Supplementary Data

Detailed Methods

Clinical studies were performed in compliance with the guidelines of good clinical practice and Declaration of Helsinki. All human subjects gave written informed consent. Data were imported from individual study data sets into one SAS dataset for each laboratory test [1]. Evaluated subjects received at least one dose of study drug.

The integrated safety database (ISDB) contains data collected from a total of 59 trials for 16 distinct, second-generation, 2′-*O*-methoxyethyl (2′MOE)-modified antisense oligonucleotides (ASOs). This collection represents 32 phase 1 (sixteen 2′MOE ASOs), 21 phase 2 (ten 2′MOE ASOs), and 6 phase 3 (one 2′MOE ASO) [2–7] trials. Forty-three of these trials were randomized placebo controlled (sixteen 2′MOE ASOs), 13 were open label (five 2′MOE ASOs)—4 of which were drug–drug interaction trials (three 2′MOE ASOs), and 2 trials were long-term open-label extensions (one 2′MOE ASO).

Supplementary Table S1. 2′-*O*-Methoxyethyl Antisense Oligonucleotide Trials in Integrated Safety Database

	Phase 1		*Phase 2*		*Phase 3*		*2′MOE ASO, systemic*	
Count, n	*Trials*	*Subjects*	*Trials*	*Subjects*	*Trials*	*Subjects*	*Trials*	*Subjects*
RCT	20	956	18[a]	1,049	5	699	43[a]	2,704
OL	5	78	3	340	1	143	9	561
DDI	4	84	0	0	0	0	4	84
Other[b]	3	127	0	0	0	0	3	127
Total	32	1,245	21	1,389	6	842	59	3,476

[a]One trial excluded from the phase 2 RCT data set (0 placebo, 2 active). [b]Includes two trials with crossover design and one single-dose tolerability trial with protocol-specified exposure to corticosteroids.

2′MOE, 2′-*O*-methoxyethyl; ASOs, antisense oligonucleotides; DDI, drug–drug interaction; OL, open label; RCT, randomized placebo-controlled trial.

Data are presented by the incidence of platelet events and descriptive summary statistics of platelet test results. Analyses on the incidence of platelet events were based on confirmed test results, as defined in table footnotes. Baseline (BSLN) was defined as the last value before the first dose. All study data were included for analyses of the incidence of events. Any exceptions are indicated by footnote in the respective tables. Two subject inclusion criteria were used for the incidence analyses. One criterion included subjects who had at least one post-BSLN measure to evaluate the incidence of confirmed post-BSLN platelets $<0.7\times$BSLN, $<0.5\times$BSLN, <LLN, <75 K/μL, and <50 K/μL. The second criterion included subjects who had a BSLN value in the normal range and at least one post-BSLN measure to evaluate the incidence of confirmed threshold events by the following five platelet count brackets, <LLN to 100, <100–75, <75–50, <50–25, and <25 K/μL.

Supplementary Table S2. Baseline Characteristics of 2′-*O*-Methoxyethyl Antisense Oligonucleotide Systemic Dataset (52 Trials, Randomized Placebo-Controlled Trial/Open Label)

Systemic RCT/OL			*2′MOE ASO dose (mg/week)*					
	Placebo	*ASO total*	*>0–75*	*>75–175*	*>175–275*	*>275–375*	*>375–475*	*>475*
n	784	2,407	167	365	1,329	270	235	41
Gender								
Female	330 (42.1%)	1,086 (45.1%)	37 (22.2%)	156 (42.7%)	652 (49.1%)	135 (50.0%)	96 (40.9%)	10 (24.4%)
Male	454 (57.9%)	1,321 (54.9%)	130 (77.8%)	209 (57.3%)	677 (50.9%)	135 (50.0%)	139 (59.1%)	31 (75.6%)
Race								
White	652 (83.2%)	2,069 (86.0%)	140 (83.8%)	304 (83.3%)	1,137 (85.6%)	254 (94.1%)	201 (85.5%)	33 (80.5%)
Black	78 (9.9%)	180 (7.5%)	16 (9.6%)	28 (7.7%)	101 (7.6%)	8 (3.0%)	20 (8.5%)	7 (17.1%)
Asian	25 (3.2%)	78 (3.2%)	4 (2.4%)	16 (4.4%)	49 (3.7%)	2 (0.7%)	6 (2.6%)	1 (2.4%)
Hispanic	7 (0.9%)	17 (0.7%)	0 (0.0%)	7 (1.9%)	4 (0.3%)	0 (0.0%)	6 (2.6%)	0 (0.0%)
Other	22 (2.8%)	62 (2.6%)	7 (4.2%)	10 (2.7%)	37 (2.8%)	6 (2.2%)	2 (0.9%)	0 (0.0%)
Age, years								
Mean (SD)	50.2 (13.6)	50.6 (13.9)	41.3 (13.2)	46.9 (13.9)	53.2 (13.1)	53.4 (12.8)	47.1 (14.1)	39.9 (15.3)
BMI, kg/m^2	780	2,326	167	361	1,252	270	235	41
Mean (SD)	28.5 (4.8)	28.6 (5.3)	26.1 (3.2)	27.8 (5.4)	29.2 (5.4)	29.5 (5.1)	27.3 (4.8)	26.9 (4.2)
Platelets, K/μL								
N	780	2,390	161	361	1,323	270	235	41
Mean (SD)	241 (62)	245 (67)	239 (54)	252 (62)	241 (65)	247 (62)	260 (97)	227 (54)

