Figure 1

Unmodified sequences		Modified sequences		Modified siRNA
sense strand sequence (5´-3´) 17mer	antisense strand sequence (5´-3´) 22mer	sense strand sequence (5´-3´) 17mer	antisense strand sequence (5´-3´) 22mer	
ACAAUUUUAGGCUCAAA	UUUGAGCCUAAAAUUGUCUAAU	ascsaaUfUfUfuaggcucaaa(GalNAc)	usUfsugagccuaaaaUfuGfucusasaU	1
CUACAUCAAGACUAAUA	UAUUAGUCUUGAUGUAGUGGGU	csusacAfUfCfaagacuaaua(GalNAc)	usAfsuuagucuugauGfuAfgugsgsgU	2
UAGACAAUUUUAGGCUA	UAGCCUAAAAUUGUCUAAACAU	usasgaCfAfAfuuuuaggcua(GalNAc)	usAfsgccuaaaauugUfcUfaaascsaU	3
ACUACAUCAAGACUAAA	UUUAGUCUUGAUGUAGUGGGAU	ascsuaCfAfUfcaagacuaaa(GalNAc)	usUfsuagucuugaugUfaGfuggsgsaU	4
AAUUUUAGGCUCAAAAA	UUUUUGAGCCUAAAAUUGUCUU	asasuuUfUfAfggcucaaaaa(GalNAc)	usUfsuuugagccuaaAfaUfuguscsuU	5
GGACCCUCUAUAUUUCA	UGAAAUAUAGAGGGUCCACUUU	gsgsacCfCfUfcuauauuuca(GalNAc)	usGfsaaauauagaggGfuCfcacsusuU	6
UGGACCCUCUAUAUUUA	UAAAUAUAGAGGGUCCACUUUU	usgsgaCfCfCfucuauauuua(GalNAc)	usAfsaauauagagggUfcCfacususuU	7
CAUCAAGACUAAUCUUA	UAAGAUUAGUCUUGAUGUAGUU	csasucAfAfGfacuaaucuua(GalNAc)	usAfsagauuagucuuGfaUfguasgsuU	8
AUCAAGACUAAUCUUGA	UCAAGAUUAGUCUUGAUGUAGU	asuscaAfGfAfcuaaucuuga(GalNAc)	usCfsaagauuagucuUfgAfugusasgU	9
UACAUCAAGACUAAUCA	UGAUUAGUCUUGAUGUAGUGGU	usascaUfCfAfagacuaauca(GalNAc)	usGfsauuagucuugaUfgUfagusgsgU	10
UGGACUAUCCUCUUGUA	UACAAGAGGAUAGUCCAUGCAU	usgsgaCfUfAfuccucuugua(GalNAc)	usAfscaagaggauagUfcCfaugscsaU	11
AGUAUAUCCAGCCGAUA	UAUCGGCUGGAUAUACUGUCCU	asgsuaUfAfUfccagccgaua(GalNAc)	usAfsucggcuggauaUfaCfuguscscU	12
AGUGGACCCUCUAUAUA	UAUAUAGAGGGUCCACUUUUGU	asgsugGfAfCfccucuauaua(GalNAc)	usAfsuauagagggucCfaCfuuususgU	13
CUUUUGCAUGGACUAUA	UAUAGUCCAUGCAAAAGCAUUU	csusuuUfGfCfauggacuaua(GalNAc)	usAfsuaguccaugcaAfaAfgcasusuU	14
UCGUAUGCAGAAUAUUA	UAAUAUUCUGCAUACGAUUUAU	uscsguAfUfGfcagaauauua(GalNAc)	usAfsauauucugcauAfcGfauususaU	15
GGACUAUCCUCUUGUUA	UAACAAGAGGAUAGUCCAUGCU	gsgsacUfAfUfccucuuguua(GalNAc)	usAfsacaagaggauaGfuCfcausgscU	16
UUCUUCCUGAACGCGCA	UGCGCGUUCAGGAAGAAACUUU	ususcuUfCfCfugaacgcgca(GalNAc)	usGfscgcguucaggaAfgAfaacsusuU	17

WO 2021/113820 PCT/US2020/063617

UAGGCUCAAAAAUUAAA	UUUAAUUUUUGAGCCUAAAAUU	usasggCfUfCfaaaaauuaaa(GalNAc)	usUfsuaauuuuugagCfcUfaaasasuU	18
AAUCGUAUGCAGAAUAA	UUAUUCUGCAUACGAUUUAAAU	asasucGfUfAfugcagaauaa(GalNAc)	usUfsauucugcauacGfaUfuuasasaU	19
CAGUAUAUCCAGCCGAA	UUCGGCUGGAUAUACUGUCCCU	csasguAfUfAfuccagccgaa(GalNAc)	usUfscggcuggauauAfcUfgucscscU	20
GGUCUGACAUCAGAACA	UGUUCUGAUGUCAGACCUCUGU	gsgsucUfGfAfcaucagaaca(GalNAc)	usGfsuucugaugucaGfaCfcucsusgU	21
GUCAACAUCCUAGGACA	UGUCCUAGGAUGUUGACCUCAU	gsuscaAfCfAfuccuaggaca(GalNAc)	usGfsuccuaggauguUfgAfccuscsaU	22
CUUCCUGAACGCGCCUA	UAGGCGCGUUCAGGAAGAAACU	csusucCfUfGfaacgcgccua(GalNAc)	usAfsggcgcguucagGfaAfgaasascU	23
UGUGAAUACUGGGUUCA	UGAACCCAGUAUUCACAAAAAU	usgsugAfAfUfacuggguuca(GalNAc)	usGfsaacccaguauuCfaCfaaasasaU	24
CCACUACAUCAAGACUA	UAGUCUUGAUGUAGUGGGAGUU	cscsacUfAfCfaucaagacua(GalNAc)	usAfsgucuugauguaGfuGfggasgsuU	25
ACAUCCUAGGACAUUUA	UAAAUGUCCUAGGAUGUUGACU	ascsauCfCfUfaggacauuua(GalNAc)	usAfsaauguccuaggAfuGfuugsascU	26
GACUAUCCUCUUGUUUA	UAAACAAGAGGAUAGUCCAUGU	gsascuAfUfCfcucuuguuua(GalNAc)	usAfsaacaagaggauAfgUfccasusgU	27
UCAAAACCUCAUGUCUA	UAGACAUGAGGUUUUGAUACCU	uscsaaAfAfCfcucaugucua(GalNAc)	usAfsgacaugagguuUfuGfauascscU	28
AACUCUAUUCUGGACUA	UAGUCCAGAAUAGAGUUGCACU	asascuCfUfAfuucuggacua(GalNAc)	usAfsguccagaauagAfgUfugcsascU	29
AGCACUUCUUCCAUCGA	UCGAUGGAAGAAGUGCUUUUGU	asgscaCfUfUfcuuccaucga(GalNAc)	usCfsgauggaagaagUfgCfuuususgU	30
UCUAUUCUGGACUUUAA	UUAAAGUCCAGAAUAGAGUUGU	uscsuaUfUfCfuggacuuuaa(GalNAc)	usUfsaaaguccagaaUfaGfagususgU	31
CUGUACUGGCUAUUACA	UGUAAUAGCCAGUACAGUUCCU	csusguAfCfUfggcuauuaca(GalNAc)	usGfsuaauagccaguAfcAfguuscscU	32
CUUCUUCCAUCGAUGAA	UUCAUCGAUGGAAGAAGUGCUU	csusucUfUfCfcaucgaugaa(GalNAc)	usUfscaucgauggaaGfaAfgugscsuU	33
GUUUCUUCCUGAACGCA	UGCGUUCAGGAAGAAACUUCUU	gsusuuCfUfUfccugaacgca(GalNAc)	usGfscguucaggaagAfaAfcuuscsuU	34
AACCUCUUGUAGUUAUA	UAUAACUACAAGAGGUUAUUUU	asasccUfCfUfuguaguuaua(GalNAc)	usAfsuaacuacaagaGfgUfuaususuU	35
CUGGACUUUAUUACUUA	UAAGUAAUAAAGUCCAGAAUAU	csusggAfCfUfuuauuacuua(GalNAc)	usAfsaguaauaaaguCfcAfgaasusaU	36
AUCAAAACCUCAUGUCA	UGACAUGAGGUUUUGAUACCAU	asuscaAfAfAfccucauguca(GalNAc)	usGfsacaugagguuuUfgAfuacscsaU	37

