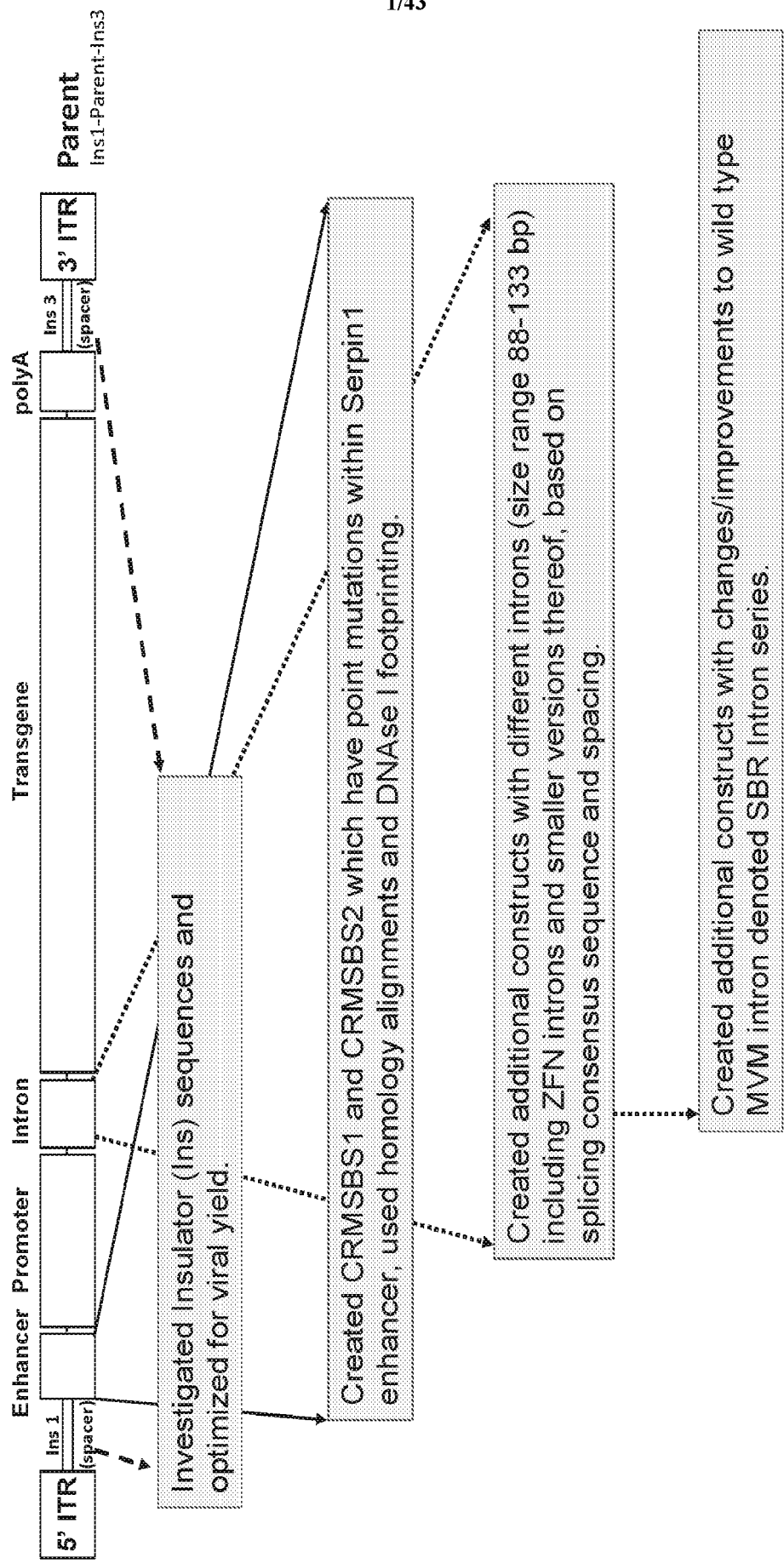




Figure

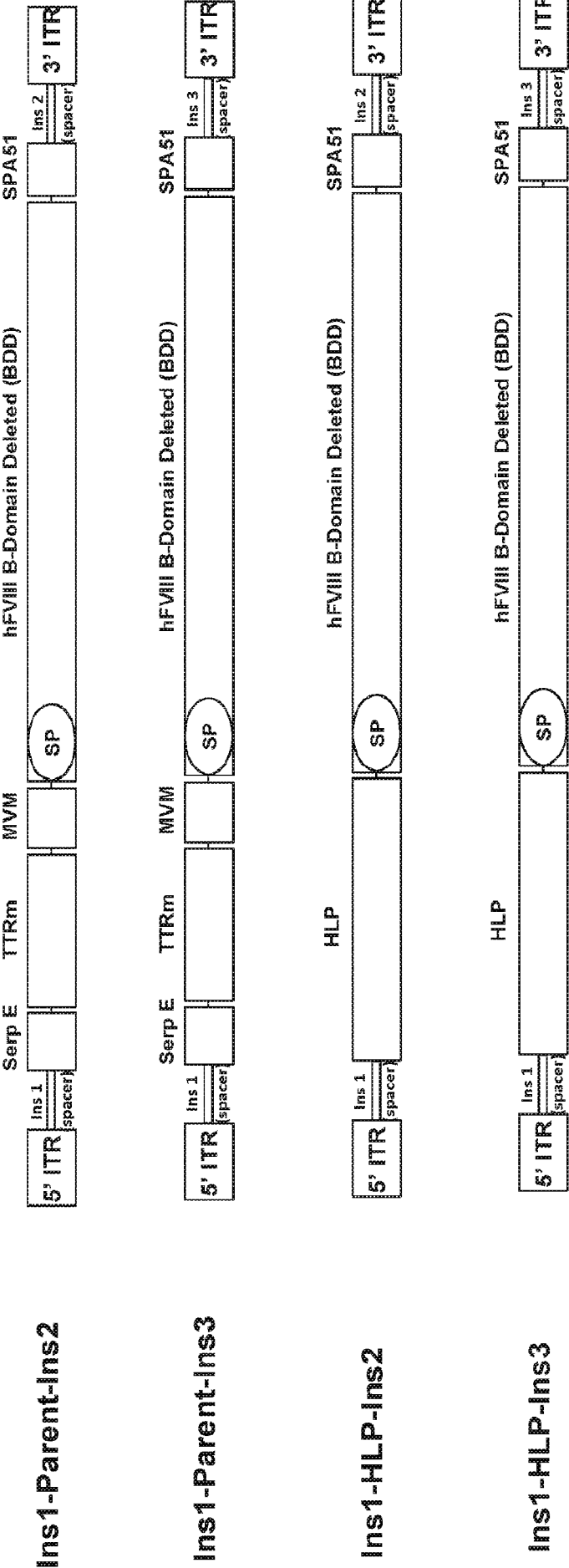


Figure 2

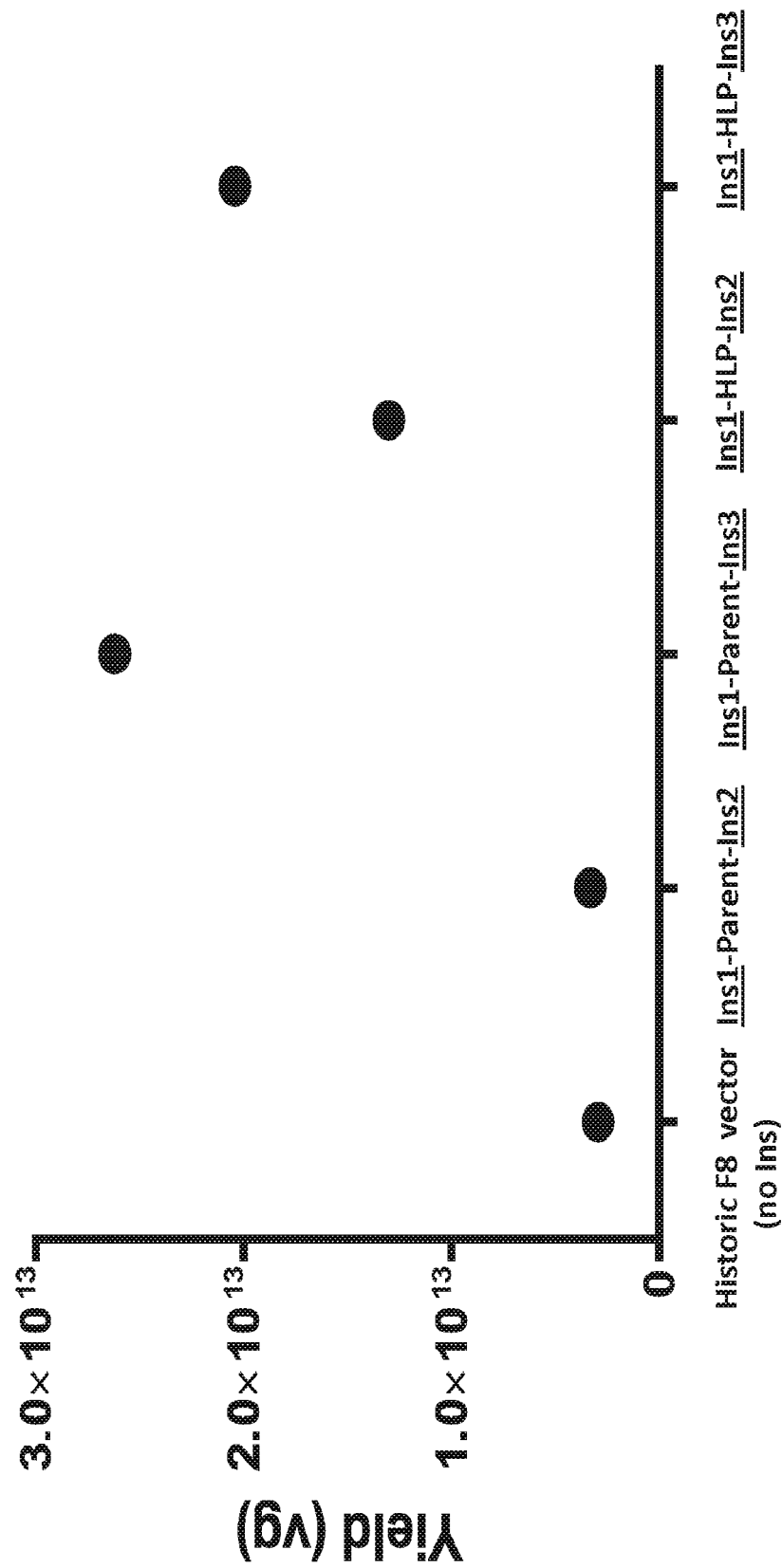


Figure 1

Enhancer Modifications

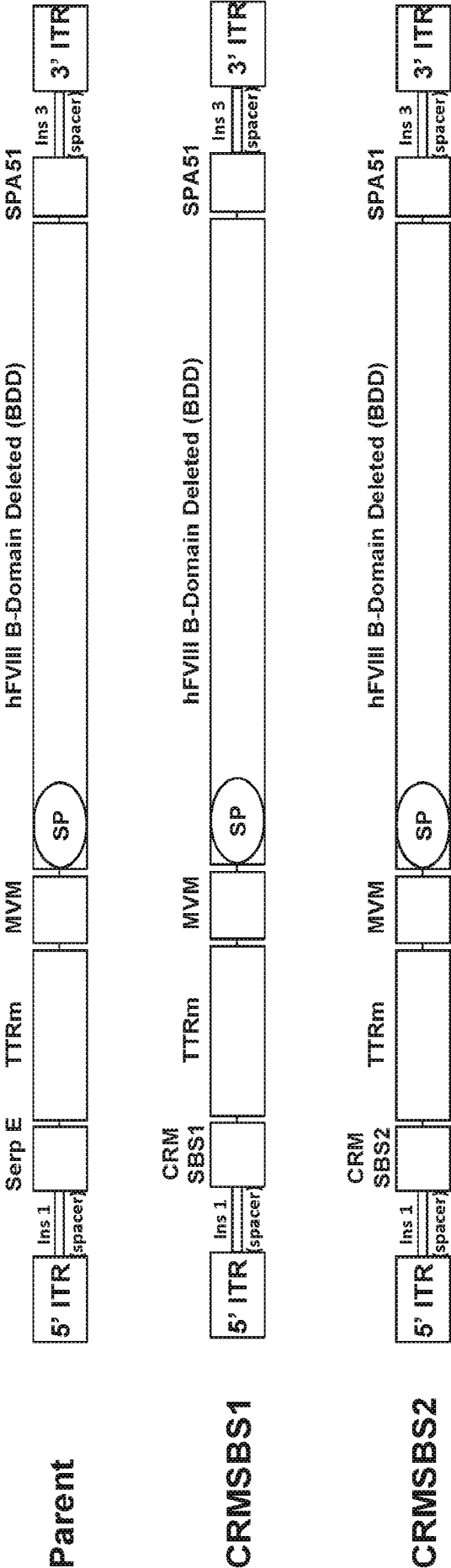
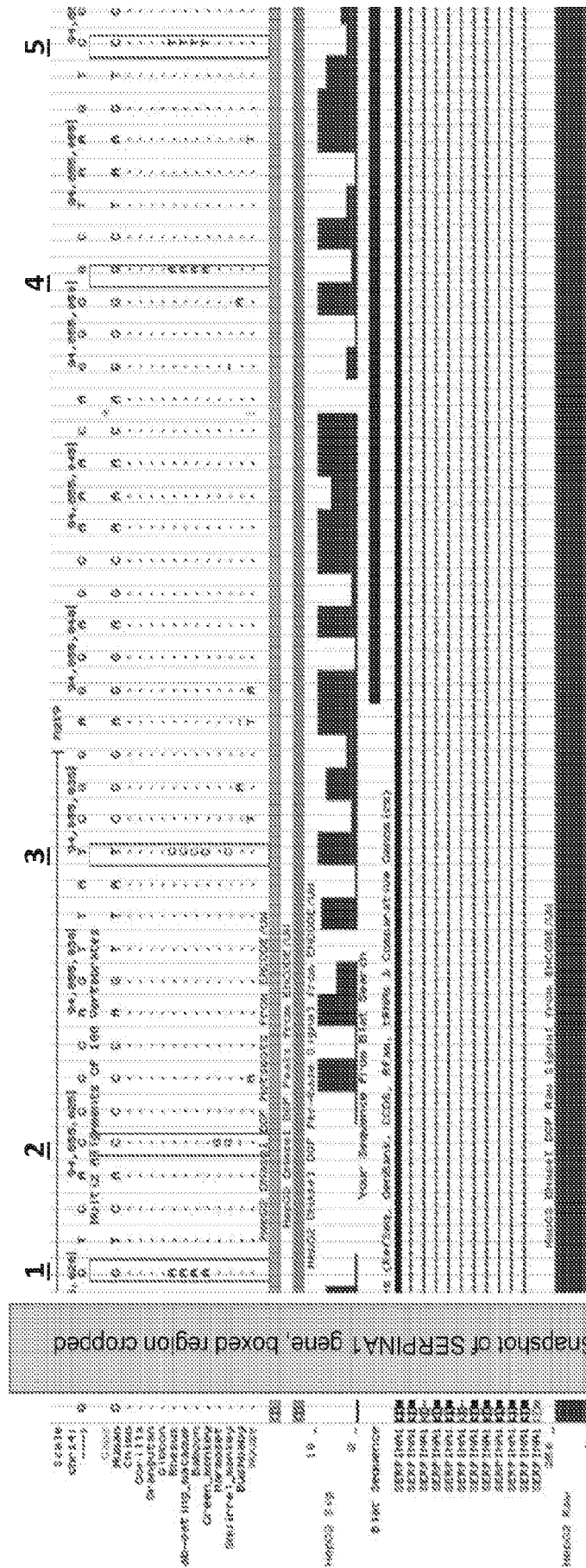