Supplementary Table S3. Data Excluded from 2′-*O*-Methoxyethyl Antisense Oligonucleotide Systemic Dataset Analysis

Trial design	*2′MOE ASOs,* n	*Trials,* n	*Subjects,* n
Drug–drug interaction	3	4[a]	84
Oral bioavailability	1	1	24
Tolerability	1	1	60
Crossover design	2	2	67
Comparator group[b]	1	1	74

[a]See Supplementary Table S4 for results on post-BSLN platelet counts in phase 1 DDI trials.
[b]Two subjects were excluded from evaluable population of published report [8].

Phase 1 Drug–Drug Interaction Trials

Three 2′MOE ASOs were evaluated for drug–drug interactions (four trials) using a crossover trial design with all subjects exposed to a 2′MOE ASO.

Drugs tested: simvastatin, ezetimibe, warfarin, enoxaparin, metformin, glipizide, and rosiglitazone

Supplementary Table S4. Incidence of Confirmed Platelet Reductions in Four Drug–Drug Interaction Trials

Post-BSLN platelet levels		*2′MOE ASO dose (mg/week)*					
Confirmed,[a] n *(%)*	*ASO total*	*>0–75*	*>75–175*	*>175–275*	*>275–375*	*>375–475*	*>475*
N	84	0	0	84	0	0	0
<0.7×BSLN	1 (1.2)			1 (1.2)			
<0.5×BSLN	0 (0)			0 (0)			
<LLN	2 (2.4)			2 (2.4)			
<75 K/μL	0 (0)			0 (0)			
<50 K/μL	0 (0)			0 (0)			
n[b]	82	0	0	82	0	0	0
LLN-100 K/μL	2 (2.4)			2 (2.4)			
<100–75 K/μL	0 (0)			0 (0)			
<75–50 K/μL	0 (0)			0 (0)			
<50–25 K/μL	0 (0)			0 (0)			
<25 K/μL	0 (0)			0 (0)			

[a]Confirmed was defined as a consecutive (next) abnormal laboratory value after the initial observation. If there was no consecutive test to confirm, then the initial observation was presumed confirmed.

[b]Number of subjects with normal BSLN platelet counts and with post-BSLN values. Lowest confirmed category was reported for each subject.