AGACUGUUCAAGUAGCA	UGCUACUUGAACAGUCUUAAAU	asgsacUfGfUfucaaguagca(GalNAc)	usGfscuacuugaacaGfuCfuuasasaU	38
AUCAUGGCCACAUCGUA	UACGAUGUGGCCAUGAUUUCUU	asuscaUfGfGfccacaucgua(GalNAc)	usAfscgauguggccaUfgAfuuuscsuU	39
CGUAUGCAGAAUAUUCA	UGAAUAUUCUGCAUACGAUUUU	csgsuaUfGfCfagaauauuca(GalNAc)	usGfsaauauucugcaUfaCfgaususuU	40
UUGAAGCAGUGGUUGGA	UCCAACCACUGCUUCAAAUUGU	ususgaAfGfCfagugguugga(GalNAc)	usCfscaaccacugcuUfcAfaaususgU	41
ACUCUAUUCUGGACUUA	UAAGUCCAGAAUAGAGUUGCAU	ascsucUfAfUfucuggacuua(GalNAc)	usAfsaguccagaauaGfaGfuugscsaU	42
CAGGGAAGGUUUAAGAA	UUCUUAAACCUUCCCUGUGUAU	csasggGfAfAfgguuuaagaa(GalNAc)	usUfscuuaaaccuucCfcUfgugsusaU	43
AUGUAUUAUAGAAUGCA	UGCAUUCUAUAAUACAUGUGAU	asusguAfUfUfauagaaugca(GalNAc)	usGfscauucuauaaauAfcAfugusgsaU	44
AAGUGGACCCUCUAUAA	UUAUAGAGGGUCCACUUUUGGU	asasguGfGfAfcccucuauaa(GalNAc)	usUfsauagaggguccAfcUfuuusgsgU	45
GAAUGAGUGCACAGCUA	UAGCUGUGCACUCAUUCUGUGU	gsasauGfAfGfugcacagcua(GalNAc)	usAfsgcugugcacucAfuUfcugsusgU	46
UCUUCUGUAUAACUCUA	UAGAGUUAUACAGAAGACAGAU	uscsuuCfUfGfuauaacucua(GalNAc)	usAfsgaguuauacagAfaGfacasgsaU	47
GCUGGGACAGUAUAUCA	UGAUAUACUGUCCCAGCAUUAU	gscsugGfGfAfcaguauauca(GalNAc)	usGfsauauacuguccCfaGfcaususaU	48
AGCACAAGAUUAUGGCA	UGCCAUAAUCUUGUGCUUGGAU	asgscaCfAfAfgauuauggca(GalNAc)	usGfsccauaaucuugUfgCfuugsgsaU	49
UGAUAGAUGGAAUACUA	UAGUAUUCCAUCUAUCAGACUU	usgsauAfGfAfuggaauacua(GalNAc)	usAfsguauuccaucuAfuCfagascsuU	50
UUACACAGGGAAGGUUA	UAACCUUCCCUGUGUAAAUAAU	ususacAfCfAfgggaagguua(GalNAc)	usAfsaccuucccuguGfuAfaausasaU	51
AUAAUGCUGGGACAGUA	UACUGUCCCAGCAUUAUUCACU	asusaaUfGfCfugggacagua(GalNAc)	usAfscugucccagcaUfuAfuucsascU	52
GUGAAUACUGGGUUCAA	UUGAACCCAGUAUUCACAAAAU	gsusgaAfUfAfcuggguucaa(GalNAc)	usUfsgaacccaguauUfcAfcaasasaU	53
AGGUUUAAGACUGUUCA	UGAACAGUCUUAAACCUUCCCU	asgsguUfUfAfagacuguuca(GalNAc)	usGfsaacagucuuaaAfcCfuucscscU	54
GUAUAUCCAGCCGAUCA	UGAUCGGCUGGAUAUACUGUCU	gsusauAfUfCfcagccgauca(GalNAc)	usGfsaucggcuggauAfuAfcugsuscU	55
AGGUCAACAUCCUAGGA	UCCUAGGAUGUUGACCUCAAAU	asgsguCfAfAfcauccuagga(GalNAc)	usCfscuaggauguugAfcCfucasasaU	56
GCUUUAUCUCAACCUGA	UCAGGUUGAGAUAAAGCUGCCU	gscsuuUfAfUfcucaaccuga(GalNAc)	usCfsagguugagauaAfaGfcugscscU	57

