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(Continued)

Figure 1A

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Figure 1B

CS12-FL-AA

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Figure 2

CS12-CRM8.2-Vr

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Figure 3A

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Figure 3B

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CRM8

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Kozak

ccacc (SEQ ID NO:7)

Poly-A

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3'-ITR

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Figure 4

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Figure 5A

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(Continued)

Figure 5B

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Figure 5C

10/28

CS12-CRM8.2-V

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(Continued)

Figure 6A

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Figure 6B

CS04-FL-NA

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(Continued)

Figure 7A

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(SEQ ID NO: 37)

Figure 7B

NG1: V S N N V S N N A T N N A T N (SEQ ID NO:11)
GTG AGC AAC AAT GTG AGC AAC AAT GCC ACC AAT AAT GCT ACC AAC (SEQ ID NO:12)

NG4: V S N N A T N N V S N (SEQ ID NO:13)
GTG AGC AAC AAT GCC ACC AAC AAT GTG AGC AAC (SEQ ID NO:14)

NG5: V S N N A T N (SEQ ID NO:15)
GTG AGC AAT AAT GCC ACC AAC (SEQ ID NO:16)

NG6: V S N N (SEQ ID NO:17)
GTG AGC AAT AAT (SEQ ID NO:18)

NG9: R S L (SEQ ID NO:19)
AGG AGC CTG (SEQ ID NO:20)

NG10: A T N V S N N S A T S A D S A V S (SEQ ID NO:21)
GCC ACT AAT GTG TCT AAC AAC TCT GCT ACC TCT GCT GAC TCT GCT GTG AGC (SEQ ID NO:22)

NG16: A T N Y V N R S L (SEQ ID NO:23)
GCC ACC AAC TAT GTG AAC AGG AGC CTG (SEQ ID NO:24)

Figure 8A

NG17: A T N Y V N R S L S A T S A D S A V S Q N (SEQ ID NO:25)
GCC ACC AAC TAT GTG AAC AGG AGC CTG TCT TCT GCC ACC TCT GCT GAC TCT GCT GTG AGC CAG AAT (SEQ ID NO:26)

NG18: V S N N V S N A V S A V S A (SEQ ID NO:27)
GTG AGC AAC AAT GTG AGC AAT GCT GTG TCT GCT GTG TCT GCT (SEQ ID NO:28)

NG19: I T V A S A T S N I T V A S A D (SEQ ID NO:29)
ATC ACT GTG GCC TCT GCC ACC TCT AAC ATC ACT GTG GCC TCT GCT GAC (SEQ ID NO:30)

NG20: I T V T N I T V T A (SEQ ID NO:31)
ATC ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:32)

NG21: Q T V T N I T V T A (SEQ ID NO:33)
CAG ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:34)

NGV: A T N V S N N S N T S N D S N V S (SEQ ID NO:35)
GCC ACT AAT GTG TCT AAC AAC AGC AAC ACC AGC AAT GAC AGC AAT GTG TCT (SEQ ID NO:36)

