(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53806	AD-56983.2	0.74	0.89	1.14	1.16	0.10	0.06	0.02
AD-53806	AD-56983.3	0.91	1.05	1.02	1.04	0.09	0.10	0.08
AD-53806	AD-56983.4	0.40	0.57	0.83	1.05	0.03	0.02	0.08
AD-53806	AD-56983.5	0.33	0.51	0.83	0.90	0.03	0.04	0.03
AD-53806	AD-56977.3	0.44	0.49	0.62	0.95	0.17	0.16	0.06
AD-53806	AD-56977.1	0.27	0.58	0.81	0.88	0.06	0.07	0.08
AD-53806	AD-56977.2	0.41	0.60	0.81	0.90	0.01	0.07	0.12
AD-53806	AD-56976.1	0.40	0.64	0.85	0.90	0.14	0.21	0.01
AD-53806	AD-56976.2	0.37	0.47	0.70	1.01	0.09	0.10	0.13
AD-53806	AD-56980.1	0.47	0.54	0.83	0.97	0.12	0.02	0.14
AD-53806	AD-56980.2	0.44	0.55	0.81	1.08	0.15	0.11	0.08
AD-53806	AD-56984.1	0.41	0.63	0.81	1.08	0.04	0.07	0.14
AD-53806	AD-56984.2	0.32	0.58	0.86	1.04	0.02	0.17	0.07
AD-53806	AD-56987.1	0.37	0.63	0.82	1.11	0.08	0.08	0.05
AD-53806	AD-56987.2	0.33	0.59	0.79	1.02	0.05	0.05	0.13
AD-53806	AD-56991.1	0.36	0.57	0.73	1.08	0.01	0.07	0.18
AD-53806	AD-56993.1	0.41	0.54	0.75	0.99	0.12	0.09	0.06
AD-53806	AD-56995.1	0.35	0.45	0.67	1.00	0.07	0.02	0.12
AD-53806	AD-56978.1	0.35	0.67	0.88	0.91	0.04	0.22	0.05
AD-53806	AD-56978.2	0.47	0.55	0.78	1.12	0.03	0.01	0.07
AD-53806	AD-56981.1	0.45	0.65	0.86	1.08	0.01	0.16	0.15
AD-53806	AD-56985.1	0.53	0.61	1.08	1.14	0.02	0.09	0.07
AD-53806	AD-56988.1	0.62	0.81	0.91	1.13	0.01	0.05	0.20
AD-53806	AD-56988.2	0.76	0.94	0.85	1.14	0.17	0.10	0.11
AD-53806	AD-56988.3	0.55	0.79	0.86	1.19	0.04	0.05	0.16
AD-53806	AD-56982.1	0.40	0.65	0.84	1.07	0.04	0.10	0.09
AD-53806	AD-56982.2	0.38	0.50	0.70	1.01	0.03	0.03	0.08
AD-53806	AD-56986.1	0.45	0.57	0.80	1.12	0.02	0.11	0.15
AD-53806	AD-56986.2	0.49	0.59	0.79	1.04	0.01	0.05	0.17
AD-53806	AD-56989.1	0.69	0.84	0.95	1.12	0.08	0.06	0.12
AD-53806	AD-56990.1	0.49	0.56	0.79	1.08	0.03	0.02	0.13
AD-53806	AD-56992.1	0.61	0.70	0.90	1.14	0.01	0.04	0.14
AD-53806	AD-56992.2	0.48	0.63	0.87	0.99	0.05	0.10	0.07
AD-53806	AD-56994.1	0.88	0.89	0.97	1.11	0.02	0.06	0.13
AD-53806	AD-56994.2	0.34	0.42	0.73	0.98	0.01	0.05	0.05
AD-53806	AD-56996.1	0.50	0.59	0.77	0.95	0.07	0.12	0.10
AD-53806	AD-57001.1	0.44	0.54	0.77	1.08	0.01	0.05	0.12

(continued)