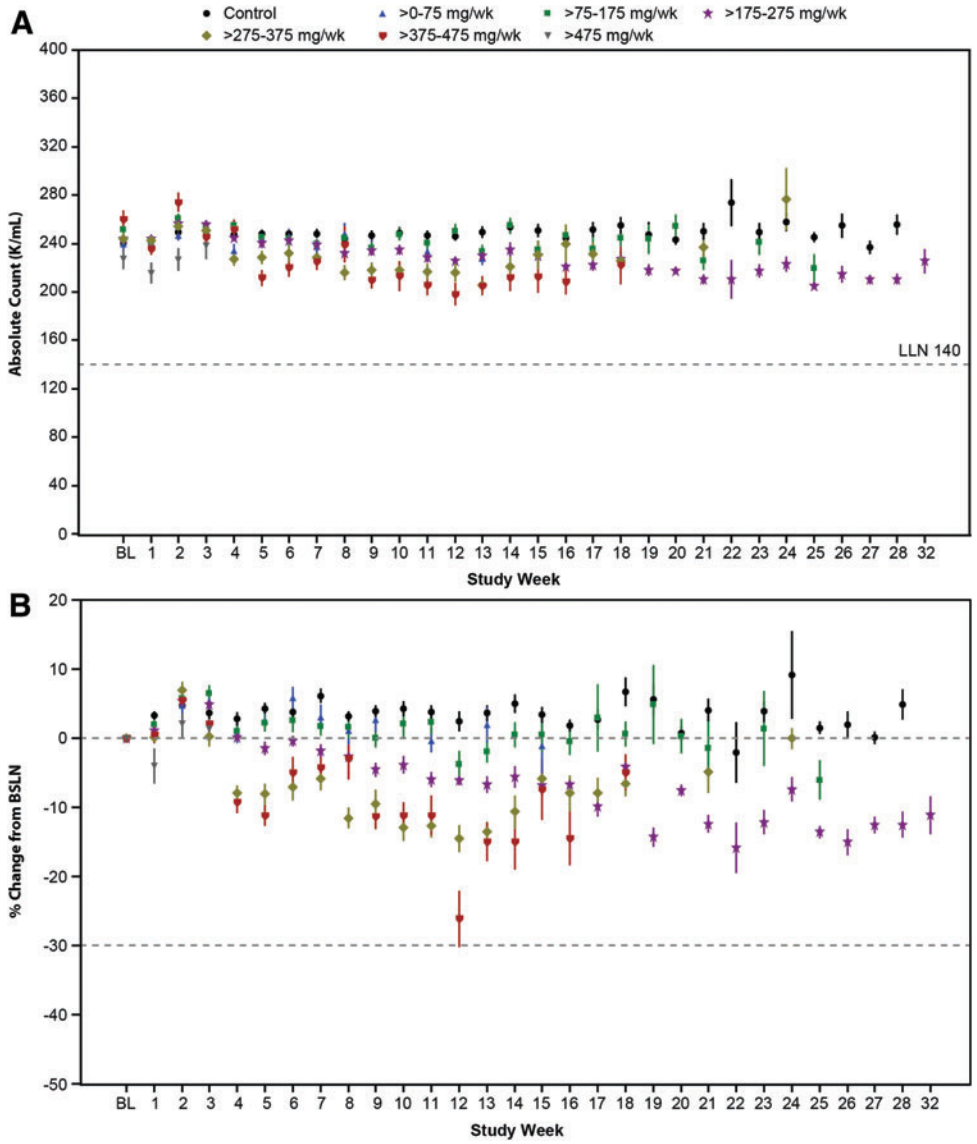
BSLN, baseline; LLN, lower limit of normal.

Randomized Placebo-Controlled Trials

Supplementary Table S5. Baseline Characteristics of Randomized Placebo-Controlled Dataset (42 Trials, Phase 1 to Phase 3)

Randomized placebo-controlled			*2′MOE ASO dose (mg/week)*					
	Placebo	*ASO total*	*>0–75*	*>75–175*	*>175–275*	*>275–375*	*>375–475*	*>475*
n	784	1,915	164	318	1,013	177	202	41
Gender								
Female	330 (42.1%)	815 (42.6%)	36 (22.0%)	148 (46.5%)	468 (46.2%)	67 (37.9%)	86 (42.6%)	10 (24.4%)
Male	454 (57.9%)	1,100 (57.4%)	128 (78.0%)	170 (53.5%)	545 (53.8%)	110 (62.1%)	116 (57.4%)	31 (75.6%)
Race								
White	652 (83.2%)	1,601 (83.6%)	137 (83.5%)	263 (82.7%)	836 (82.5%)	163 (92.1%)	169 (83.7%)	33 (80.5%)
Black	78 (9.9%)	171 (8.9%)	16 (9.8%)	26 (8.2%)	94 (9.3%)	8 (4.5%)	20 (9.9%)	7 (17.1%)
Asian	25 (3.2%)	72 (3.8%)	4 (2.4%)	15 (4.7%)	44 (4.3%)	2 (1.1%)	6 (3.0%)	1 (2.4%)
Hispanic	7 (0.9%)	16 (0.8%)	0 (0.0%)	6 (1.9%)	4 (0.4%)	0 (0.0%)	6 (3.0%)	0 (0.0%)
Other	22 (2.8%)	51 (2.7%)	7 (4.3%)	8 (2.5%)	34 (3.4%)	4 (2.3%)	1 (0.5%)	0 (0.0%)
Age, years								
Mean (SD)	50.2 (13.6)	49.8 (13.4)	41.3 (13.3)	50.0 (13.2)	52.5 (12.6)	49.9 (11.9)	48.0 (13.5)	39.9 (15.3)
BMI, kg/m^2								
Mean (SD)	28.5 (4.8)	28.2 (5.0)	26.1 (3.2)	28.1 (5.3)	28.9 (5.2)	28.3 (4.3)	27.2 (4.8)	26.9 (4.2)
Platelets, K/μL								
Mean (SD)	240.5 (61.7)	246.5 (68.4)	239.4 (53.7)	251.6 (63.0)	244.3 (64.7)	244.1 (60.5)	261.0 (103.1)	227.2 (54.1)

