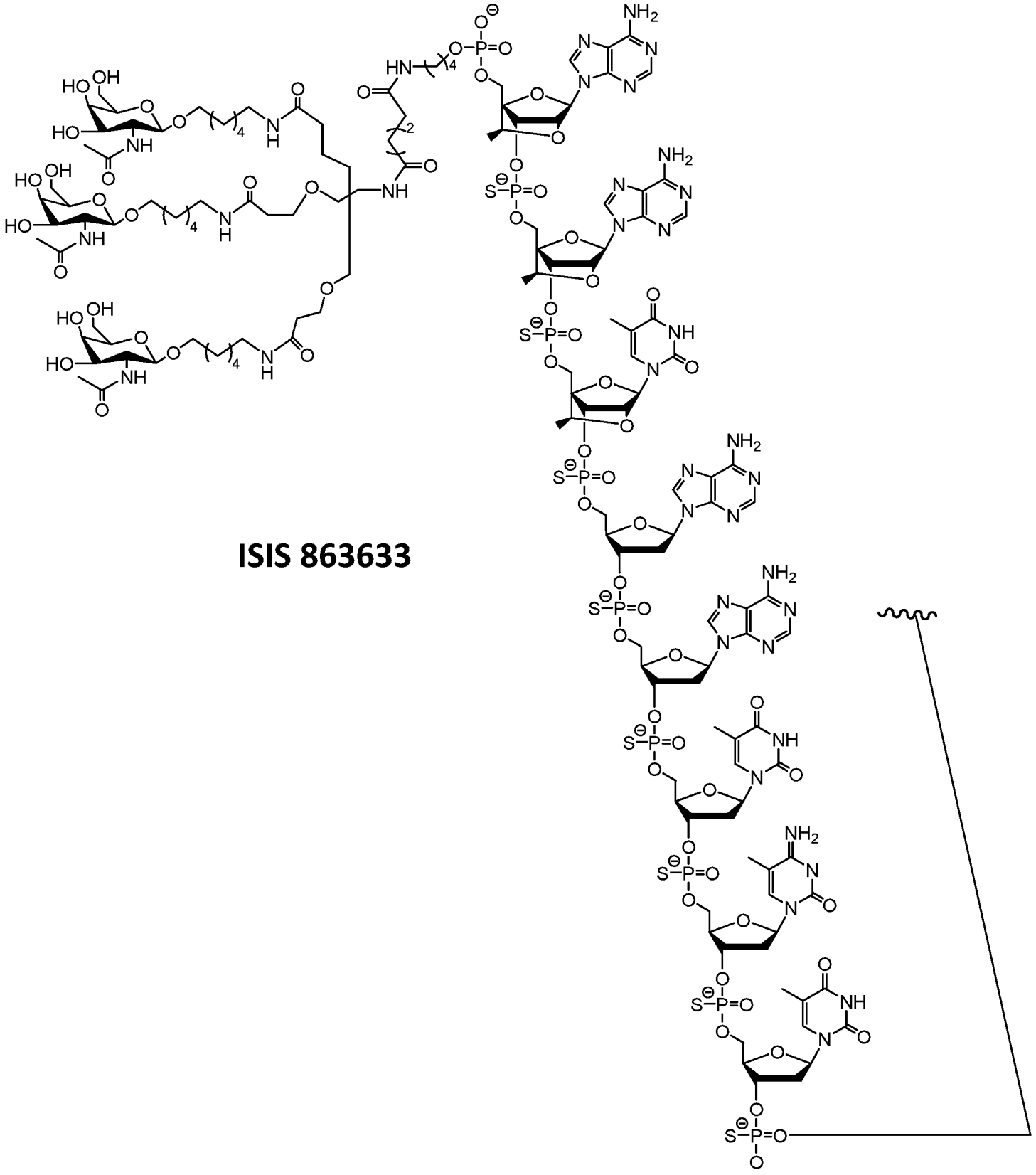

"Unconjugated oligonucleotide" (antisense oligomer)
Cepadacursen

FIG. 3



ISIS 863633

FIG. 4

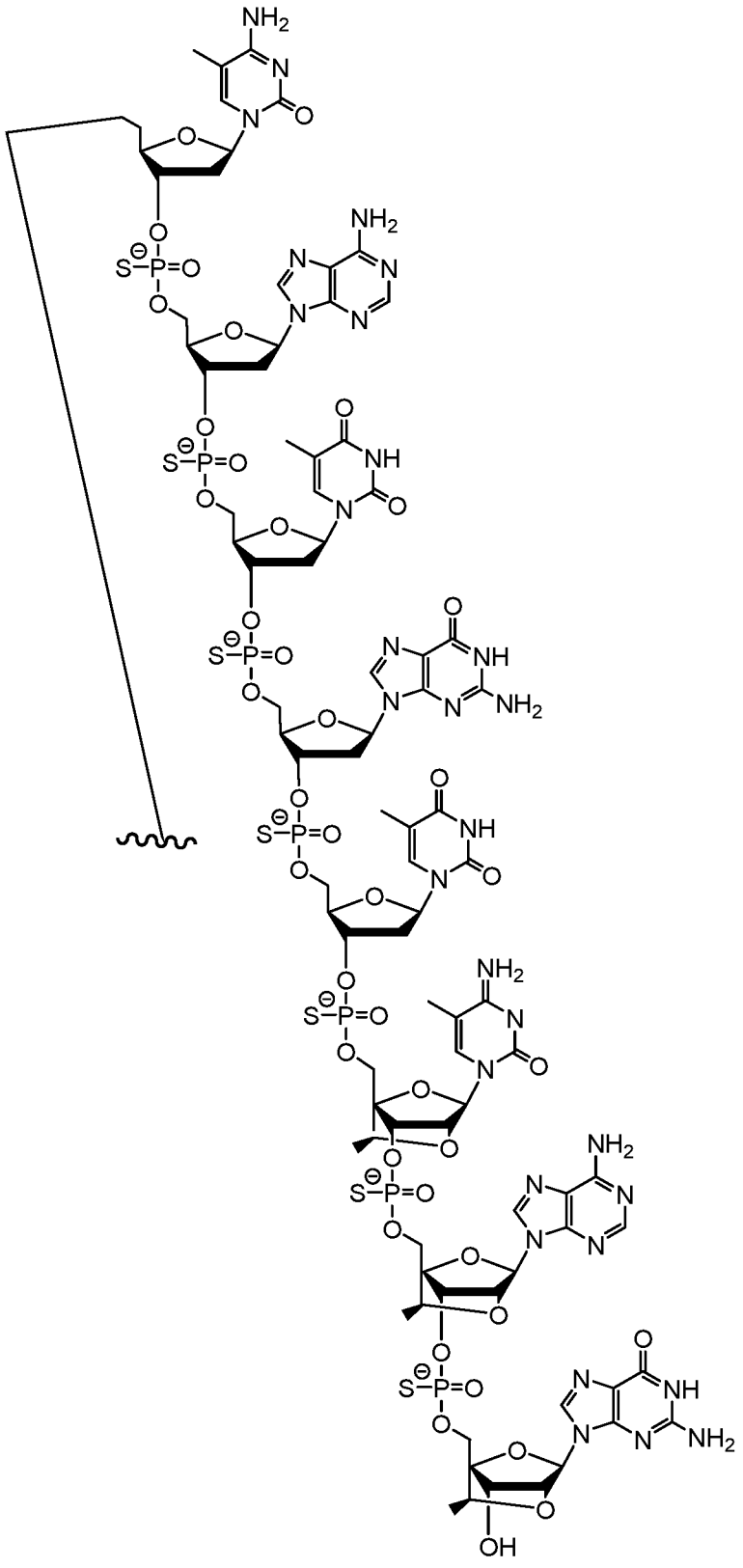


FIG. 4

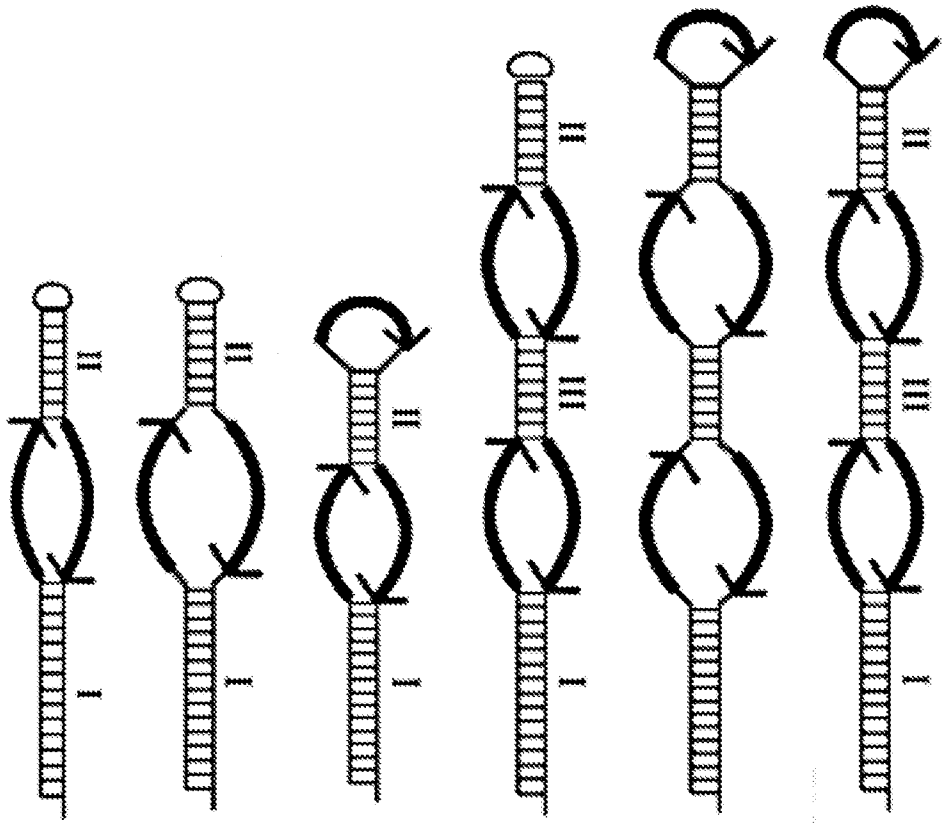
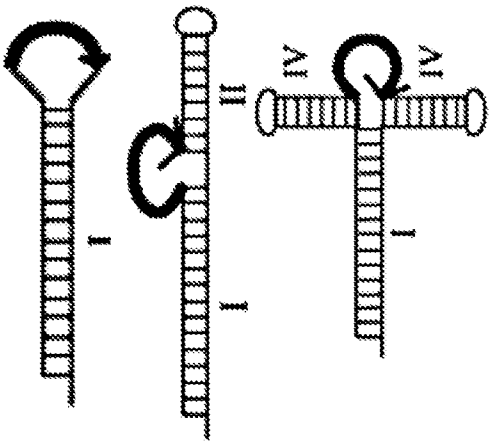
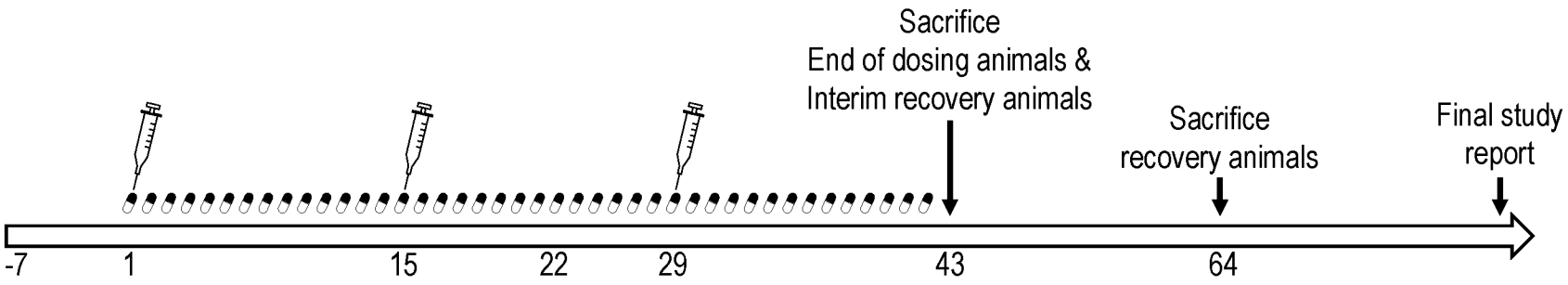


FIG. 5





- ☐ PD:PCSK9 & lipids) on days -7, pre-dose, 4, 8, 15, 22, 29, 36, 43, 50, 57 and 64
- ☐ PK:(G1-6) at predose & 0.5, 1.5, 3.5, and 8 hours postdose on days 1, 15 & 29