Parent duplex	Duplex ID	200nM Avg	20nM Avg	2nM Avg	0.2nM-384	200nM SD	20nM SD	2nM SD
AD-53806	AD-57007.1	0.62	0.68	0.91	1.11	0.04	0.02	0.19
AD-53806	AD-57013.1	0.65	0.78	0.94	1.17	0.05	0.04	0.22
AD-53806	AD-57019.1	0.57	0.74	0.87	1.14	0.01	0.09	0.13
AD-53806	AD-57022.1	0.46	0.48	0.72	0.98	0.14	0.01	0.17
AD-53806	AD-57025.1	0.37	0.47	0.68	0.92	0.04	0.11	0.06
AD-53806	AD-56997.1	0.41	0.56	0.77	0.88	0.00	0.10	0.09
AD-53806	AD-57002.1	0.46	0.58	0.81	1.04	0.03	0.03	0.08
AD-53806	AD-57008.1	0.68	0.75	0.91	1.13	0.02	0.03	0.15
AD-53806	AD-57014.1	0.80	0.82	0.99	1.17	0.02	0.01	0.12
AD-53806	AD-57020.1	0.51	0.53	0.81	1.07	0.17	0.03	0.07
AD-53806	AD-57020.2	0.37	0.46	0.68	1.02	0.04	0.07	0.13
AD-53806	AD-57026.1	0.34	0.51	0.68	0.97	0.01	0.08	0.06
AD-53806	AD-57003.1	0.76	0.90	0.94	1.11	0.02	0.16	0.11
AD-53806	AD-57009.1	0.81	0.88	0.93	0.98	0.01	0.03	0.10
AD-53806	AD-57015.1	0.72	0.92	0.90	1.04	0.01	0.05	0.15
AD-53806	AD-57023.1	0.41	0.50	0.75	1.00	0.08	0.07	0.06
AD-53806	AD-57027.1	0.38	0.46	0.68	0.93	0.11	0.00	0.07
AD-53806	AD-56998.1	0.45	0.57	0.94	0.98	0.01	0.06	0.11
AD-53806	AD-57004.1	0.39	0.61	0.80	1.13	0.03	0.04	0.13
AD-53806	AD-57010.1	0.43	0.64	0.81	1.00	0.01	0.07	0.15
AD-53806	AD-57016.1	0.44	0.71	0.80	0.97	0.01	0.25	0.05
AD-53806	AD-56999.2	0.49	0.60	0.69	1.04	0.04	0.02	0.16
AD-53806	AD-56999.1	0.39	0.55	0.68	0.96	0.01	0.09	0.10
AD-53806	AD-57021.1	0.40	0.58	0.71	1.02	0.03	0.03	0.11
AD-53806	AD-57024.1	0.41	0.49	0.68	1.02	0.14	0.00	0.10
AD-53806	AD-57005.1	0.45	0.56	0.87	1.06	0.03	0.03	0.20
AD-53806	AD-57011.1	0.53	0.63	0.92	1.02	0.02	0.07	0.10
AD-53806	AD-57017.1	0.48	0.60	0.81	1.07	0.00	0.01	0.12
AD-53806	AD-57000.2	0.50	0.60	0.74	0.93	0.04	0.01	0.02
AD-53806	AD-57000.3	0.54	0.49	0.72	0.97	0.22	0.08	0.00
AD-53806	AD-57000.1	0.70	0.76	0.80	0.95	0.02	0.05	0.04
AD-53806	AD-57006.2	0.48	0.75	0.76	0.94	0.00	0.31	0.12
AD-53806	AD-57006.3	0.45	0.57	0.71	0.98	0.08	0.09	0.12
AD-53806	AD-57006.1	0.64	0.76	0.84	0.97	0.00	0.11	0.10
AD-53806	AD-57012.1	0.53	0.83	0.79	0.93	0.04	0.42	0.02
AD-53806	AD-57018.1	0.67	0.73	0.72	0.93	0.07	0.04	0.03

[0439] siRNAs with a variety of chemical modifications based on the parent sequences of AD-53815 and AD-53806 were also screened for *in vitro* efficacy by transfection in Hep3B cells at 10nM and 0.1nM. The results of this structure-activity relationship screen are shown in Table 7, and are expressed as the average fraction message remaining relative to control +/- SD.

Table 7. Efficacy screens for lead optimization of AD-53815 and AD-53806 by transfection in a human cells.

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-53815.5	0.14	0.05	0.24	ND
AD-53815	AD-53815.4	0.18	0.07	0.38	ND
AD-53815	AD-56633.1	0.18	0.10	0.24	ND
AD-53815	AD-56617.1	0.13	0.06	0.25	ND
AD-53815	AD-56623.1	0.14	0.05	0.24	ND
AD-53815	AD-56629.1	0.14	0.02	0.17	ND
AD-53815	AD-56635.1	0.12	0.02	0.22	ND
AD-53815	AD-56641.1	0.15	0.01	0.16	ND
AD-53815	AD-56625.1	0.12	0.03	0.29	ND
AD-53815	AD-56631.1	0.13	0.01	0.20	ND
AD-53815	AD-56637.1	0.22	0.14	0.16	ND
AD-53815	AD-56643.1	0.18	0.08	0.16	ND
AD-53815	AD-56649.1	0.16	0.00	0.19	ND
AD-53815	AD-56655.1	0.24	0.11	0.24	ND
AD-53815	AD-56615.1	0.15	0.00	0.32	ND
AD-53815	AD-56621.1	0.20	0.07	0.41	ND
AD-53815	AD-56627.1	0.17	0.04	0.31	ND
AD-53815	AD-56639.1	0.19	0.08	0.24	ND
AD-53815	AD-56645.1	0.19	0.09	0.27	ND
AD-53815	AD-56651.1	0.29	0.09	0.68	ND
AD-53815	AD-56610.1	0.21	0.11	0.23	ND
AD-53815	AD-56616.1	0.16	0.04	0.29	ND
AD-53815	AD-56622.1	0.18	0.07	0.36	ND
AD-53815	AD-56628.1	0.28	0.07	0.60	ND
AD-53815	AD-56634.1	0.16	0.04	0.29	ND
AD-53815	AD-56640.1	0.21	0.09	0.26	ND
AD-53815	AD-56646.1	0.27	0.21	0.37	ND
AD-53815	AD-56652.1	0.26	0.08	0.29	ND
AD-53815	AD-56611.1	0.35	0.11	0.96	ND
AD-53815	AD-56647.1	0.17	0.09	0.13	ND
AD-53815	AD-56653.1	0.17	0.09	0.28	ND
AD-53815	AD-56612.1	0.17	0.07	0.24	ND
AD-53815	AD-56618.1	0.14	0.00	0.26	ND
AD-53815	AD-56624.1	0.15	0.02	0.27	ND
AD-53815	AD-56630.1	0.13	0.01	0.24	ND