UGGGUUCACCAAAAAUA	UAUUUUUGGUGAACCCAGUAUU	usgsggUfUfCfaccaaaaaua(GalNAc)	usAfsuuuuuggugaaCfcCfagusasuU	58
GUCUGAUAGAUGGAAUA	UAUUCCAUCUAUCAGACUUCUU	gsuscuGfAfUfagauggaaua(GalNAc)	usAfsuuccaucuaucAfgAfcuuscsuU	59
AAUAAUGCUGGGACAGA	UCUGUCCCAGCAUUAUUCACCU	asasuaAfUfGfcugggacaga(GalNAc)	usCfsugucccagcauUfaUfucascscU	60
UCUGAUAGAUGGAAUAA	UUAUUCCAUCUAUCAGACUUCU	uscsugAfUfAfgauggaauaa(GalNAc)	usUfsauuccaucuauCfaGfacususcU	61
AAGCACAAGAUUAUGGA	UCCAUAAUCUUGUGCUUGGAUU	asasgcAfCfAfagauuaugga(GalNAc)	usCfscauaaucuuguGfcUfuggsasuU	62
GGGUUCACCAAAAAUCA	UGAUUUUUGGUGAACCCAGUAU	gsgsguUfCfAfccaaaaauca(GalNAc)	usGfsauuuuuggugaAfcCfcagsusaU	63
CAGAGGUCUGACAUCAA	UUGAUGUCAGACCUCUGUGAAU	csasgaGfGfUfcugacaucaa(GalNAc)	usUfsgaugucagaccUfcUfgugsasaU	64
GAAAGAUUUCCCUAGCA	UGCUAGGGAAAUCUUUCAAAUU	gsasaaGfAfUfuucccuagca(GalNAc)	usGfscuagggaaaucUfuUfcaasasuU	65
GAUUUCCCUAGCCUCUA	UAGAGGCUAGGGAAAUCUUUCU	gsasuuUfCfCfcuagccucua(GalNAc)	usAfsgaggcuagggaAfaUfcuususcU	66
UCAAGUAGCAUUCCAAA	UUUGGAAUGCUACUUGAACAGU	uscsaaGfUfAfgcauuccaaa(GalNAc)	usUfsuggaaugcuacUfuGfaacsasgU	67
AGAAUGAGUGCACAGCA	UGCUGUGCACUCAUUCUGUGUU	asgsaaUfGfAfgugcacagca(GalNAc)	usGfscugugcacucaUfuCfugusgsuU	68
UCAAGACUAAUCUUGUA	UACAAGAUUAGUCUUGAUGUAU	uscsaaGfAfCfuaaucuugua(GalNAc)	usAfscaagauuagucUfuGfaugsusaU	69
UCCACCAAAAGUGGACA	UGUCCACUUUUGGUGGACUUCU	uscscaCfCfAfaaaguggaca(GalNAc)	usGfsuccacuuuuggUfgGfacususcU	70
GUUCACCAAAAAUCCAA	UUGGAUUUUUGGUGAACCCAGU	gsusucAfCfCfaaaaauccaa(GalNAc)	usUfsggauuuuugguGfaAfcccsasgU	71
UUCCAAUCUGUAGCCAA	UUGGCUACAGAUUGGAAUGCUU	ususccAfAfUfcuguagccaa(GalNAc)	usUfsggcuacagauuGfgAfaugscsuU	72
AAGAUUUCCCUAGCCUA	UAGGCUAGGGAAAUCUUUCAAU	asasgaUfUfUfcccuagccua(GalNAc)	usAfsggcuagggaaaUfcUfuucsasaU	73
AUUACUGGAGCUGGGCA	UGCCCAGCUCCAGUAAUGAGAU	asusuaCfUfGfgagcugggca(GalNAc)	usGfscccagcuccagUfaAfugasgsaU	74
AUUAUGGCCUGUAUUGA	UCAAUACAGGCCAUAAUCUUGU	asusuaUfGfGfccuguauuga(GalNAc)	usCfsaauacaggccaUfaAfucususgU	75
CACAGGGAAGGUUUAAA	UUUAAACCUUCCCUGUGUAAAU	csascaGfGfGfaagguuuaaa(GalNAc)	usUfsuaaaccuucccUfgUfguasasaU	76
UGUUCAAGUAGCAUUCA	UGAAUGCUACUUGAACAGUCUU	usgsuuCfAfAfguagcauuca(GalNAc)	usGfsaaugcuacuugAfaCfaguscsuU	77

GAAGUCUGAUAGAUGGA	UCCAUCUAUCAGACUUCUUACU	gsasagUfCfUfgauagaugga(GalNAc)	usCfscaucuaucagaCfuUfcuusascU	78
UAAGAAGUCUGAUAGAA	UUCUAUCAGACUUCUUACGACU	usasagAfAfGfucugauagaa(GalNAc)	usUfscuaucagacuuCfuUfacgsascU	79
ACACAGGGAAGGUUUAA	UUAAACCUUCCCUGUGUAAAUU	ascsacAfGfGfgaagguuuaa(GalNAc)	usUfsaaaccuucccuGfuGfuaasasuU	80
GUGCAACUCUAUUCUGA	UCAGAAUAGAGUUGCACCGUUU	gsusgcAfAfCfucuauucuga(GalNAc)	usCfsagaauagaguuGfcAfccgsusuU	81
AUUUGAGGUCAACAUCA	UGAUGUUGACCUCAAAUGUCUU	asusuuGfAfGfgucaacauca(GalNAc)	usGfsauguugaccucAfaAfuguscsuU	82
GCACUUCUUCCAUCGAA	UUCGAUGGAAGAAGUGCUUUUU	gscsacUfUfCfuuccaucgaa(GalNAc)	usUfscgauggaagaaGfuGfcuususuU	83
UGAGGUCAACAUCCUAA	UUAGGAUGUUGACCUCAAAUGU	usgsagGfUfCfaacauccuaa(GalNAc)	usUfsaggauguugacCfuCfaaasusgU	84
GUAUGCAUGAUAAUGAA	UUCAUUAUCAUGCAUACAUCUU	gsusauGfCfAfugauaaugaa(GalNAc)	usUfscauuaucaugcAfuAfcauscsuU	85
AAGAAGUCUGAUAGAUA	UAUCUAUCAGACUUCUUACGAU	asasgaAfGfUfcugauagaua(GalNAc)	usAfsucuaucagacuUfcUfuacsgsaU	86
CAUGUAUUAUAGAAUGA	UCAUUCUAUAAUACAUGUGAAU	csasugUfAfUfuauagaauga(GalNAc)	usCfsauucuauaauaCfaUfgugsasaU	87
CUCUUGUAGUUAUAAAA	UUUUAUAACUACAAGAGGUUAU	csuscuUfGfUfaguuauaaaa(GalNAc)	usUfsuuauaacuacaAfgAfggususaU	88
AAGUCUGAUAGAUGGAA	UUCCAUCUAUCAGACUUCUUAU	asasguCfUfGfauagauggaa(GalNAc)	usUfsccaucuaucagAfcUfucususaU	89
CACAGAGGUCUGACAUA	UAUGUCAGACCUCUGUGAAAGU	csascaGfAfGfgucugacaua(GalNAc)	usAfsugucagaccucUfgUfgaasasgU	90
GGUGCAACUCUAUUCUA	UAGAAUAGAGUUGCACCGUUUU	gsgsugCfAfAfcucuauucua(GalNAc)	usAfsgaauagaguugCfaCfcgususuU	91
ACUGGGUUCACCAAAAA	UUUUUGGUGAACCCAGUAUUCU	ascsugGfGfUfucaccaaaaa(GalNAc)	usUfsuuuggugaaccCfaGfuaususcU	92
CAUAUUGUUCCAGCAAA	UUUGCUGGAACAAUAUGGGAUU	csasuaUfUfGfuuccagcaaa(GalNAc)	usUfsugcuggaacaaUfaUfgggsasuU	93
AUUCCAAUCUGUAGCCA	UGGCUACAGAUUGGAAUGCUAU	asususCfAfAfucuguagcca(GalNAc)	usGfsgcuacagauugGfaAfugcsusaU	94
GAAUACUUACCAAUAAA	UUUAUUGGUAAGUAUUCCAUCU	gsasauAfCfUfuaccaauaaa(GalNAc)	usUfsuauugguaaguAfuUfccasuscU	95
UGAAUACUGGGUUCACA	UGUGAACCCAGUAUUCACAAAU	usgsaaUfAfCfuggguucaca(GalNAc)	usGfsugaacccaguaUfuCfacasasaU	96
CCAUUUAAAGGUGGACA	UGUCCACCUUUAAAUGGAAAAU	cscsauUfUfAfaagguggaca(GalNAc)	usGfsuccaccuuuaaAfuGfgaasasaU	97