- ☐ Clinical chemistry & Hematology on Days -7, pre-dose, 15, 29, 43 and 64
- ☐ Clinical observations: Usual parameters + indicators of increased intestinal mobility (i.e. loose stool)

Sacrifice: End of Dosing, End of Recovery

- ☐ Histopath: Liver/kidney/GI tract (extensive):
- ☐ Biodistribution: Liver/kidney/intestine (duodenum, jejunum, ileum and colon

FIG. 6

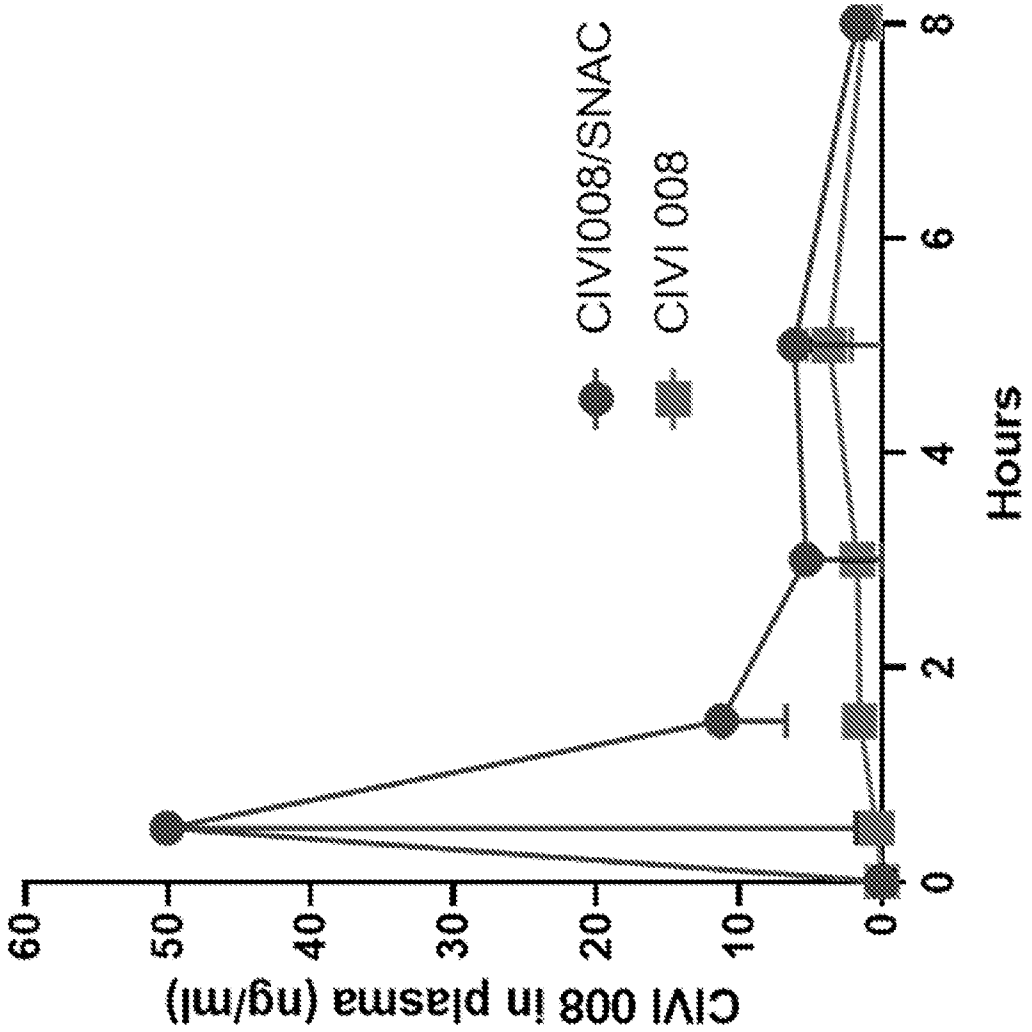

CIVI008/SNAC
CIVI 008
CIVI 008 in plasma (ng/ml)
Hours
0
10
20
30
40
50
60
0
2
4
6
8