Figure 4



CRMSBS1 = Changes at 1, 2, 3, 4
CRMSBS2 = Changes at 1, 3, 4, 5

Figure 5

Intron Modifications: CRMSBS1

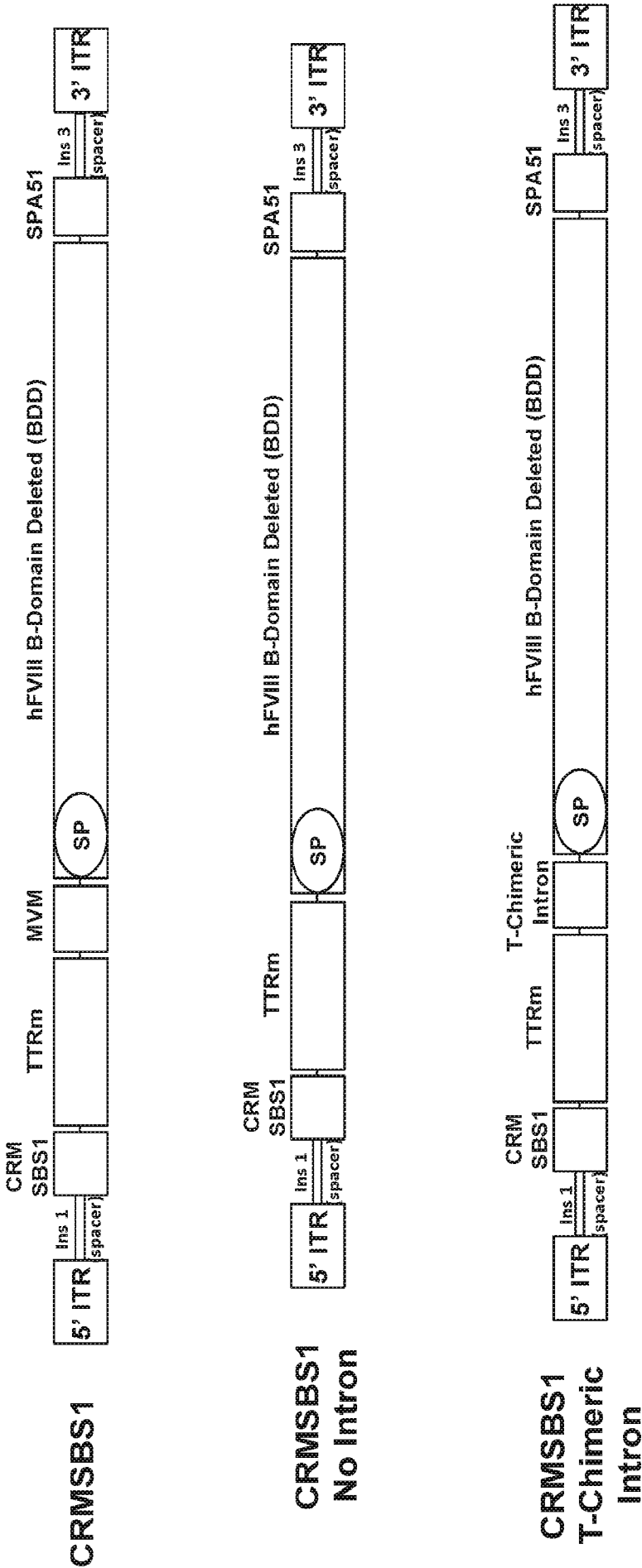


Figure 6

Intron Modifications: CRMSBS2

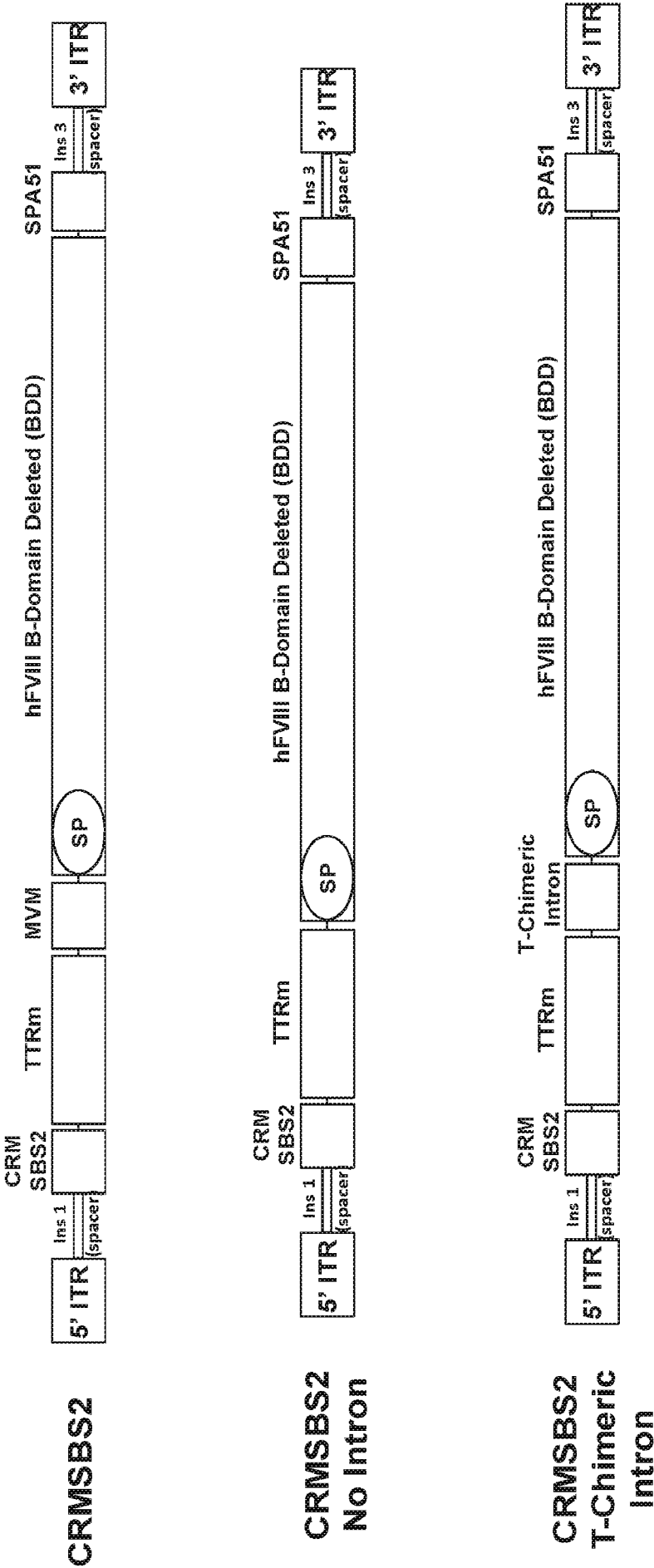


Figure 7

Figure 8A

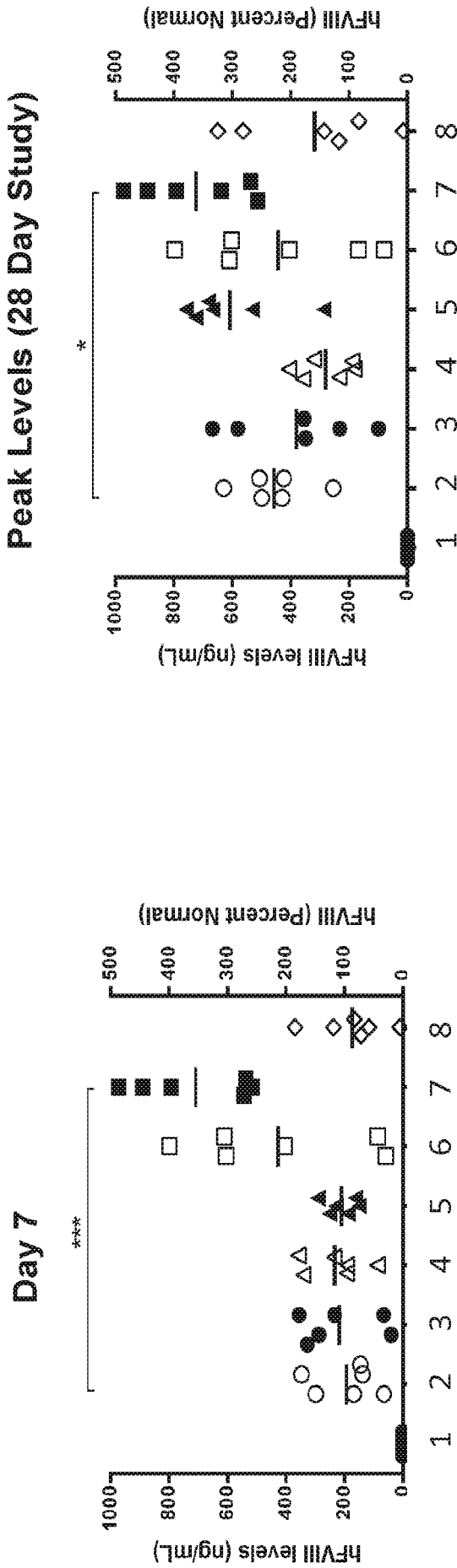
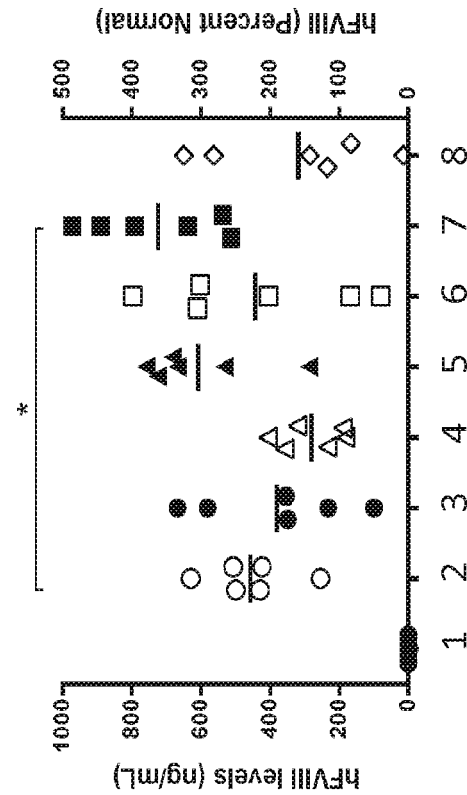


Figure 8B

Peak Levels (28 Day Study)



Number	Name	Figure with Map
1	Formulation	-
2	Parent	Fig 4
3	CRMSBS1	Fig 4
4	CRMSBS1 No intron	Fig 6
5	CRMSBS1 T-chimeric intron	Fig 6
6	CRMSBS2	Fig 4
7	CRMSBS2 No intron	Fig 7
8	CRMSBS2 T-chimeric intron	Fig 7

Figure 9A

Human Factor VIII (hFVIII) mRNA

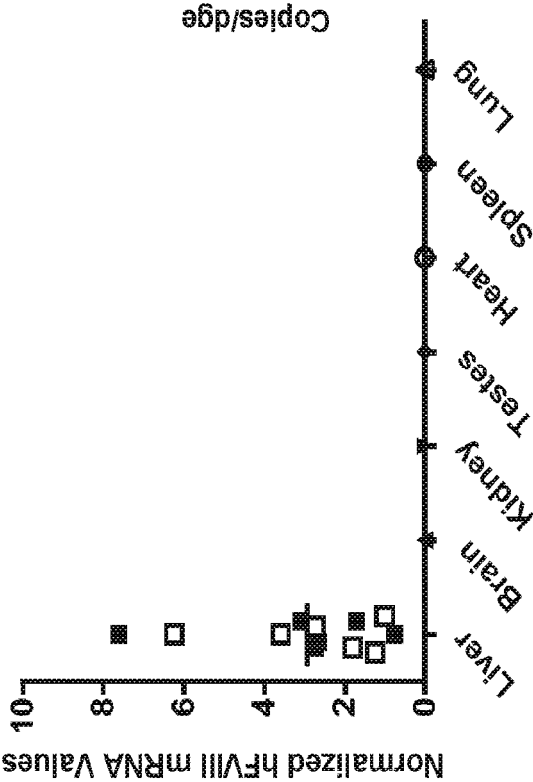
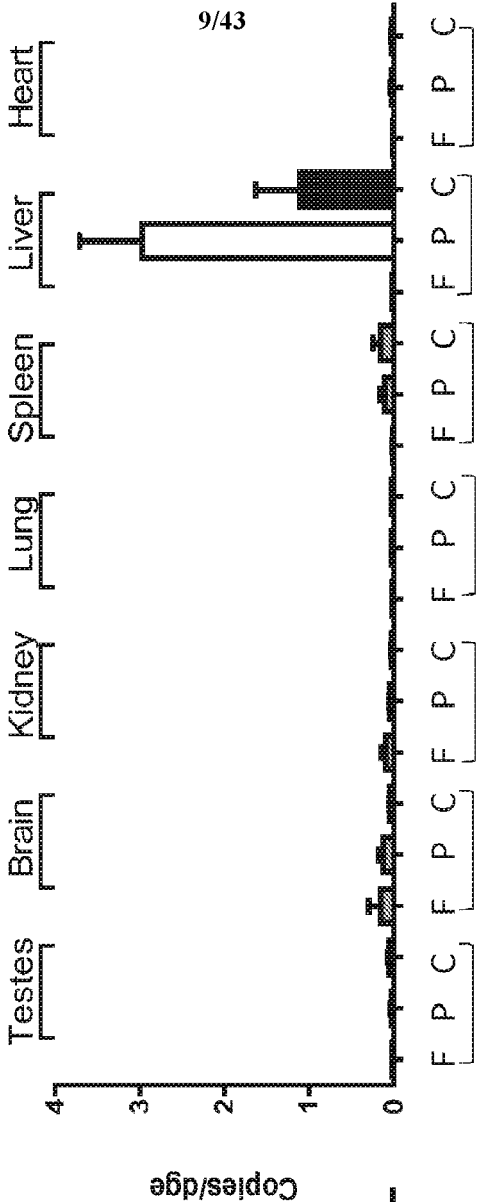