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-56636.1	0.17	0.08	0.22	ND
AD-53815	AD-56642.1	0.12	0.03	0.13	ND
AD-53815	AD-56648.1	0.15	0.05	0.21	ND
AD-53815	AD-56654.1	0.22	0.10	0.24	ND
AD-53815	AD-56613.1	0.17	0.07	0.40	ND
AD-53815	AD-56619.1	0.21	0.12	0.30	ND
AD-53815	AD-56614.1	0.12	0.01	0.23	ND
AD-53815	AD-56620.1	0.12	0.02	0.15	ND
AD-53815	AD-56626.1	0.14	0.03	0.20	ND
AD-53815	AD-56632.1	0.12	0.02	0.21	ND
AD-53815	AD-56638.1	0.15	0.10	0.23	ND
AD-53815	AD-56644.1	0.23	0.11	0.17	ND
AD-53815	AD-56650.1	0.13	0.03	0.20	ND
AD-53815	AD-56656.1	0.26	0.03	0.27	ND
AD-53815	AD-56662.1	0.13	0.06	0.18	ND
AD-53815	AD-56668.1	0.19	0.05	0.20	ND
AD-53815	AD-56673.1	0.18	0.05	0.21	ND
AD-53815	AD-56678.1	0.17	0.00	0.20	ND
AD-53815	AD-56683.1	0.29	0.22	0.27	ND
AD-53815	AD-56688.1	0.19	0.02	0.18	ND
AD-53815	AD-56657.1	0.18	0.14	0.34	ND
AD-53815	AD-56663.1	0.11	0.04	0.18	ND
AD-53815	AD-56669.1	0.11	0.02	0.31	ND
AD-53815	AD-56674.1	0.14	0.00	0.21	ND
AD-53815	AD-56679.1	0.14	0.05	0.19	ND
AD-53815	AD-56684.1	0.14	0.03	0.19	ND
AD-53815	AD-56689.1	0.18	0.09	0.18	ND
AD-53815	AD-56693.1	0.19	0.11	0.21	ND
AD-53815	AD-56658.1	0.19	0.13	0.30	ND
AD-53815	AD-56664.1	0.15	0.07	0.20	ND
AD-53815	AD-56670.1	0.18	0.10	0.26	ND
AD-53815	AD-56680.1	0.27	0.05	0.31	ND
AD-53815	AD-56685.1	0.14	0.02	0.28	ND
AD-53815	AD-56690.1	0.10	0.03	0.18	ND
AD-53815	AD-56694.1	0.15	0.06	0.17	ND
AD-53815	AD-56659.1	0.16	0.04	0.27	ND
AD-53815	AD-56665.1	0.14	0.06	0.26	ND
AD-53815	AD-56671.1	0.11	0.01	0.29	ND

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53815	AD-56676.1	0.14	0.06	0.20	ND
AD-53815	AD-56681.1	0.15	0.03	0.30	ND
AD-53815	AD-56686.1	0.15	0.03	0.26	ND
AD-53815	AD-56691.1	0.11	0.02	0.16	ND
AD-53815	AD-56695.1	0.14	0.06	0.24	ND
AD-53815	AD-56660.1	0.10	0.03	0.37	ND
AD-53815	AD-56666.1	0.18	0.13	0.22	ND
AD-53815	AD-56672.1	0.14	0.02	0.35	ND
AD-53815	AD-56677.1	0.15	0.04	0.23	ND
AD-53815	AD-56682.1	0.14	0.06	0.28	ND
AD-53815	AD-56687.1	0.24	0.01	0.53	ND
AD-53815	AD-56692.1	0.09	0.01	0.36	ND
AD-53815	AD-56696.1	0.16	0.09	0.26	ND
AD-53815	AD-56661.1	0.21	0.15	0.48	ND
AD-53815	AD-56667.1	0.22	0.16	0.26	ND
AD-53806	AD-53806.11	0.19	0.05	0.25	0.06
AD-53806	AD-53806.13	0.21	0.07	0.21	0.16
AD-53806	AD-53806.12	0.21	0.08	0.21	0.02
AD-53806	AD-53806.5	0.22	0.01	0.29	0.06
AD-53806	AD-53806.6	0.24	0.07	0.33	0.12
AD-53806	AD-53806.7	0.19	0.02	0.24	0.11
AD-53806	AD-53806.8	0.20	0.01	0.23	0.05
AD-53806	AD-53806.9	0.22	0.01	0.19	0.06
AD-53806	AD-53806.10	0.17	0.01	0.21	0.07
AD-53806	AD-56979.1	0.18	0.00	0.29	0.14
AD-53806	AD-56979.2	0.24	0.11	0.24	0.12
AD-53806	AD-56975.3	0.26	0.09	0.28	0.18
AD-53806	AD-56975.4	0.35	0.02	0.50	0.23
AD-53806	AD-56975.5	0.17	0.01	0.21	0.18
AD-53806	AD-56975.1	0.24	0.09	0.32	0.12
AD-53806	AD-56975.2	0.19	0.04	0.16	0.02
AD-53806	AD-56983.1	0.17	0.01	0.32	0.18
AD-53806	AD-56983.2	0.28	0.07	0.63	0.15
AD-53806	AD-56983.3	1.22	0.61	0.83	0.02
AD-53806	AD-56983.4	0.25	0.10	0.24	0.10
AD-53806	AD-56983.5	0.17	0.01	0.26	0.15
AD-53806	AD-56977.3	0.31	0.11	0.28	0.23
AD-53806	AD-56977.1	0.22	0.04	0.34	0.12