FIG. 7

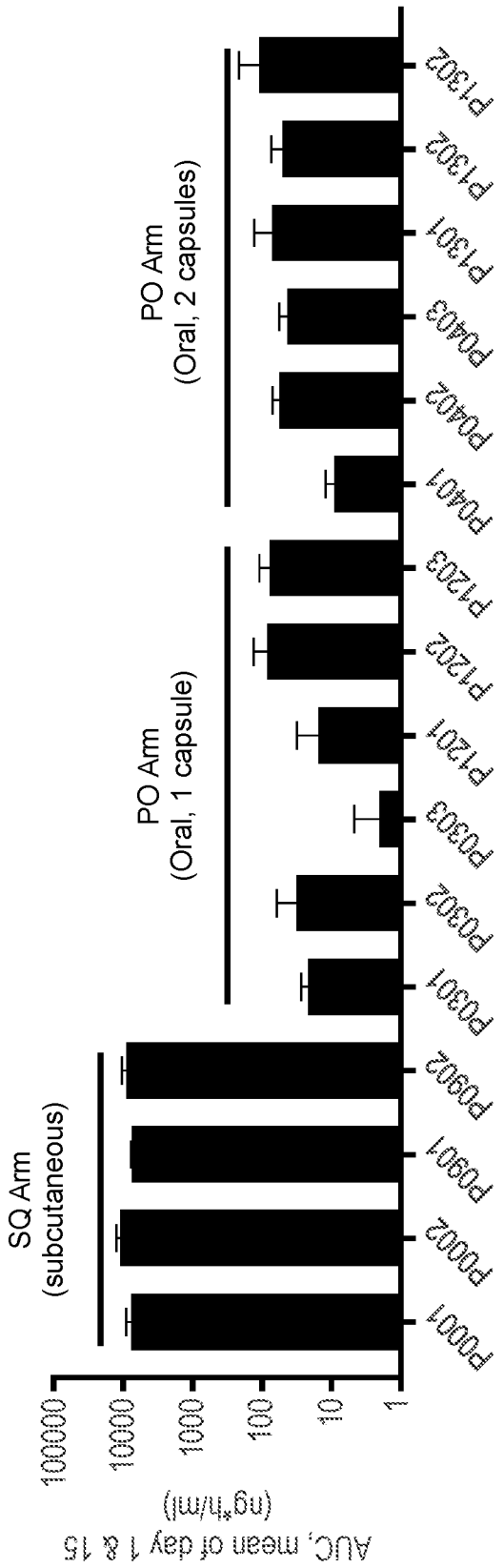

AUC, mean of day 1 & 15
(ng*h/ml)
100000
10000
1000
100
10
1
SQ Arm
(subcutaneous)
PO Arm
(Oral, 1 capsule)
PO Arm
(Oral, 2 capsules)
P0001
P0002
P0901
P0902
P0301
P0302
P0303
P1201
P1202
P1203
P0401
P0402
P0403
P1301
P1302
P1302

FIG. 8

Dose group	End of dosing (µg/gram tissue)	End of recovery (µg/gram tissue)
SQ Q2W x 3	33.8 (19.1)	N.A.
1 capsule QD x 42	2.3 (1.2)	0.6 (0.2)
2 capsules QD x 42	4.0 (1.6)	0.9 (0.7)

FIG. 9

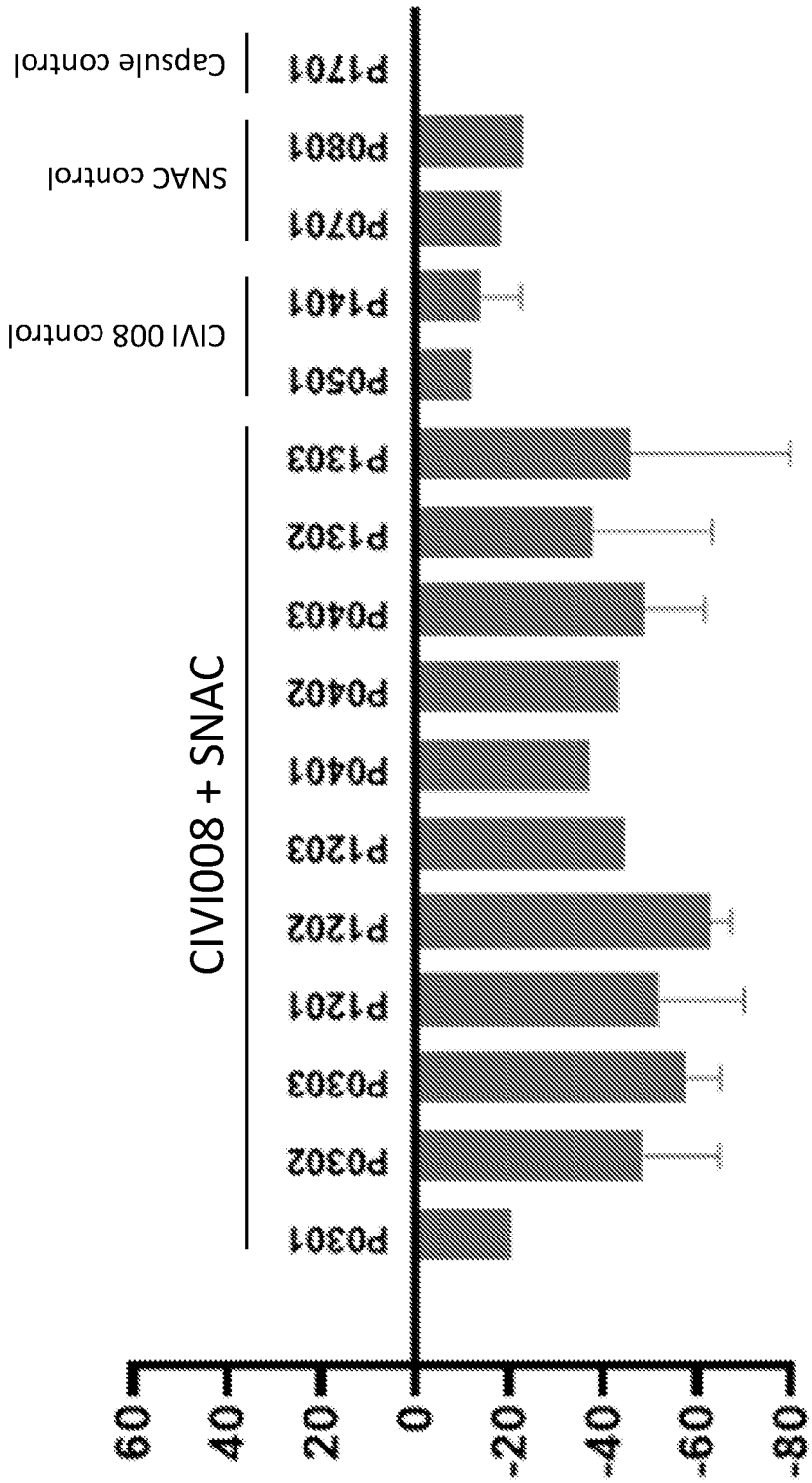

Mean PCSK9 % change from baseline (day 35 & 42)
60
40
20
0
-20
-40
-60
-80
P0301
P0302
P0303
P1201
P1202
P1203
P0401
P0402
P0403
P1302
P1303
P0501
P1401
P0701
P0801
P1701
CIVI008 + SNAC
CIVI 008 control
SNAC control
Capsule control

FIG. 10

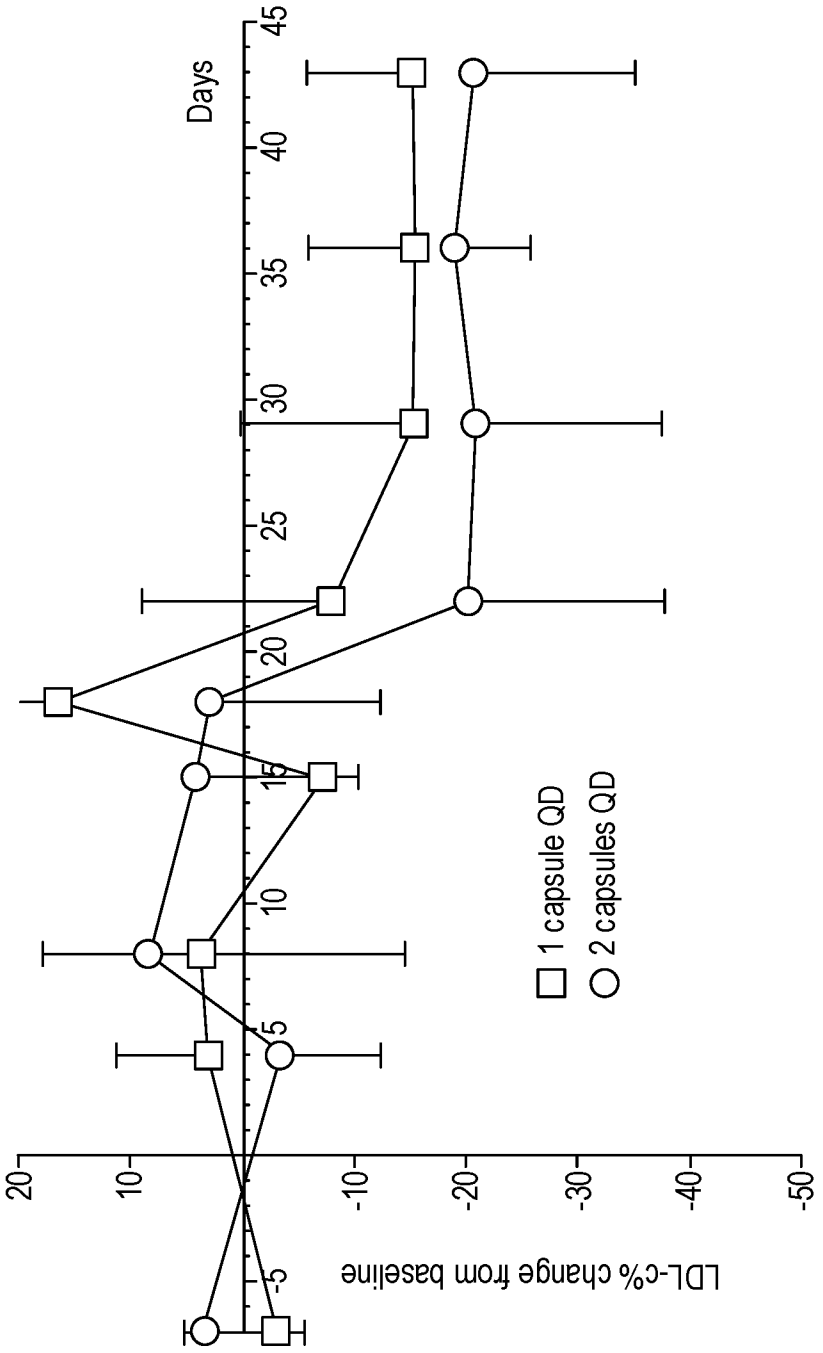

Days
45
40
35
30
25
20
15
10
5
-5
20
10
-10
-20
-30
-40
-50
LDL-c% change from baseline
1 capsule QD
2 capsules QD