Figure 9B

Vector Genomes (VGs), AAV2/6 Biodistribution



Name	Symbol
Formulation	F
Parent	P
CRMSBS2 No Intron	C

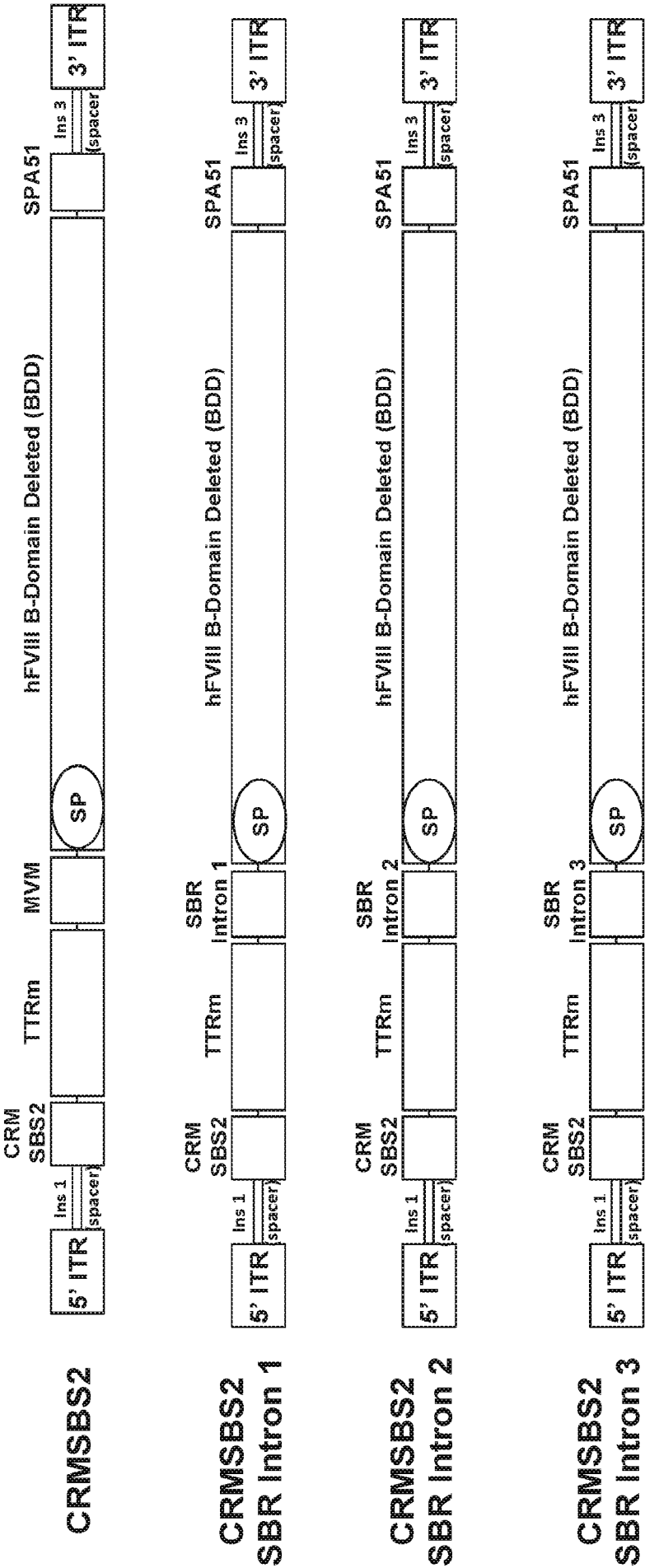


Figure 10

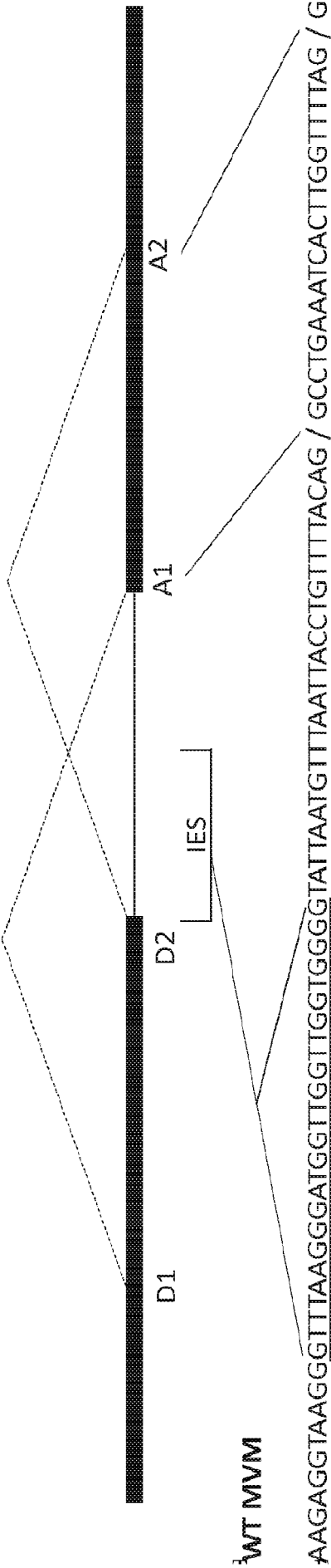


Figure 11

SBR Intron 1.

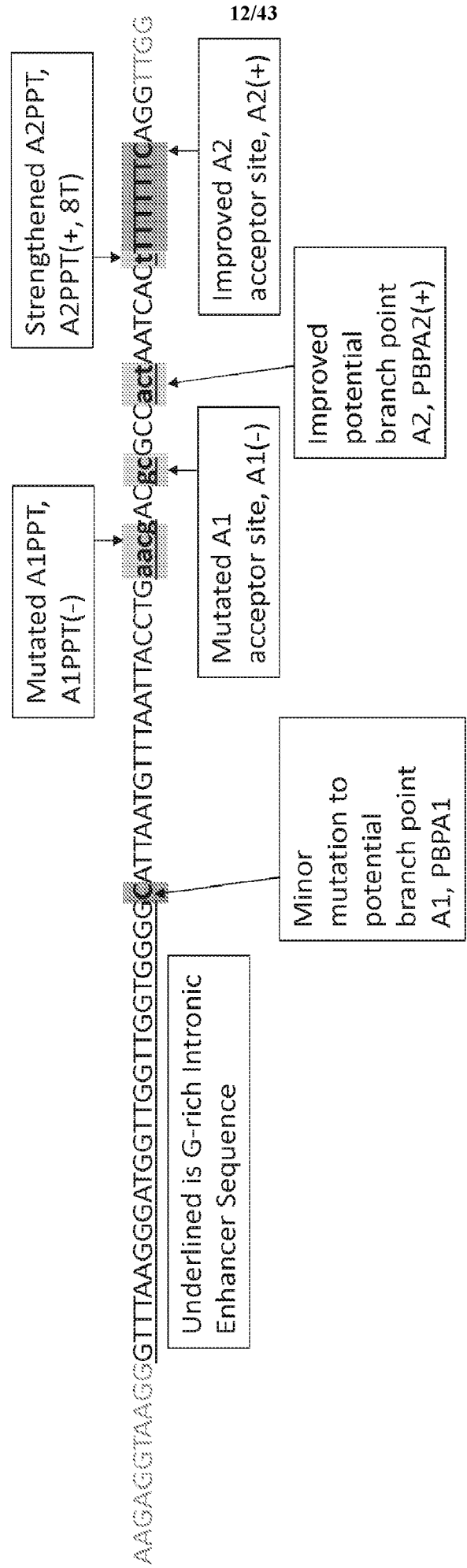


Figure 12

Figure 13

SBR Intron 2.

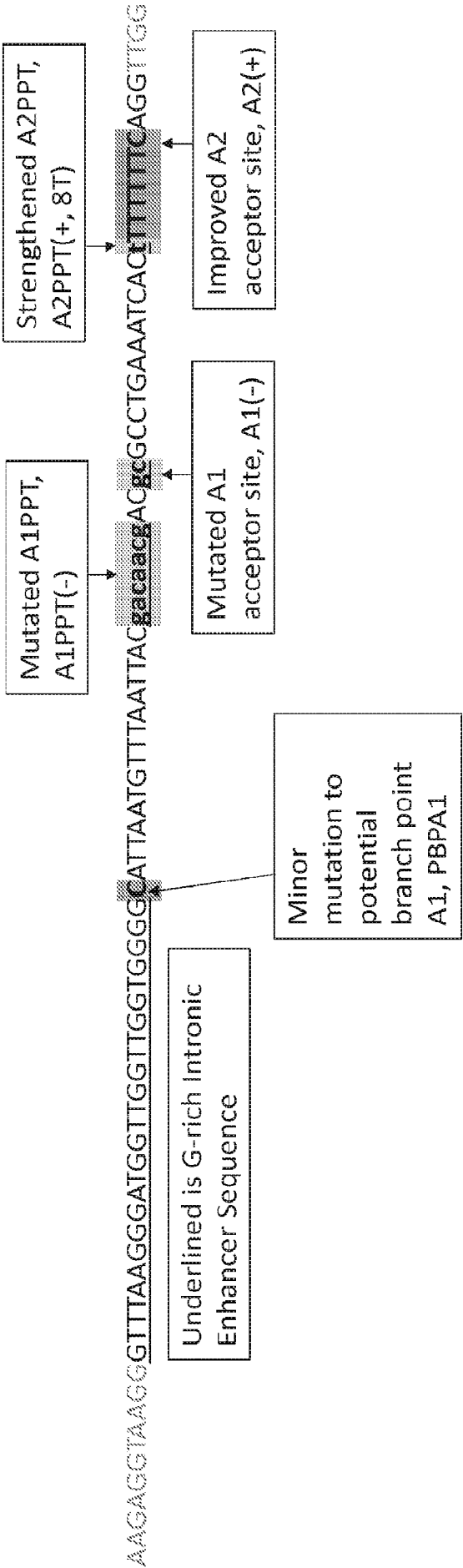


Figure 14

SBR Intron 3.

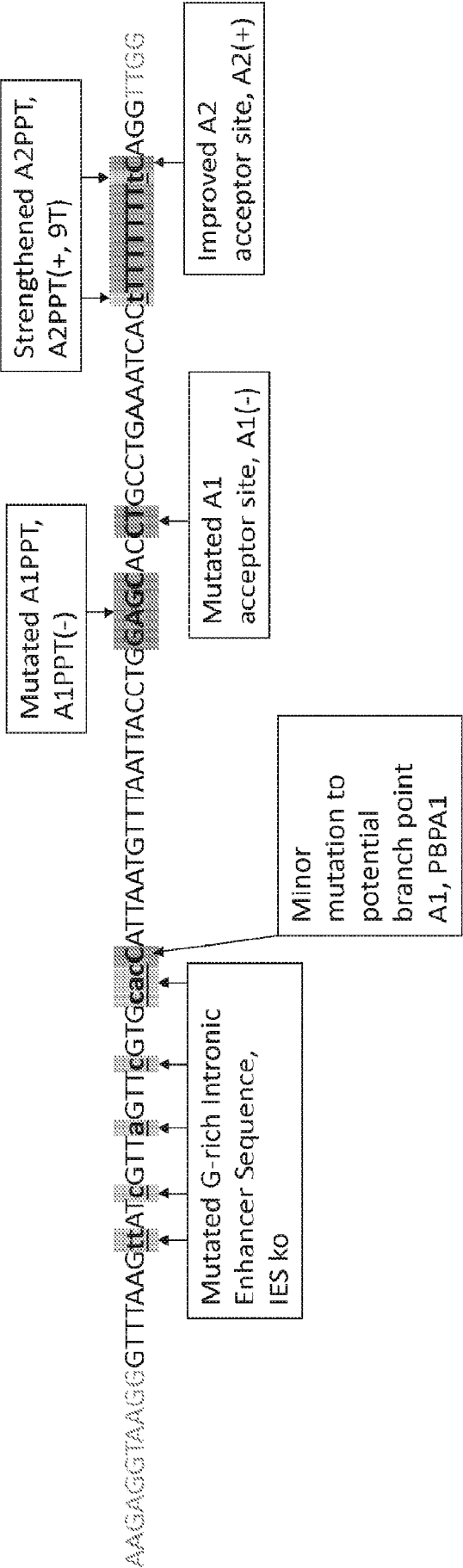


Figure 15A

Day 7

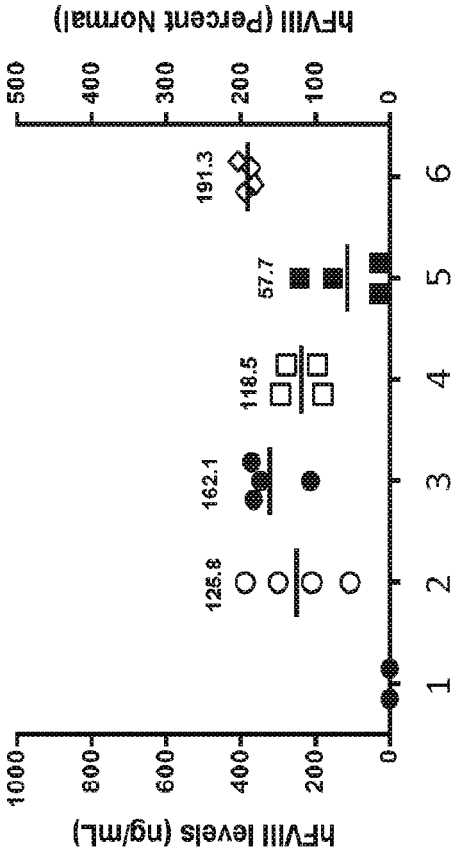
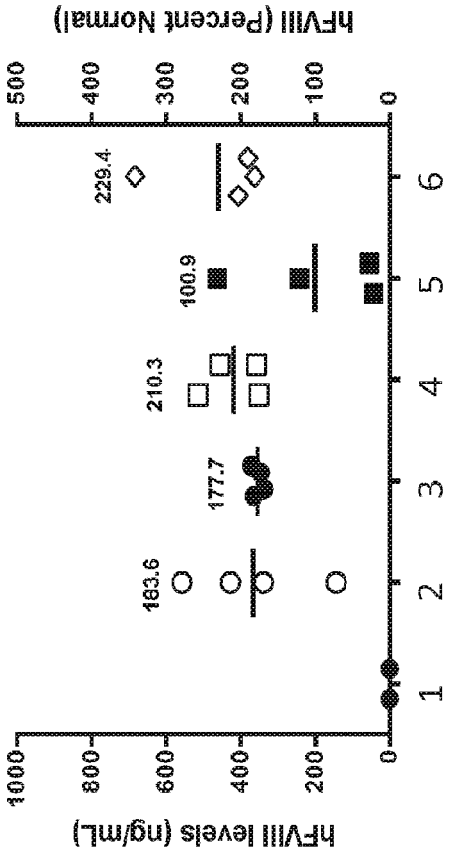


Figure 15B

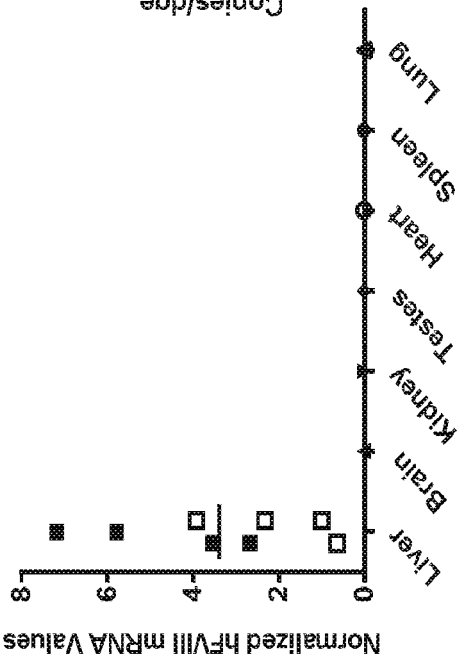
Peak Levels (28 Day Study)



Number	Name	Figure with Map
1	Formulation	-
2	Parent	Fig 4
3	CRMSBS2	Fig 7
4	CRMSBS2 SBR Intron 1	Fig 8
5	CRMSBS2 SBR Intron 2	Fig 8
6	CRMSBS2 SBR Intron 3	Fig 8

