

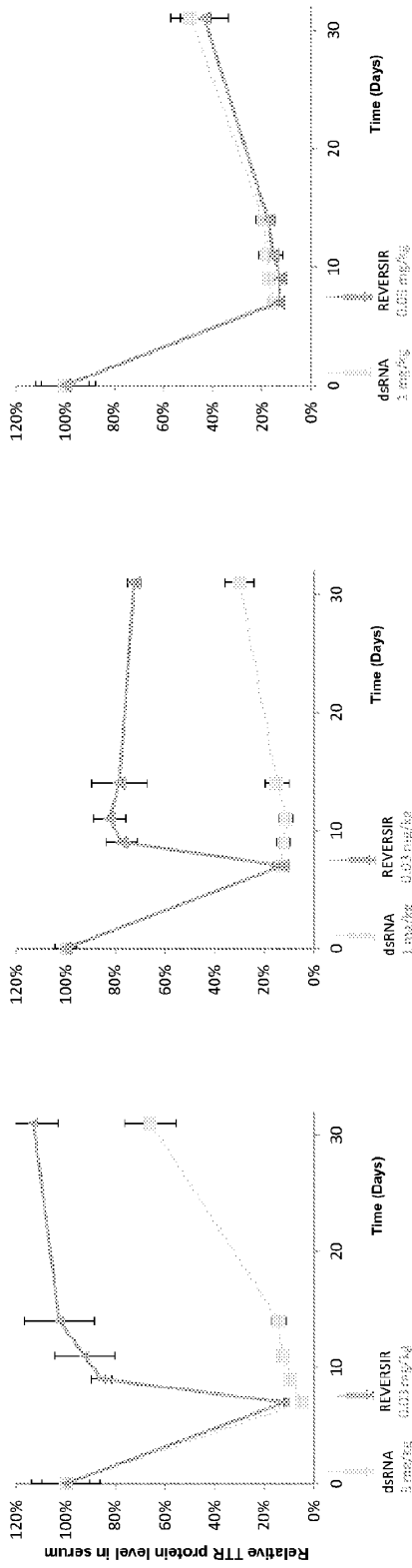


FIG. 1C

FIG. 1B

FIG. 1A

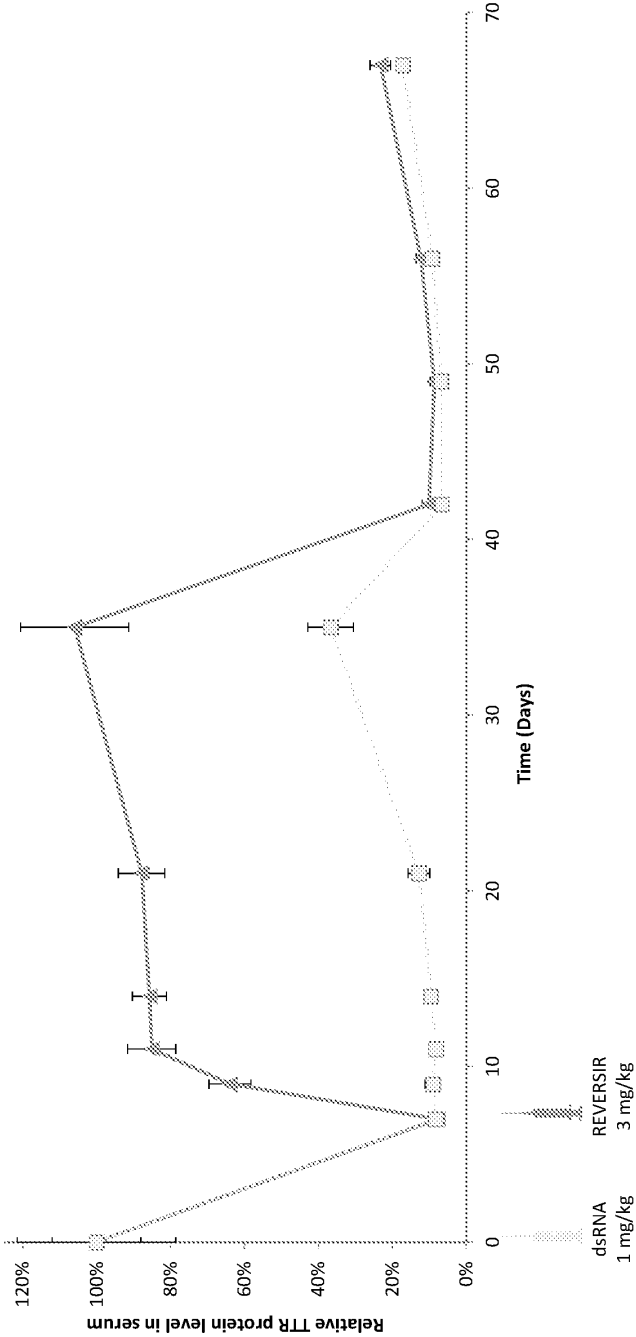


FIG. 2

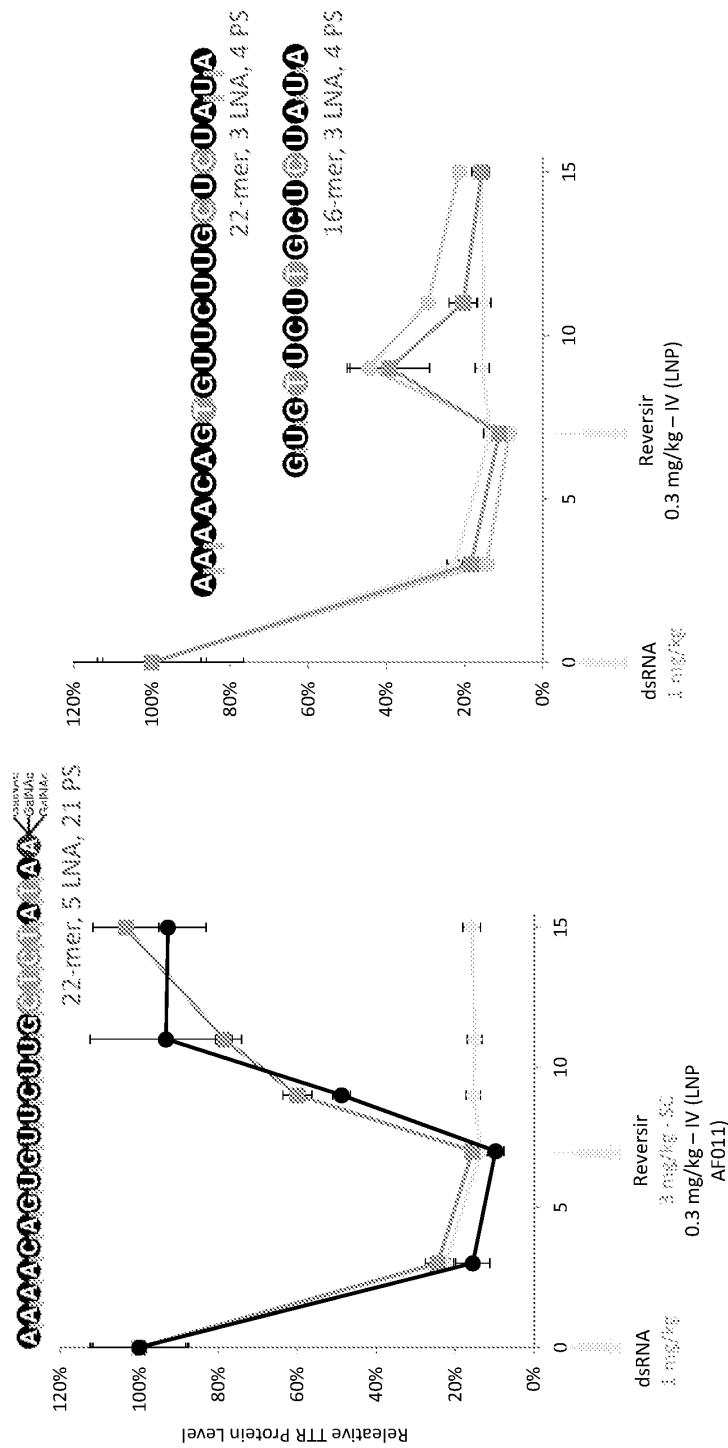
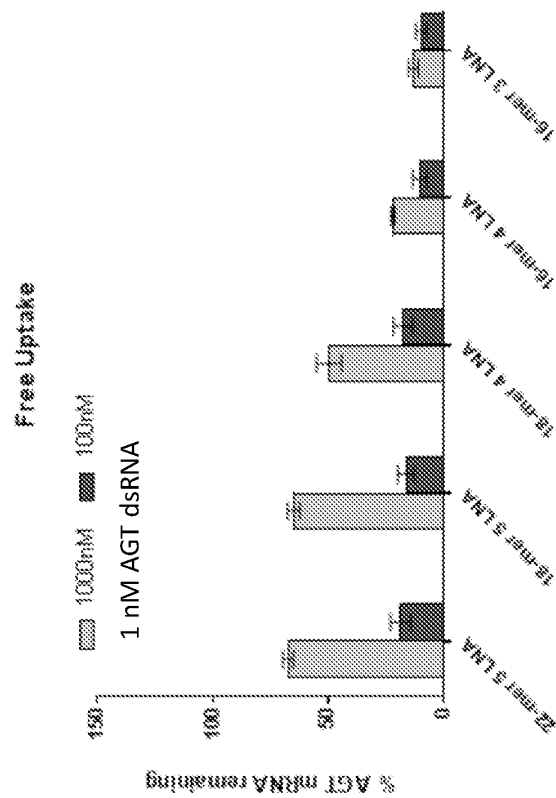
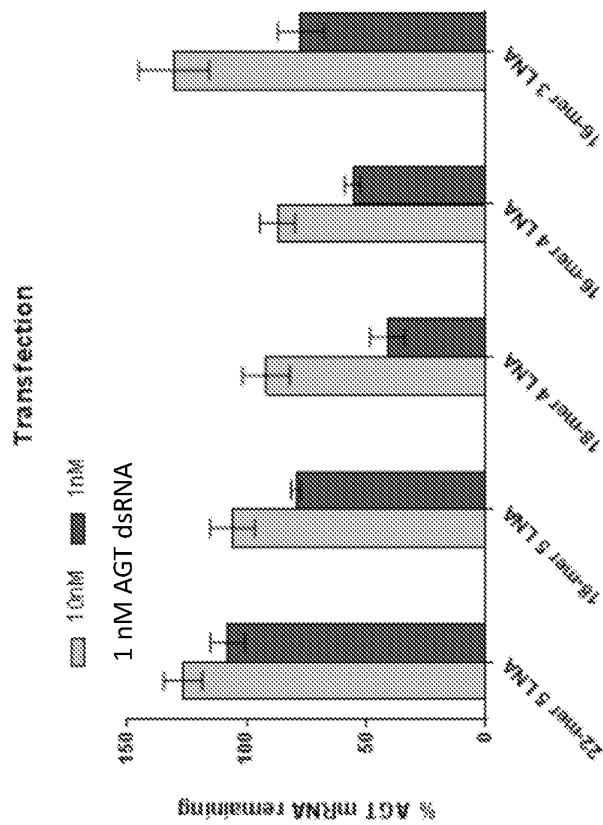