FIG. 11A

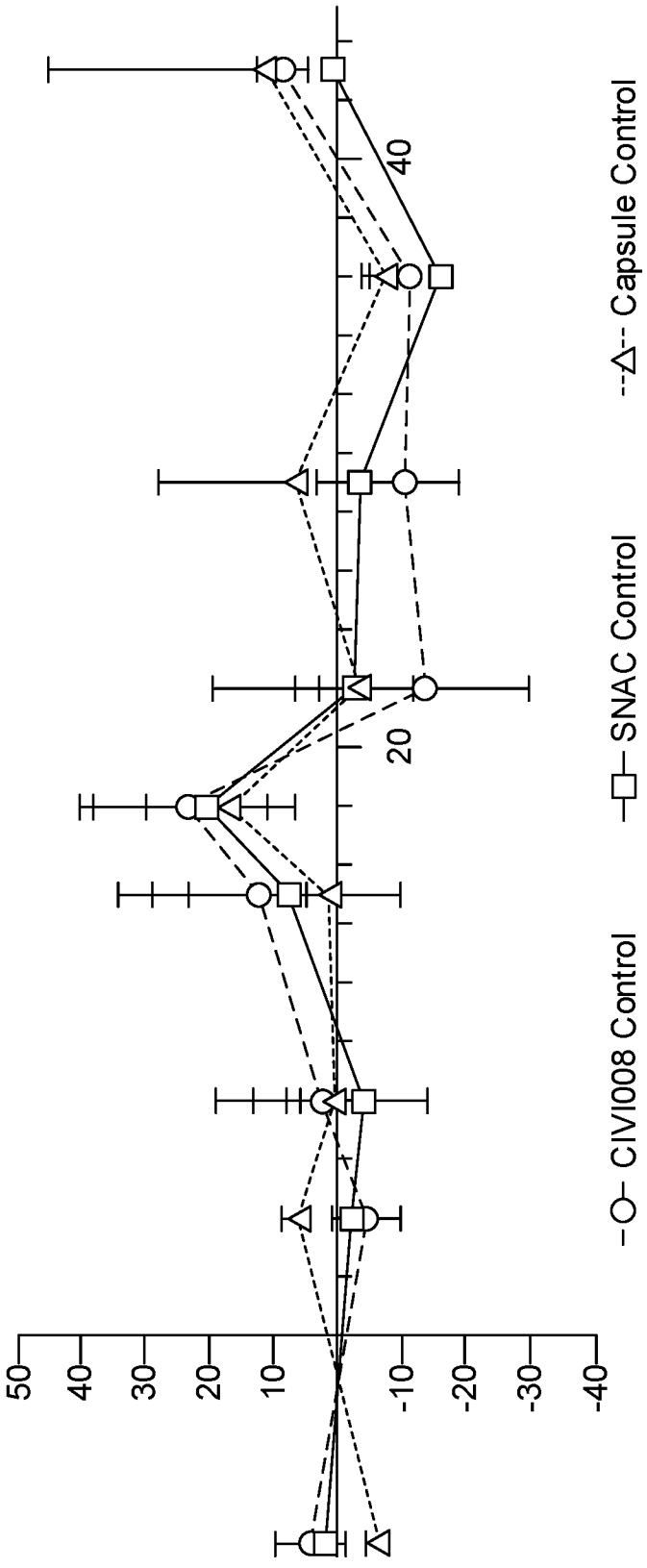

LDL % change from baseline
50
40
30
20
10
-10
-20
-30
-40
20
40
CIVI008 Control
SNAC Control
Capsule Control

FIG. 11B

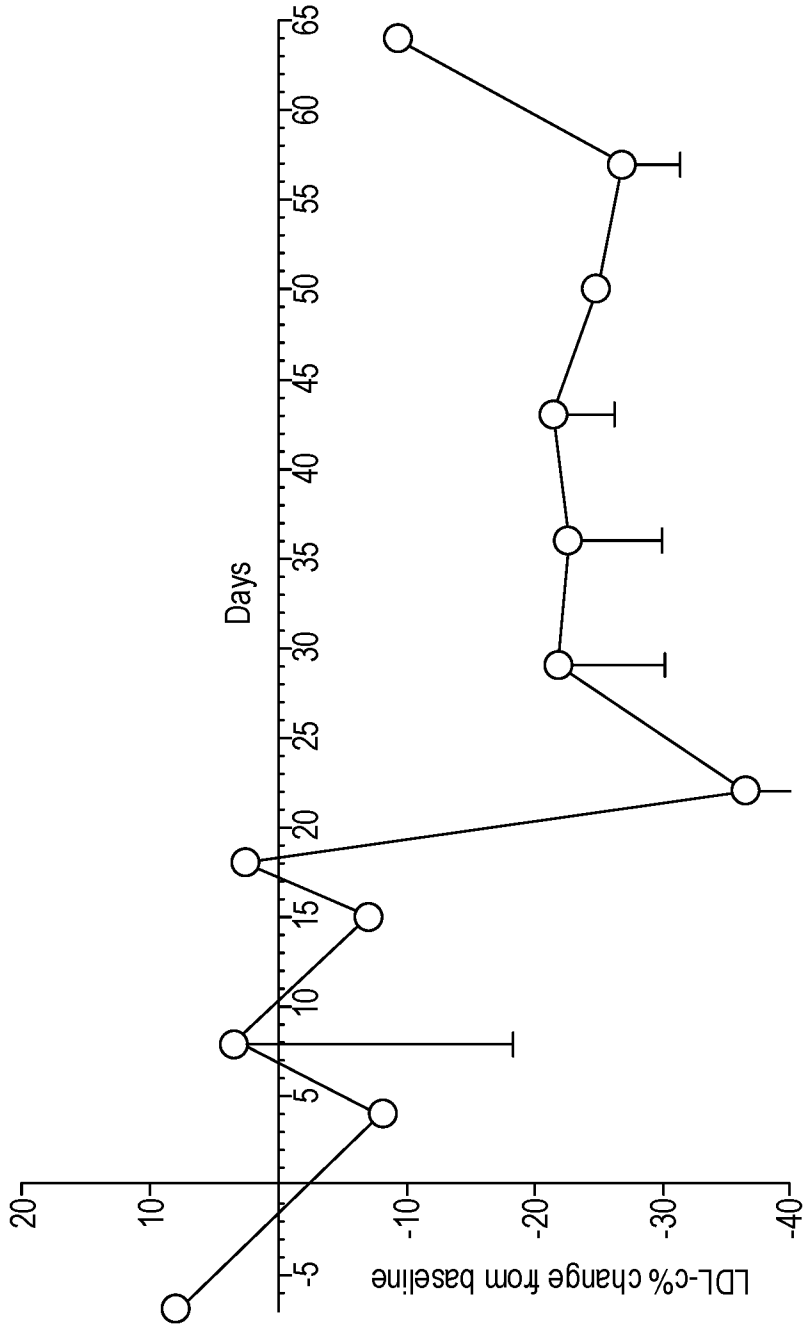
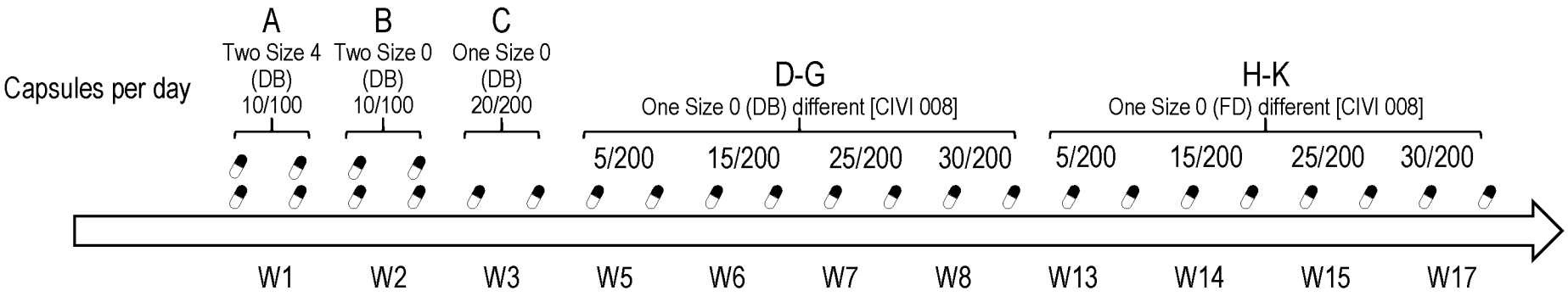