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53806	AD-56977.2	0.22	0.05	0.29	0.16
AD-53806	AD-56976.1	0.21	0.09	0.34	0.20
AD-53806	AD-56976.2	0.17	0.03	0.25	0.04
AD-53806	AD-56980.1	0.22	0.04	0.20	0.02
AD-53806	AD-56980.2	0.19	0.01	0.20	0.06
AD-53806	AD-56984.1	0.24	0.11	0.22	0.10
AD-53806	AD-56984.2	0.19	0.01	0.21	0.10
AD-53806	AD-56987.1	0.19	0.05	0.29	0.19
AD-53806	AD-56987.2	0.24	0.03	0.24	0.09
AD-53806	AD-56991.1	0.17	0.01	0.17	0.08
AD-53806	AD-56993.1	0.14	0.09	0.22	0.06
AD-53806	AD-56995.1	0.19	0.07	0.27	0.13
AD-53806	AD-56978.1	0.27	0.12	0.36	0.12
AD-53806	AD-56978.2	0.24	0.03	0.20	0.01
AD-53806	AD-56981.1	0.22	0.03	0.28	0.17
AD-53806	AD-56985.1	0.21	0.00	0.28	0.04
AD-53806	AD-56988.1	0.20	0.02	0.24	0.02
AD-53806	AD-56988.2	0.20	0.03	0.27	0.13
AD-53806	AD-56988.3	0.23	0.03	0.27	0.01
AD-53806	AD-56982.1	0.23	0.06	0.24	0.00
AD-53806	AD-56982.2	0.21	0.06	0.18	0.07
AD-53806	AD-56986.1	0.23	0.05	0.20	0.06
AD-53806	AD-56986.2	0.24	0.04	0.25	0.13
AD-53806	AD-56989.1	0.31	0.02	0.43	0.00
AD-53806	AD-56990.1	0.27	0.00	0.28	0.10
AD-53806	AD-56992.1	0.27	0.06	0.31	0.01
AD-53806	AD-56992.2	0.22	0.10	0.30	0.14
AD-53806	AD-56994.1	0.97	0.05	0.85	0.09
AD-53806	AD-56994.2	0.22	0.09	0.26	0.01
AD-53806	AD-56996.1	0.18	0.04	0.31	0.08
AD-53806	AD-57001.1	0.24	0.09	0.23	0.08
AD-53806	AD-57007.1	0.25	0.01	0.27	0.03
AD-53806	AD-57013.1	0.30	0.08	0.33	0.02
AD-53806	AD-57019.1	0.29	0.03	0.28	0.02
AD-53806	AD-57022.1	0.20	0.06	0.21	0.05
AD-53806	AD-57025.1	0.23	0.12	0.25	0.15
AD-53806	AD-56997.1	0.20	0.05	0.25	0.11
AD-53806	AD-57002.1	0.21	0.07	0.28	0.01

(continued)

Parent duplex	Duplex ID	Trans 10nM Avg	Trans 10nM SD	Trans 0.1nM Avg	Trans 0.1nM SD
AD-53806	AD-57008.1	0.26	0.01	0.31	0.01
AD-53806	AD-57014.1	0.32	0.03	0.43	0.05
AD-53806	AD-57020.1	0.19	0.00	0.23	0.01
AD-53806	AD-57020.2	0.20	0.08	0.28	0.22
AD-53806	AD-57026.1	0.34	0.24	0.37	0.24
AD-53806	AD-57003.1	0.34	0.04	0.45	0.15
AD-53806	AD-57009.1	0.30	0.07	0.40	0.02
AD-53806	AD-57015.1	0.32	0.01	0.47	0.04
AD-53806	AD-57023.1	0.17	0.06	0.27	0.13
AD-53806	AD-57027.1	0.20	0.03	0.19	0.11
AD-53806	AD-56998.1	0.23	0.09	0.29	0.24
AD-53806	AD-57004.1	0.24	0.13	0.30	0.12
AD-53806	AD-57010.1	0.23	0.09	0.23	0.11
AD-53806	AD-57016.1	0.21	0.03	0.23	0.06
AD-53806	AD-56999.2	0.25	0.10	0.35	0.05
AD-53806	AD-56999.1	0.24	0.08	0.28	0.21
AD-53806	AD-57021.1	0.18	0.04	0.29	0.17
AD-53806	AD-57024.1	0.20	0.09	0.28	0.11
AD-53806	AD-57005.1	0.18	0.10	0.29	0.17
AD-53806	AD-57011.1	0.21	0.07	0.26	0.12
AD-53806	AD-57017.1	0.20	0.07	0.29	0.21
AD-53806	AD-57000.2	0.20	0.04	0.29	0.21
AD-53806	AD-57000.3	0.22	0.11	0.30	0.16
AD-53806	AD-57000.1	0.25	0.14	0.38	0.33
AD-53806	AD-57006.2	0.22	0.14	0.31	0.18
AD-53806	AD-57006.3	0.19	0.09	0.31	0.25
AD-53806	AD-57006.1	0.20	0.12	0.41	0.29
AD-53806	AD-57012.1	0.16	0.05	0.36	0.17
AD-53806	AD-57018.1	0.20	0.37	0.10	0.14

[0440] To determine whether any of the siRNAs from the *in vitro* SAR screen are more effective at silencing PCSK9 than the parent siRNA (AD-53815) PCSK9 transgenic mice were administered a single 3 mg/kg dose of the siRNAs shown in Figure 4, and 72 hours post-dosing, PCSK9 protein levels were determined by ELISA assay. The results, shown in Figure 5, demonstrate that AD-57928 is surpringly effective at silencing PCSK9. Figure 6 shows that, not only does a single dose of AD-57928 effectively knock-down PCSK9 protein, but there is also a dose response using AD-57928.