AAGUUUCUUCCUGAACA	UGUUCAGGAAGAAACUUCUGUU	asasguUfUfCfuuccugaaca(GalNAc)	usGfsuucaggaagaaAfcUfucusgsuU	98
AGAUUAUGGCCUGUAUA	UAUACAGGCCAUAAUCUUGUGU	asgsauUfAfUfggccuguaua(GalNAc)	usAfsuacaggccauaAfuCfuugsusgU	99
ACUUGGAGUCGUUGGUA	UACCAACGACUCCAAGUAGGAU	ascsuuGfGfAfgucguuggua(GalNAc)	usAfsccaacgacuccAfaGfuagsgsaU	100
UACUGGGUUCACCAAAA	UUUUGGUGAACCCAGUAUUCAU	usascuGfGfGfuucaccaaaa(GalNAc)	usUfsuuggugaacccAfgUfauuscsaU	101
UAAAGCUAACACAGGAA	UUCCUGUGUUAGCUUUAAUUUU	usasaaGfCfUfaacacaggaa(GalNAc)	usUfsccuguguuagcUfuUfaaususuU	102
GCUCAAAAAUUAAAGCA	UGCUUUAAUUUUUGAGCCUAAU	gscsucAfAfAfaauuaaagca(GalNAc)	usGfscuuuaauuuuuGfaGfccusasaU	103
ACAUGUAUUAUAGAAUA	UAUUCUAUAAUACAUGUGAAAU	ascsauGfUfAfuuauagaaua(GalNAc)	usAfsuucuauaauacAfuGfugasasaU	104
CCAUAUUGUUCCAGCAA	UUGCUGGAACAAUAUGGGAUGU	cscsauAfUfUfguuccagcaa(GalNAc)	usUfsgcuggaacaauAfuGfggasusgU	105
UCAUGGCCACAUCGUCA	UGACGAUGUGGCCAUGAUUUCU	uscsauGfGfCfcacaucguca(GalNAc)	usGfsacgauguggccAfuGfauususcU	106
AUUUCCCUAGCCUCUUA	UAAGAGGCUAGGGAAAUCUUUU	asususuCfCfCfuagccucuua(GalNAc)	usAfsagaggcuagggAfaAfucususuU	107
UAUAUCCAGCCGAUCUA	UAGAUCGGCUGGAUAUACUGUU	usasuaUfCfCfagccgaucua(GalNAc)	usAfsgaucggcuggaUfaUfacusgsuU	108
CAAGACUAAUCUUGUUA	UAACAAGAUUAGUCUUGAUGUU	csasagAfCfUfaaucuuguua(GalNAc)	usAfsacaagauuaguCfuUfgausgsuU	109
CAAGGACUGAACCAGAA	UUCUGGUUCAGUCCUUGUGUAU	csasagGfAfCfugaaccagaa(GalNAc)	usUfscugguucagucCfuUfgugsusaU	110
CCACCAAAAGUGGACCA	UGGUCCACUUUUGGUGGACUUU	cscsacCfAfAfaaguggacca(GalNAc)	usGfsguccacuuuugGfuGfgacsusuU	111
GAUUAUGGCCUGUAUUA	UAAUACAGGCCAUAAUCUUGUU	gsasuuAfUfGfgccuguauua(GalNAc)	usAfsauacaggccauAfaUfcuusgsuU	112
GAAUACUGGGUUCACCA	UGGUGAACCCAGUAUUCACAAU	gsasauAfCfUfggguucacca(GalNAc)	usGfsgugaacccaguAfuUfcacsasaU	113
CACCAAAAGUGGACCCA	UGGGUCCACUUUUGGUGGACUU	csasccAfAfAfaguggaccca(GalNAc)	usGfsgguccacuuuuGfgUfggascsuU	114
UACUUACCAAUAAGAAA	UUUCUUAUUGGUAAGUAUUCCU	usascuUfAfCfcaauaagaaa(GalNAc)	usUfsucuuauugguaAfgUfauuscscU	115
AGAUUAAUUACCUGUCA	UGACAGGUAAUUAAUCUUGUUU	asgsauUfAfAfuuaccuguca(GalNAc)	usGfsacagguaauuaAfuCfuugsusuU	116
CGGUGCAACUCUAUUCA	UGAAUAGAGUUGCACCGUUUUU	csgsguGfCfAfacucuauuca(GalNAc)	usGfsaauagaguugcAfcCfguususuU	117

ACGGUGCAACUCUAUUA	UAAUAGAGUUGCACCGUUUUGU	ascsggUfGfCfaacucuauua(GalNAc)	usAfsauagaguugcaCfcGfuuusugU	118
AGUAGCAUUCCAAUCUA	UAGAUUGGAAUGCUACUUGAAU	asgsuaGfCfAfuuccaaucua(GalNAc)	usAfsgauuggaaugcUfaCfuugsasaU	119

Figure 2

		siRNA activity (dual dose) in PHH			
		10nM		0.1nM	
		MV remaining		MV remaining	
Corresponding position of AS strand position 2 in NM_178135.4	siRNA	Remaining mRNA [%]	SD	Remaining mRNA [%]	SD
1747	1	24.7	6.8	24.9	2.9
2210	2	34.0	13.5	26.6	4.1
1744	3	30.0	8.7	26.7	4.8
2209	4	26.6	9.7	26.9	5.3
1749	5	29.7	8.3	27.2	5.0
1588	6	29.1	10.4	27.6	1.0
1587	7	27.8	8.4	27.8	1.5
2213	8	37.1	12.4	27.9	4.2
2214	9	29.5	12.0	29.3	5.2
2211	10	31.0	8.4	30.0	7.4
2270	11	38.0	10.0	30.6	11.5
449	12	52.4	15.5	31.3	5.6
1585	13	30.9	7.5	31.5	7.0
2262	14	31.4	7.8	31.6	7.4
926	15	22.0	2.3	32.1	3.5
2271	16	41.4	7.6	32.8	10.9
895	17	26.5	4.9	32.8	11.3
1754	18	39.0	7.8	32.9	7.3
924	19	18.4	3.3	33.0	3.0
448	20	58.5	10.9	33.9	3.3
672	21	56.0	22.5	34.5	6.8
507	22	46.8	5.1	34.5	7.0
897	23	31.2	0.6	34.7	2.5
740	24	40.5	12.6	34.8	7.5
2207	25	41.1	14.8	34.9	8.9
511	26	42.9	9.9	35.1	10.3
2272	27	30.9	7.7	35.6	9.7