Mean platelet results over time



SUPPLEMENTARY FIG. S1. Mean platelet results over time in the randomized placebo-controlled dataset. **(A)** Absolute count and **(B)** % change from BSLN.

Supplementary Table S6. Incidence of Confirmed Platelet Reductions in Randomized Placebo-Controlled Trials (42 Trials, Phase 1 to Phase 3)

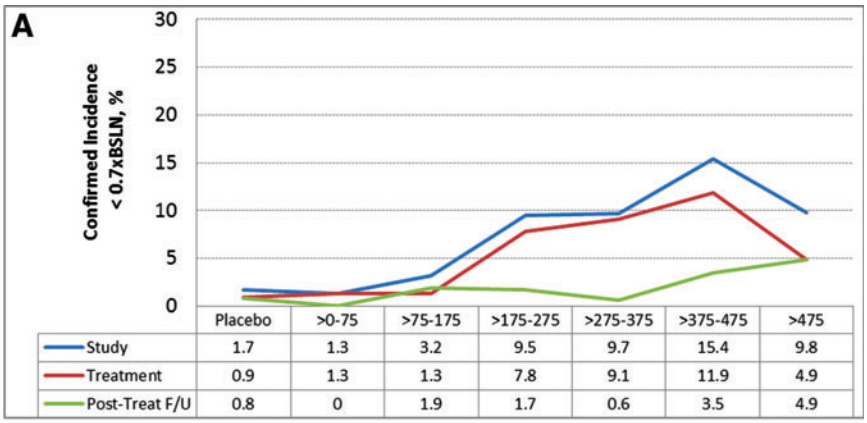
Post-BSLN platelet count			*2′MOE ASO dose (mg/week)*					
Confirmed,[a] n *(%)*	*Placebo*	*ASO total*	*>0–75*	*>75–175*	*>175–275*	*>275–375*	*>375–475*	*>475*
n	777	1,877	158	315	986	176	201	41
<0.7×BSLN	13 (1.7)	158 (8.4)	2 (1.3)	10 (3.2)	94 (9.5)	17 (9.7)	31 (15.4)	4 (9.8)
<0.5×BSLN	2 (0.3)	17 (0.9)	0 (0)	0 (0)	8 (0.8)	0 (0)	9 (4.5)	0 (0)
n	777	1,878	158	315	987	176	201	41
<LLN	24 (3.1)	103 (5.5)	2 (1.3)	7 (2.2)	63 (6.4)	12 (6.8)	15 (7.5)	4 (9.8)
<75 K/μL	1 (0.1)	3 (0.2)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.5)	1 (2.4)
<50 K/μL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
n[b]	749	1,788	155	298	936	170	189	40
LLN-100 K/μL	13 (1.7)	74 (4.1)	1 (0.6)	5 (1.6)	42 (4.5)	11 (6.5)	12 (6.3)	3 (7.5)
<100–75 K/μL	0 (0)	3 (0.2)	0 (0)	0 (0)	2 (0.2)	0 (0)	1 (0.5)	0 (0)
<75–50 K/μL	1 (0.1)	1 (0.06)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	0 (0)
<50–25 K/μL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<25 K/μL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Confirmed was defined as a consecutive (next) abnormal laboratory value after the initial observation. If there was no consecutive test to confirm, then the initial observation was presumed confirmed.
[b]Number of subjects with normal BSLN platelet counts and with post-BSLN values. Lowest confirmed category was reported for each subject.