FIG. 3B

FIG. 3A



		24h transfection of REVERSIR		24h transfection of REVERSIR		24h free uptake of REVERSIR		24h free uptake of REVERSIR		
		Dose - Unit		Dose - Unit		Dose - Unit		Dose - Unit		
		1 - nM		10 - nM		1000 - nM		100 - nM		
REVERSIR sets	REVERSIR	avg	SD	avg	SD	avg	SD	avg	SD	
	22-mer - 5 LNA	107.9	7.2	126.7	8.0	67.4	2.3	18.7	4.5	
	18-mer - 5 LNA	79.4	2.0	105.9	9.4	65.0	2.7	16.5	3.6	
	18-mer - 4 LNA	40.8	7.3	91.9	9.8	49.6	5.4	17.7	4.0	
	16-mer - 4 LNA	55.6	3.4	87.1	7.5	22.1	0.9	19.4	3.2	
	16-mer - 3 LNA	77.2	9.8	130.5	14.8	13.2	2.2	9.7	2.5	
		REVERSIR								LNA
22-mer - 5 LNA		UCCGUCGAUCCGACAAUUGCG								

FIG. 5

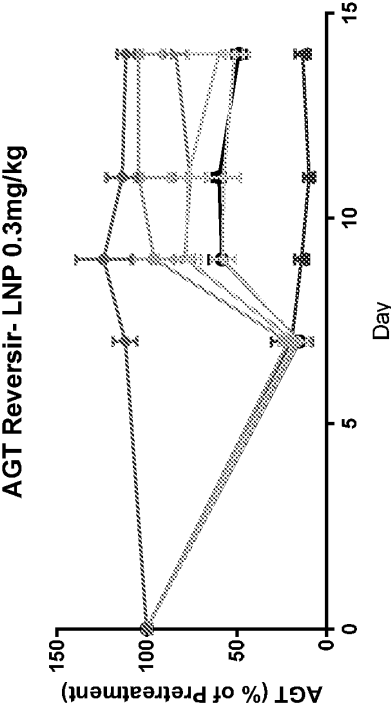


FIG. 6A

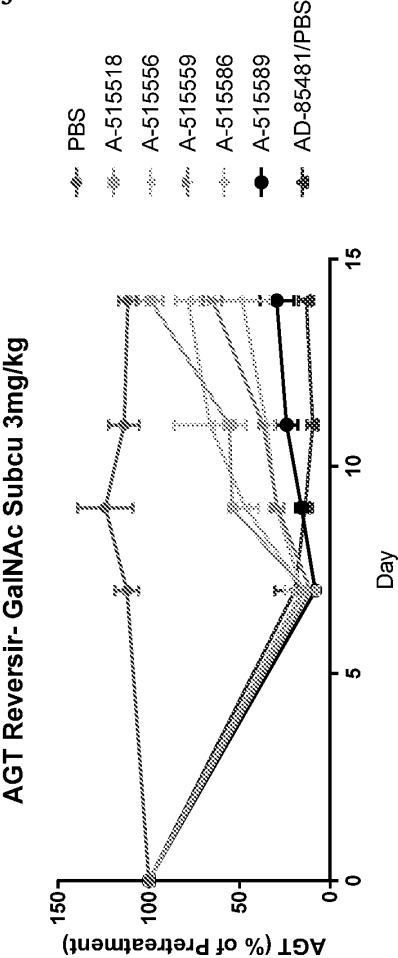


FIG. 6B

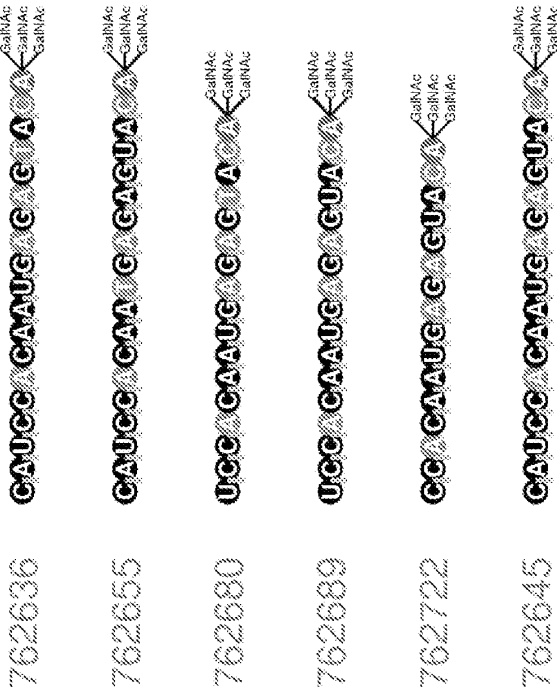


FIG. 7A

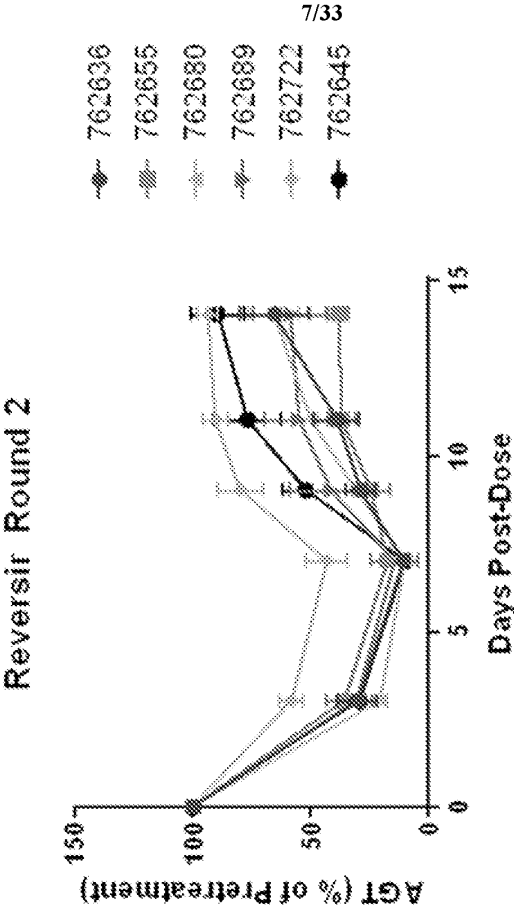
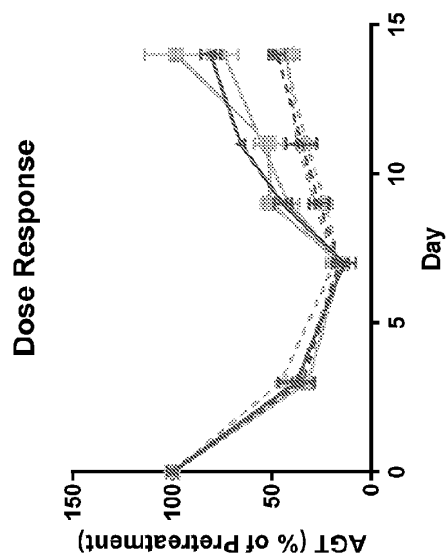
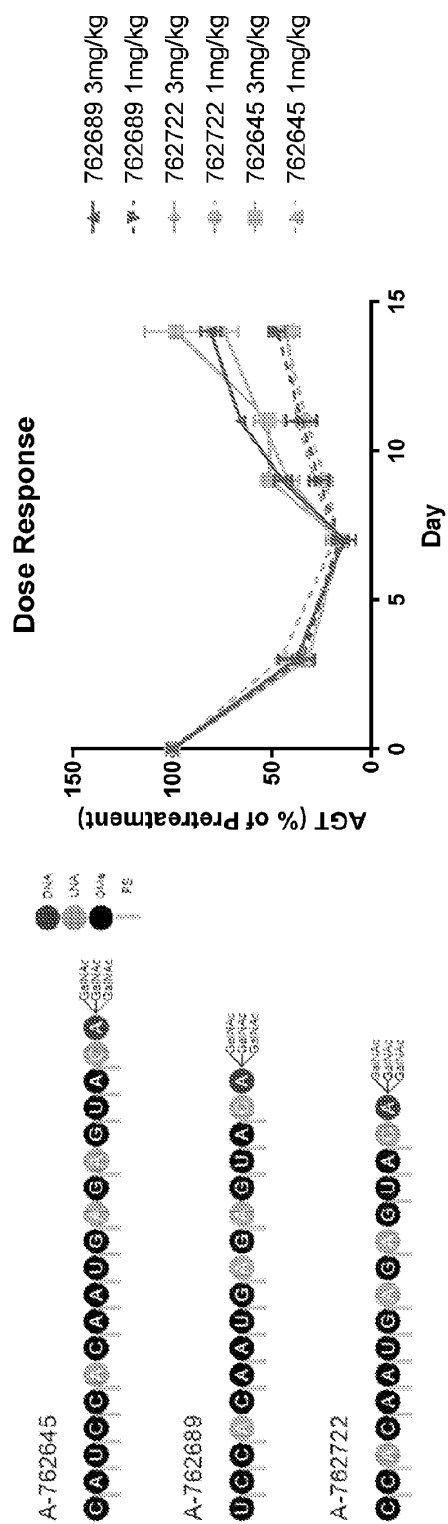