Figure 16A

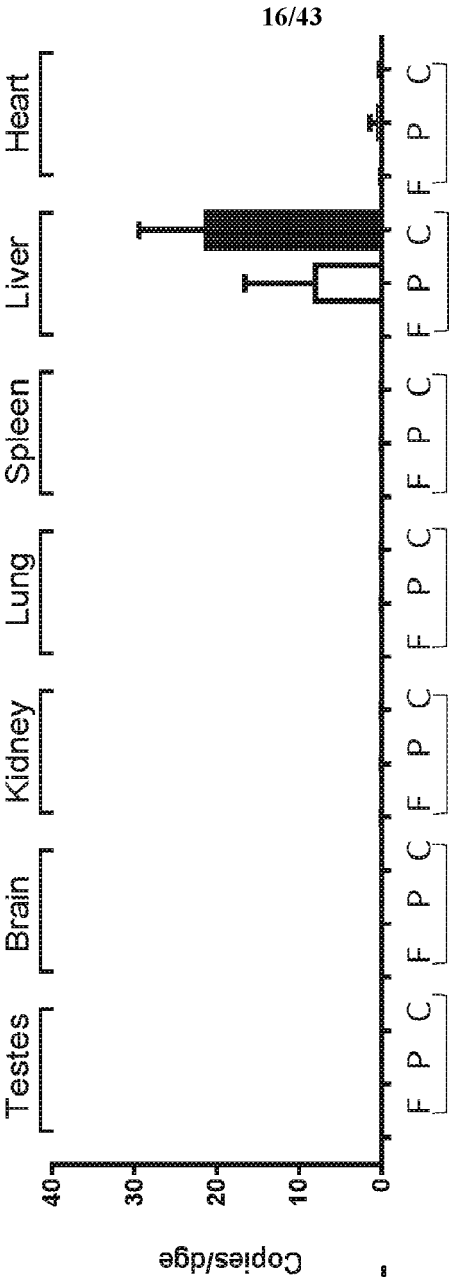
Human Factor VIII (hFVIII) mRNA



Open symbols: Parent
Filled symbols: CRMSBS2 SBR Intron

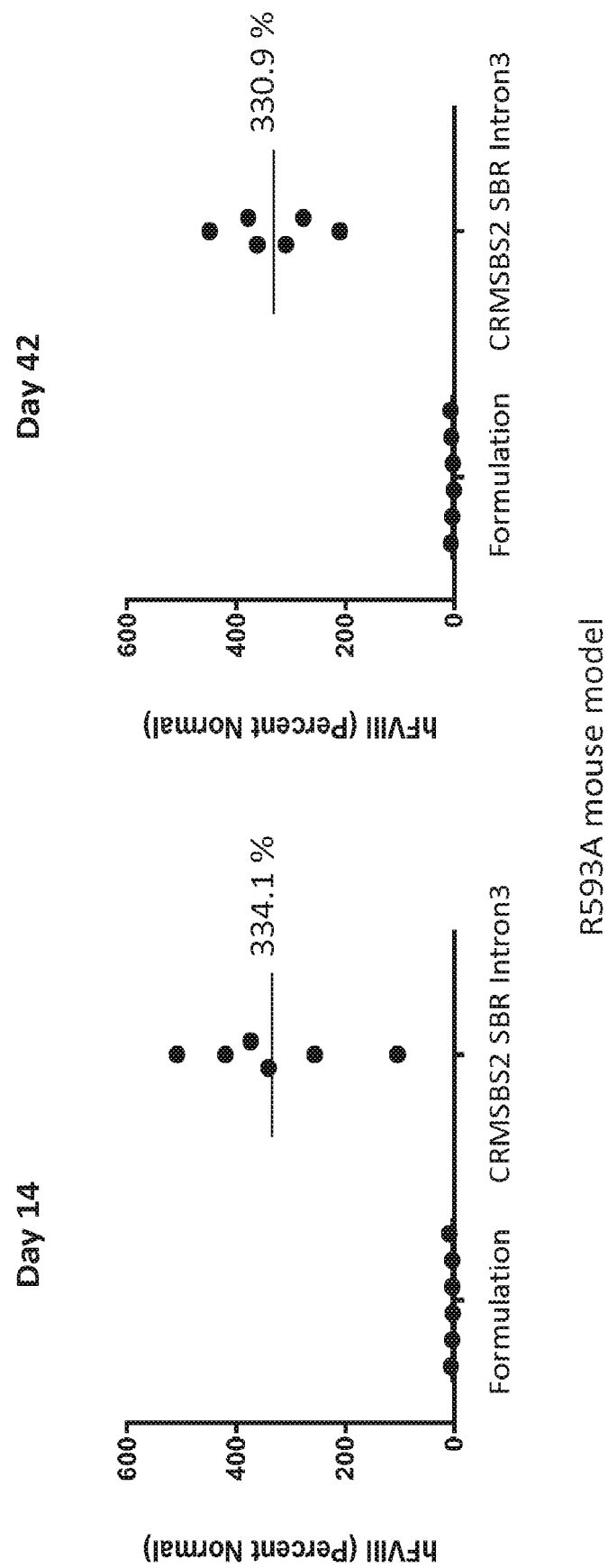
Figure 16B

Vector Genomes (VGs), AAV2/6 Biodistribution



Name	Symbol
Formulation	F
Parent	P
CRMSBS2 SBR Intron 3	C

Figure 17B



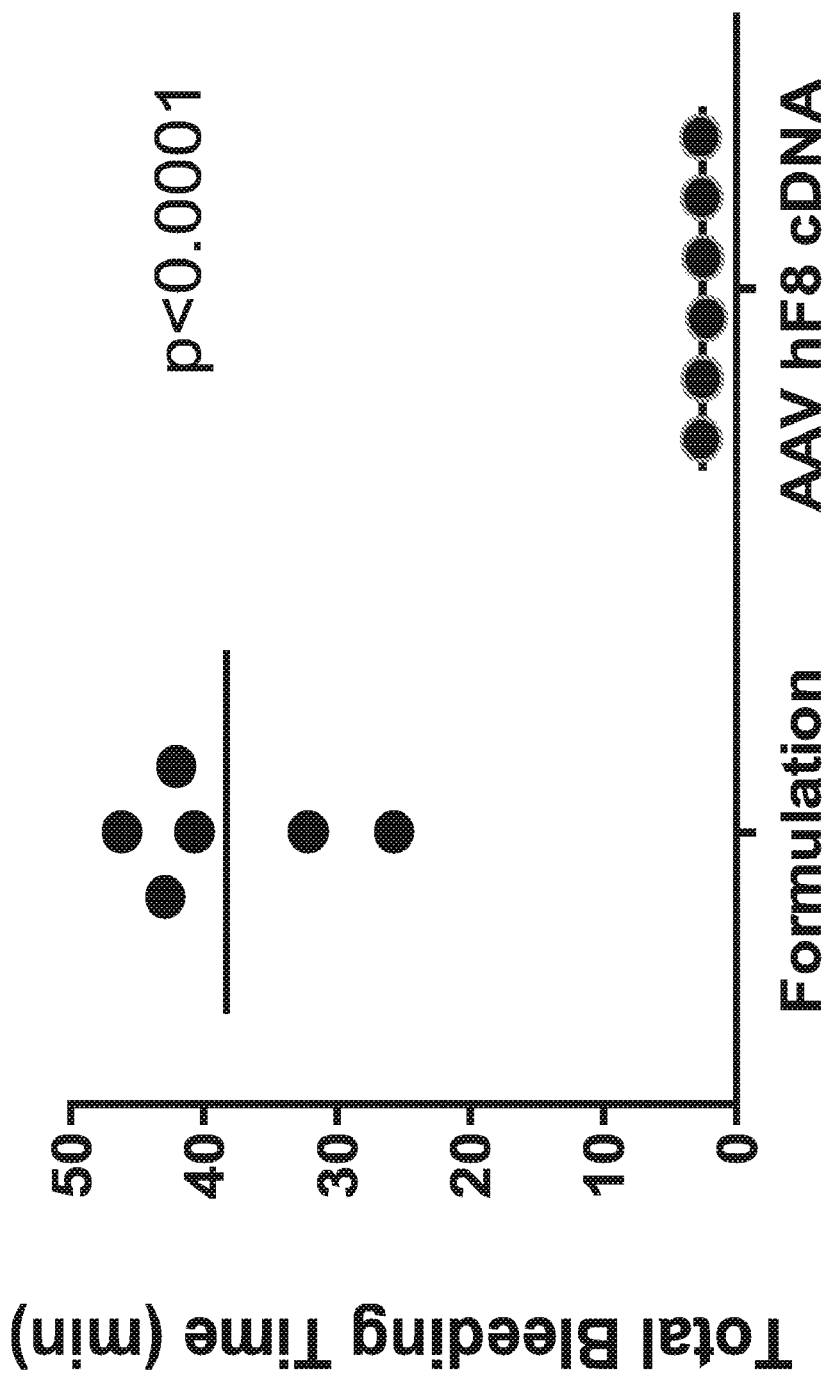


Figure 18

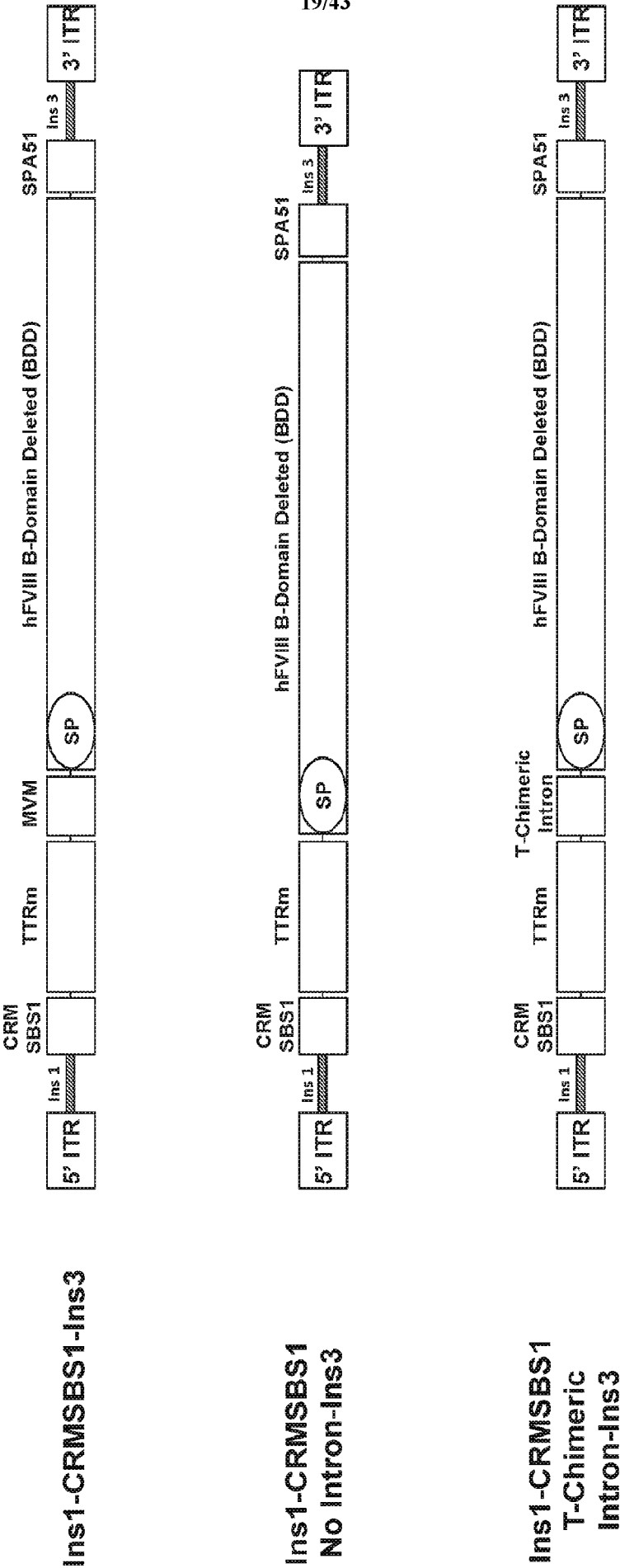


Figure 19

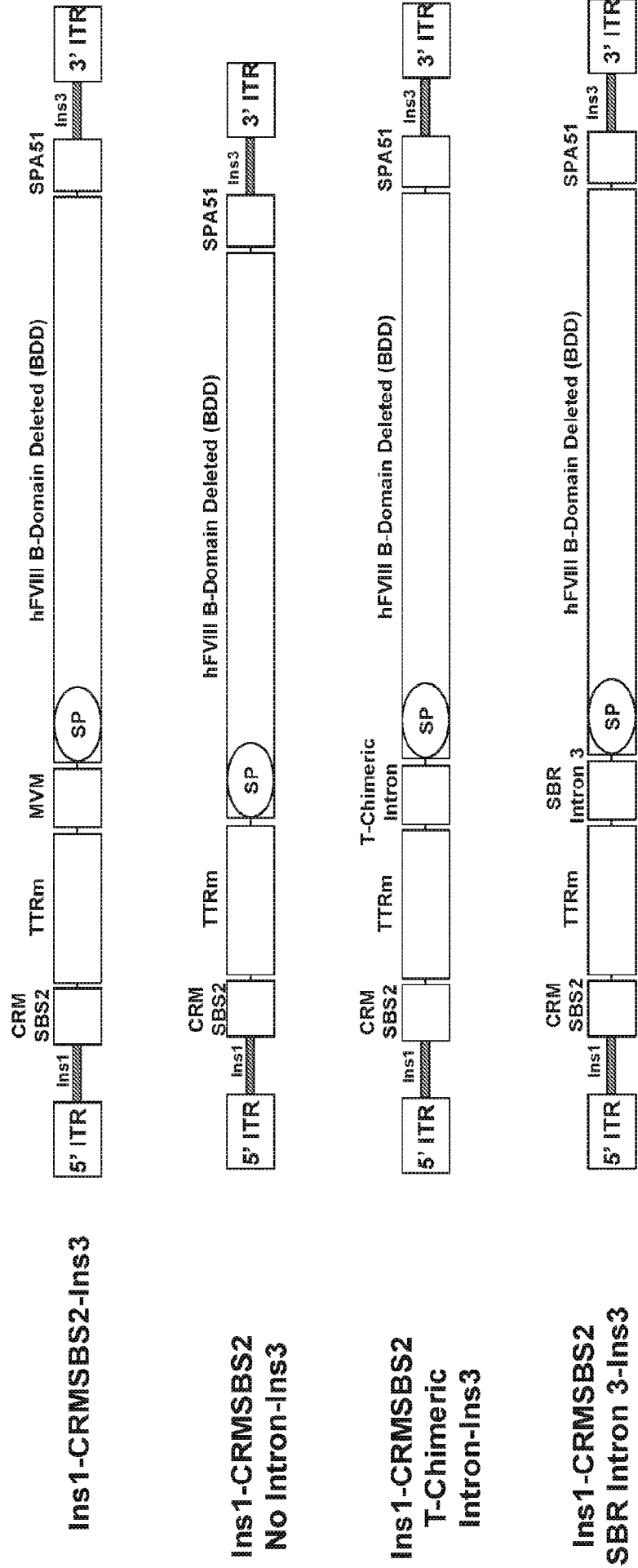
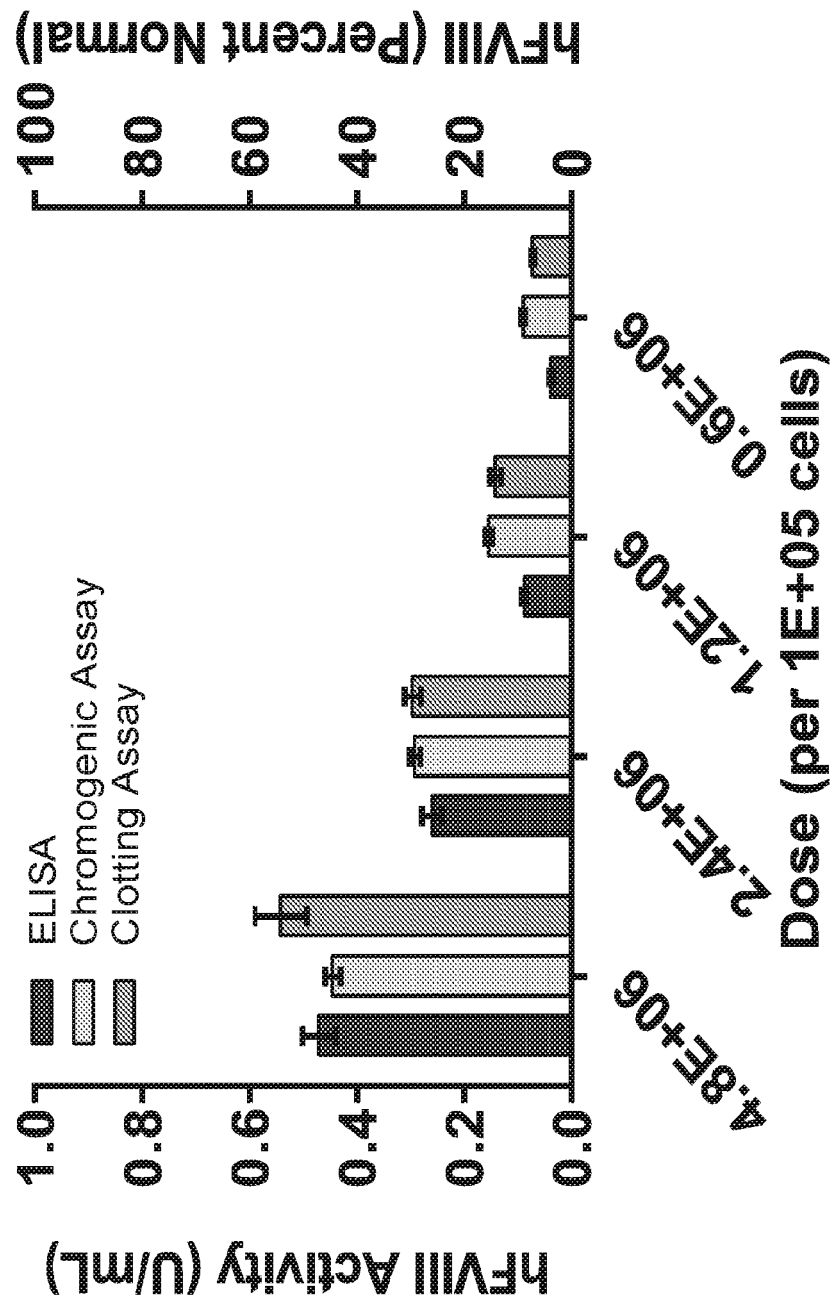
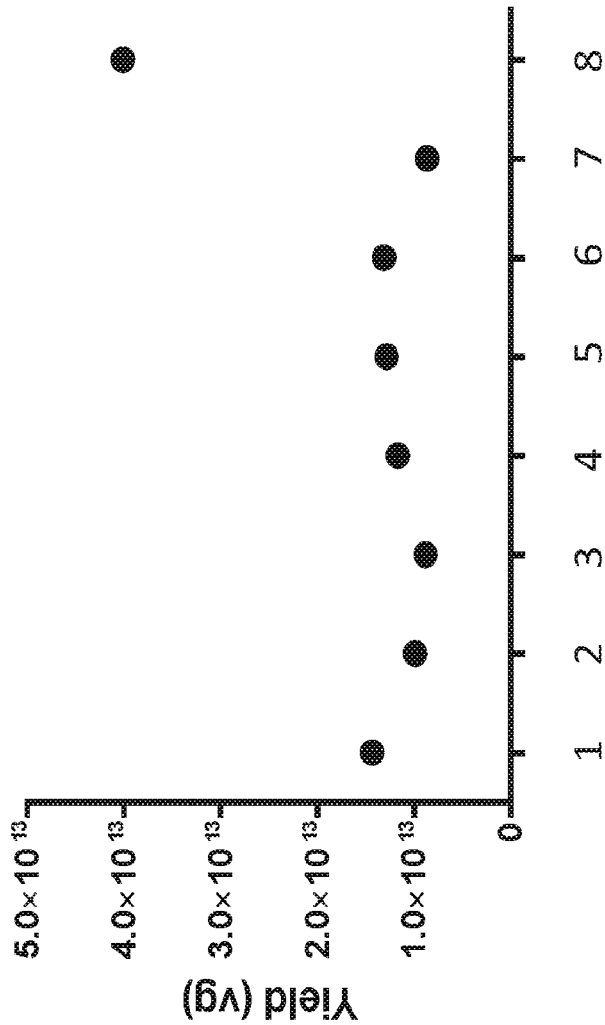