LDL-c% change from baseline
20
10
-5
-10
-20
-30
-40
Days
5
10
15
20
25
30
35
40
45
50
55
60
65

FIG. 12



Animals: 10 non-naive HNPs (5m/5F)
PK: at pre-dose & 0.5, 1.5, 3 and 5 hours post dose on dosing days
Clinical observations: Twice weekly
Clinical chemistry: days -7 and end of dosing

FIG. 13

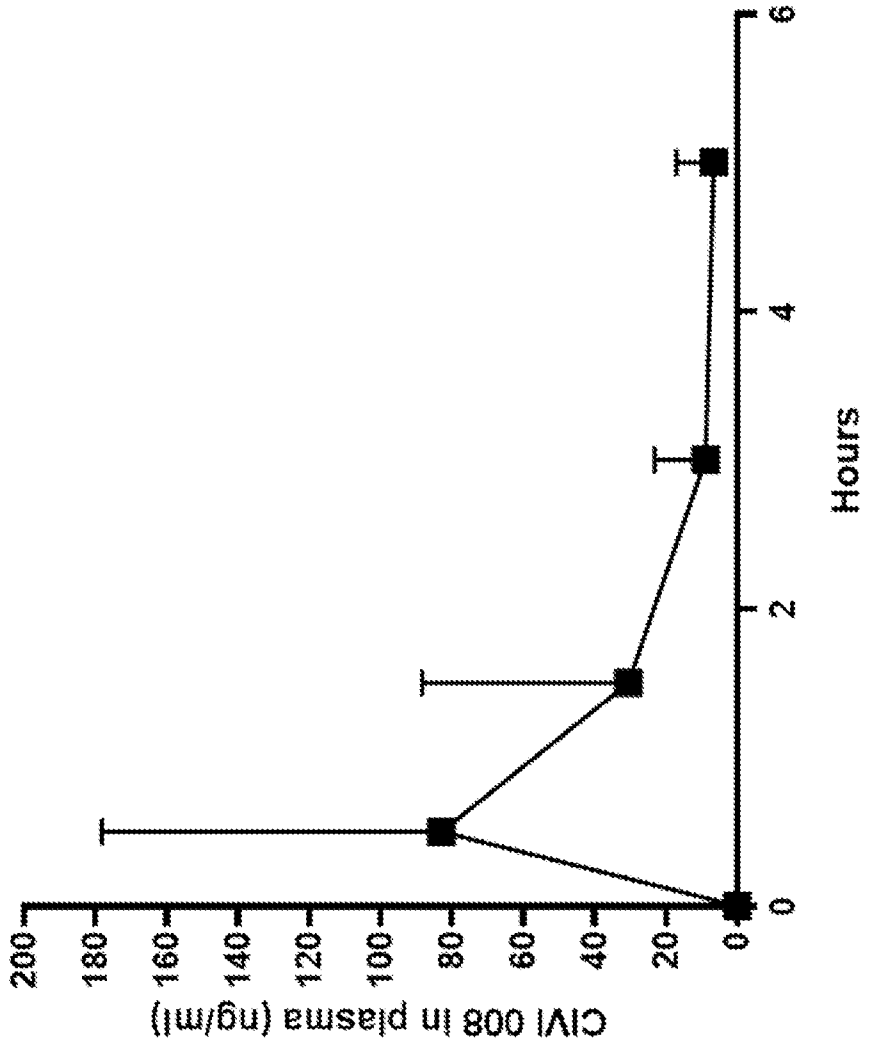
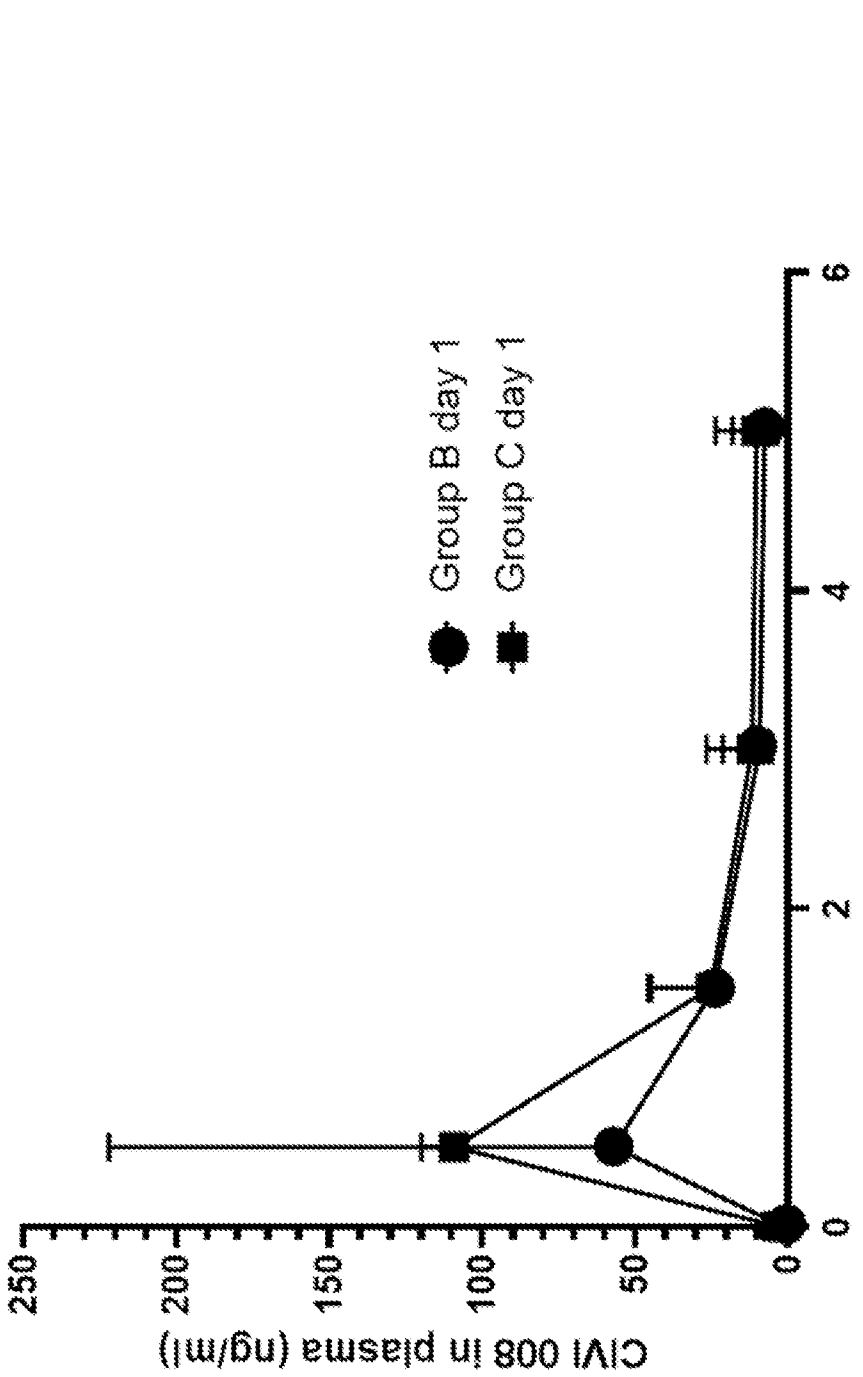

CIVI 008 in plasma (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
2
4
6
Hours

FIG. 14

	No. animals	Mean AUC_{0-5} (ng*ml*h)	SD	Mean C_{max} (ng/ml)	SD
CIVI008/SNAC	6	67.1	50.7	50,7	52,3
CIVI008/5-CNAC	10	122,5	98.6	106.9	91.2

FIG. 15

SUBSTITUTE SHEET (RULE 26)



	No. Capsules	No. Animals	Mean AUC_{0-5} ($ng*ml*h$)	SD	Mean C_{max} (ng/ml)	SD
Group B	2	10	97.0	87.9	60.8	64.6
Group C	1	10	144.8	101.2	116.9	114.1