FIG. 7B



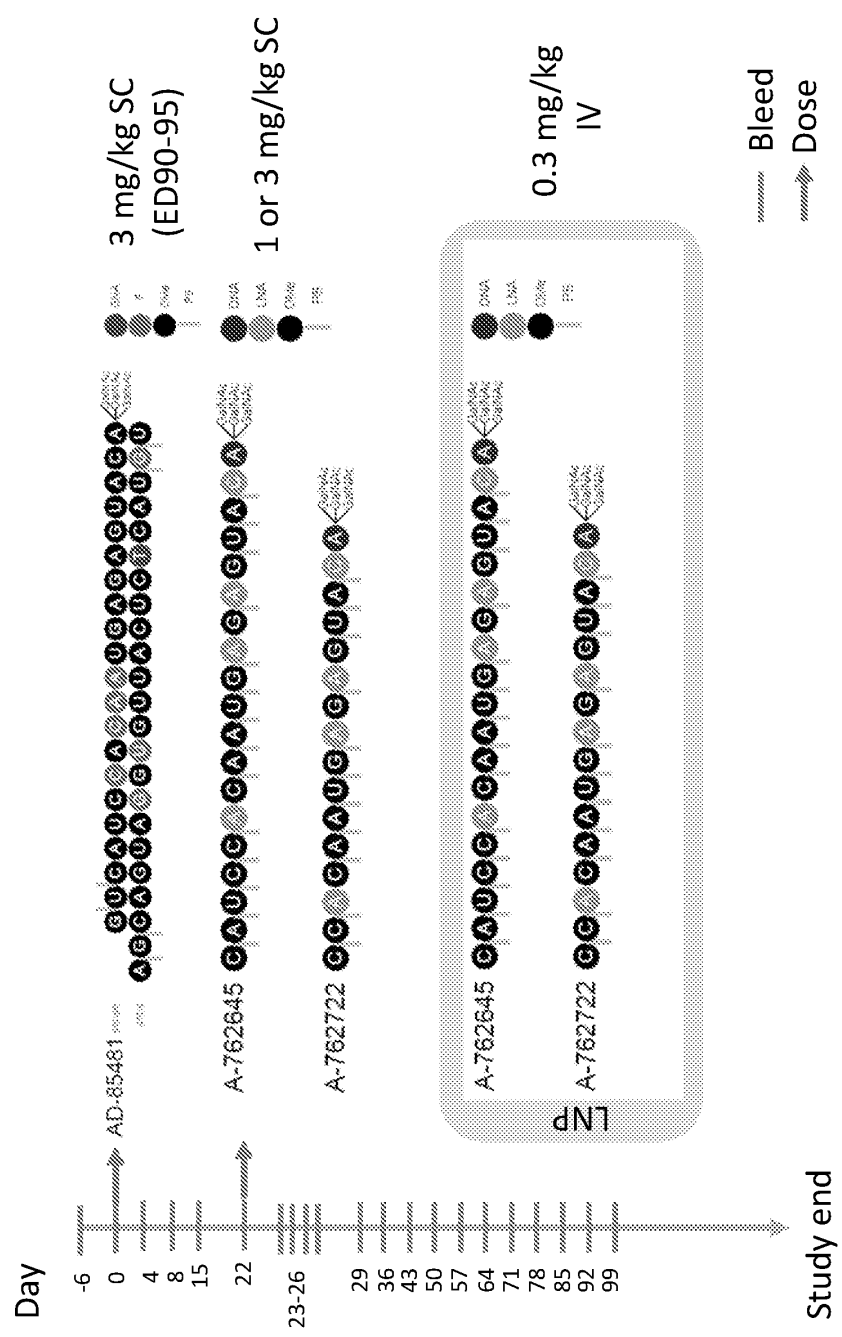


FIG. 9

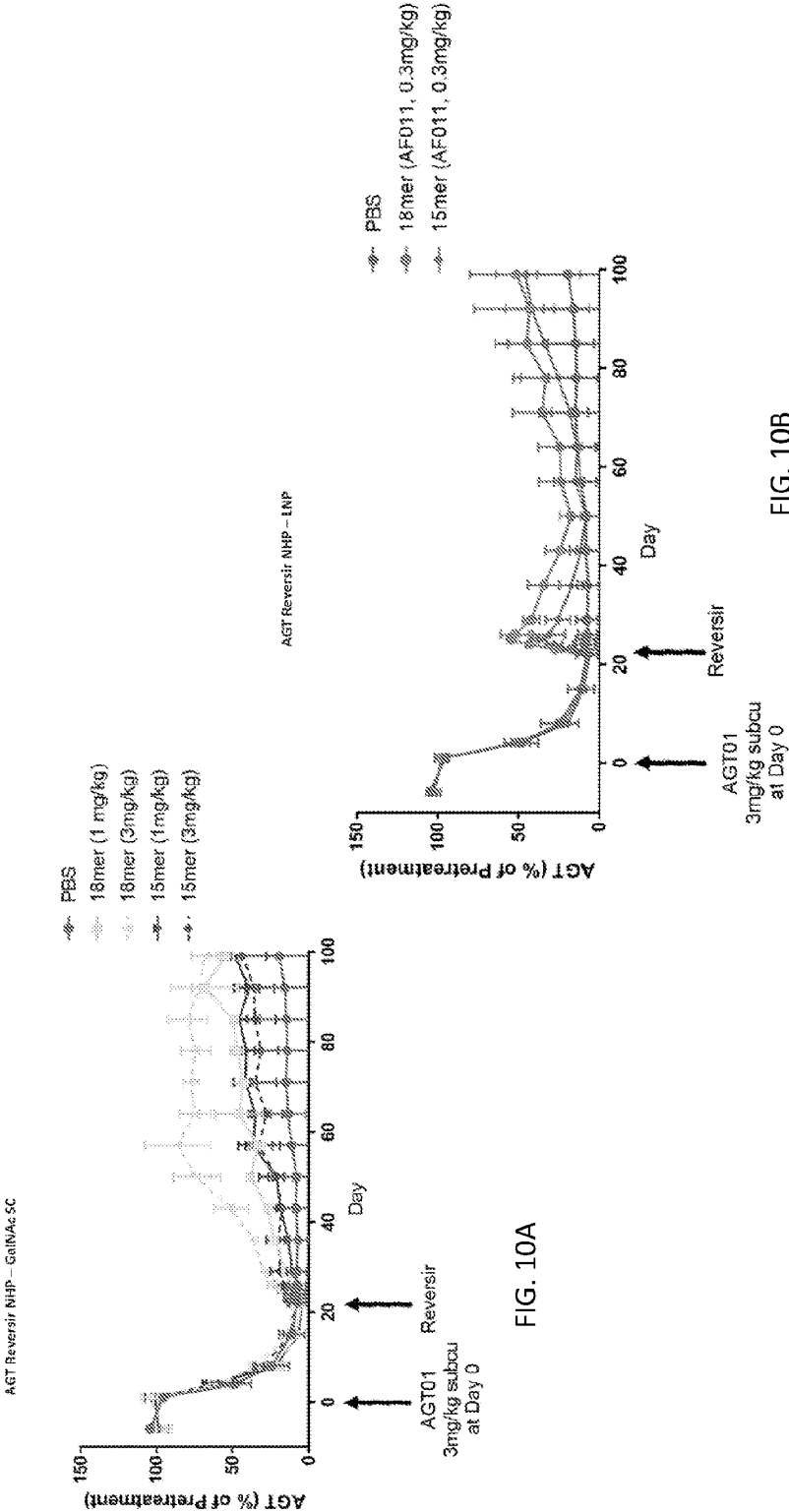


FIG. 10A

FIG. 10B

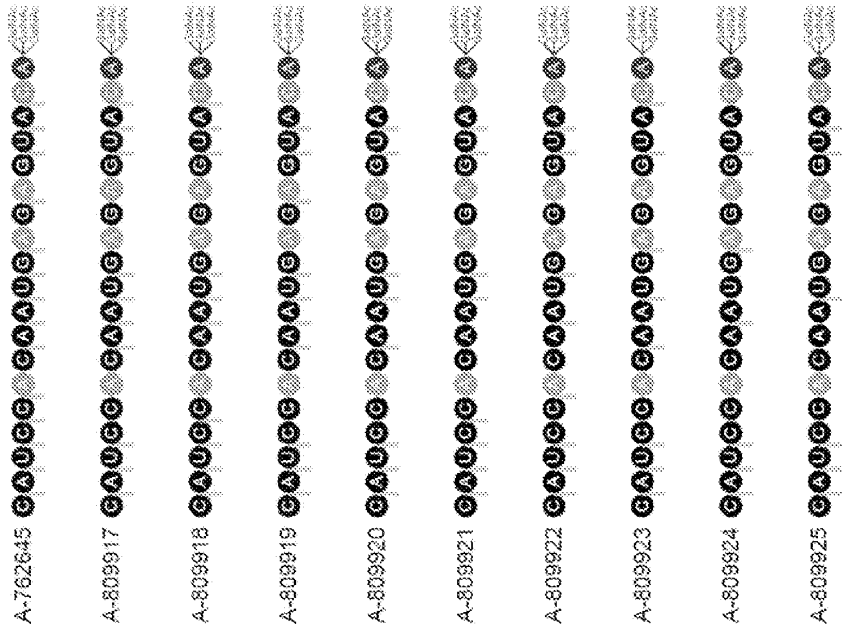


FIG. 11A

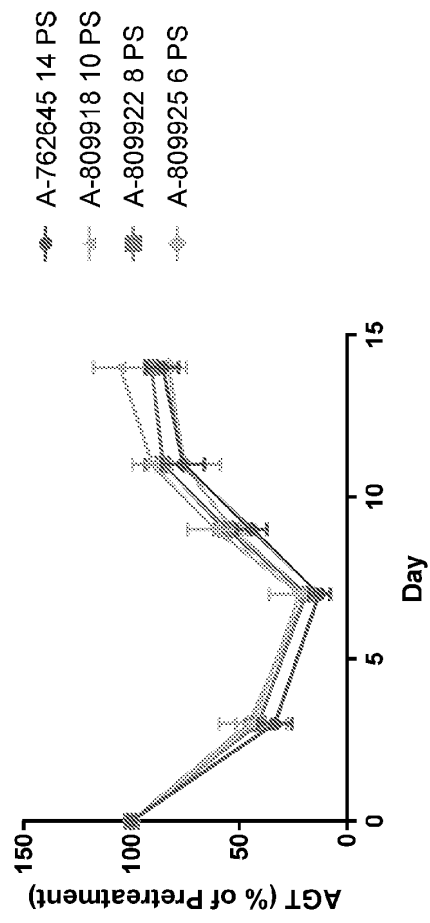


FIG. 11B

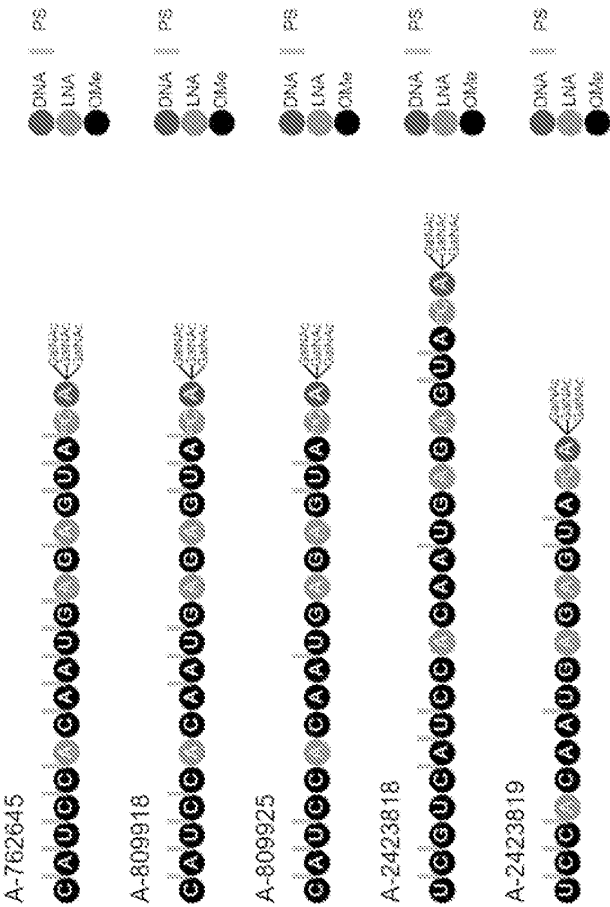


FIG. 12A

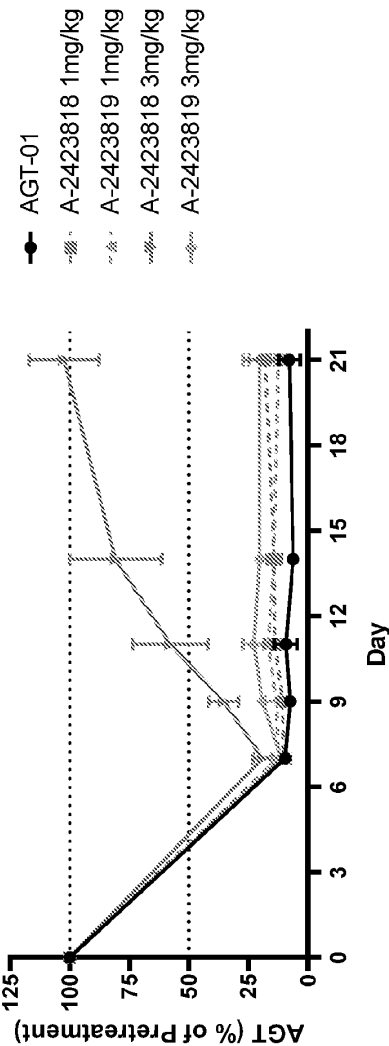
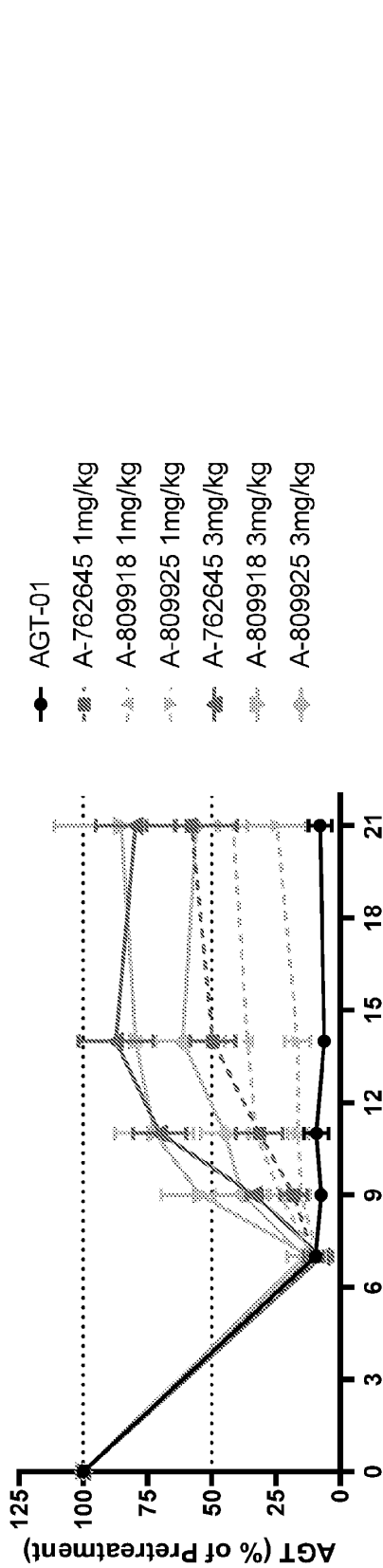