Figure 8B

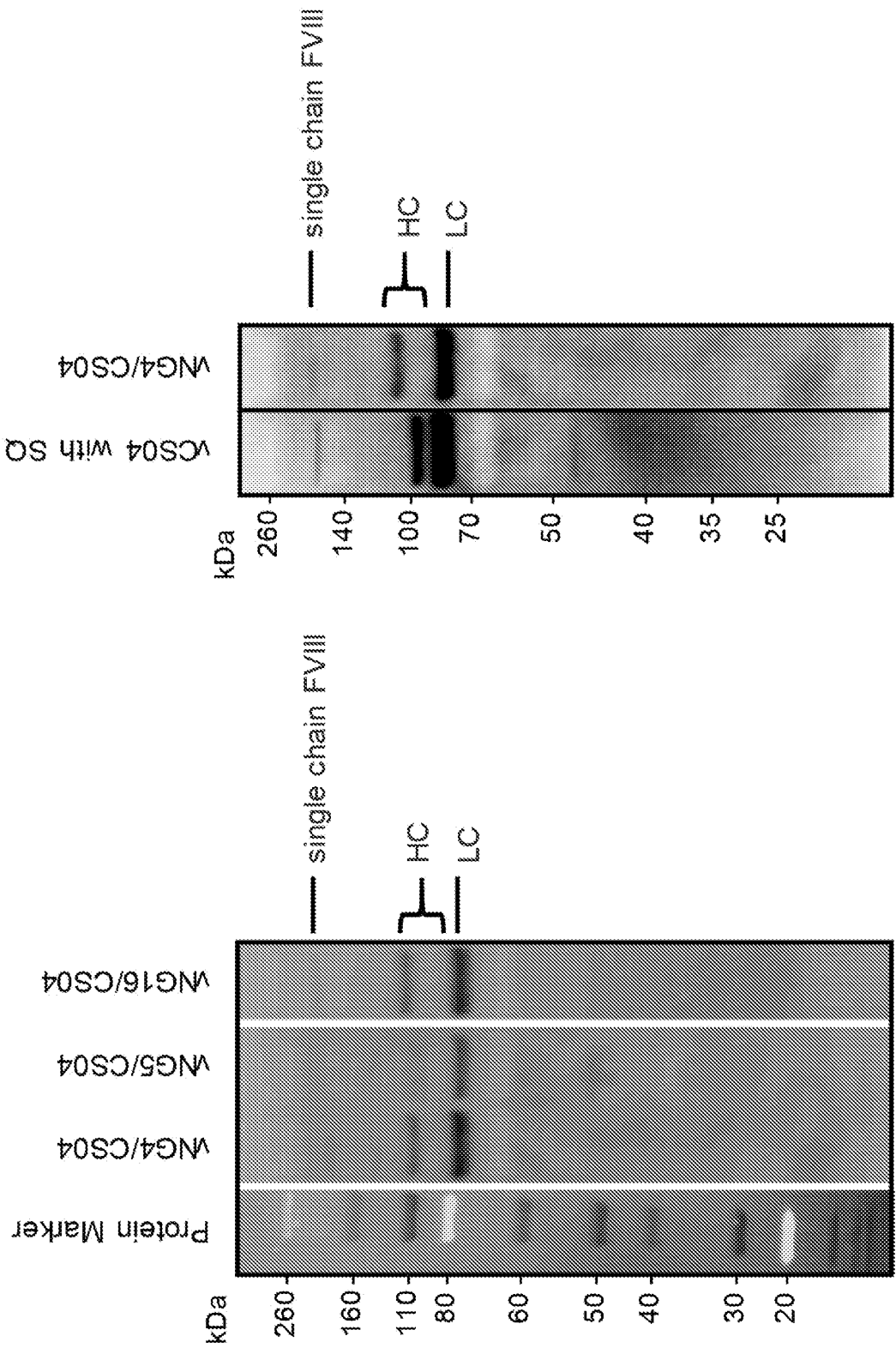


Figure 9

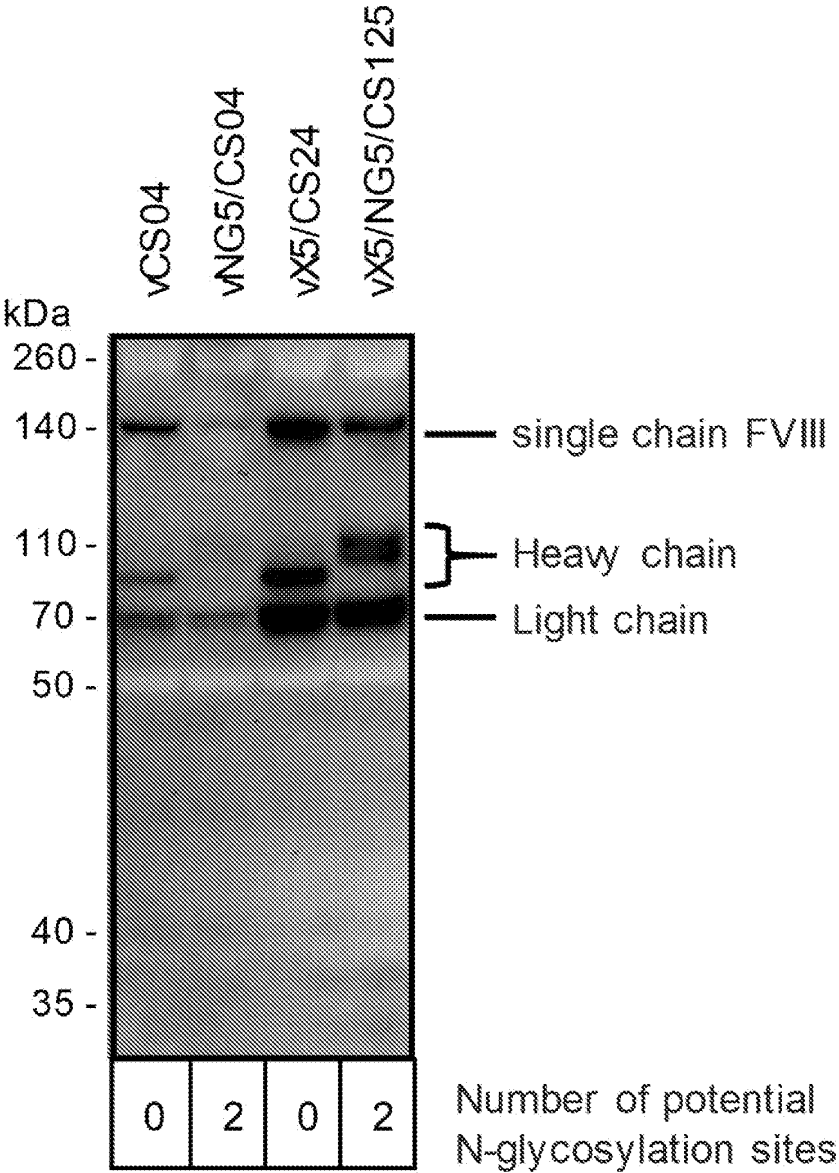


Figure 10

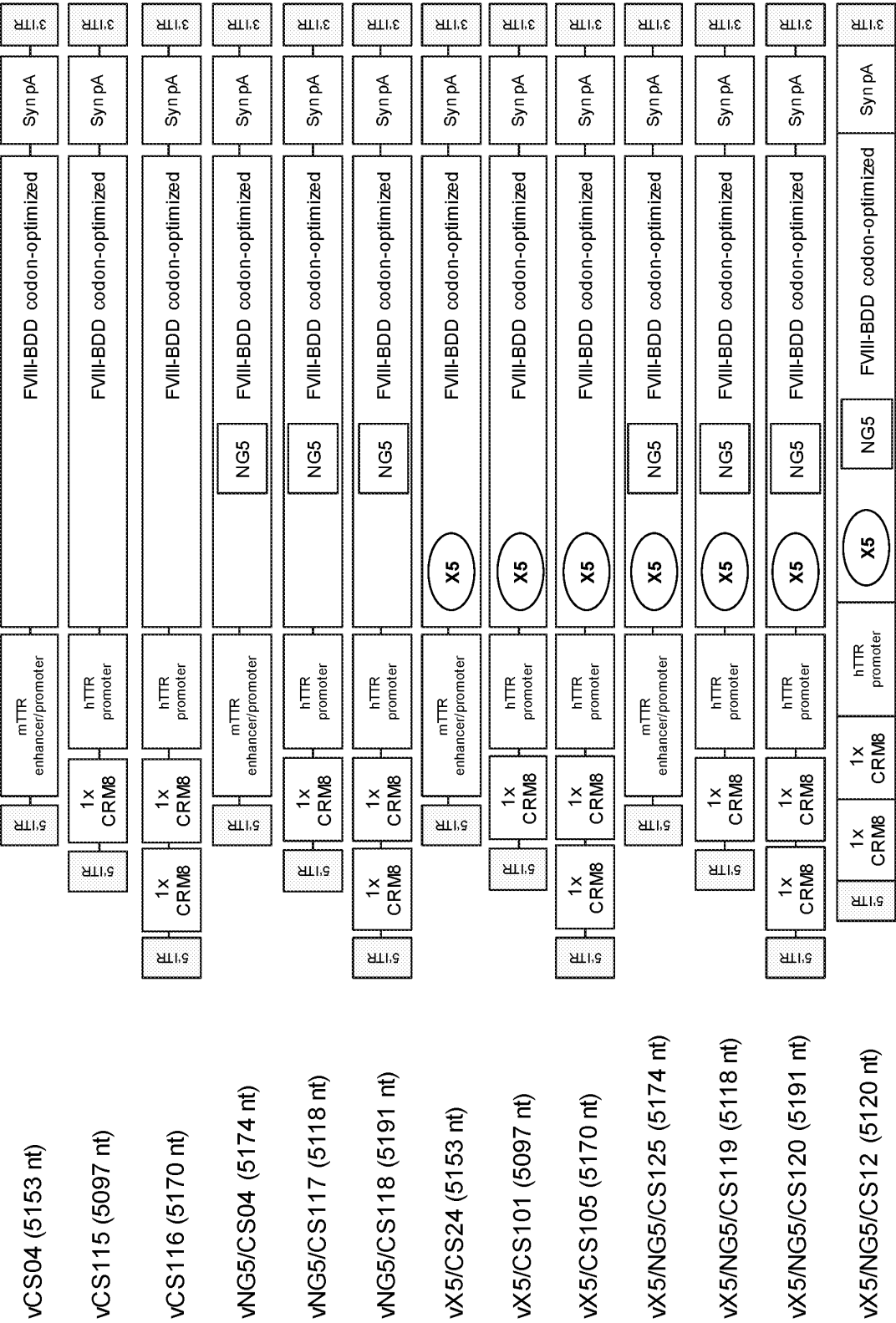


Figure 11

Vector	Promoter	CDS	Sequence modi- fication(s)	In vivo biopotency ("Line E" mice)				In vitro biopotency (HepG2 cells)		
				Number of mice	Average FVIII Expression at day 14 [IU/mL]	Standard Deviation	Fold expression increase	BPU	Standard Deviation	Fold expression increase*