FIG. 16

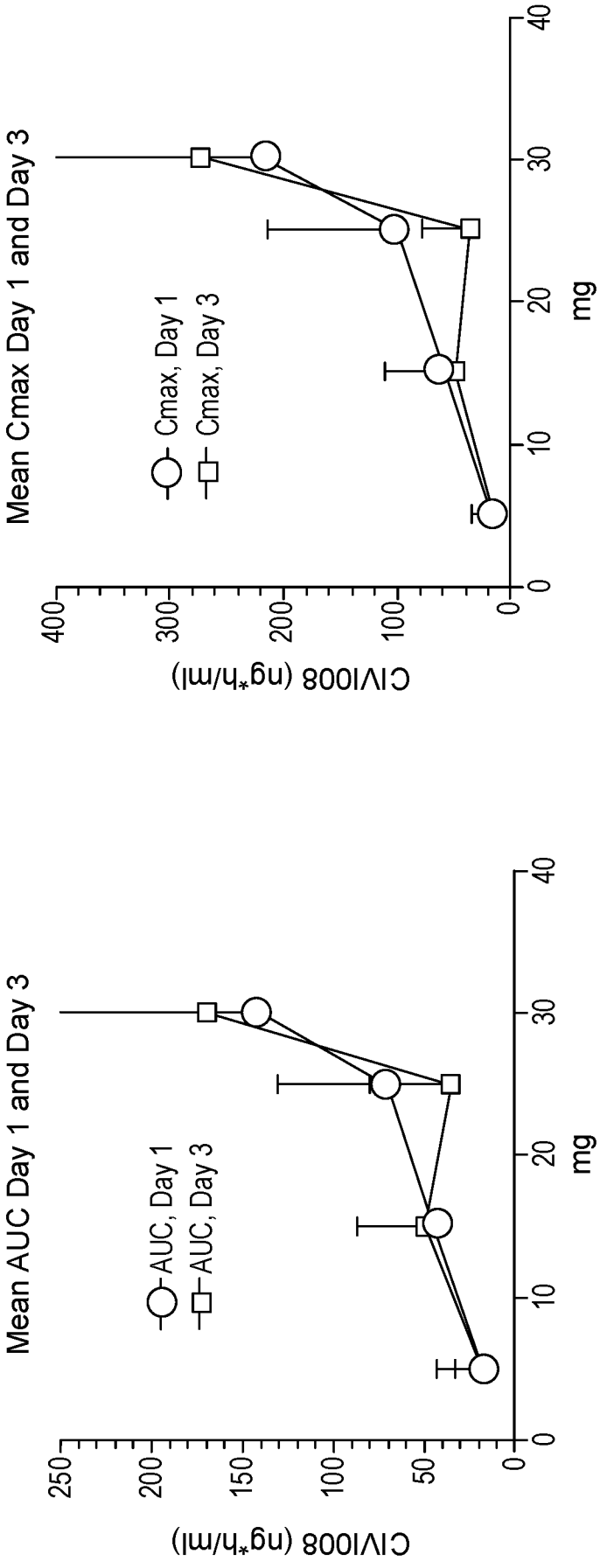

Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CIV1008 (ng*h/ml)
mg
0
50
100
150
200
250
0
10
20
30
40
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CIV1008 (ng*h/ml)
mg
0
100
200
300
400
0
10
20
30
40

FIG. 17

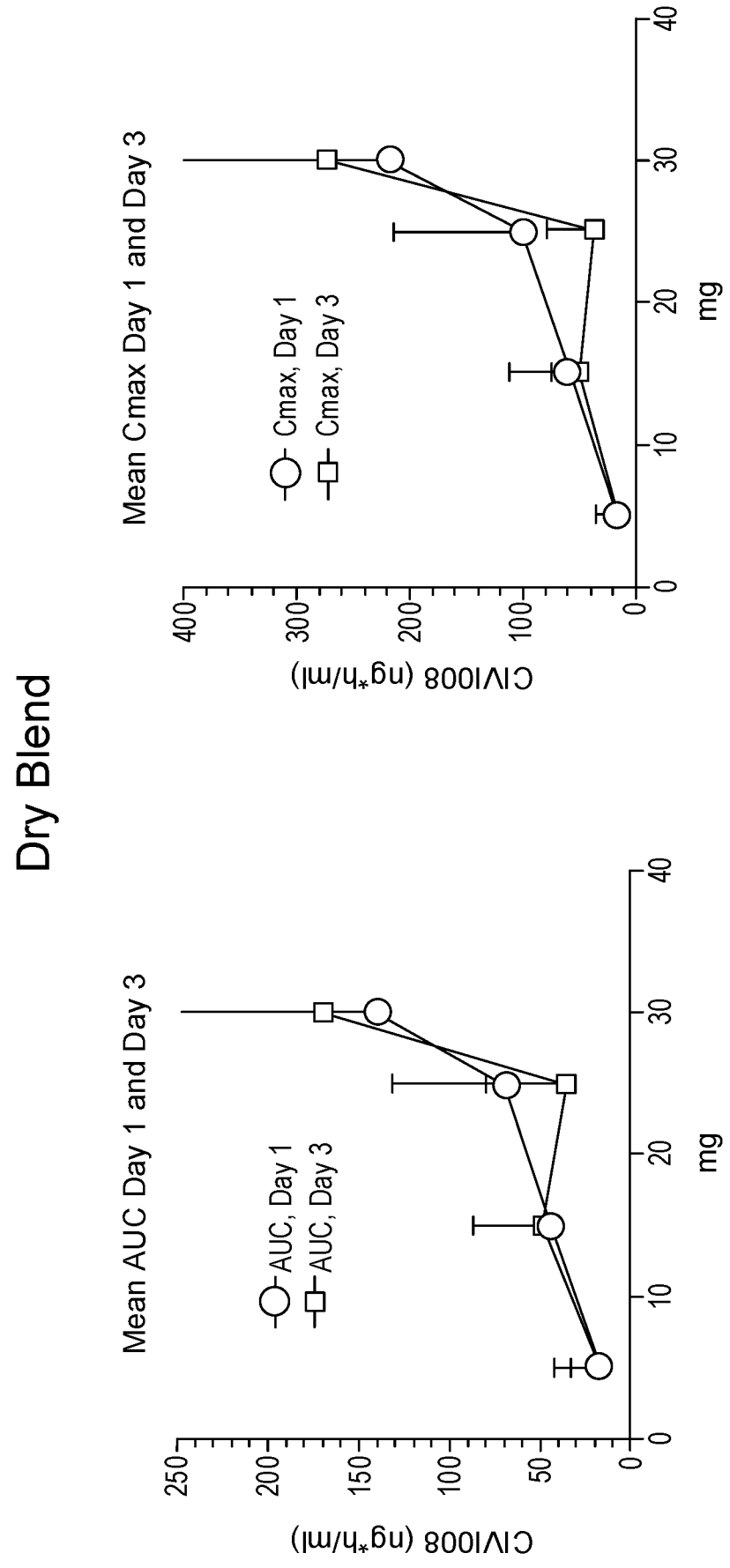

Dry Blend
Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CL/F/008 (ng*h/ml)
mg
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CL/F/008 (ng*h/ml)
mg

FIG. 18A

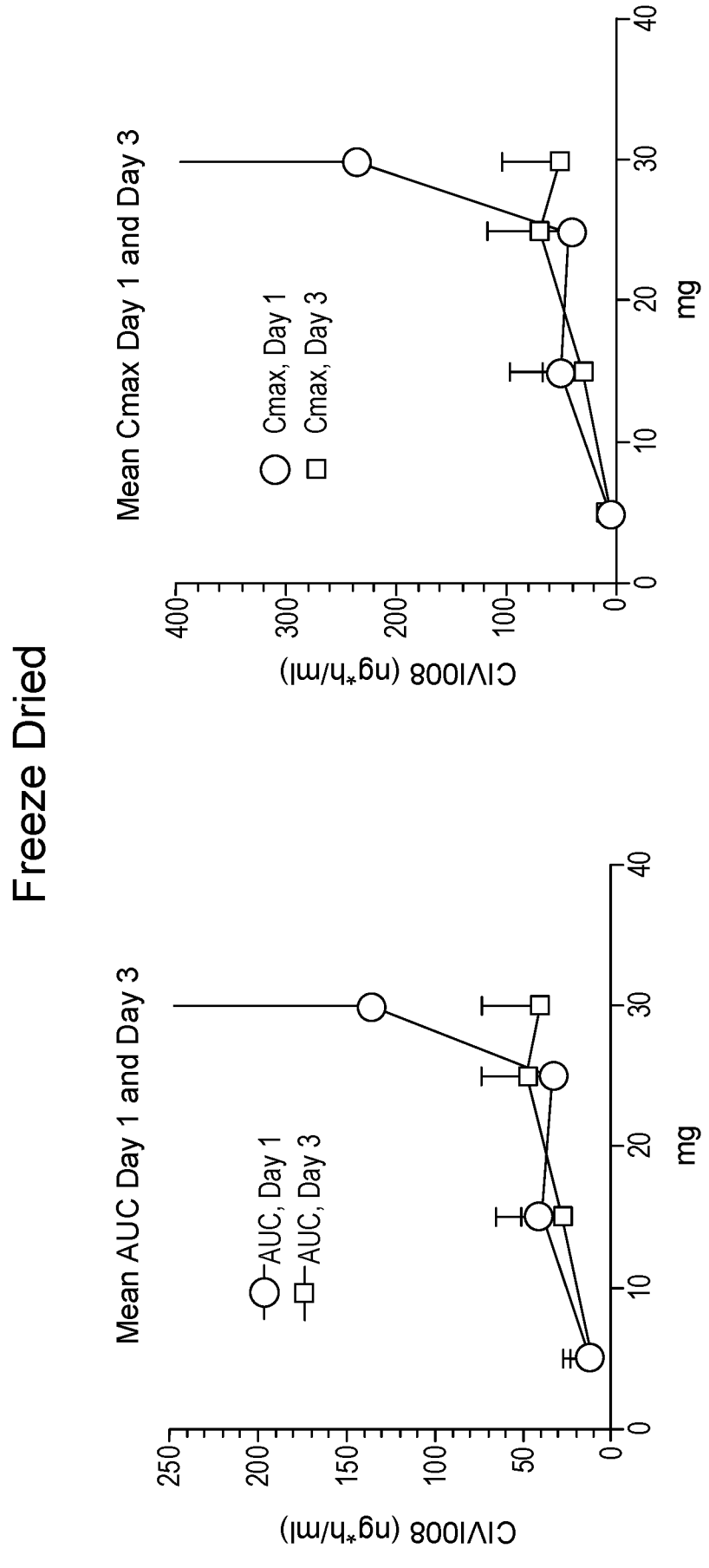

Freeze Dried
Mean Cmax Day 1 and Day 3
Cmax, Day 1
Cmax, Day 3
CIV1008 (ng*h/ml)
mg
Mean AUC Day 1 and Day 3
AUC, Day 1
AUC, Day 3
CIV1008 (ng*h/ml)
mg