Example 4. Split Dosing Study Using AD-57928

[0441] The ability of AD-57928 to suppress expression of PCSK9 protein was assessed by measuring levels of human PCSK9 (hPCSK9) protein in serum of hPCSK9 transgenic mice following administration of AD-57928. AD-57928 was administered subcutaneously using six different dosing schedules that included a "loading phase" during the first week (one dose of 0.5 mg/kg, 1 mg/kg or 2 mg/kg daily for 5 subsequent days), followed by a "maintenance phase" (once or

twice weekly dosing of either 0.5 mg/kg, 1 mg/kg or 2 mg/kg for 5 weeks), as is described in Table 8 below. The last dose was administered at day 38. Each dosing schedule was tested using a group of 3 mice that included two males and one female. A control group received injections with PBS.

Table 8. Dosing Schedules for administration of AD-57928

Test Article	Week 1		Weeks 2-6	
	Loading Dose (mg/kg)	Total Dose (mg/kg)	Maintenance dose (mg/kg)	Total Weekly Dose (mg/kg)
PBS	5x	0	2x	0
AD-57928	5x2	10	2x2	4
AD-57928	5x2	10	1x2	2
AD-57928	5x1	5	2x1	2
AD-57928	5x1	5	1x1	1
AD-57928	5x0.5	2.5	2x0.5	1
AD-57928	5x0.5	2.5	1x0.5	0.5

[0442] Serum was collected 3 days prior to administration of the first dose and on days 1, 4, 7, 10, 14, 17, 21, 24, 28, 31, 35, 38, 42, 45, 52, 59 and 65 after the first dose. PCSK9 protein levels in serum were assessed by ELISA assay. The results are shown in Figures 6, 7 and 8.

[0443] Reduced of hPCSK9 serum protein levels were observed 72 hours following the first dose, and were sustained through day 38. Administration of AD-57928 at the loading doses of 5x2 mg/kg, 5x1 mg/kg and 5x0.5 mg/kg resulted in ~90%, ~70% and ~60% reduction of hPCSK9 serum protein levels, respectively (see Figures 6-8). In the group dosed using the 2x maintenance dosing schedule, the reduced levels of hPCSK9 were sustained for 1 week longer than in the group dosed using the 1x maintenance dosing schedule, and returned to baseline 4 weeks after the last dose (see Figures 6-8).

Example 5. Phosphorothioate Titration

[0444] In order to determine the effect of the number and position of phosphorothioate modifications on the ability of dsRNA to inhibit the expression of PCSK9, a number of siRNAs based on the parent sequences of AD-57928, AD-53806 and AD-53830 as shown in Table 9 were prepared and tested. To determine whether any of the siRNAs are more effective at silencing PCSK9 than AD-57928, PCSK9 transgenic mice were administered a single 0.3 mg/kg dose of the siRNA in Table 9, and 72 hours post-dosing, PCSK9 protein levels were determined by ELISA assay. The results, shown in Figure 9, demonstrate that AD-57928 is surpringly effective at silencing PCSK9. AD-58893, AD-58894, AD-58896, AD-58897, AD-58898 and AD-58899 were also able to silence PCSK9 as compared to the control.

Table 9. siRNAs used in phosphorothiate titration experiment

Duplex ID	Sense Sequence	SEQ ID NO:	Antisense Sequence	SEQ ID NO:	Chemistry
AD-57928	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgU fL96	1557	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs asa	1567	TOFFEE with 6 PS, and 3OMe on 3'end of AS
AD-58893	CfsuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf L96	1558	asCfaAfaAfgCfaAfaacAfgGfuCfuAfgas a	1568	TOFFEE with 3 outer PS
AD-58894	CfusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUf L96	1559	aCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsa a	1569	TOFFEE with 3 inner PS
AD-58895	CfuAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL 96	1560	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgs asa	1570	TOFFEE with just 4 antisense PS
AD-58896	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgU fL96	1561	aCfaAfaAfgCfaAfaacAfgGfuCfuAfgaa	1571	TOFFEE with just 2 sense PS
AD-58897	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfg UfL96	1562	asCfsasAfaAfgCfaAfaacAfgGfuCfuAfsg sasa	1572	TOFFEE with 9 PS
AD-58898	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfg UfL96	1563	asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfs gsasa	1573	TOFFEE with 10PS
AD-58899	CfsusAfsgAfcCfuGfUfUfuUfgCfuUfuUfsg UfL96	1564	asCfsaAfaAfgCfsaAfaacAfsgGfuCfuAfs gsasa	1574	TOFFEE with 11PS
AD-58900	CfsasAfgCfaGfaCfAfUfuUfaUfcUfuUfuU fL96	1565	asAfsaAfaGfaUfaAfaugUfcUfgCfuUfgs csu	1575	6PS version of AD-53806
AD-58902	UfsusUfuCfuAfgAfCfCfuGfuUfuUfgCfuU fL96	1566	asAfsgCfaAfaAfcAfgguCfuAfgAfaAfas gsu	1576	6PS version of AD-53830

Example 6. Liver Drug Levels of AD-57928 and AD-58895

[0445] The goal of this study was to quantify siRNA levels in the liver of wild-type mice in order to define appropriate conditions for drug level screening. The siRNAs used in the experiment were AD-57928 and AD-58895 (that produced no decrease in PCSK9 protein level in Example 5). AD-58895 was used as a comparator to define timepoints at which a difference in drug level reflective of efficacy is observable.