vCS04	mTTR promoter/enhancer	CS04	-	44	2.1	1.7	1.0 (ref.)	1.0	0.6	1.0 (ref.)
vCS115	1xCRM8/hTTR	CS04	-	8	2.5	0.9	1.2	2.1	n.a.	2.2
vCS116	2xCRM8/hTTR	CS04	-	8	1.9	0.6	0.9	3.6	n.a.	3.7
vNG5/CS04	mTTR promoter/enhancer	CS04	NG5	8	4.0	2.6	1.9	0.6	n.a.	0.6
vNG5/CS117	1xCRM8/hTTR	CS04	NG5	7	3.2	1.0	1.5	1.5	0.1	1.5
vNG5/CS118	2xCRM8/hTTR	CS04	NG5	7	2.9	1.8	1.4	2.3	n.a.	2.4
vX5/CS24	mTTR promoter/enhancer	CS04	X5	16	6.5	2.1	3.1	3.8	1.9	4.0
vX5/CS101	1xCRM8/hTTR	CS04	X5	7	5.2	3.2	2.5	7.0	n.a.	7.3
vX5/CS105	2xCRM8/hTTR	CS04	X5	8	5.1	2.8	2.5	20.3	n.a.	21.2
vX5/NG5/CS125	mTTR promoter/enhancer	CS04	NG / X5	8	9.3	2.8	4.5	3.0	1.0	3.2
vX5/NG5/CS119	1xCRM8/hTTR	CS04	NG / X5	8	7.6	5.8	3.6	13.6	4.4	14.2
vX5/NG5/CS120	2xCRM8/hTTR	CS04	NG / X5	8	11.4	5.0	5.5	19.0	n.a.	19.8