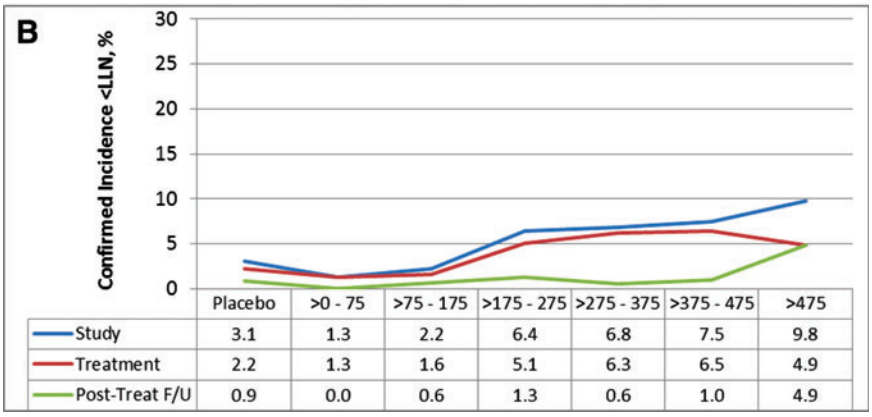
Supplementary Table S7. Platelet Reductions Occurred Predominantly on Treatment in 2′-*O*-Methoxyethyl Antisense Oligonucleotide-Treated Subjects

			2′MOE ASO dose (mg/week)					
Confirmed,[a] n *(%)*	*Placebo* (n=*784*)	*ASO total* (n=*1,915*)	*>0–75* (n=*164*)	*>75–175* (n=*318*)	*>175–275* (n=*1,013*)	*>275–375* (n=*177*)	*>375–475* (n=*202*)	*>475* (n=*41*)
(A) Platelets <0.7×BSLN								
n	777	1,877	158	315	986	176	201	41
Study period	13 (1.7)	158 (8.4)	2 (1.3)	10 (3.2)	94 (9.5)	17 (9.7)	31 (15.4)	4 (9.8)
Treatment period	7 (0.9)	125 (6.7)	2 (1.3)	4 (1.3)	77 (7.8)	16 (9.1)	24 (11.9)	2 (4.9)
Follow-up period	6 (0.8)	33 (1.8)	0 (0.0)	6 (1.9)	17 (1.7)	1 (0.6)	7 (3.5)	2 (4.9)
(B) Platelets <LLN								
n	777	1,878	158	315	987	176	201	41
Study period	24 (3.1)	103 (5.5)	2 (1.3)	7 (2.2)	63 (6.4)	12 (6.8)	15 (7.5)	4 (9.8)
Treatment period	17 (2.2)	83 (4.4)	2 (1.3%)	5 (1.6)	50 (5.1)	11 (6.3)	13 (6.5)	2 (4.9)
Follow-up period	7 (0.9)	20 (1.1)	0 (0.0)	2 (0.6)	13 (1.3)	1 (0.6)	2 (1.0)	2 (4.9)

Incidence of (A) post-BSLN platelets <0.7×BSLN and (B) post-BSLN platelets <LLN.
[a]Confirmed was defined as a consecutive (next) abnormal laboratory value after the initial observation. If there was no consecutive test to confirm, then the initial observation was presumed confirmed.



	Placebo	>0-75	>75-175	>175-275	>275-375	>375-475	>475
Study	1.7	1.3	3.2	9.5	9.7	15.4	9.8
Treatment	0.9	1.3	1.3	7.8	9.1	11.9	4.9
Post-Treat F/U	0.8	0	1.9	1.7	0.6	3.5	4.9



	Placebo	>0 - 75	>75 - 175	>175 - 275	>275 - 375	>375 - 475	>475
Study	3.1	1.3	2.2	6.4	6.8	7.5	9.8
Treatment	2.2	1.3	1.6	5.1	6.3	6.5	4.9
Post-Treat F/U	0.9	0.0	0.6	1.3	0.6	1.0	4.9

SUPPLEMENTARY FIG. S2. Incidence of platelet reductions during treatment and follow-up. **(A)** Post-BSLN platelets $<0.7\times$BSLN and **(B)** post-BSLN platelets <LLN.

Statistical test for dose response in mean platelet levels

Doses >75 mg/week produced greater reductions in platelet levels compared with placebo and the difference was statistically significant (Supplementary Table S8). Comparing adjacent 2′MOE ASO dose levels, the higher dose level always produced a greater reduction than the lower dose group in the mean percent change from BSLN in platelet counts. However, the difference was only statistically significant between the >175–275 and >75–175 mg/week as well as the >275–375 and >175–275 mg/week dose groups.