712	28	21.5	4.8	36.1	7.9
1524	29	32.6	10.7	36.1	10.0
539	30	68.6	14.4	36.3	10.8
1527	31	37.2	16.3	36.6	9.7
1790	32	45.5	10.8	36.8	6.8
543	33	59.8	5.9	38.0	11.5
893	34	46.9	7.0	38.3	8.8
2368	35	29.7	4.2	38.4	15.3
1533	36	42.3	17.5	38.5	12.5
711	37	27.1	6.0	38.8	14.0
1339	38	34.6	14.7	39.8	13.5
568	39	52.8	5.1	39.9	12.3
927	40	19.9	7.0	40.0	5.2
946	41	32.4	4.0	40.1	8.7
1525	42	33.9	14.1	40.1	14.8
1326	43	37.1	8.5	40.2	4.7
2247	44	49.5	14.7	40.6	14.9
1584	45	25.9	5.2	40.8	5.3
1398	46	32.3	6.4	41.1	6.2
1556	47	33.7	15.4	41.1	10.9
441	48	90.2	26.8	41.2	13.4
768	49	26.7	3.3	41.3	14.7
817	50	33.4	12.7	41.3	11.1
1321	51	35.0	1.8	41.5	5.7
436	52	62.7	15.0	41.9	12.1
741	53	41.5	6.7	42.3	7.6
1332	54	39.6	7.8	42.3	4.0
450	55	73.1	21.5	42.6	6.2
505	56	68.0	6.9	42.8	8.0
1437	57	36.7	9.8	43.2	10.6
749	58	34.1	4.0	43.3	10.7
814	59	30.2	11.4	43.7	14.6
435	60	72.8	12.7	43.8	13.5
815	61	51.7	16.0	43.8	11.5
767	62	40.5	5.2	44.1	11.9
750	63	28.9	3.6	44.5	11.5
668	64	39.6	16.9	44.5	9.5
1477	65	40.4	11.4	44.6	14.5
1481	66	31.0	6.7	44.6	15.2
1346	67	37.4	12.4	44.6	1.7
1397	68	37.8	6.6	44.8	7.3
2215	69	40.8	17.3	44.8	4.4
1576	70	46.1	6.7	45.3	14.3
752	71	31.3	2.3	45.6	11.7
1356	72	34.4	8.2	45.9	9.0
1479	73	30.1	7.0	46.2	12.9

201	74	85.5	24.8	46.4	9.4
776	75	78.1	10.7	46.5	22.2
1324	76	29.3	6.6	47.0	20.0
1343	77	35.6	13.1	47.0	10.3
811	78	46.6	16.5	47.4	14.6
808	79	55.5	21.6	47.8	5.4
1323	80	28.9	1.6	48.5	10.8
1520	81	42.5	9.2	48.8	11.7
500	82	128.5	25.8	48.9	28.2
540	83	65.2	10.7	49.5	1.5
503	84	87.9	5.8	49.9	11.9
1007	85	18.1	4.8	50.3	8.9
809	86	23.1	7.7	50.8	15.0
2246	87	63.8	15.0	51.6	18.5
2371	88	39.5	9.6	53.1	12.5
812	89	45.0	20.6	53.1	13.2
666	90	48.9	11.1	53.3	15.5
1519	91	34.5	9.3	54.1	10.3
747	92	48.9	10.8	54.6	19.7
631	93	52.7	16.1	55.3	20.0
1355	94	43.4	11.4	55.4	16.1
826	95	43.2	10.6	55.6	14.4
742	96	58.0	15.1	56.6	2.5
1265	97	48.1	2.1	57.5	16.5
891	98	49.6	10.0	57.6	8.5
774	99	28.0	5.1	57.8	10.4
133	100	76.3	23.8	57.9	22.8
746	101	37.2	4.9	58.0	19.4
1767	102	82.9	18.0	58.4	4.7
1757	103	86.3	11.6	59.7	1.3
2245	104	72.2	16.4	59.8	4.6
630	105	102.1	17.0	62.1	4.4
569	106	53.4	3.9	62.4	9.5
1482	107	33.3	5.9	62.5	15.2
451	108	53.9	14.1	62.9	10.9
2216	109	39.1	15.8	65.5	6.7
43	110	146.3	17.4	68.2	19.4
1577	111	73.8	0.3	69.6	14.3
775	112	52.8	14.2	72.6	6.5
743	113	96.6	29.6	73.0	18.5
1578	114	50.3	17.5	81.8	2.4
829	115	44.2	8.2	84.5	12.3
1126	116	47.3	6.9	86.9	24.9
1518	117	42.8	15.7	87.9	14.8
1517	118	45.9	7.8	88.8	19.3
1349	119	57.6	15.4	92.8	3.4

FIGURE 3

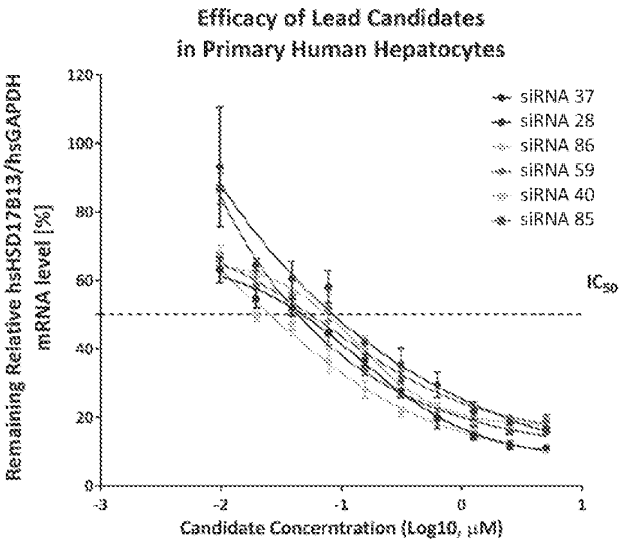
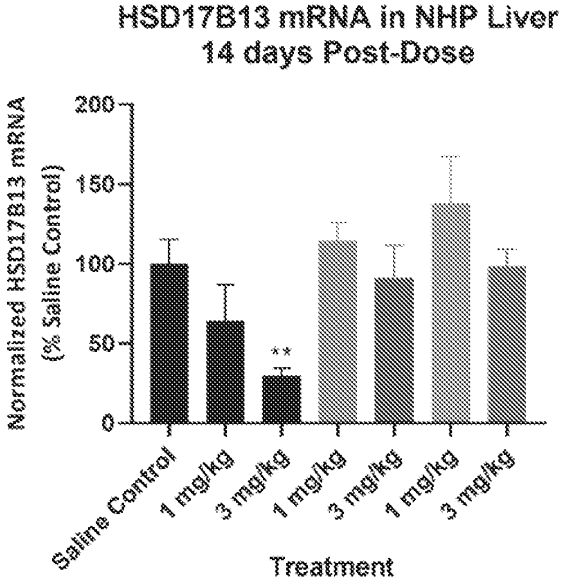