Figure 20

Figure 21

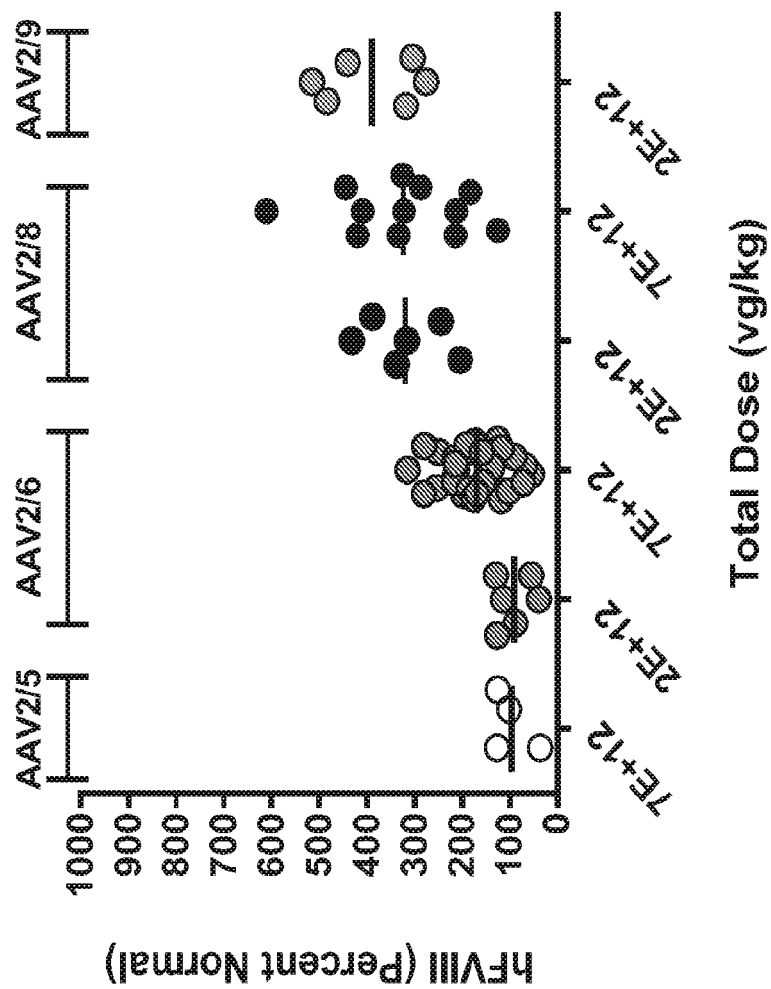




Name	Number
Ins1-Parent-Ins3	1
Ins1-CRMSBS1-Ins3	2
Ins1-CRMSBS1 No intron-Ins3	3
Ins1-CRMSBS1 T-chimeric Intron- Ins3	4
Ins1-CRMSBS2-Ins3	5
Ins1-CRMSBS2 No Intron-Ins3	6
Ins1-CRMSBS2 T-chimeric Intron-Ins3	7
Ins1-CRMSBS2 SBR Intron 3-Ins3	8

Figure 22

Figure 23



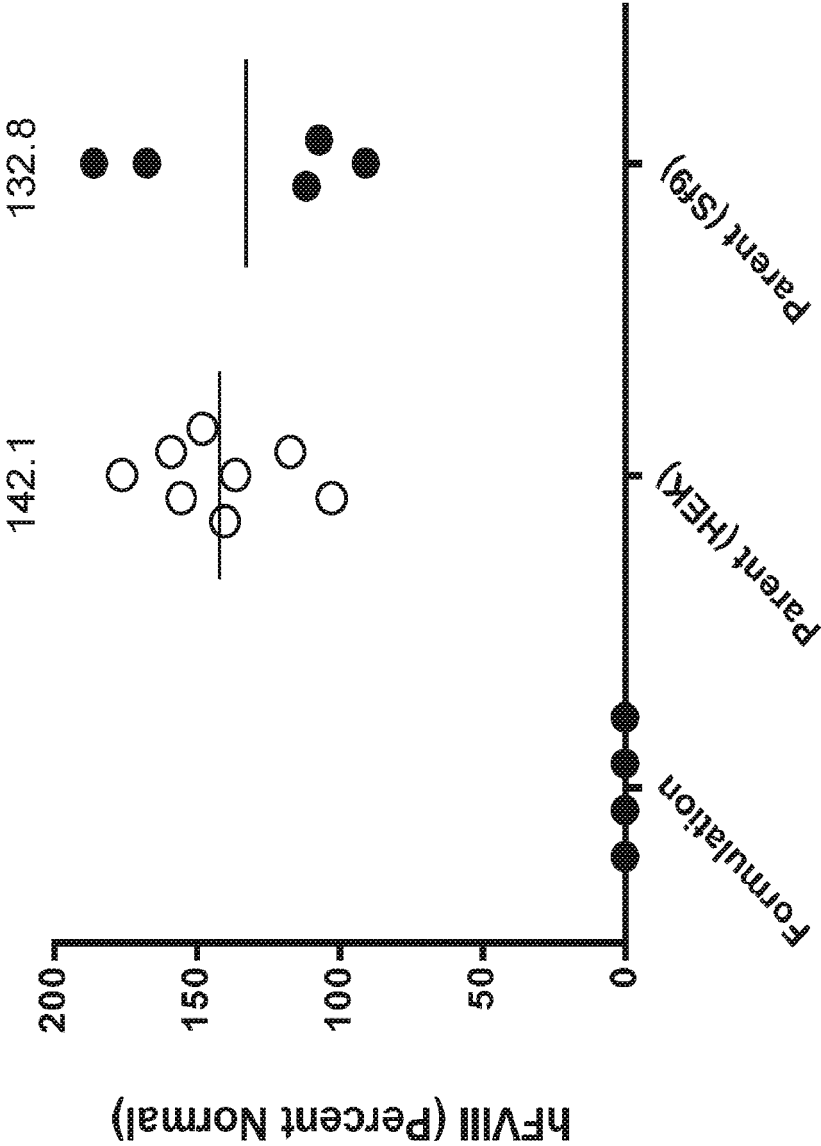


Figure 24

Figure 25A

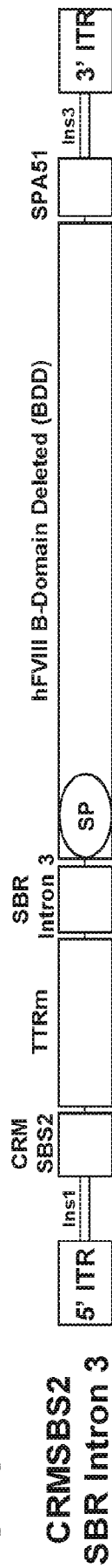
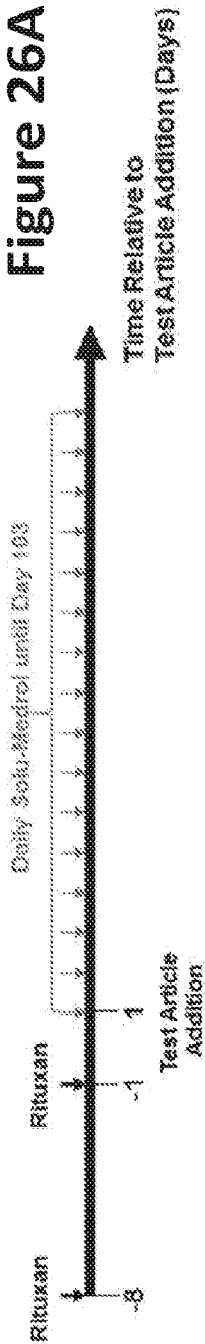


Figure 26A



Group	No of Animals	Test Article Identification	AAV Transgene Description	Serotype	Total rAAV Dose (vg/kg)
	Male				
Immunosuppression Regimen- Pre-Test Article Injection					
1	1	SGMO.01	Formulation Buffer	NA	0
2	3	SGMO.02	hF8 cDNA 1	AAV2/6	2E+11
3	3	SGMO.03	hF8 cDNA 1	AAV2/6	6E+11
4	3	SGMO.04	hF8 cDNA 1	AAV2/6	2E+12
5	3	SGMO.05	hF8 cDNA 1	AAV2/6	6E+12
Immunosuppression Regimen- Post-Test Article Injection					
6	1	SGMO.06	hF8 cDNA 1	NA	0
7	3	SGMO.07	hF8 cDNA 1	AAV2/6	2E+12
8	3	SGMO.08	hF8 cDNA 1	AAV2/6	6E+12

Figure 26B

Group	No of Animals		Test Article Identification	AAV Transgene Description	Serotype	Total rAAV Dose (vg/kg)
		Male				
Redose at Day 56 of Group 2						
2	3		SGMO.A	hF8 cDNA 1	AAV2/6	9E+11

Vg - vector genome

Figure 27

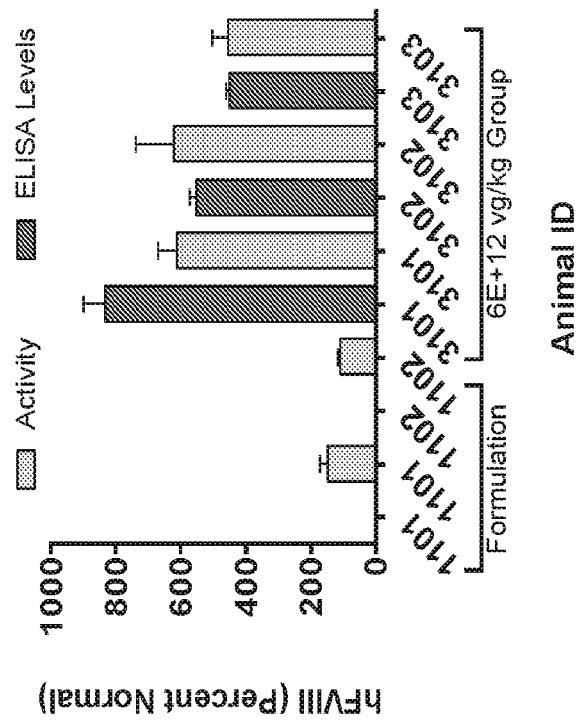


Figure 28A

Formulation
Control Group
(Animal ID 1101)

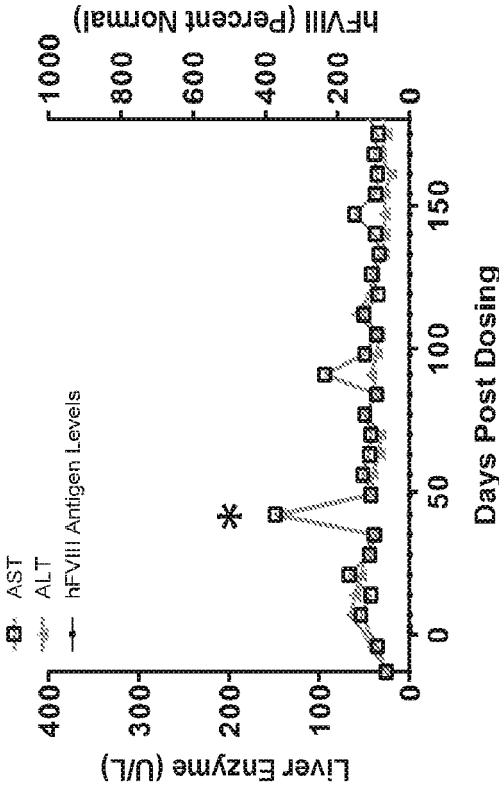
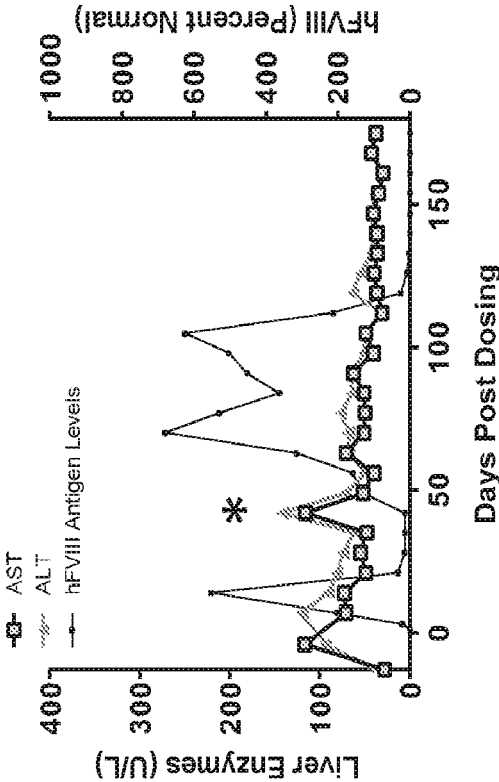


Figure 28B

Group 3
6E+12 vg/kg
(Animal ID 3102)



* Elevated levels observed post-liver biopsies (day 41)