FIG. 12B

FIG. 12C

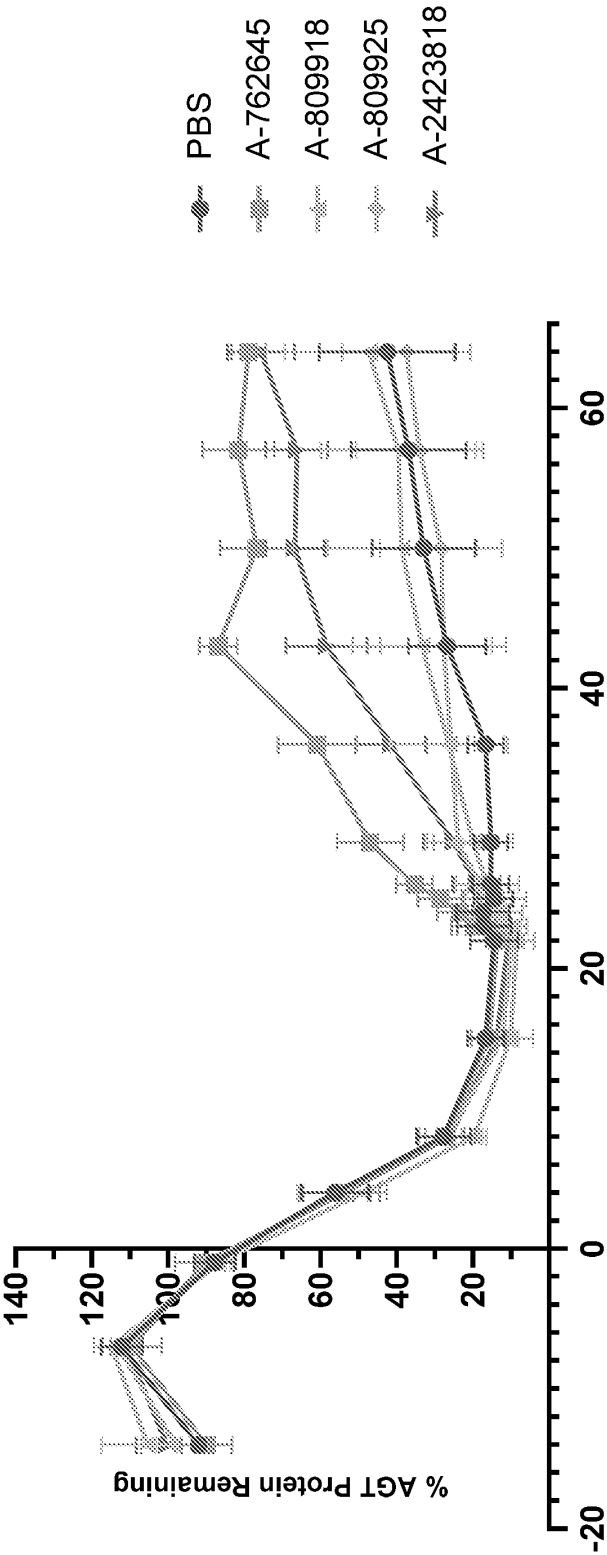


FIG. 13A

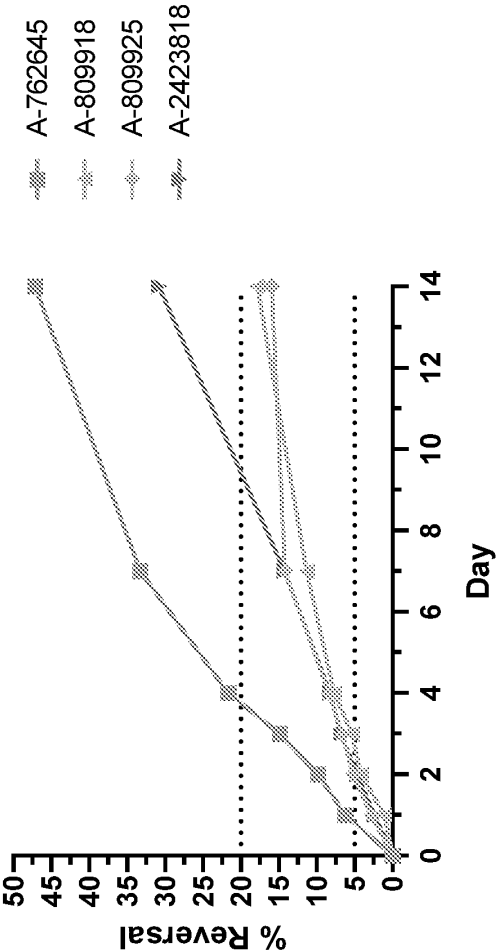


FIG. 13B

A-762645	
Day	% Reversal
0	0.0
1	6.2
2	9.9
3	14.9
4	21.7
7	33.3
14	47.2

FIG. 13C