FIGURE 4



**p<0.01, One-way ANOVA with Tukey multiple comparisons test performed on log-transformed data; mean±SEM

FIGURE 5

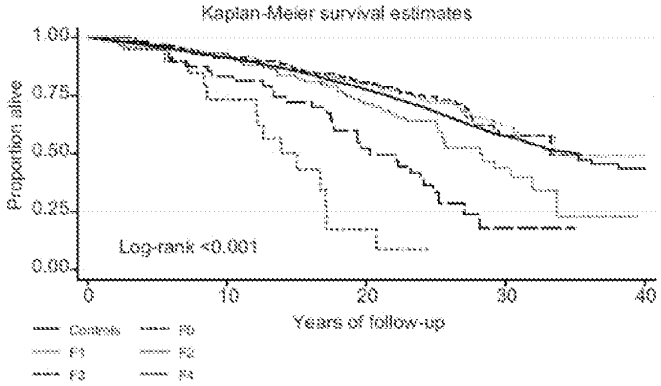
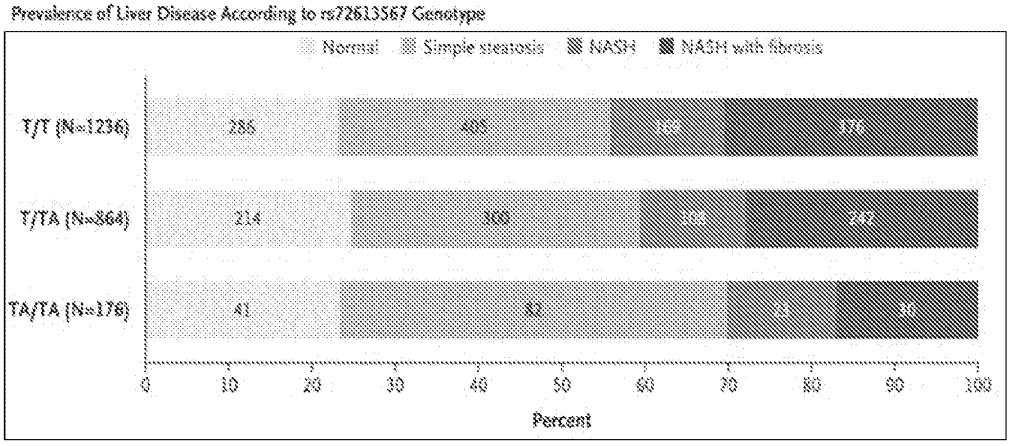


FIGURE 6



Abul-Husn, et al. NEJM. 2018

FIGURE 7

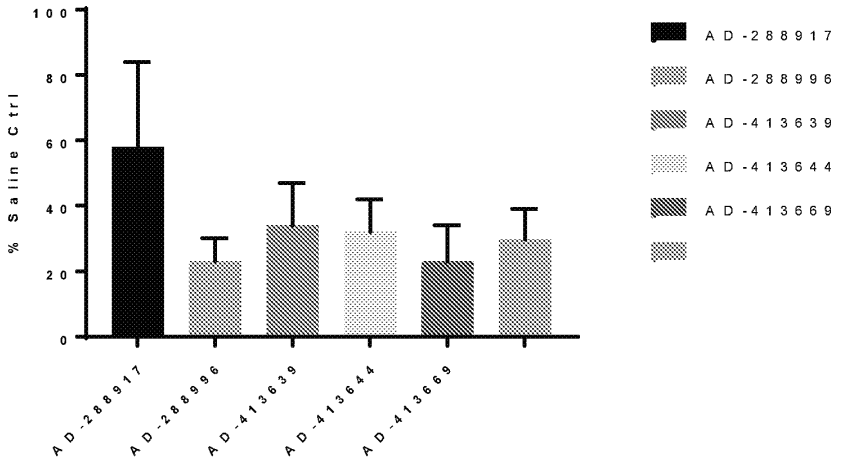

100
80
60
40
20
0
% Saline Ctrl
AD-288917
AD-288996
AD-413639
AD-413644
AD-413669
AD-288917
AD-288996
AD-413639
AD-413644
AD-413669

FIGURE 8

Dosing Regimen	Clinical Signs Study Duration	Terminal Clinical Chemistry Study Day 2-3	MTD (AUC) in mM	Presence of Human Variant	HHP Analysis Study Candidate
10mg/kg SD	Body weight plateau	mild elevation of liver enzymes	37.6	Y	
60mg/kg SD	Body weight decrease	strong elevation of liver enzymes			
30mg/kg q2d x 6	Body weight decrease	strong elevation of liver enzymes			
20mg/kg SD	No findings	No findings	117.4	Y	Y
60mg/kg SD	No findings	No findings			
30mg/kg q2d x 6	Body weight decrease	Mild elevation of liver enzymes			
20mg/kg SD	No findings	No findings	25.5	Not for Variant C	Y
60mg/kg SD	No findings	No findings			
30mg/kg q2d x 6	Body weight plateau	No findings			
20mg/kg SD	No findings	No findings	53.1	Not for Variant C	Y
60mg/kg SD	No findings	Mild elevation in bilirubin			
30mg/kg q2d x 6	No findings	Elevated bilirubin			
20mg/kg SD	No findings	No findings	36.5	Not for Variant F	
60mg/kg SD	No findings	No findings			
30mg/kg q2d x 6	Body weight plateau	No findings			
20mg/kg SD	No findings	No findings	62.4	Not for Variant F	
60mg/kg SD	Body weight decrease	strong elevation of liver enzymes			
30mg/kg q2d x 6	Body weight decrease	strong elevation of liver enzymes			