FIG. 18B

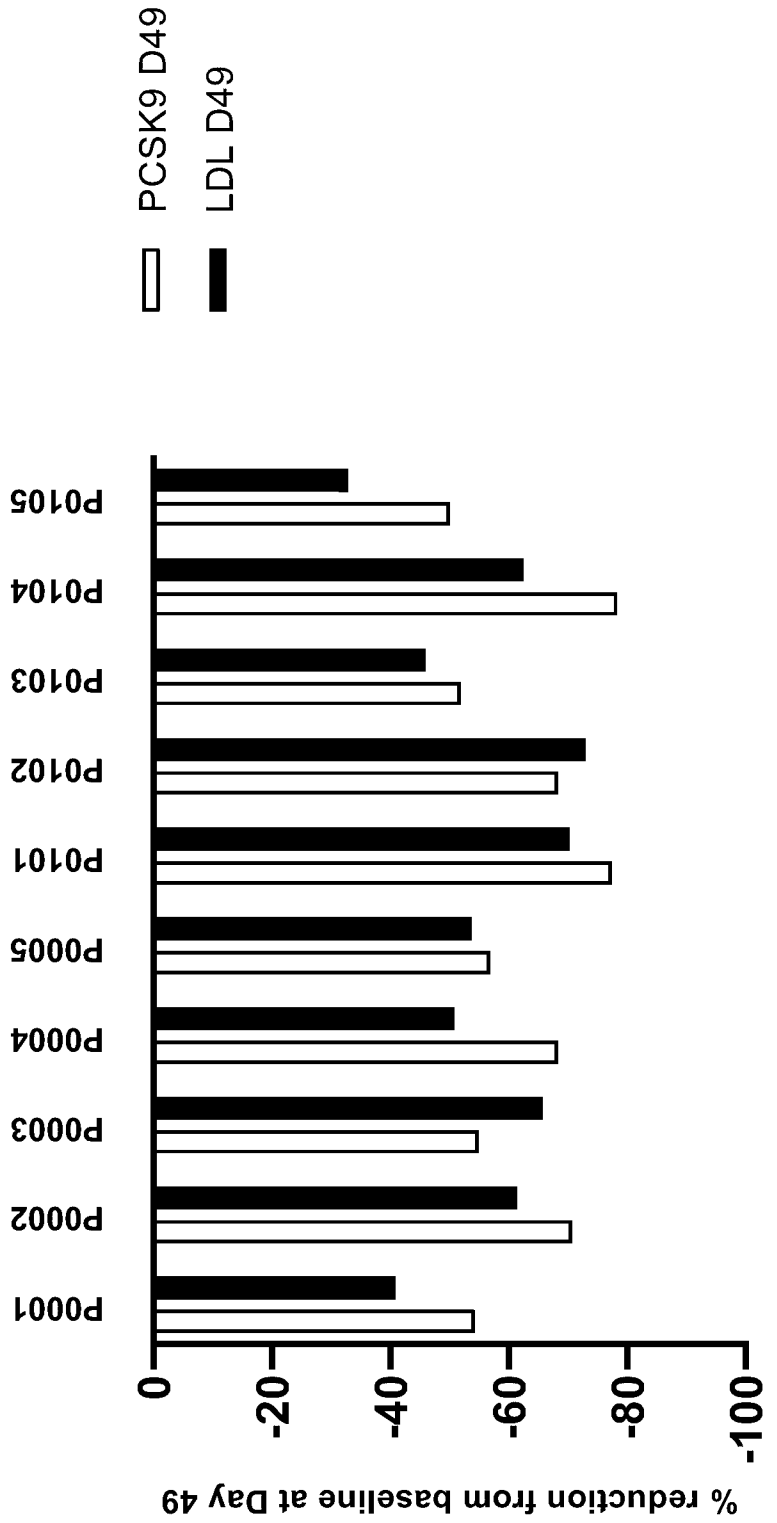

PCSK9 D49
LDL D49
P0105
P0104
P0103
P0102
P0101
P0005
P0004
P0003
P0002
P0001
0
-20
-40
-60
-80
-100
% reduction from baseline at Day 49