Supplementary Table S8. Subject-Level Meta-analysis in Mean % Change from Baseline, Treatment Period

Comparison type/comparison	*ASO dose-level/ placebo*	*No. of trials*	n	*LS mean (% change from BSLN)*	*LS mean difference (ASO-placebo)*	*95% CI*
Placebo comparison						
>0–75 mg/week vs. placebo	2′MOE ASO	12	80	2	−2.1	−5.2, 1.0
	Placebo	12	106	4.1	—	—
>75–175 mg/week vs. placebo	2′MOE ASO	20	173	−3.4	−9.3	−14.9, −3.6
	Placebo	20	216	5.9	—	—
>175–275 mg/week vs. placebo	2′MOE ASO	27	823	−8.9	−10.8	−13.0, −8.5
	Placebo	27	523	1.9	—	—
>275–375 mg/week vs. placebo	2′MOE ASO	15	150	−12.9	−18.7	−22.2, −15.2
	Placebo	15	156	5.8	—	—
>375–475 mg/week vs. placebo	2′MOE ASO	14	137	−17.8	−22.6	−30.0, −15.2
	Placebo	14	160	4.9	—	—
Adjacent 2′MOE ASO dose-level comparison						
>0–75 mg/week vs. placebo	High dose	12	80	2	−2.1	−5.2, 1.0
	Low dose	12	106	4.1	—	—
>75–175 mg/week vs. >0–75 mg/week	High dose	12	74	1.3	−0.7	−5.0, 3.5
	Low dose	12	80	2	—	—
>175–275 mg/week vs. >75–175 mg/week	High dose	17	191	−11.2	−7.9	−11.3, −4.6
	Low dose	17	164	−3.3	—	—
>275–375 mg/week vs. >175–275 mg/week	High dose	10	97	−11.4	−3.7	−6.9, −0.4
	Low dose	10	113	−7.7	—	—
>375–475 mg/week vs. >275–375 mg/week	High dose	6	39	−10.2	−3.3	−7.9, 1.3
	Low dose	6	39	−6.9	—	—

Statistics: analysis only included data from subjects assigned to receive multiple SC doses. ANCOVA with protocol and dose category as factor variables, and BSLN platelet value as a covariate was applied for statistical analysis. Negative estimates mean that the high-dose category had a larger reduction in platelet change (% scale) compared with the low-dose category. 95% CIs that did not include 0 were statistically significant at the two-sided 5% significance level.

SC, subcutaneous.

Statistical test for dose response in the incidence of platelet reductions >30% from BSLN

An increase in incidence of confirmed post-BSLN platelet reductions >30% from BSLN was observed when comparing each successive dose level with placebo as well as adjacent 2′MOE ASO dose levels with an increased risk in higher dose levels (Supplementary Table S9). When compared with placebo, increasing 2′MOE ASO dose levels had greater reductions in platelet levels and were statistically significant for doses >175 mg/week. Comparing adjacent dose levels, estimated incidence was greater and statistically significant at the 5% level only for the >175–275 mg/week group when compared with the >75–175 mg/week group.

Supplementary Table S9. Subject-Level Meta-analysis of the Incidence of Platelet Reductions >30% from Baseline (<0.7 × BSLN), Treatment Period

Comparison type/comparison	*No. of trials*	*Low ASO dose-level/placebo events*/n	*High ASO dose-level events*/n	*Mantel-Haenszel risk difference/100 patients (high-low)*	*95% CI*
Placebo comparison					
>0–75 mg/week vs. placebo	12	1/106	2/80	2	−2.0, 6.0
>75–175 mg/week vs. placebo	20	2/216	3/172	0.8	−1.5, 3.0
>175–275 mg/week vs. placebo	27	7/522	74/824	7.6	5.4, 9.7
>275–375 mg/week vs. placebo	15	0/156	11/149	7.4	3.5, 11.3
>375–475 mg/week vs. placebo	14	2/160	24/132	16.7	10.5, 22.8
Adjacent 2′MOE ASO dose-level comparison					
>0–75 mg/week vs. placebo	12	1/106	2/80	2	−2.0, 6.0
>75–175 mg/week vs. >0–75 mg/week	12	2/80	1/74	−1.3	−5.8, 3.2
>175–275 mg/week vs. >75–175 mg/week	17	3/163	11/191	5.1	0.9, 9.3
>275–375 mg/week vs. >175–275 mg/week	10	2/113	6/96	3.8	−1.0, 8.7
>375–475 mg/week vs. >275–375 mg/week	6	0/39	2/39	5.0	−1.9, 11.9

Statistics: analysis evaluated data from subjects assigned to receive multiple SC doses. The stratified Mantel-Haenszel method for common risk difference, with protocol as the stratification factor, was used to test for differences between 2′MOE ASO dose groups and placebo, as well as between 2′MOE ASO dose levels. Positive estimates mean that the high-dose category had a greater percent with a platelet reduction >30% during the treatment period compared with the low-dose category. 95% CIs that did not include 0 are statistically significant at the two-sided 5% significance level.