[0446] A total of 33 C57B6 female mice were used in the experiment (3 mice per group). These mice were administered a single subcutaneous dose of either AD-57928, AD-58895 or PBS as a control. Livers were collected at 4, 24, 48, 72, 96 and 168 hours post-dose. Duplicate tissue aliquots per sample were collected, and the concentration of siRNA in the liver was measured using a newly designed antisense sequence specific qRT-PCR assay. The measured amount of AD-57928 and AD-58895 per gram of liver over time is shown in Figure 10, and the amount of AD-57928 and AD-58895 expressed as a percentage of total theretical dose is shown in Figure 11. The limit of detection (LOD) of the qRT-PCR assay was ~1 ng/ g of liver, and the assay showed good performance and accurate duplicates reproducibility. The results indicate that AD-57928 is more stable in the liver and AD-58895 is less stable, and both can be detected across all timepoints. At 7 days post dose, the level of AD-57928 is >100 fold above the LOD of the qRT-PCR assay, and the level of AD-58895 is >10 fold above LOD. The concentrations of AD-57928 and AD-58895 differ on average >10 fold according to their predicted stability and the observed efficacy. The timepoint between 72 and 120 hours post dose may be appropriate for siRNA concentration based screens.

Example 7. Optimization of AD-57928

[0447] In order to enhance the *in vivo* activity and stability of AD-57928, additional iRNA agents based on the parent sequences of AD-57928 were prepared and tested (Table 10; the "Sense" sequences in Table 10 are disclosed as SEQ ID NOS: 1653-1658, respectively, in order of appearance, and the "Antisense" sequences are disclosed as SEQ ID NOS: 1659-1664, respectively, in order of appearance; the same sense and antisense sequences disclosed in Table 10 are also disclosed in Figure 12A).

[0448] The unmodified sense and antisense sequences for AD-60212 are:

Sense - 5'- CUAGACCUGUTUUGCUUUUGU - 3' (A-122088.3; SEQ ID NO:1665); and
Antisense - 5'- ACAAAAGCAAAACAGGUCUAGAA - 3'(A-120190.19; SEQ ID NO:1666).

[0449] In general, these compounds contained fewer 2'-fluro modifications and fluoro-modified uridines were removed. The *in vitro* potency of these duplexes was tested by transfection of HeLa and Hep3b cells. As shown in Figure 12B, AD-59849, AD-59228, and AD-60212 have IC_{50} values comparable to the parent (AD-57928).

[0450] The ability of these duplexes to persist *in vivo* in the liver was also determined by administering 1 mg/kg of each duplex to wild-type mice and determining the siRNA level by quantitative PCR. As depicted in Figure 13, all of the duplexes show greater persistence in the liver than the parent duplex starting at the post-120 hours administration timepoint.

[0451] The ability of these duplexes to suppress expression of PCSK9 protein was also assessed *in vivo* by measuring levels of PCSK9 protein, LDL, HDL, total cholesterol (Tc), triglycerides (Tgs), alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in the serum of non-human primates (NHP). The presence of injection site reation was also monitored. The duplexes were administered using a dosing schedule that included a "loading phase" during the first week (one dose of 2 mg/kg daily for 5 subsequent days, qdx5), followed by a "maintenance phase" (three weekly doses of 2 mg/kg for 3 weeks, qwx3), as is described in Table 11 below.

Table 10. Additional iRNA Agents.

Duplex	Sense ID	Sense	AntiSense ID	Antisense
AD-57928 (parent)	A-117428	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	A-117429	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa
AD-59849	A-121244	CfsusAfgAfcCfuGfUfUfuUfgcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-60688	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-121239	asCfsaAfaagCfaAfaacAfgGfucuAfgsasa
AD-59223	A-120188	csusagacCfuGfuuuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-60212	A-122088	csusagacCfuGfudTuugcuuuuguL96	A-120190	asCfsaAfAfAfgCfaAfaAfcAfgGfuCfuagsasa
AD-59228	A-120197	CfsusAfgAfcCfuGfUfUfuUfgCfsuUfsuUfsgsUfsL96	A-120202	asCfsaAfaAfsgCfaAfaacAfgGfuCfsuAfgsasa

Table 11. Dosing Schedules

Test Article	Group Number	N	Dose Level (mg/kg)	Dose Frequency	Cumulative dose (mg/kg)
AD-57928	1	3 females	2	qdx5+qwx3, 8 doses	16
AD-59849	2		2	qdx5+qwx3, 8 doses	16
AD-60688	3		2	qdx5+qwx3, 8 doses	16
AD-59223	4		2	qdx5+qwx3, 8 doses	16
AD-60212	5		2	qdx5+qwx3, 8 doses	16
AD-59228	6		2	qdx5+qwx3, 8 doses	16
Blood : Days -9, -6, -3, 4, 7, 10, 14, 17, 21, 24, 28, 31, 35, 42, 49, 56, 63 (first dose, Day 1) Injection site observation: Yes Readouts: PCSK9 protein, LDL, HDL, Tc, Trigs, ALT, AST, ALP					

[0452] As shown in Figures 14A and 14B, all compounds except for AD-60688 achieve greater than 80% PCSK9 silencing and individual animals in the AD-60212 group achieve greater than 90% PCSK9 silencing. Figure 15 demonstrates that, in the absence of statins, all compounds except for AD-60688 achieve 60% LDL cholesterol lowering and individual animals in the AD-59223 group achieve up to 77% LDL cholesterol lowering. Surprisingly, and as depicted in Figure 18, the indicated agents maintained cholesterol lowering 46 days following the last dose of the indicated agents. Even more surprisingly, and as depicted in Figure 19, AD-60212 and AD-59849 maintain up to 60% LDL cholesterol lowering to at least day 120 (93 days after the final dose), longer than any effect observed for an RNAi agent *in vivo*, indicating that, following a loading phase, these compounds may be administered at a frequency of once a month, once every two months, once every three months, once every four months, once every five months, or once every six months during the maintenance phase.