Figure 29B

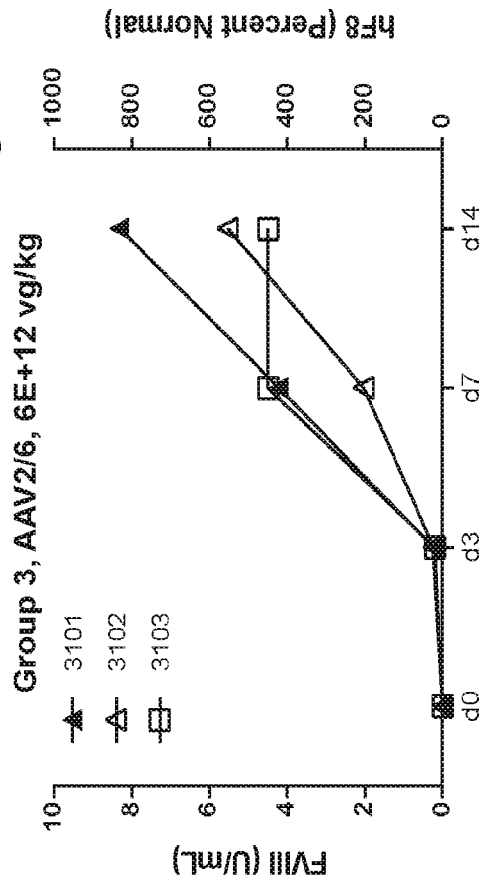


Figure 29D

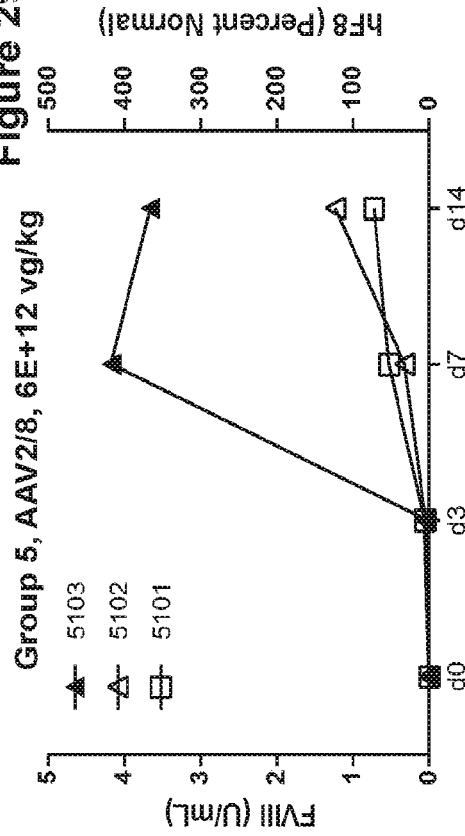


Figure 30

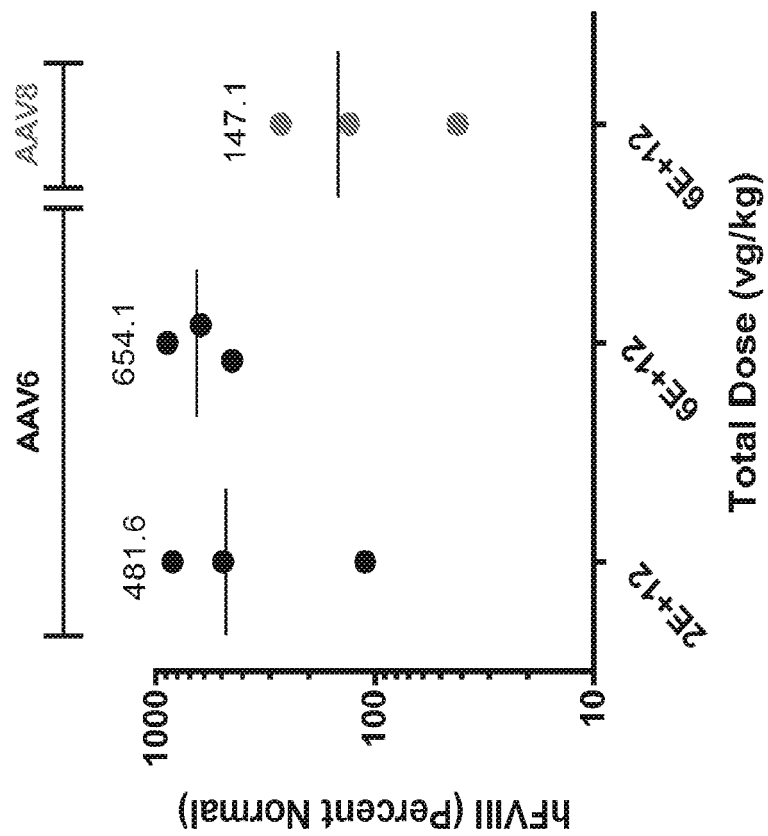


Figure 31A

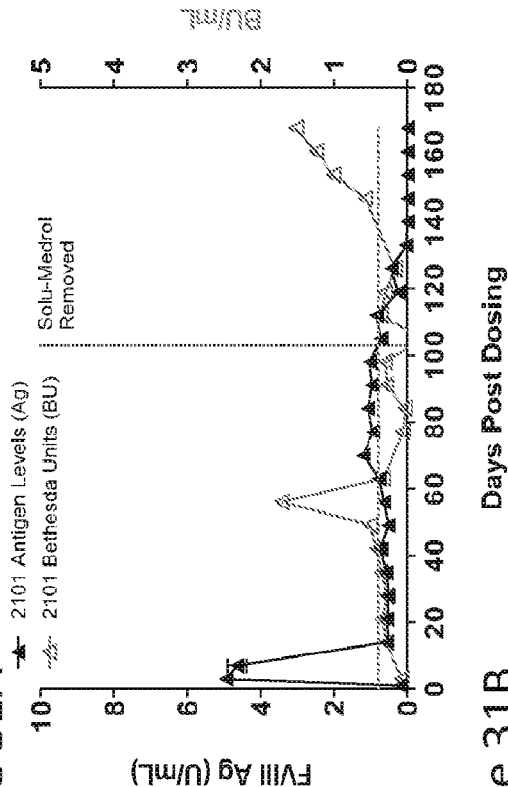


Figure 31C

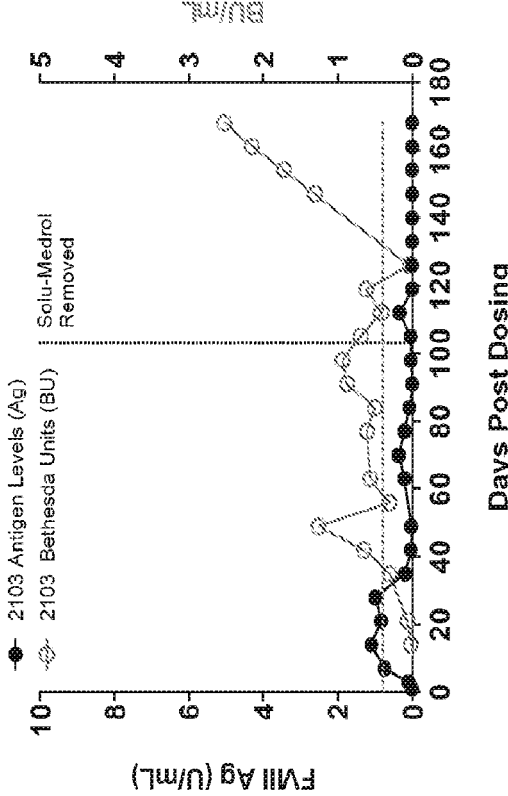
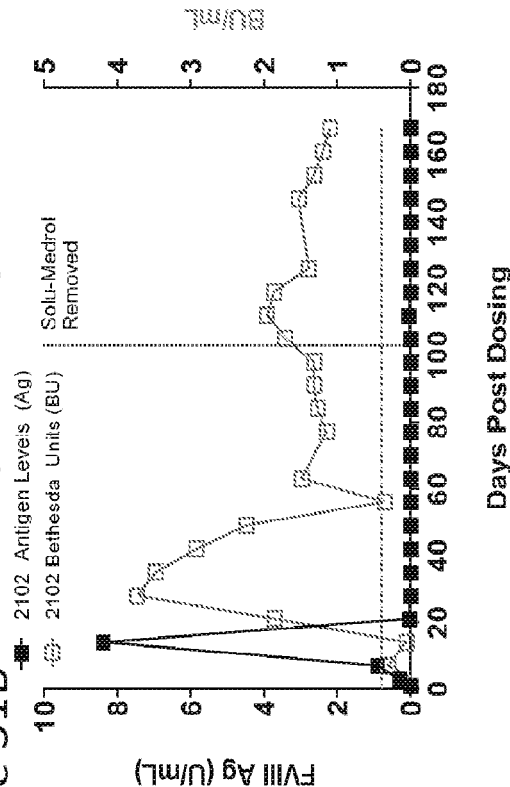


Figure 31B



Group 2, AAV2/6, 2E+12 vg/kg

Figure 32A

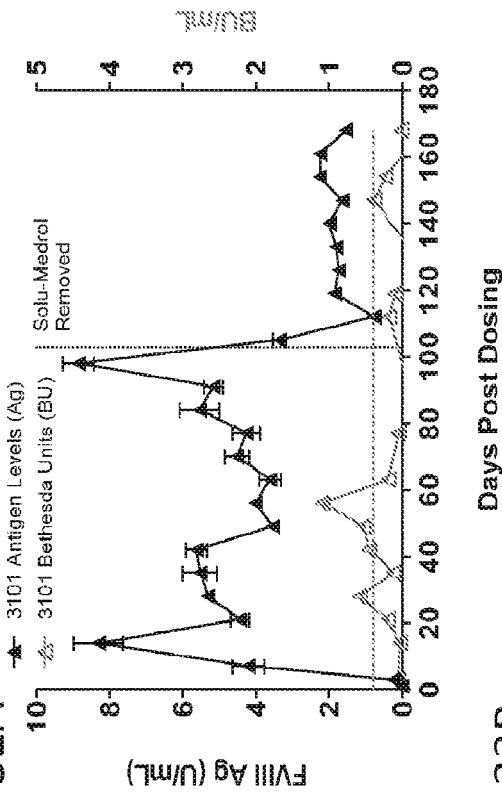


Figure 32C

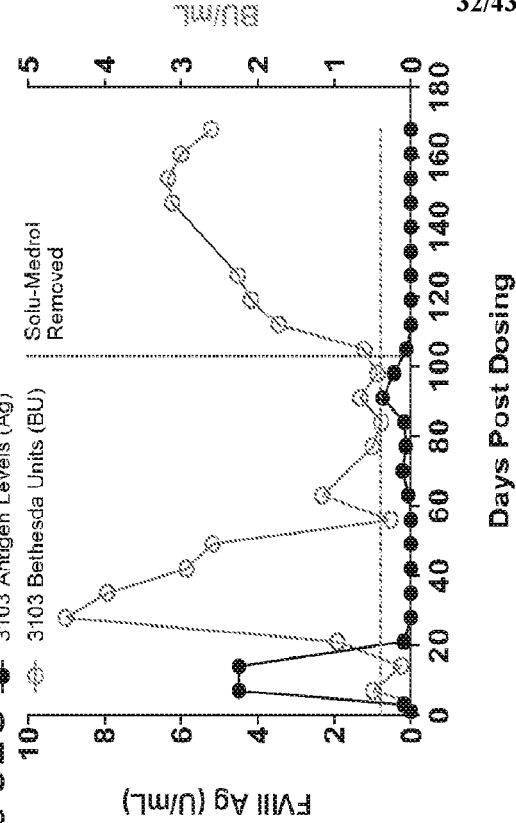
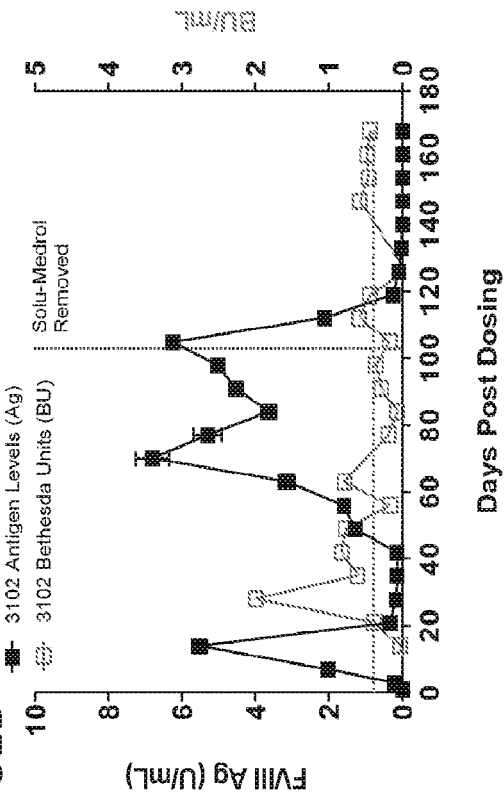