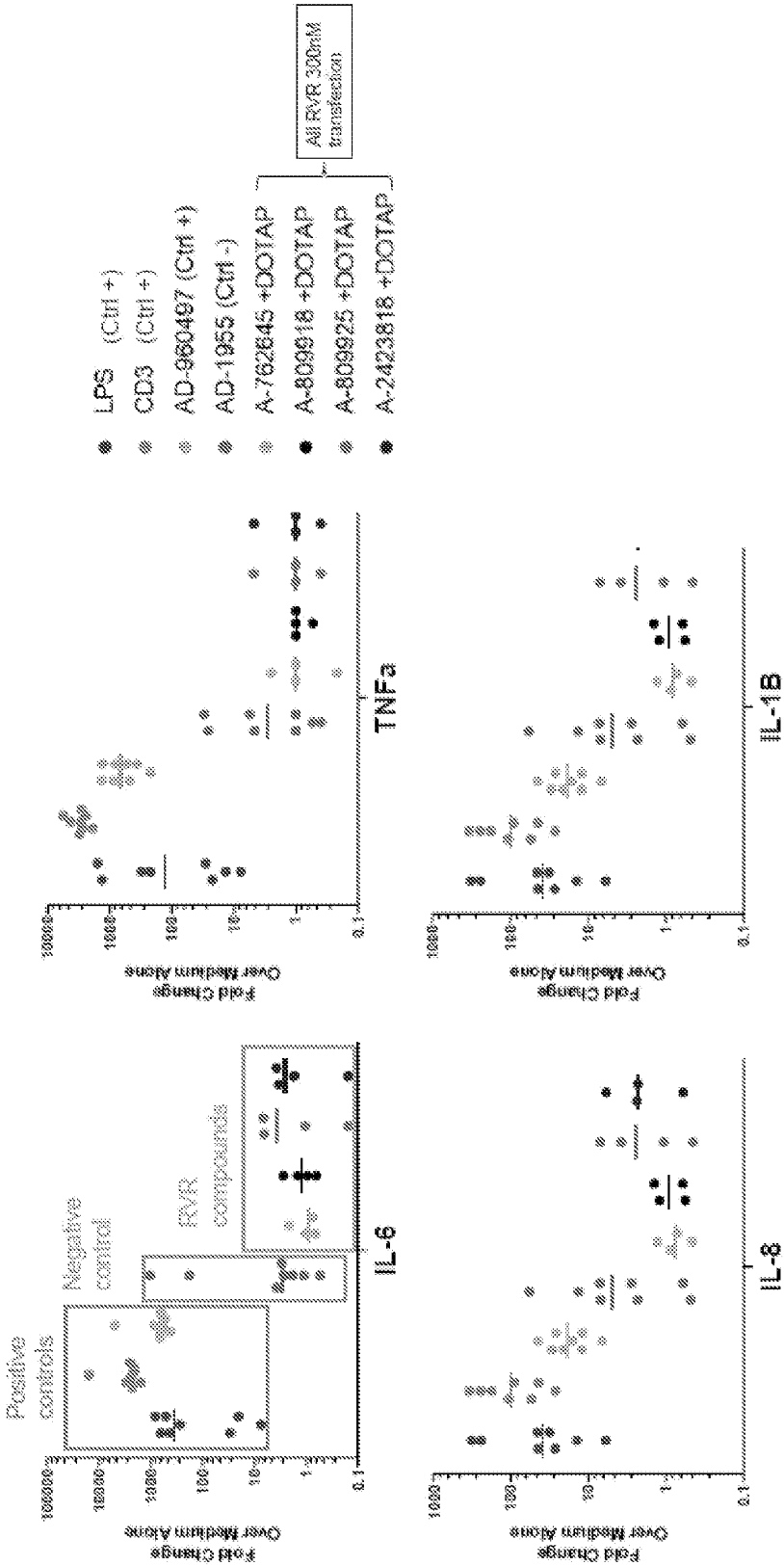


FIG. 14A

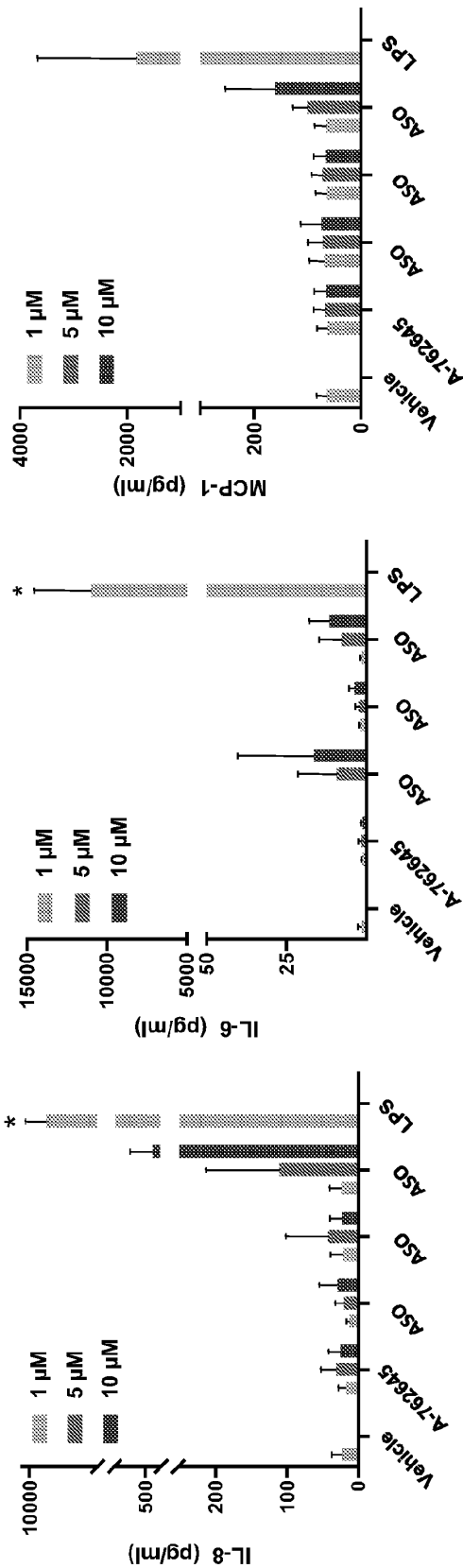


FIG. 14B

Day 99 (77 days post RVR dosing) in NHP

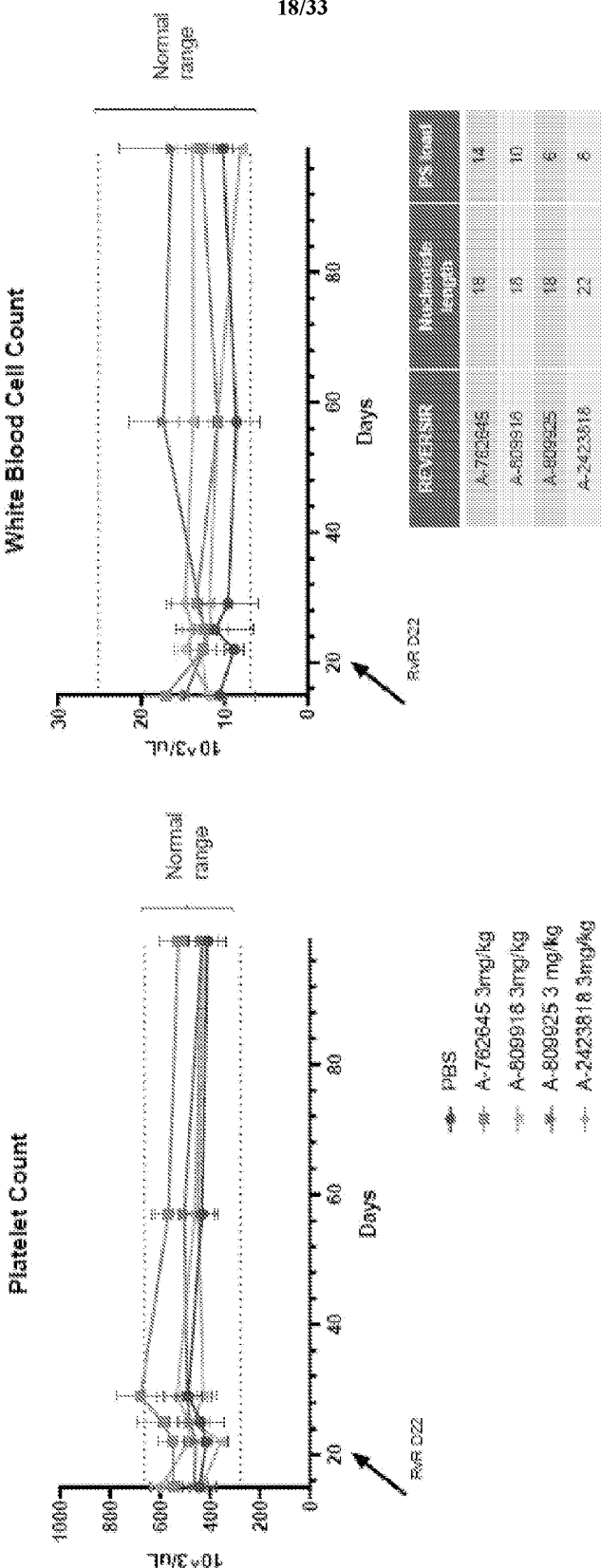
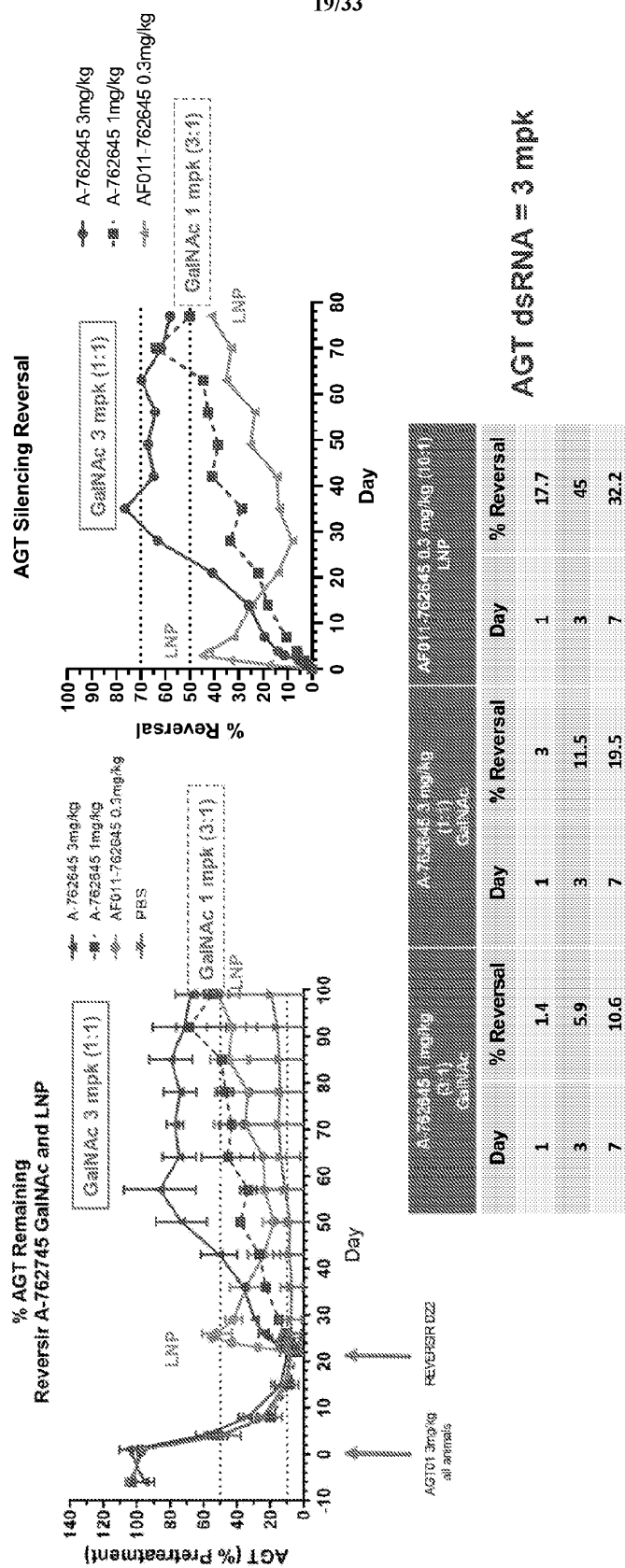