Example 8. Preparation of Additional AD-57928-Based PCSK9 Sequences

[0453] Additional iRNA agents based on the parent sequences of AD-57928 were prepared (see Table 12, below) and tested *in vitro* for potency by transfecting HeLa and Hep3B cells with these agents. The IC_{50} values for these agents are shown in Table 13.

Table 12. PCSK9 sequences

Duplex ID	Sense strand	Sense (5' to 3')	SEQ ID NO:	Antisense	Antisense (5' to 3')	SEQ ID NO:
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1577	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1605
AD-60928.1	A-122701.2	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgAfL96	1578	A-122702.2	usCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1606
AD-60929.1	A-122703.2	GfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1579	A-122704.2	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfcsusu	1607
AD-60930.1	A-122705.2	GfsasAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1580	A-122706.2	asCfsaAfaAfgCfaAfaacAfgGfuCfuUfcsusu	1608
AD-60931.1	A-122707.3	GfsasUfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1581	A-122708.2	asCfsaAfaAfgCfaAfaacAfgGfuCfaUfcsusu	1609
AD-60932.1	A-122707.4	GfsasUfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1582	A-122709.2	asCfsaAfaAfgCfaAfaacAfgGfuCfaUfcsasa	1610
AD-60933.1	A-122710.2	CfsasUfcAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1583	A-122711.2	asCfsaAfaAfgCfaAfaacAfgGfuGfaUfgsasa	1611
AD-60934.1	A-122712.2	CfsusUfcUfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1584	A-122713.2	asCfsaAfaAfgCfaAfaacAfgGfaGfaAfgsasa	1612
AD-60927.1	A-122714.2	CfsusAfcUfgCfuGfUfUfuUfgCfuUfuUfgUfL96	1585	A-122715.2	asCfsaAfaAfgCfaAfaacAfgCfaGfuAfgsasa	1613
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1586	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1614
AD-60906.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1587	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1615
AD-60907.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1588	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1616
AD-60908.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1589	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1617
AD-60909.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1590	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1618
AD-60910.1	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1591	A-122313.1	asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afg sasa	1619
AD-60911.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1592	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1620
AD-60912.1	A-122308.1	(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1593	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1621
AD-60913.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1594	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1622
AD-60914.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1595	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1623
AD-60915.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh) Uf(Uyh)Uf(Gyh)UfL96	1596	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1624
AD-57928.45	A-117428.1	CfsusAfgAfcCfuGfUfUfuUfgCfuUfuUfgUfL96	1597	A-117429.1	asCfsaAfaAfgCfaAfaacAfgGfuCfuAfgsasa	1625

(continued)

Duplex ID	Sense strand	Sense (5' to 3')	SEQ ID NO:	Antisense	Antisense (5' to 3')	SEQ ID NO:
AD-60916.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1598	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1626
AD-60917.1	A-122307.1	Cfsus(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1599	A-122313.1	asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afgsasa	1627
AD-60918.1	A-122308.1	(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1600	A-122309.1	asCfsaAfaAfgCf(Ayh)AfaacAfgGfuCfuAfgsasa	1628
AD-60919.1	A-122308.1	(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1601	A-122310.1	asCfsaAfaAfgCfa(Ayh)aacAfgGfuCfuAfgsasa	1629
AD-60920.1	A-122308.1	(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1602	A-122311.1	asCfsaAfaAfgCfaAf(Ayh)acAfgGfuCfuAfgsasa	1630
AD-60921.1	A-122308.1	(Cyh)u(Ayh)(Gyh)(Ayh)(Cyh)CfuGfUfUfuUf(Gyh)Cf(Uyh)Uf(Uyh)Uf(Gyh)UfL96	1603	A-122312.1	asCfsaAfaAfgCfaAfa(Ayh)cAfgGfuCfuAfgsasa	1631
AD-60922.1	A-122308.1		1604	A-122313.1	asCfsaAfaAfgCf(Ayh)AfaacAf(Gyh)GfuCf(Uyh)Afgsasa	1632

Table 13. IC_{50} values for the iRNA agents identified in Table 12.

Duplex ID	Hela IC_{50}(nM)	Hep3b IC_{50}(nM)
AD-57928.47	0.0026	0.0005
AD-60928.1	0.0000	0.0009
AD-60929.1	0.0010	0.0027
AD-60930.1	0.0055	0.0019
AD-60931.1	0.0028	0.0019
AD-60932.1	0.0039	0.0036
AD-60933.1	0.0349	0.1518
AD-60934.1	0.2115	0.5420
AD-60927.1	>10	-
AD-57928.45	<3.57225e-005	0.0007
AD-60906.1	0.0048	0.0007
AD-60907.1	0.0001	<3.57225e-005
AD-60908.1	0.0003	0.0072
AD-60909.1	-	0.0142
AD-60910.1	0.0001	0.0030
AD-60911.1	0.0955	0.1935
AD-60912.1	0.1834	0.4106
AD-60913.1	0.2693	0.5715
AD-60914.1	0.2292	0.4319
AD-60915.1	0.2069	0.3185
AD-57928.45	0.0057	0.0027
AD-60916.1	0.0802	0.2040
AD-60917.1	0.1420	0.0976
AD-60918.1	0.4101	0.3268
AD-60919.1	0.3202	0.5143
AD-60920.1	0.5199	0.5978
AD-60921.1	0.7969	2.0875
AD-60922.1	1.1078	1.0307