Figure 32B



Group 3, AAV2/6, 6E+12 vg/kg

Group 4, AAV2/8, 6E+12 vg/kg

Figure 33A

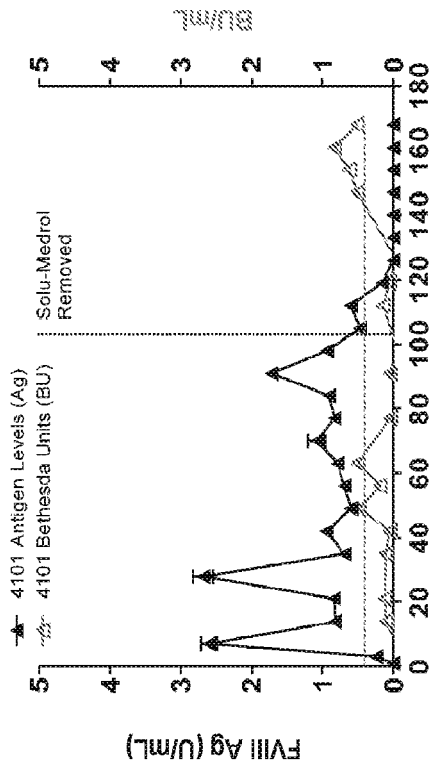


Figure 33B

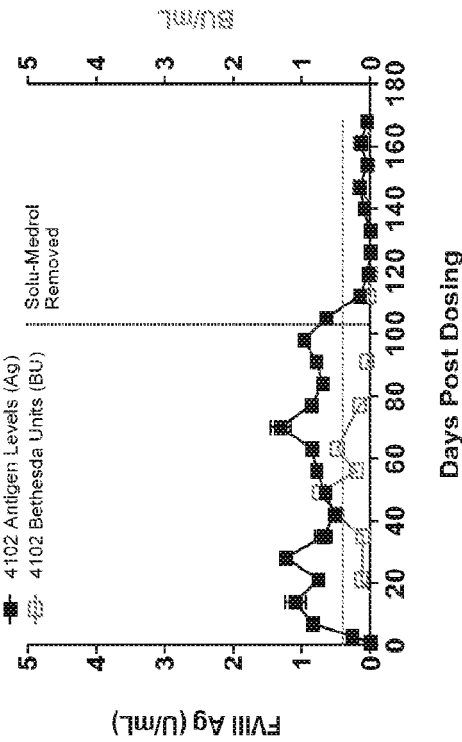


Figure 33C

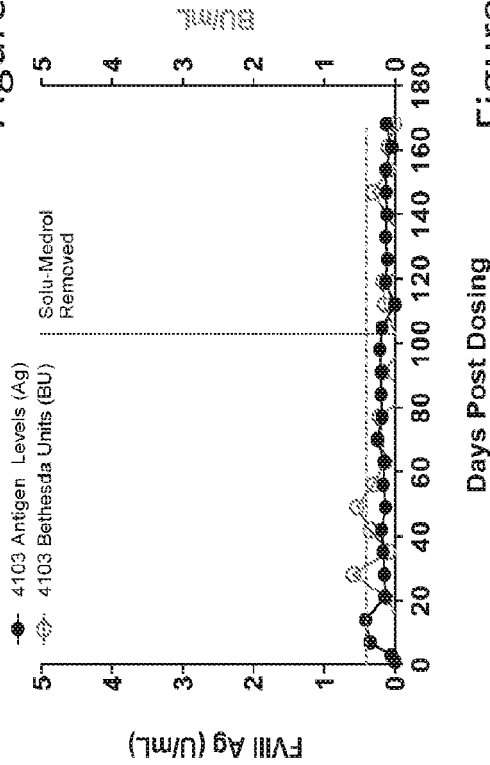


Figure 33D

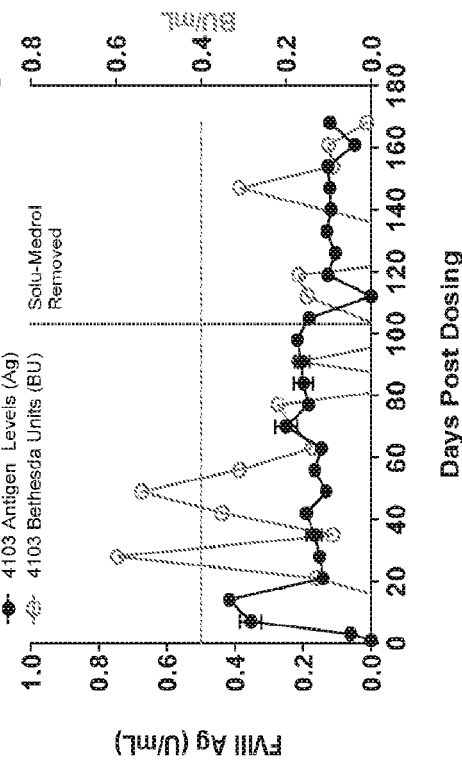


Figure 34A

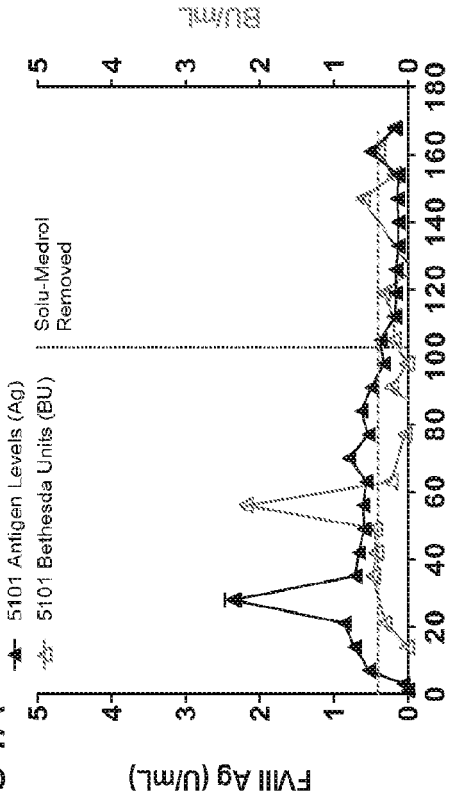


Figure 34B

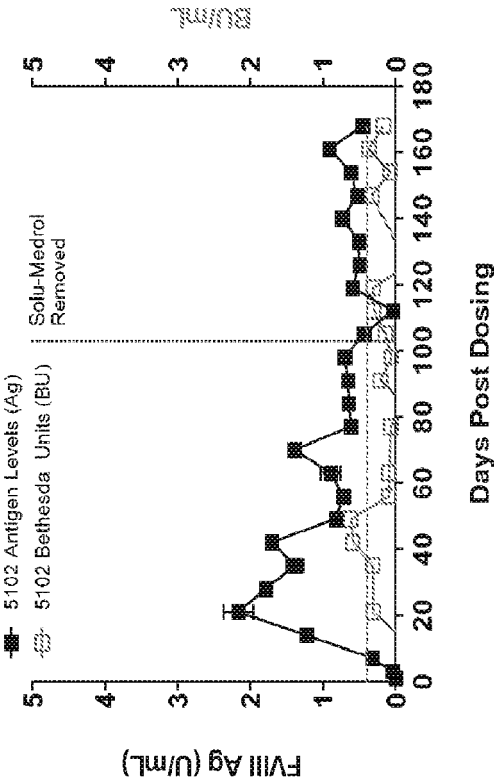
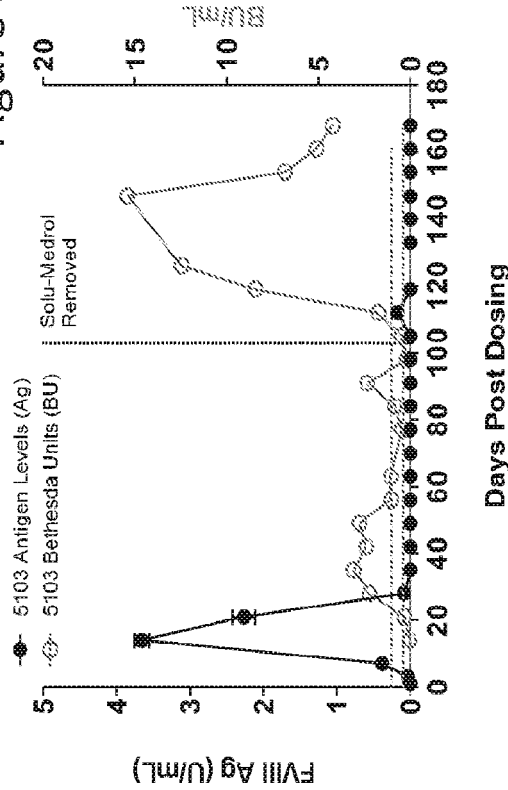


Figure 34C



Group 5, AAV2/8, 6E+12 vg/kg

Figure 34D

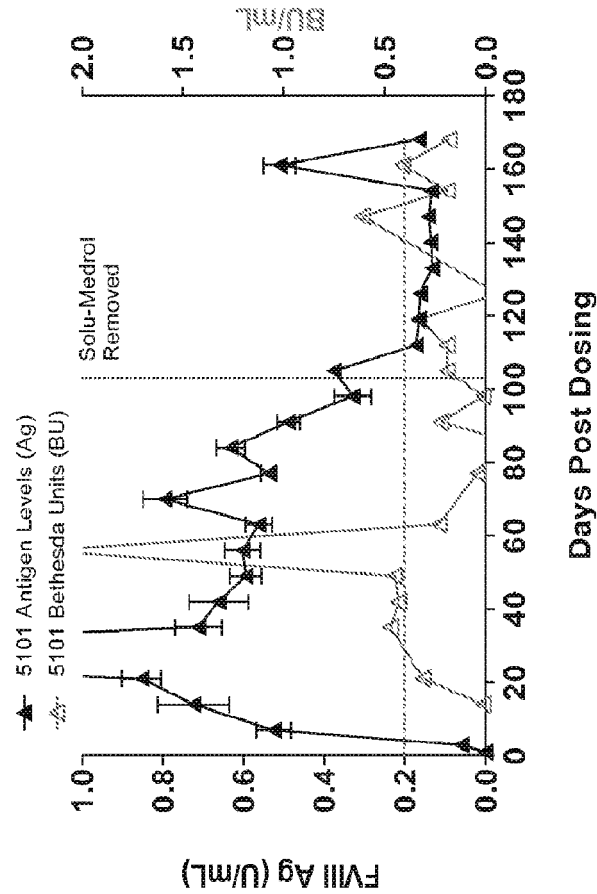
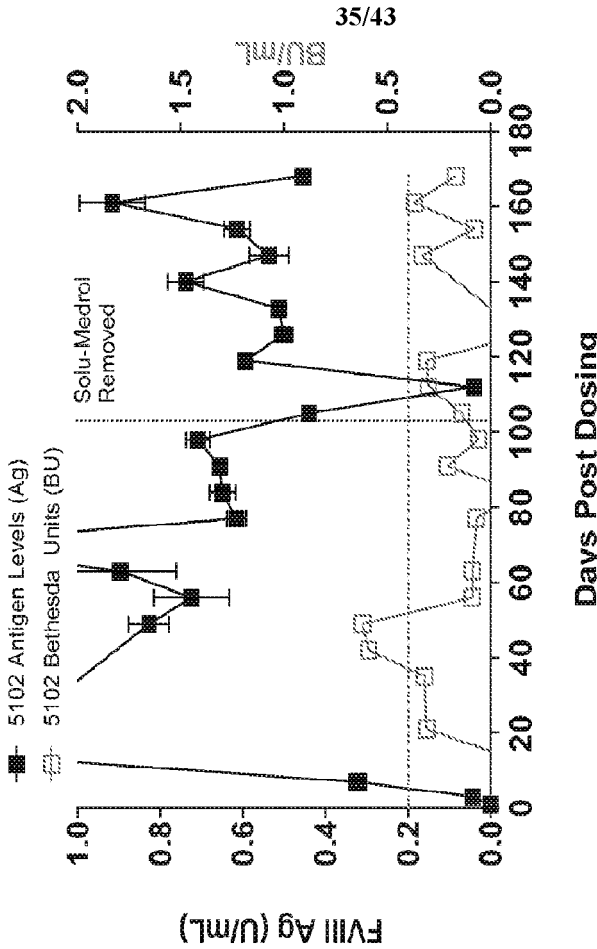


Figure 34E



Group 5, AAV2/8, 6E+12 vg/kg

Figure 35A

Formulation Control Group 1

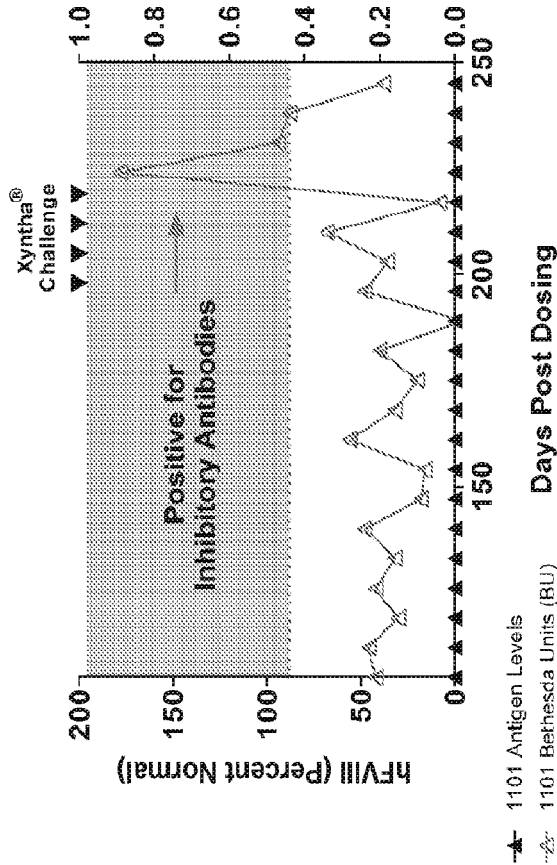
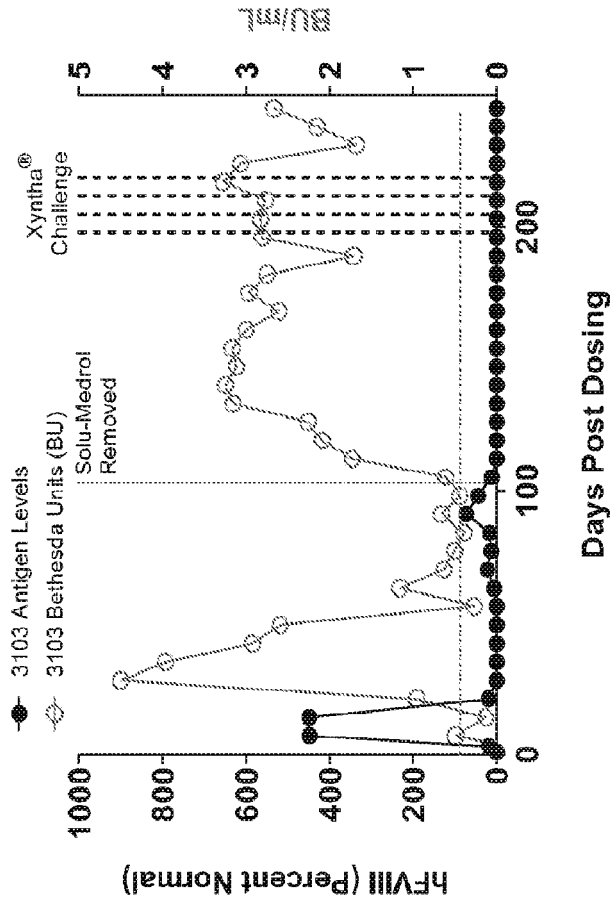