WO 2021/113820 PCT/US2020/063617

FIGURE 9A

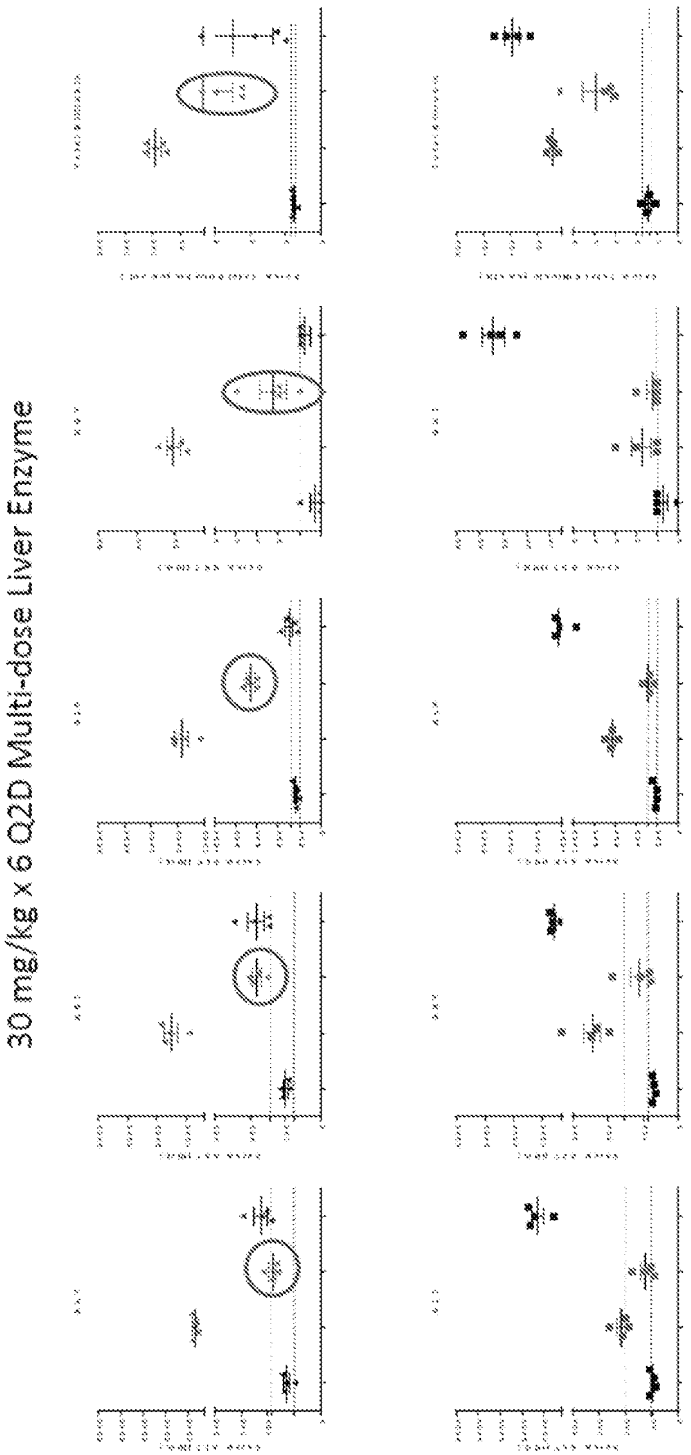


FIGURE 9B

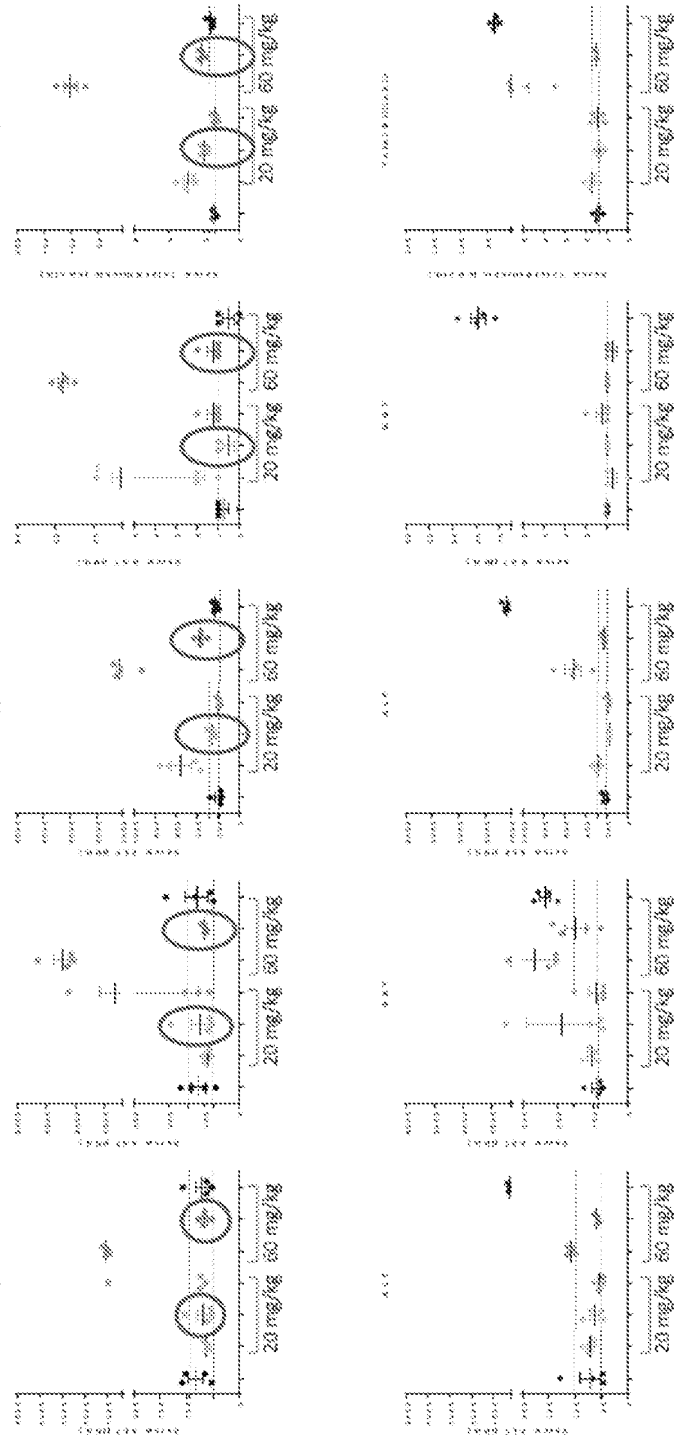
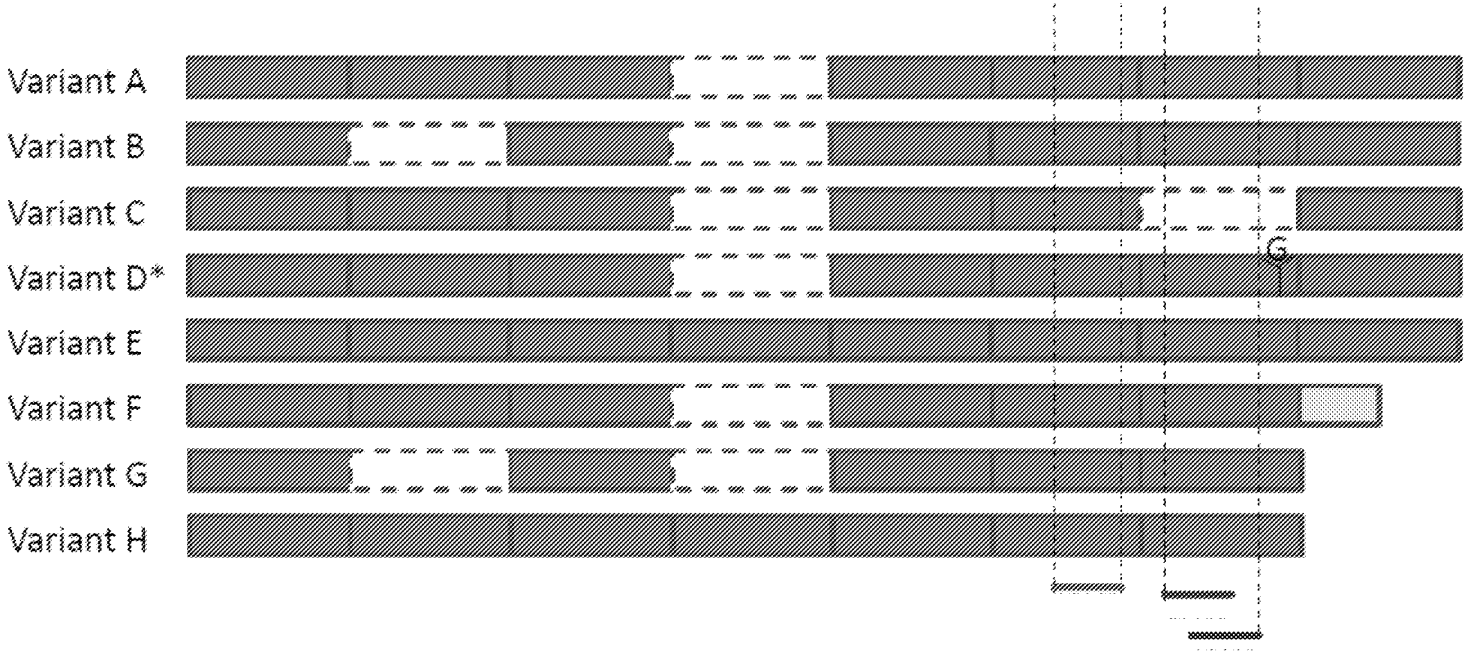