Figure 12

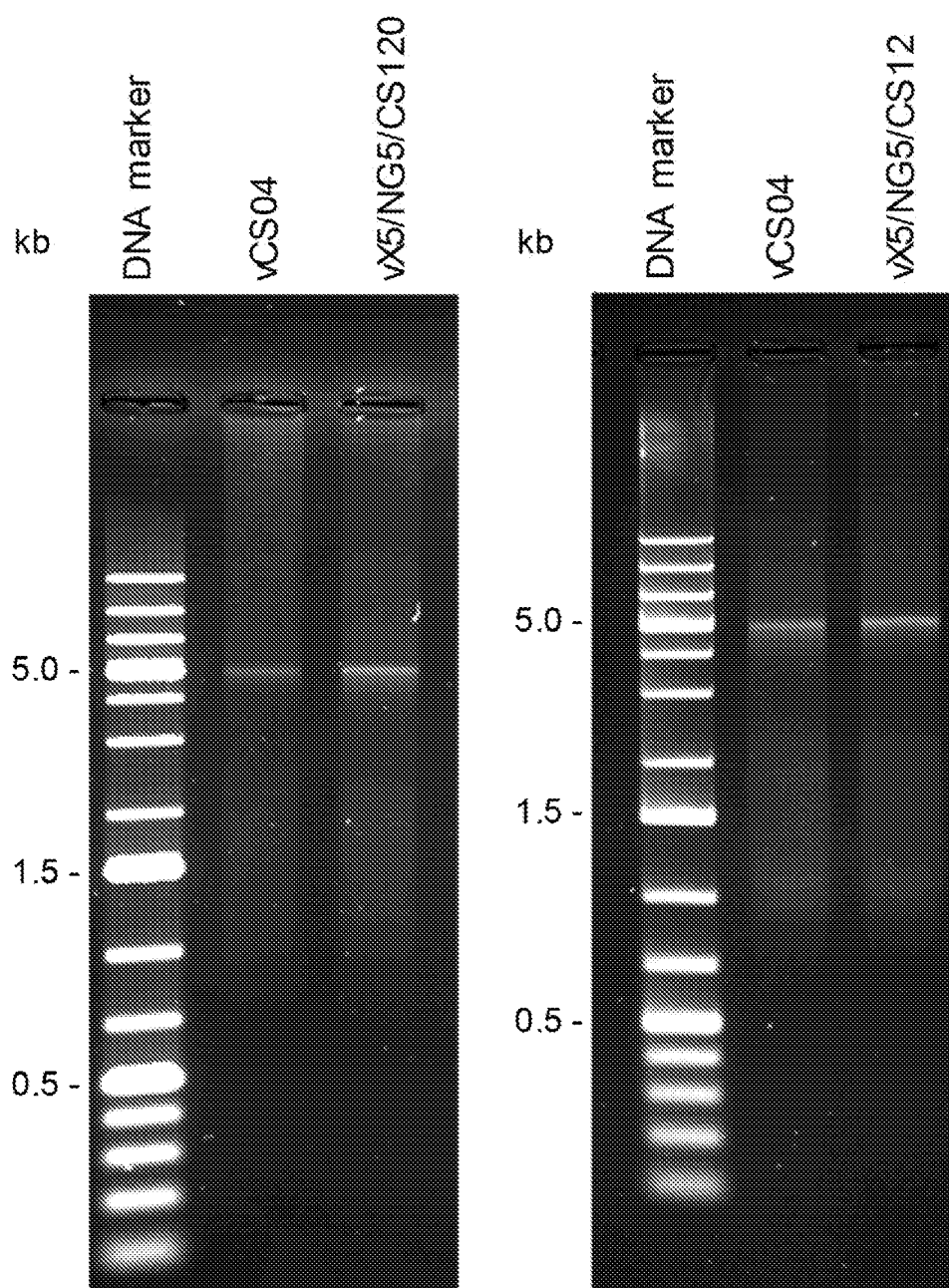


Figure 13

Vector	Promoter	CDS	Sequence modification (s)	In vivo biopotency				In vitro biopotency		
				Dosis [vg/kg]	Number of mice	Average FVIII Expression at day 14 [IU/mL]	Standard Deviation	Fold expression increase	BPU	Stand-ard Devi-ation
vCS04	mTTR promoter/enhancer	CS04	-	1.0E+12	16	0.3	0.1	1.0*	1.0	0.1
				4.0E+12	16	2.5	0.9	-	-	-
vX5/NG5/CS120	2xCRM8/hTTR	CS04	NG / X5	1.0E+12	7	4.3	1.7	14.5*	16.7	5.1
vX5/NG5/CS12	2xCRM8/hTTR	CS04	NG / X5, size-reduced	5.0E+11	24	1.5	0.8	-	24.2	8.1
				1.0E+12	24	4.2	1.3	14.0*	-	-

Figure 14

Human wild-type FVIII



Refacto-type BDD-FVIII



Figure 15

hFVIII-FL-AA

```

mqielstcfff lcllrfcfsa trryylgave lswdymqsdl gelpvdarfp prvpksfpfn
tsvvykktlf veftdhlfni akprppwmgf lgptiqaevy dtvvitlknm ashpvsilhav
gvsywkaseg aeyddqtsqr ekeddkvfpg gshtyvwqvl kengpmasdp lcltysylsh
vdlvkdlmsg ligallvcre gslakektqt lkhkfillfav fddegkshwse tknslmqdrd
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rqasleispi tfltaqtllm dlqgflfch issqhhdgme aykvkdscepe epqlrmkne
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nhmsnktts knmemvqqkk egpipdaqn pdmsffkmlf lpesarwiqr thgknslnsg
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```

Figure 16

BDL004 - agc ttcagccaga atccacctgt cctgaaacgc caccagagg (SEQ ID NO:40)

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BDLNG4 - agcttcagccagaatGTGAGCAACAATGCCACCAACAATGTGAGCAACccacctgtcctgaaacgccaccagagg (SEQ ID NO:42)

BDLNG5 - agcttcagccagaatGTGAGCAATAATGCCACCAACccacctgtcctgaaacgccaccagagg (SEQ ID NO:43)