Figure 35B

Treatment Group 3



hFVIII Levels never recovered,
Robust BU Levels

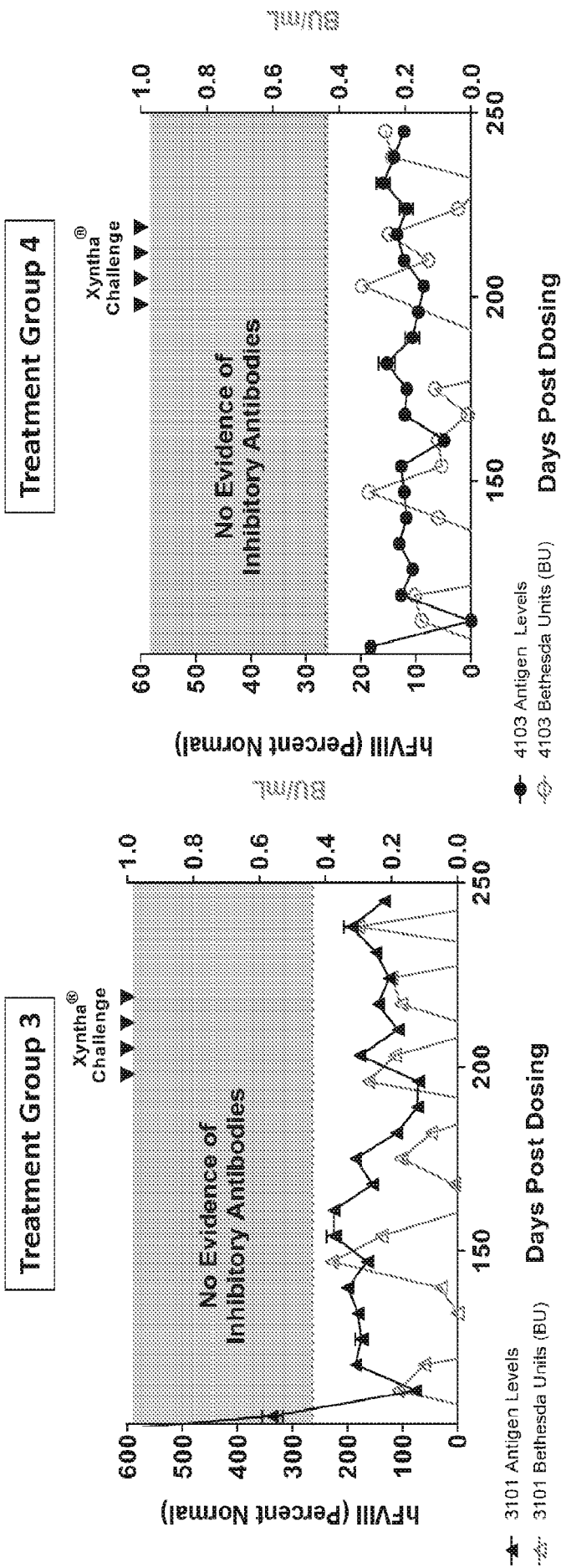


Figure 35C

hFVIII Levels stable ~150%

Figure 35D

hFVIII Levels stable ~10%

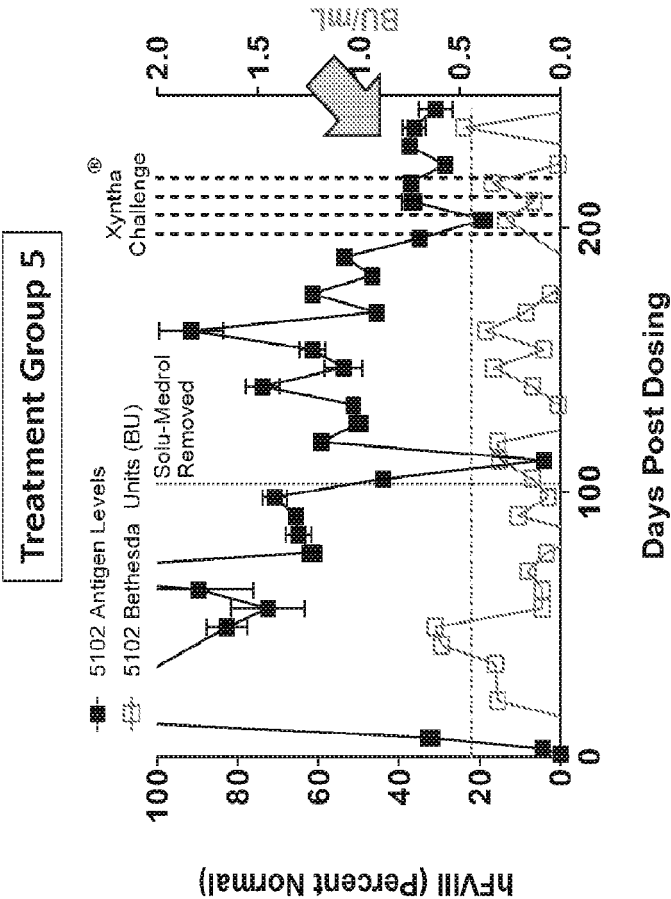


Figure 35F

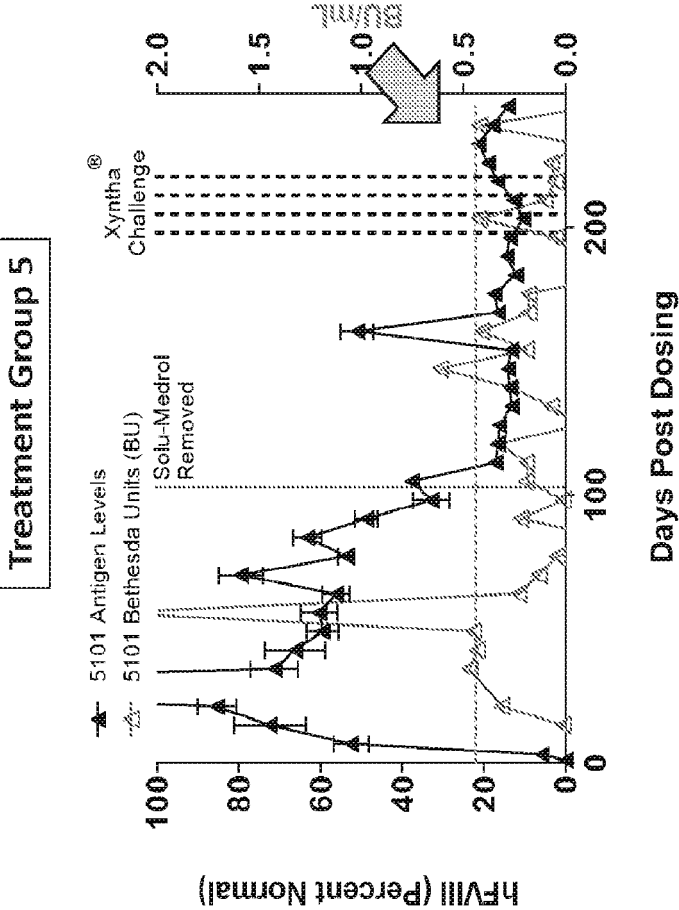


Figure 35E

Figure 36A

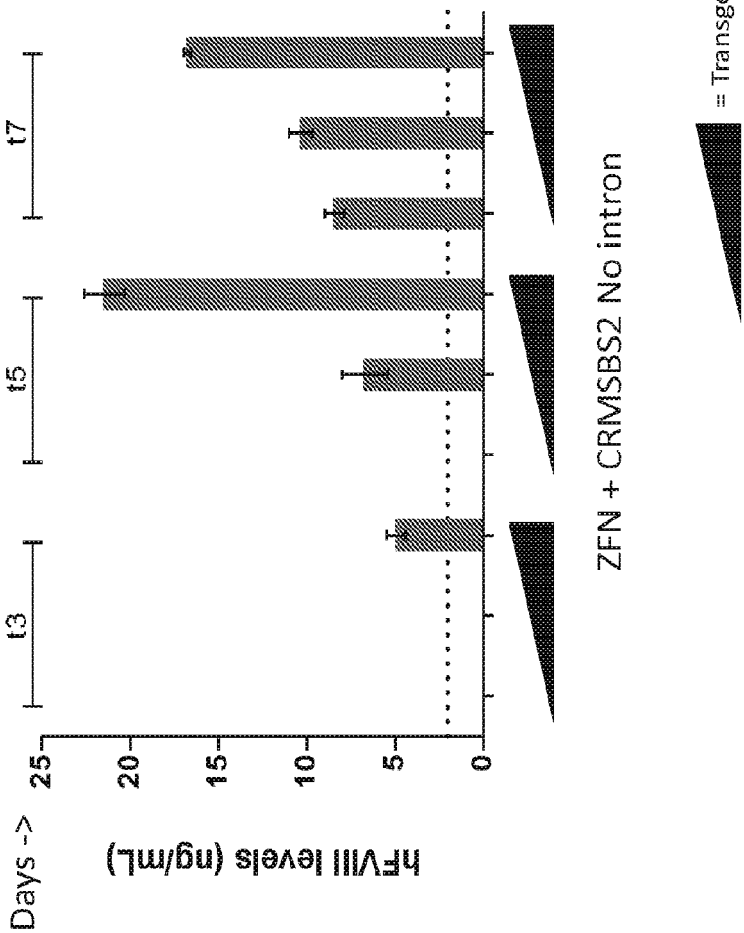
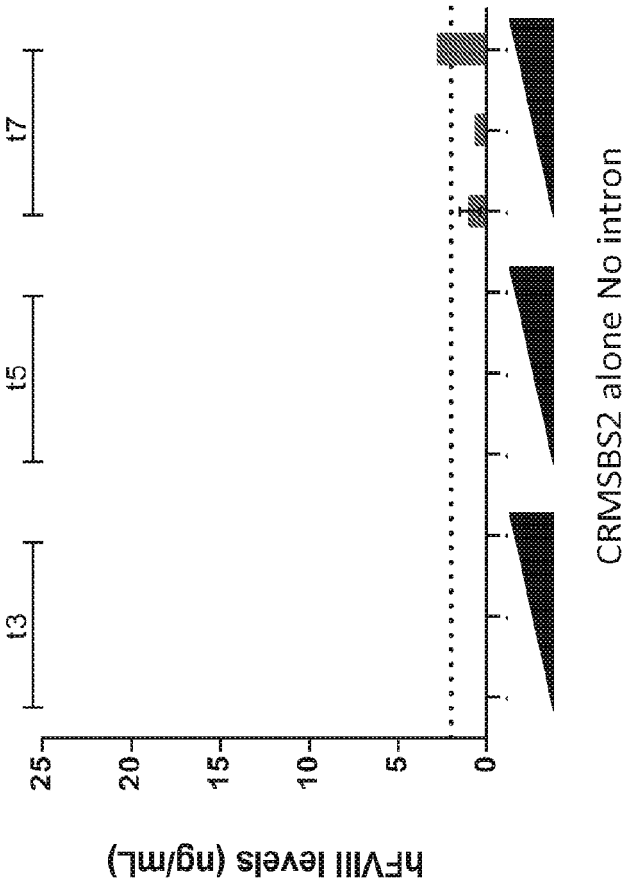
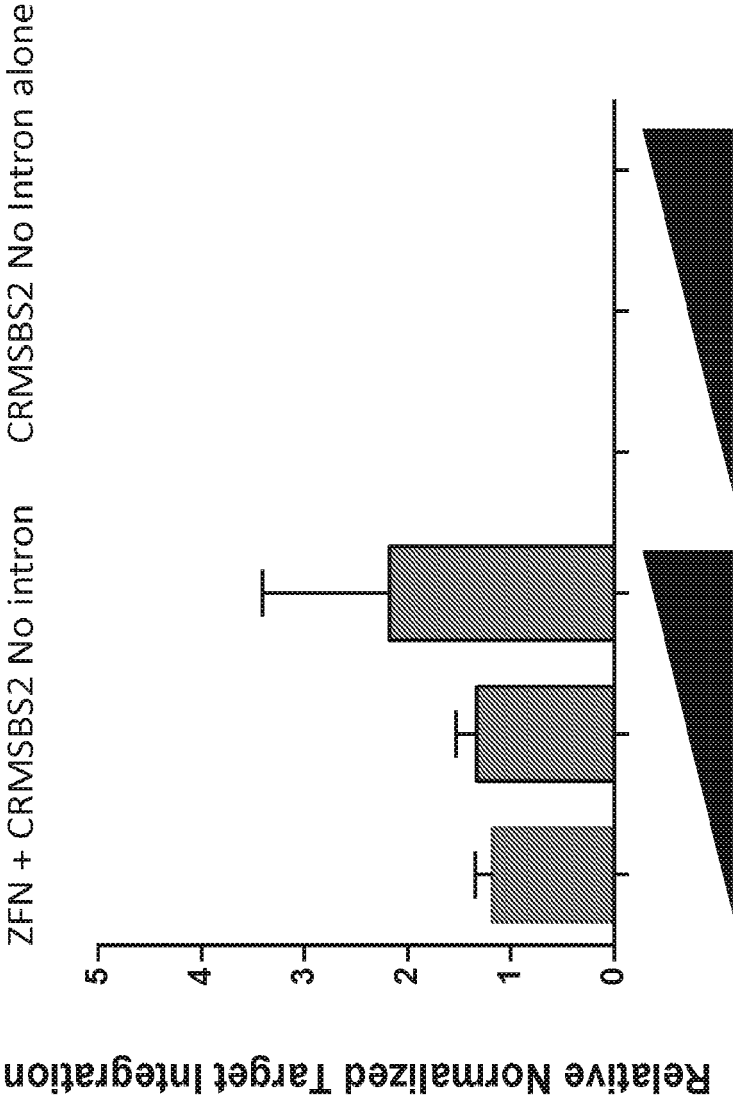


Figure 36B





= 3.0E+04 -> 1.2E+05

Figure 37

Figure 39

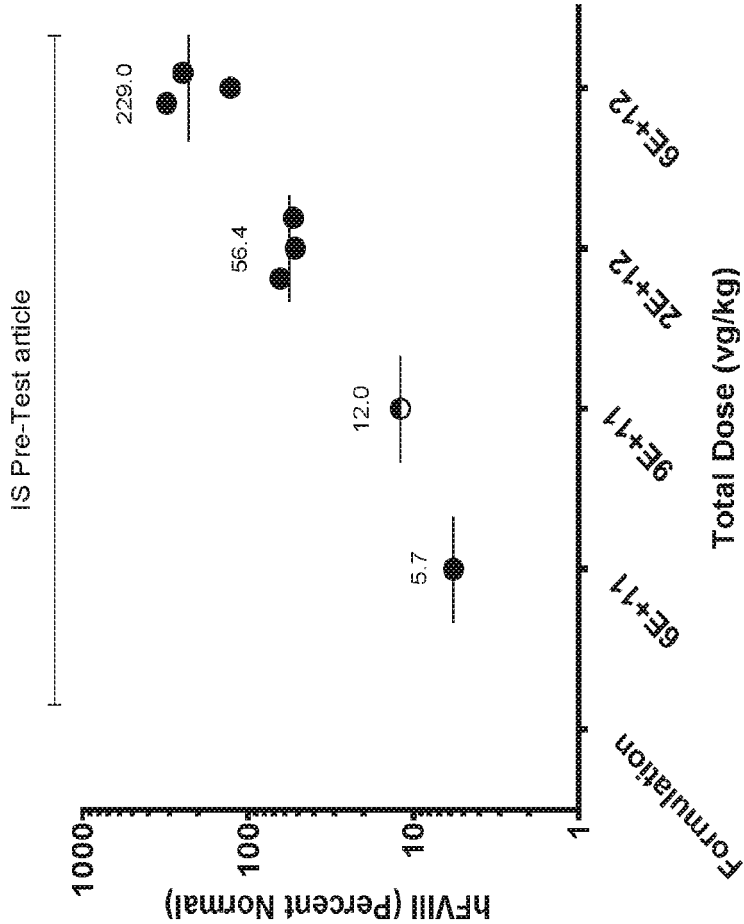
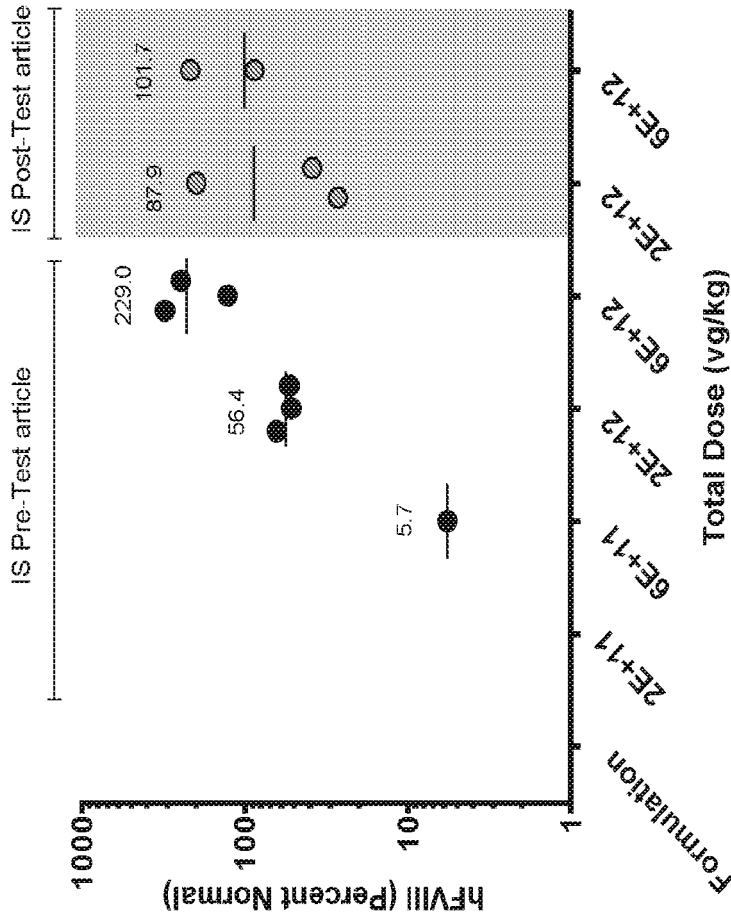


Figure 38



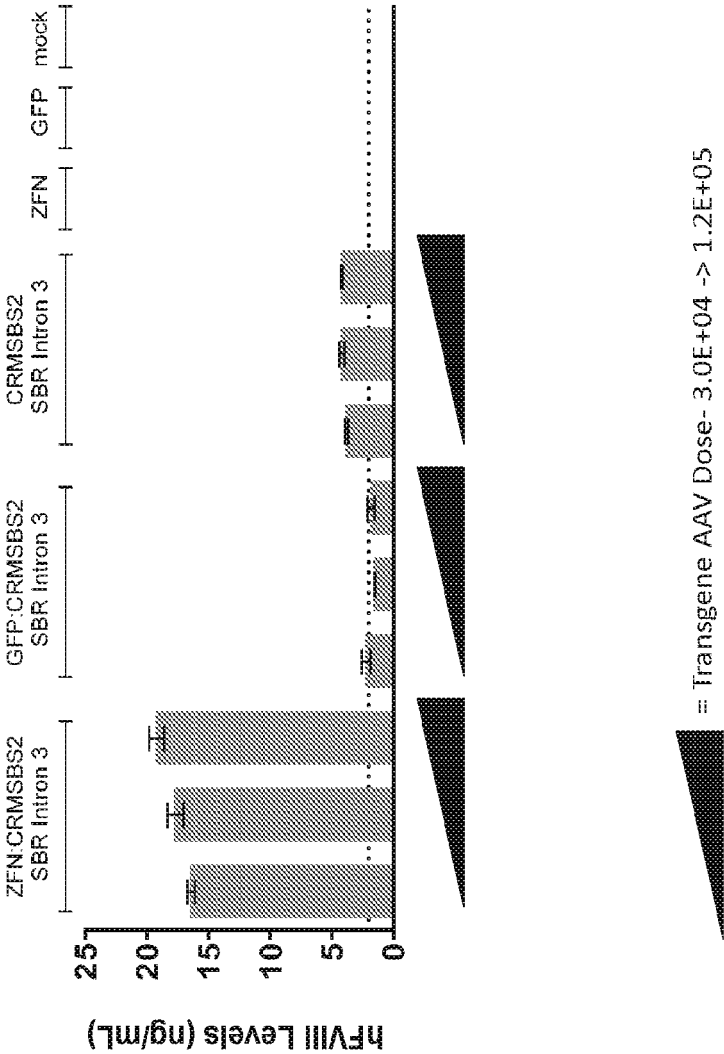


Figure 40A

Figure 40B