FIG. 14C



zilebesiran 10 mpk

Numeric PD profile of the first 7 days of RVR dosing

Day post dose	Day post RVR dose	zilebesiran 10mpk +PBS	zilebesiran 10mpk +RVR 10mpk (n=2)	zilebesiran 10mpk +RVR 30mpk	zilebesiran 10mpk +RVR 30mpk split (10mpk Q24hx3)
Pre (D-7&1)	NA	100	100	100	100
22	0	3.3	3.3	3.0	4.6
23	1	4.0	4.1	4.5	7.8
24	2	4.0	4.0	3.6	14.6
25	3	0.7	0.8	1.2	27.1
26	4	11.4	17.5	22.3	51.2
29	7	3.7	23.1	28.7	65.2

Q24h dosing every 24 hours. mpk: mg/kg

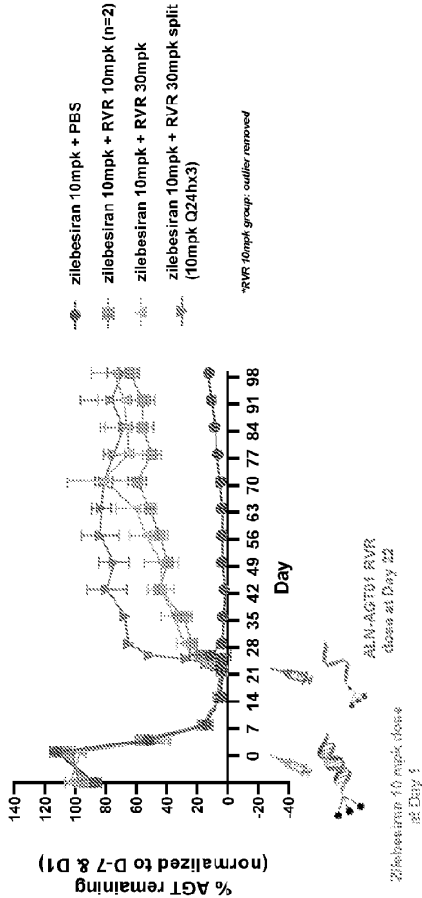


FIG. 15B

% AGT Remaining

	0	1	2	3	4	7	14	36
PBS CTL	22	23	24	25	26	29	34	36
10 mpk SC	3.5	3.9	4.1	3.6	3.6	3.7	2.9	2.9
20 mpk SC	4.7	5.9	17.1	21.2	28.3	32.8	36.2	36.0
30 mpk SC	3.1	4.7	6.7	10.2	16.5	25.8	35.2	35.2
10 mpk IV	3.0	4.5	6.8	14.2	22.3	28.7	19.1	22.7
20 mpk IV	3.6	6.3	9.1	12.1	17.5	19.1	22.5	22.5
30 mpk IV	2.8	4.5	9.7	13.7	20.2	22.5	35.4	35.4

- PBS CTL
- 10 mpk SC
- 20 mpk SC
- 30 mpk SC
- 10 mpk IV
- 20 mpk IV
- 30 mpk IV

Reversal SC vs IV

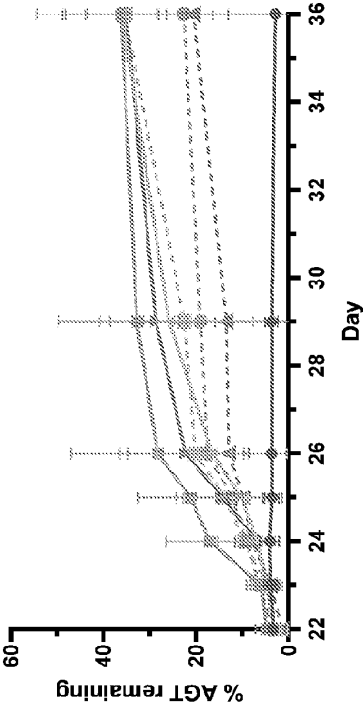


FIG. 15C

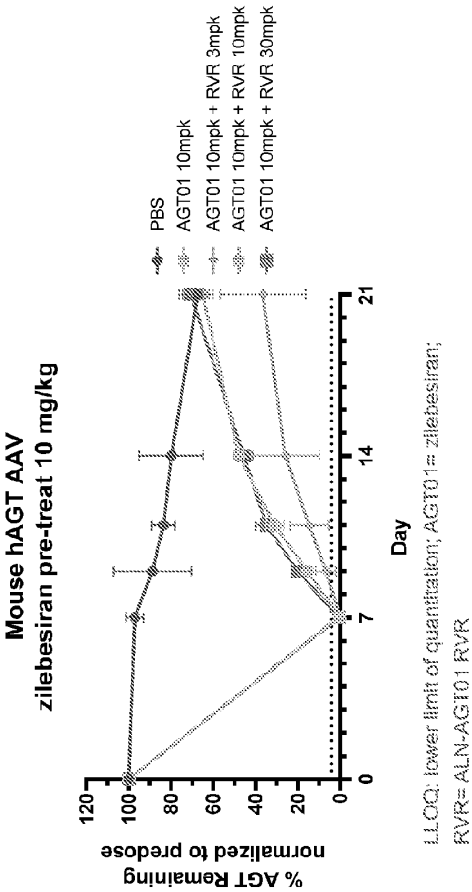


FIG. 16A

Treatment days		% AGT remaining				
Day post zil ebs do se	Day post RV R dose	Zilebe 10 mpk +PBS	Zilebe 10 mpk +RVR 3mpk	Zilebe 10 mpk +RVR 10mpk	Zilebe 10mpk +RVR 30 mpk	
Pre- (D0)	NA	100	100	100	100	
7	0	1.32	LLOQ	LLOQ	1.10	
9	2	LLOQ	6.75	15.53	20.13	
11	4	LLOQ	14.55	30.83	34.89	
14	7	LLOQ	25.90	48.04	45.58	
21	14	LLOQ	36.69	65.07	70.65	

Treatment days			% AGT remaining		
Day post zilaib dose	Day post RVR dose		Zilebe 3mpk +PBS	Zilebe 3 mpk +RVR 3mpk	Zilebe 3 mpk +RVR 10mpk
Pre- (D0)	NA		NA	100	100
7	0		NA	32.6	4.06
9	2		NA	22.12	35.42
11	4		NA	44.35	55.3
14	7		NA	59.27	71.96
21	14		NA	69.54	70.9

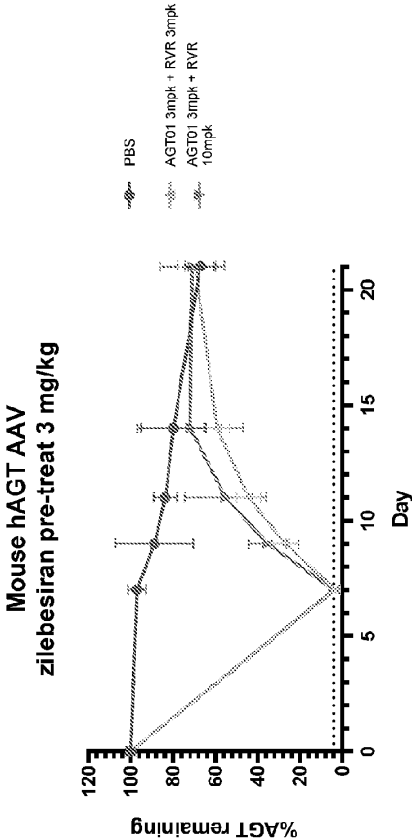
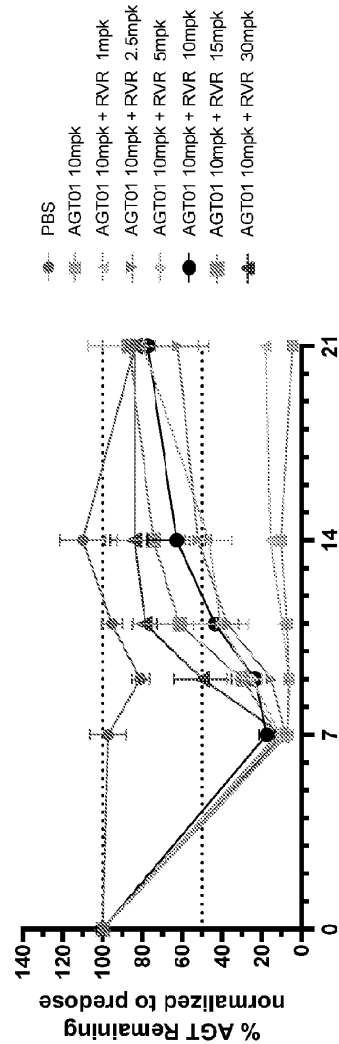


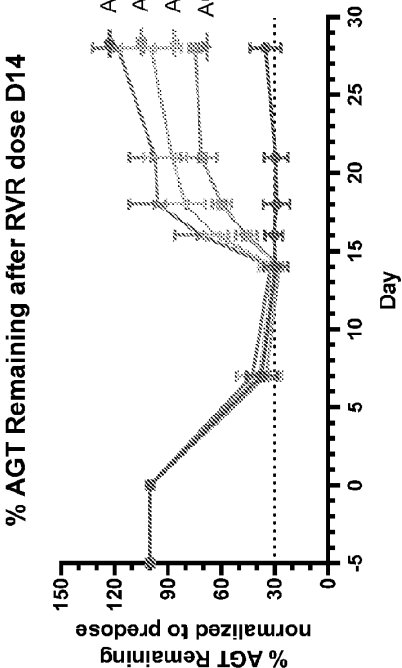
FIG. 16B

% AGT Remaining after RVR dose D7



Treatment days			% AGT remaining					
Day post zile	Day post RVR dose	Day post zile + RVR	Zilebe 10 mpk	Zilebe 10 mpk + RVR 1mpk	Zilebe 10 mpk + RVR 2.5mpk	Zilebe 10 mpk + RVR 5mpk	Zilebe 10 mpk + RVR 10mpk	Zilebe 10 mpk + RVR 30mpk
0	N/A		100.0	100.0	100.0	100.0	100.0	100.0
7	0		7.1	6.8	7.8	10.8	17.5	9.8
9	2		6.3	6.1	15.2	25.0	23.2	45.6
11	4		7.3	9.7	37.2	40.7	43.5	78.7
14	6		10.3	15.7	52.1	46.7	62.9	83.7
21	13		4.5	18.1	62.3	79.7	77.3	83.5