Example 9. Repeat-Dose Efficacy of AD-57928

[0454] The repeat-dose efficacy of AD-57928 in suppressing expression of PCSK9 protein was assessed *in vivo* by measuring the levels of PCSK9 protein, LDL, HDL, total cholesterol (Tc), triglycerides (Tgs), alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in the serum of non-human primates (NHP). The presence of injection site reation was also monitored. AD-57928 duplexes were subcutaneously administered using the dosing schedules described in Table 14 below. Group 5 animals were re-dosed with a single 25 mg/kg dose on day 92. One additional group of animals was administered a single dose of 25 mg/kg. "2xw" is two times per week; "q2w" is once every two weeks; and "q1w" is once per week.

Table 14. Dosing Schedules

Test Article	Group Number	N	Dose Level (mg/kg)	Dose Frequency	Cumulative dose (mg)
AD-57928	1	3 females	1	2xw,12 doses	12
	2		2	2xw, 12 doses	24
	3		1	q2w, 6 doses	6
	4		2	q2w, 6 doses	12
	5		0.5	q1w, 6 doses	3
	6		1	q1w, 10 doses	10
	7		2	q1w, 10 doses	20
Blood : Days -9, -6, -3, 1 (pre-bleeds) 3-129 (efficacy bleeds) Injection site observation: Yes Readouts: PCSK9 protein, LDL, HDL, Tc, Trigs, ALT, AST, ALP					

[0455] As depicted in Figure 16A, the most effective regimen for lowering LDL was a twice weekly regimen (2xw) which achieved about a 60% reduction in LDL levels. The same cumulative dose administered less frequently was less efficacious than the twice a week regimen. Figure 16B demonstrates that the 2xw regimen achieved greater than 80% PCSK9 silencing.

[0456] Figures 17A and 17B demonstrate that a single 25 mg/kg dose of AD-57928 has the same onset of LDL and PCSK9 lowering, the same nadir of PCSK9 and LDL lowering, and equivalent rate of LDL lowering as a lower multiple-dose of 2 mg/kg AD-57928 administered two times per week (2xw). These graphs also demonstrate that there is a trend towards faster PCSK9 lowering with the single 25 mg/kg dose and that recovery of both PCSK9 levels and LDL levels starts about 20 days after nadir is reached (day 7) for the 25 mg/kg single dose. The nadir for the 25 mg/kg single dose is at Day 7.

Example 10. Tolerability of Optimized AD-57928 iRNA Agents

[0457] The additional iRNA agents prepared based on the parent sequences of AD-57928 described in Figure 12A (and Table 10) were assessed for tolerability in rats. Male rats were subcutaneously administered 225 mg/kg of the indicated iRNA agents on days 1, 8, and 15, and sacrificed and necropsied on day 16 (see Table 15). The animals were observed for any clinical symptoms on a daily basis and the body weights of the anmals were determined pre-study and weekly during the study. On day 16, blood from the animals was assessed hematologically, for coagulation and for serum chemistry; the drug metabolism and pharmacokinetics of the agents were determined using liver samples from the animals; and the heart, lungs (insufflated), kidneys, liver, spleen, testes, and first and last injection sites were analyzed for any changes. There were no changes in clinical signs, visual injection site observations, serum chemistry, coagulation or microscopic pathology of the liver, spleen lung, heart, or testes. Table 16 provides a summary of the liver weights, the final body weights, the results of the hematological analyses and the pathology severity scores for the final injection sites and kidneys for each agent tested.

Table 15. Dosing Schedules

Dose Group	TA	Dose (mg/kg)	Dose Vol. (mL/ kg)	No. Males	Dosing Schedule	Nx Day
1	PBS	0	5	3	SC on Days 1, 8, and 15	Day 16
2	AD-57928 (parent)	225		3		
3	AD-59849	225		3		
4	AD-59223	225		3		

(continued)

Dose Group	TA	Dose (mg/kg)	Dose Vol. (mL/ kg)	No. Males	Dosing Schedule	Nx Day
5	AD-59228	225		3		
6	AD-60688	225		3		
7	AD-60212	225		3		

Table 16. Tolerability Summary

	AD-57928 (parent)	AD-59849	AD-59223	AD-59228	AD-60688	AD-60212
No. PS	6	6	6	13	6	6
No. 2'F	21	15	12	21	9	12
No. dT	0	0	0	0	0	1
[Liver] (μg/g)	907±62	1139±160	1277±231	1999±424	1624±147	1258±286
Final BW (% from control)	-2.1%	-4.6%	-2.1%	-6.8%	-0.5%	-2.9%
Day 16 Hematology	No Change	No Change	↑WBC, ↑LYM, hemolysis	No Change	No Change	No Change
Day 16 Final Inj. Site Inflammation	3/3 (1.7)	3/3 (1.3)	2/3 (1.5)	3/3 (2.3)	2/3 (1.0)	3/3 (1.3)
Day 16 Basophilic Granules, Kidney	3/3 (2.0)	3/3 (2.3)	3/3 (1.0)	3/3 (2.0)	3/3 (1.3)	3/3 (1.3)

Pathology Severity Scores: 1 = minimal; 2 = slight; 3 = moderate
BW = Body Weight
WBC = White Blood Cell
LYM = Lymphocytes

SEQUENCE LISTING

[0458]

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