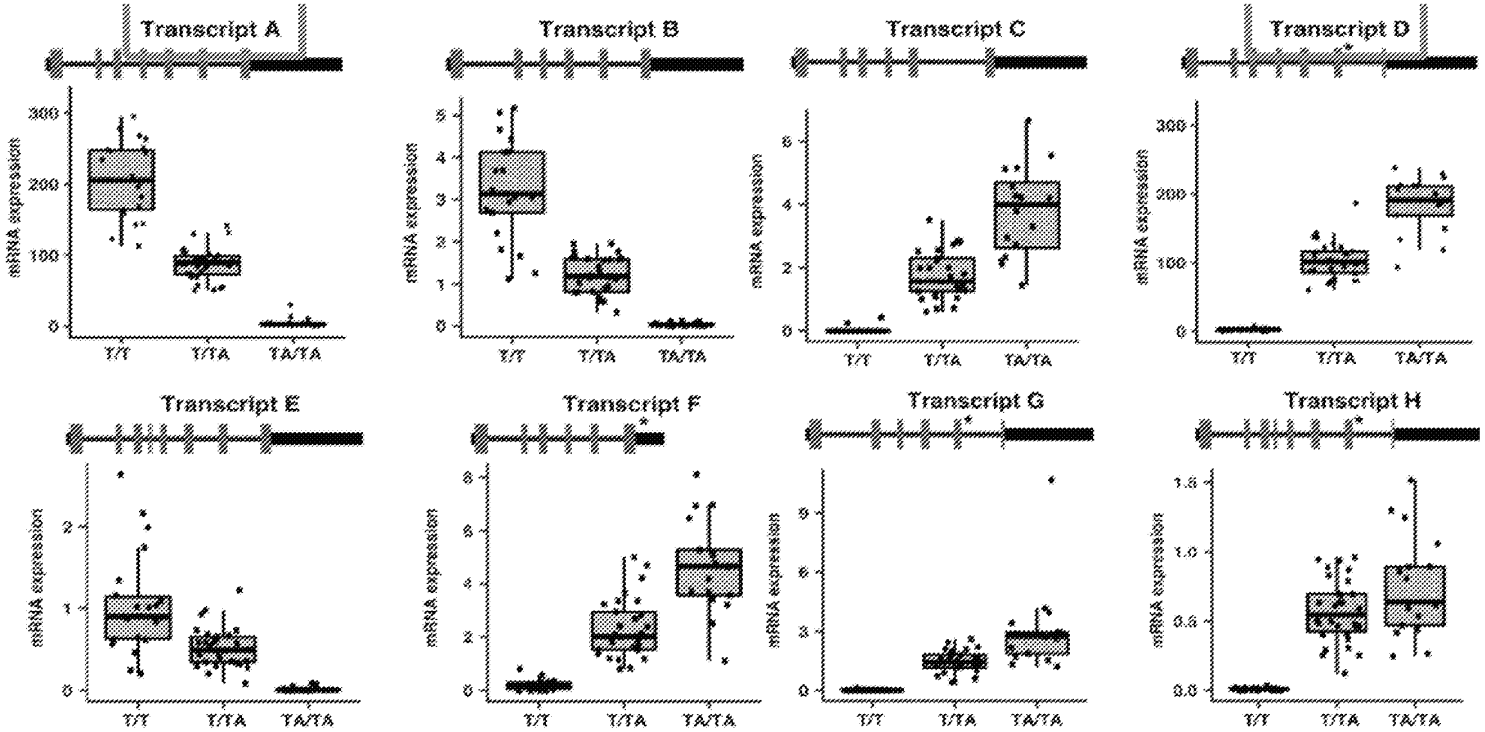
FIGURE 10A



* Variant D is the LoF truncated mutant protein that is caused by rs72613567:TA SNP and associated with milder disease in NASH – mRNA is almost identical to variant A (wt) with insertion of a single "G" that leads to early termination of translation

WO 2021/113820 PCT/US2020/063617

FIGURE 10B



- In patients without rs72613567:TA SNP, variant A is the main transcript
- In patients with rs72613567:TA SNP, variant D is the main transcript
- Other variants only account for <10% of the total transcripts – not clear if this is true in NHP (only 2 variant reported)

WO 2021/113820 PCT/US2020/063617