FIG. 17



Treatment days		% ACT remaining				
Day post zile be dose	Day post RVR dose	Zilebe 10 mpk +PBS	Zilebe 10 mpk +RVR 3mpk	Zilebe 10mp k +RVR 10mpk	Zilebe 10mpk +RVR 3 mpk x 3 12 hrs	
Pre- (D- 5)	NA	100	100	100	100	
7	0	37.3	34.7	38.6	42.6	
14	0	29.4	27.6	30.8	32.3	
16	2	30.4	46.0	62.3	71.5	
18	4	29.1	59.7	80.3	95.7	
21	7	29.5	71.0	87.5	97.2	
28	14	35.4	74.9	99.6	118.1	

FIG. 18



- PBS
- ▨ 10 mg/kg dsRNA/PBS
- ▧ 10 mg/kg dsRNA + 3 mg/kg RVR
- ▩ 10 mg/kg dsRNA + 10 mg/kg RVR
- ⊖ 10 mg/kg dsRNA + 30 mg/kg RVR

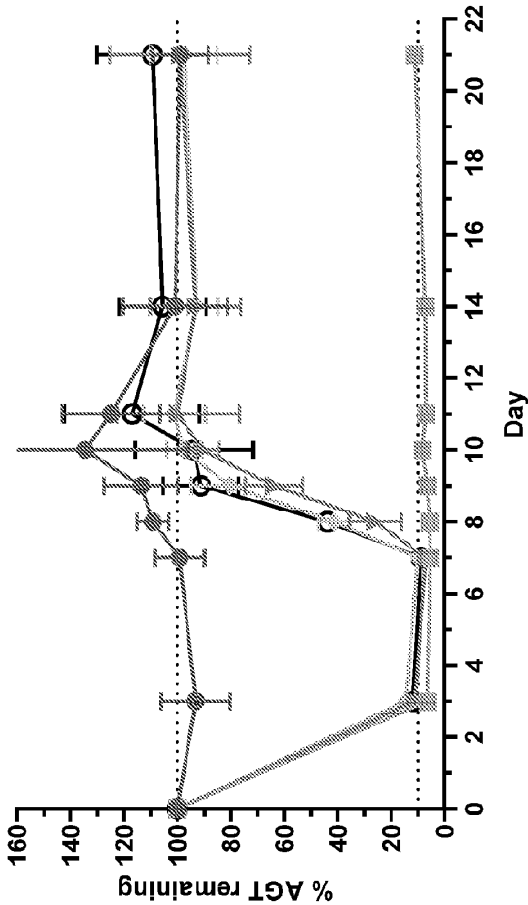


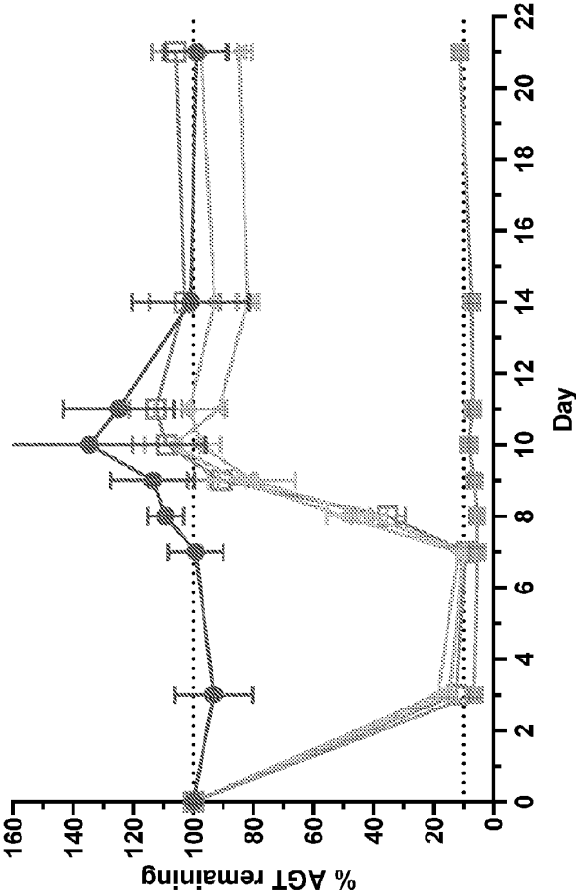
FIG. 19A

10 mg/kg dsRNA + 30 mg/kg RVR		10 mg/kg dsRNA + 10 mg/kg RVR		10 mg/kg dsRNA + 3 mg/kg RVR		10 mg/kg dsRNA/PBS		AGT dsRNA 10 mg/kg	
Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining
0	7.0	0	10.1	0	8.8	0	6.48	0	6.48
1	26.0	1	41.4	1	43.9	1	6.63	1	6.63
2	63.9	2	80.6	2	91.3	2	6.45	2	6.45
3	90.8	3	97.5	3	110.3	3	8.26	3	8.26

Day 0 is a pre-reversal dosing sample; Day 7 post dsRNA dosing and considered nadir



- PBS
- 10 mg/kg dsRNA/PBS
- ▨ 3 mg/kg dsRNA + 3 mg/kg RVR
- ◆ 10 mg/kg dsRNA + 10 mg/kg RVR
- ▩ 30 mg/kg dsRNA + 30 mg/kg RVR



10 mg/kg dsRNA + 3 mg/kg RVR			10 mg/kg dsRNA + 10 mg/kg RVR			30 mg/kg dsRNA + 30 mg/kg RVR			30 mg/kg dsRNA + 30 mg/kg RVR + 10 mg/kg dsRNA + 10 mg/kg RVR		
Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining
0	11.7	0	10.1	0	9.4	0	5.48	0	5.48	0	5.48
1	50.3	1	41.4	1	35.3	1	5.63	1	5.63	1	5.63
2	85.2	2	80.6	2	90.7	2	6.45	2	6.45	2	6.45
3	106.7	3	97.5	3	109.0	3	8.25	3	8.25	3	8.25

Day 0 is a pre-reversal dosing sample. Day 7 post dsRNA dosing and considered nadir

FIG. 19B



- PBS
- ▨ 10 mg/kg dsRNA/PBS
- ◆ 10 mg/kg dsRNA + 10 mg/kg RVR
- ★ 10 mg/kg dsRNA + 30 mg/kg RVR
- ▽ 10 mg/kg dsRNA + 1 mg/kg RVR LNP (AF-105-516448)

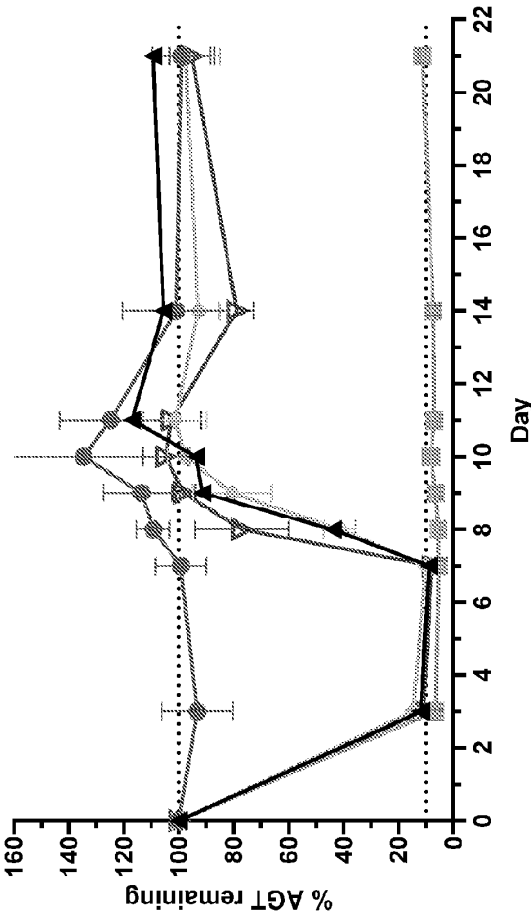


FIG. 19C

10 mg/kg dsRNA + 1 mg/kg RVR LNP		10 mg/kg dsRNA + 10 mg/kg RVR		10 mg/kg dsRNA + 30 mg/kg RVR		10 mg/kg dsRNA + 1 mg/kg RVR LNP		10 mg/kg dsRNA + 10 mg/kg RVR		10 mg/kg dsRNA + 30 mg/kg RVR		10 mg/kg dsRNA + 1 mg/kg RVR LNP	
Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining
0	7.0	0	10.1	0	7.7	0	5.5	0	7.7	0	5.5	0	5.5
1	26.0	1	41.4	1	77.0	1	5.5	1	77.0	1	5.5	1	5.5
2	63.9	2	80.6	2	98.2	2	6.4	2	98.2	2	6.4	2	6.4
3	90.8	3	97.5	3	104.8	3	8.3	3	104.8	3	8.3	3	8.3
4	99.8	4	101.2	4	102.7	4	6.9	4	102.7	4	6.9	4	6.9

Day 0 is a pre-reversal dosing sample; Day 7 post dsRNA dosing and considered nadir



- PBS
- 10 mg/kg dsRNA/PBS
- ◆ 10 mg/kg dsRNA + 10 mg/kg RVR
- ◇ 10 mg/kg dsRNA + 10 mg/kg RVR GalNAc IV

10 mg/kg dsRNA + 10 mg/kg RVR		10 mg/kg dsRNA + 10 mg/kg RVR GalNAc IV		AGT dsRNA 10 mg/kg	
Day	% AGT remaining	Day	% AGT remaining	Day	% AGT remaining
0	10.1	0	9.7	0	5.6
1	41.4	1	29.2	1	5.6
2	80.6	2	64.3	2	6.4
3	97.5	3	73.0	3	8.3

Day 0 is a pre-reversal dosing sample; Day 7 post dsRNA dosing and considered nadir