BDLNG6 - agcttcagccagaatGTGAGCAATAATccacctgtcctgaaacgccaccagagg (SEQ ID NO:44)

BDLNG9 - agcttcagccagaatAGGAGCCTGccacctgtcctgaaacgccaccagagg (SEQ ID NO:45)

BDLNG10 - agcttcagccagaatGCCACTAATGTGTGTCTAACAACTCTGCTGACTCTGCTGAGCccacctgtcctgaaacgccaccagagg (SEQ ID NO:46)

BDLNG16 - agcttcagccagaatGCCACCAACTATGTGAACAGGAGCCTGccacctgtcctgaaacgccaccagagg (SEQ ID NO:47)

BDLNG17 - agcttcagccagaatGCCACCAACTATGTGAACAGGAGCCTGTCTGCCACCTCTGCTGACTCTGCTGTGAGCCAGAAATccacctgtcctgaaacgccaccagagg (SEQ ID NO:48)

BDLNG18 - agcttcagccagaatGTGAGCAACAATGTGAGCAATGCTGTGTCTGCTGTGTCTGCTccacctgtcctgaaacgccaccagagg (SEQ ID NO:49)

BDLNG19 - agcttcagccagaatATCACTGTGGCCTCTGCCACCTCTAACATCACTGTGGCCTCTGCTGACccacctgtcctgaaacgccaccagagg (SEQ ID NO:50)

BDLNG20 - agcttcagccagaatATCACTGTGACCAACATCACTGTGACTGCCccacctgtcctgaaacgccaccagagg (SEQ ID NO:51)

BDLNG21 - agcttcagccagaatCAGACTGTGACCAACATCACTGTGACTGCCccacctgtcctgaaacgccaccagagg (SEQ ID NO:52)

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Figure 17

Plasmid backbone of CS12-CRM8.2-Vrp

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(SEQ ID NO:54)

Figure 18

pMB1 Replicon

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(SEQ ID NO:55)

Bla (ApR)

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Figure 19

CS12-CRM8.2-Vp

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(Continued)

Figure 20A

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(Continued)

Figure 20B

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Figure 20C