FIG. 19

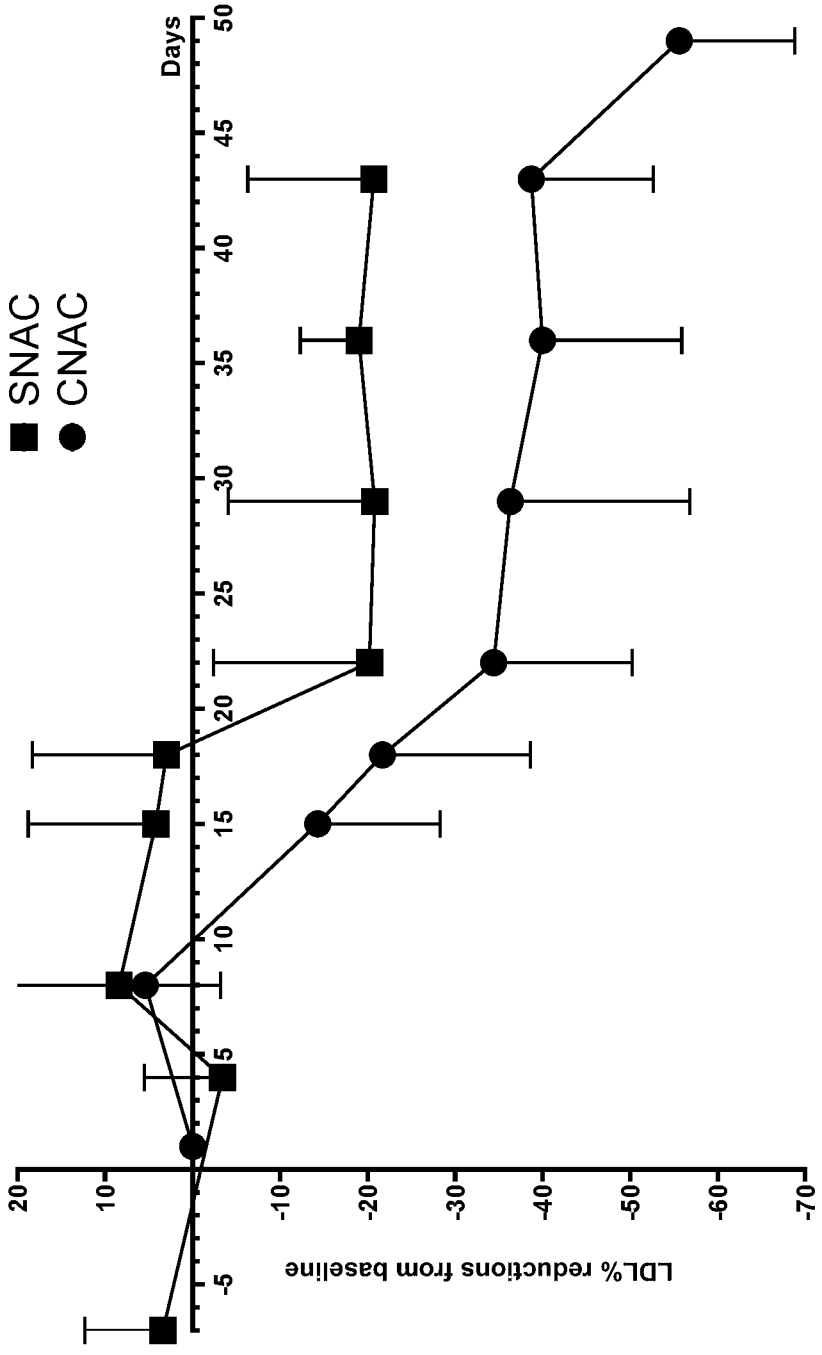
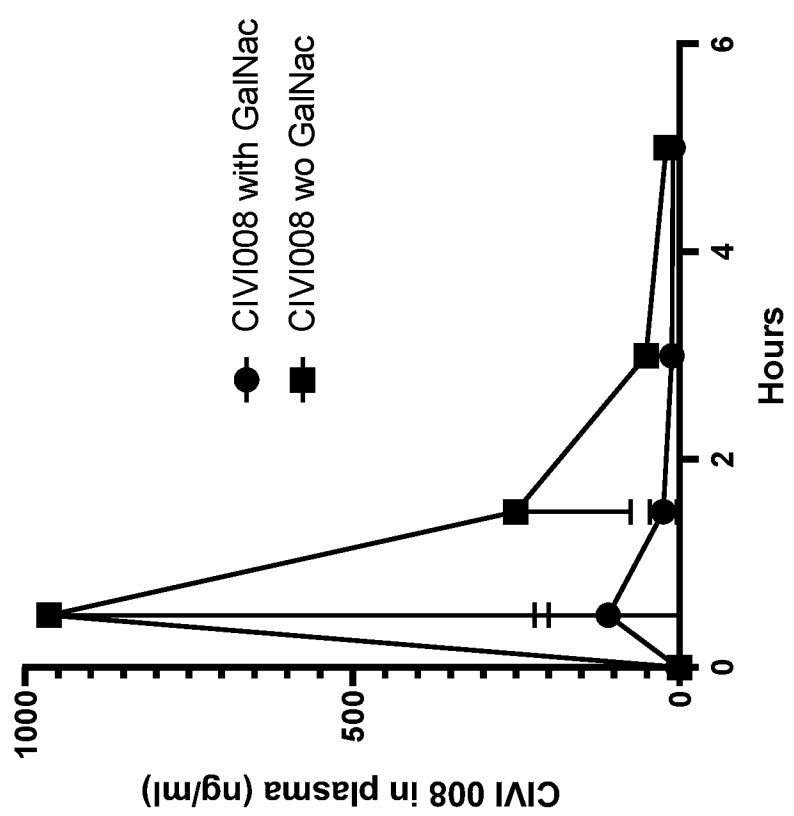
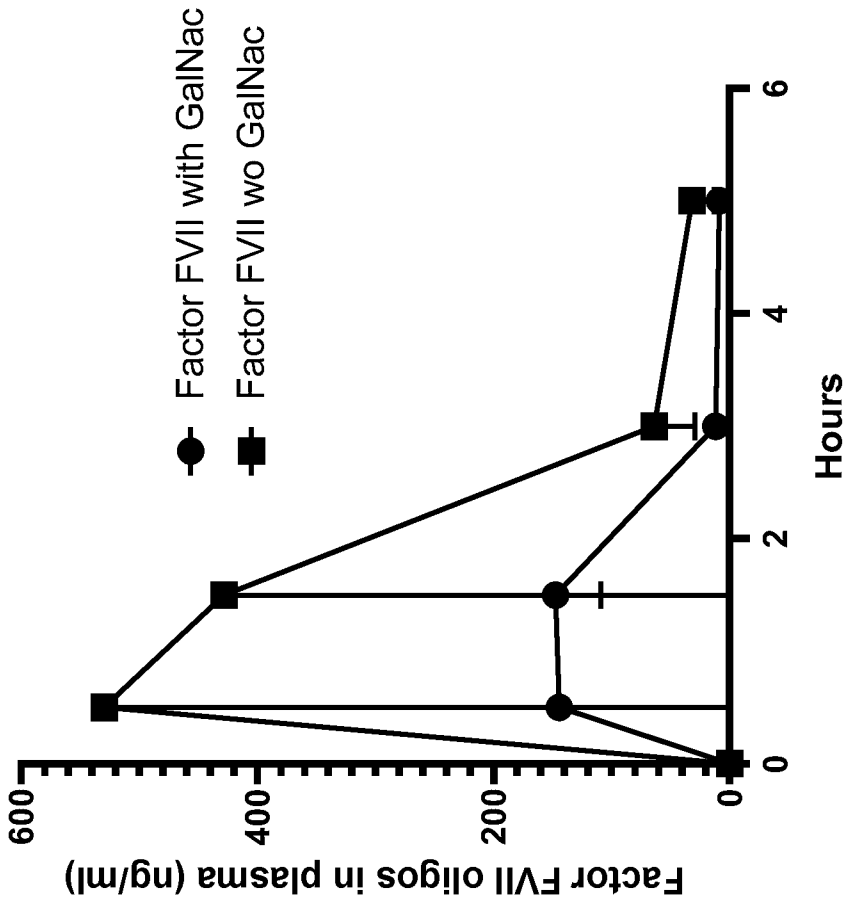

SNAC
CNAC
Days
LDL% reductions from baseline
20
10
-5
-10
-20
-30
-40
-50
-60
-70
5
10
15
20
25
30
35
40
45
50

FIG. 20



	No. animals	Mean AUC_{0-5} (ng*l*h),	SD	Mean Cmax (ng/ml)	SD	Tmax (hours)
CIVI 008 with GalNac	10	144.8	101.2	116.9	114.1	0.5-1.5
CIVI 008 wo GalNac	10	1147.7	756.3	968.0	760.4	0.5-1.5

FIG. 21



	No. animals	Mean AUC_{0-5} (ng*l*h),	SD	Mean Cmax (ng/ml)	SD	Tmax (hours)
Factor FVII with GalNac	10	322.5	358.6	184,9	179.2	0.5-1.5
Factor FVII wo GalNac	8	1109.5	811.1	743.3	646.4	05-1.5

FIG. 22

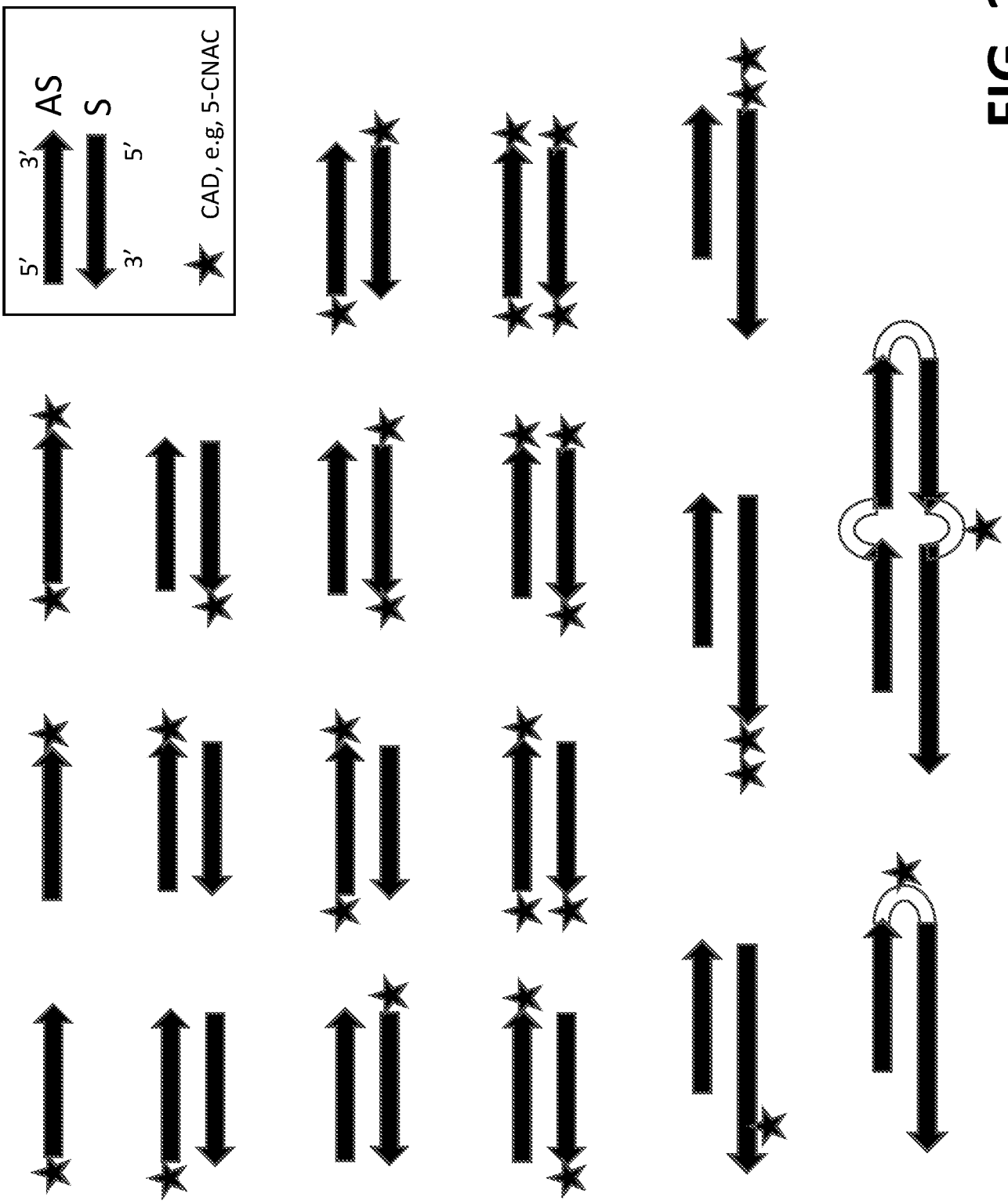


FIG. 23