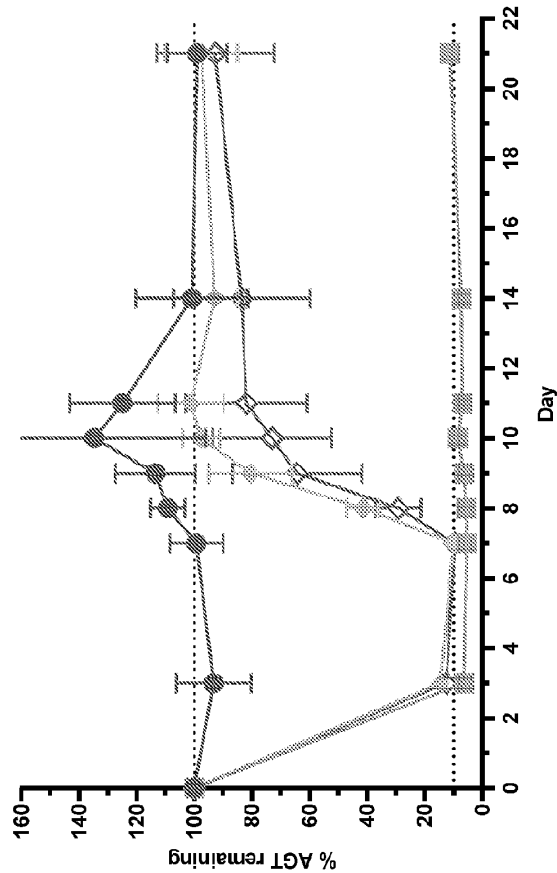


FIG. 19D

AGT RVR

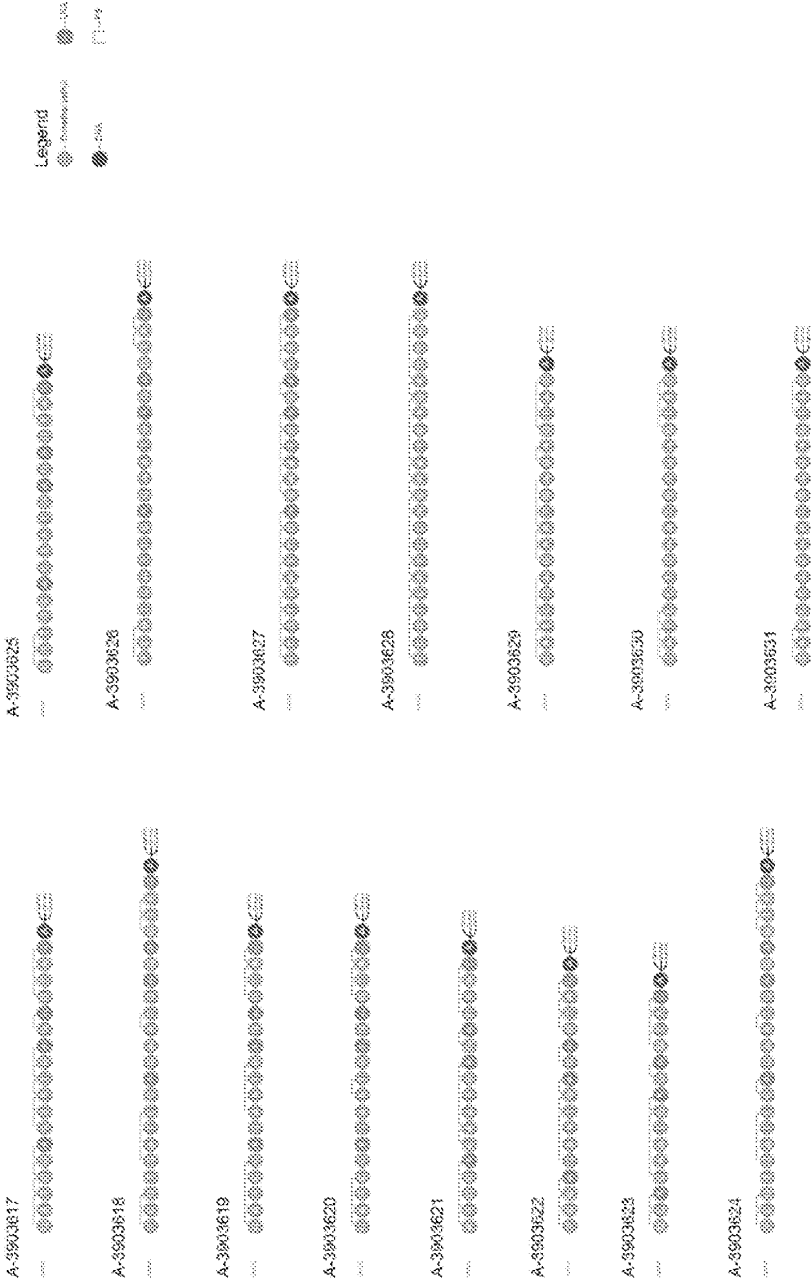


FIG. 20

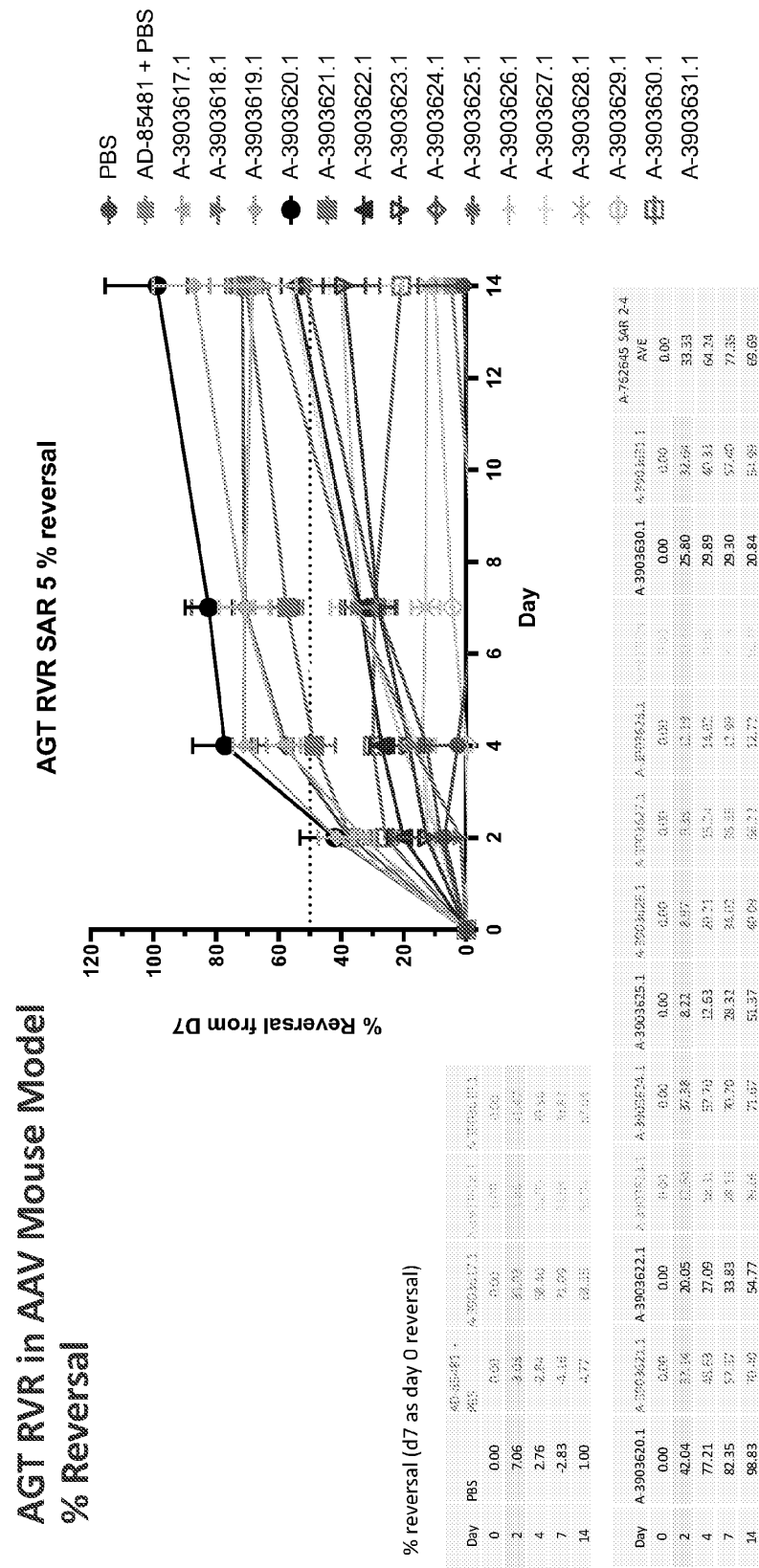
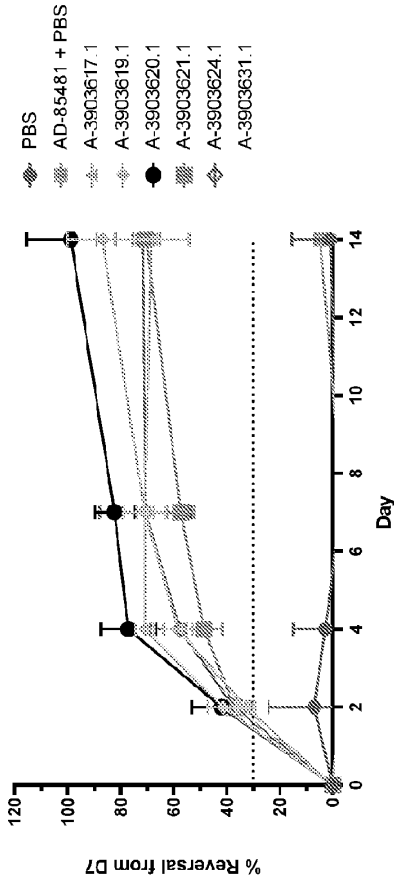


FIG. 22

% AGT Silencing Reversal >30% at Day 2 post RVR dosing

>30% Reversal at Day 2 AGT RVR SAR 5



> 30% reversal at Day 2 post RVR dose (D7 Nadir is 00 for reversal)

Day	A-3903617.1	A-3903619.1	A-3903620.1	A-3903621.1	A-3903624.1	A-3903631.1	A-762645 SAR 2.4 AVE
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	33.03	41.47	42.04	37.14	37.38	32.64	33.33
4	58.40	70.56	77.21	48.63	57.70	40.33	64.24
7	71.89	70.57	82.35	57.37	73.70	57.40	77.35
14	68.35	87.04	98.83	70.40	71.57	54.99	69.69

FIG. 23