CI, confidence interval.

Effect of Concomitant Antithrombotic Agents

Supplementary Table S10. Antithrombotic Medications Reported in 6-Month, Phase 3 Mipomersen Trials by WHO ATC Class and Preferred Medication Name

WHO ATC class/ Preferred medication name, n *(%)*	*Placebo (*n = *129)*	*Mipomersen (*n = *261)*	*Total (*n = *390)*
Subjects receiving any prior or concomitant antithrombotic medications	86 (66.7)	192 (73.6)	278 (71.3)
Platelet aggregation inhibitors excl. heparin	19 (14.7)	44 (16.9)	63 (16.2)
Clopidogrel	19 (14.7)	41 (15.7)	60 (15.4)
Asasantin	0 (0.0)	2 (0.8)	2 (0.5)
Abciximab	0 (0.0)	1 (0.4)	1 (0.3)
Cilostazol	0 (0.0)	1 (0.4)	1 (0.3)
Dipyridamole	0 (0.0)	1 (0.4)	1 (0.3)
Prasugrel	1 (0.8)	0 (0.0)	1 (0.3)
Salicylic acid and derivatives	84 (65.1)	176 (67.4)	260 (66.7)
Acetylsalicylic acid	83 (64.3)	176 (67.4)	259 (66.4)
Couldina	0 (0.0)	1 (0.4)	1 (0.3)
Salicylamide	0 (0.0)	1 (0.4)	1 (0.3)
Salicylic acid and derivatives	1 (0.8)	0 (0.0)	1 (0.3)
Heparin group	5 (3.9)	10 (3.8)	15 (3.8)
Heparin	2 (1.6)	6 (2.3)	8 (2.1)
Heparin fraction, sodium salt	2 (1.6)	1 (0.4)	3 (0.8)
Enoxaparin	1 (0.8)	7 (2.7)	8 (2.1)
Vitamin K antagonists	3 (2.3)	12 (4.6)	15 (3.8)
Warfarin sodium	3 (2.3)	12 (4.6)	15 (3.8)
Direct thrombin inhibitors	1 (0.8)	2 (0.8)	3 (0.8)
Bivalirudin	1 (0.8)	2 (0.8)	3 (0.8)

Supplementary Table S11. Incidence of Bleeding Events in 6-Month, Phase 3 Mipomersen Trials, Standardized MedDRA Query of Treatment Period

MedDRA SOC/preferred term, n *(%)*	*Placebo*	*Mipomersen*
n	129	261
Any bleeding event[a]	2 (1.6)	3 (1.1)
Antithrombotic agent, yes	2 (1.6)	2 (0.8)
Injury, poisoning, and procedural complications	1 (0.8)	1 (0.4)
Contusion	1 (0.8)	1 (0.4)
Investigations	0 (0)	1 (0.4)
Hematocrit decreased	0 (0)	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	1 (0.8)	0 (0)
Epistaxis	1 (0.8)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.4)
Ecchymosis	0 (0)	1 (0.4)
General disorders and administration site conditions	20 (15.5)	95 (36.4)
Injection site hematoma	18 (14.0)	83 (31.8)
Injection site hemorrhage	2 (1.6)	16 (6.1)

Table shows any bleeding event reported as possibly related, related, or of unknown relationship to study drug during the treatment period. SOC denotes system organ class.

[a]Events reported under the general disorders and administration site conditions SOC were excluded from the any bleeding event analysis.

Effect of 2′MOE ASO treatment on coagulation [9–12]

Supplementary Table S12. Incidence of Abnormal Coagulation Times in Randomized Placebo-Controlled Trials During Steady-State Conditions of the Drug Elimination Phase

Incidence of abnormal coagulation[a]			*ASO dose (mg/week)*					
n *(%)*	*Placebo*	*ASO total*	*>0–75*	*>75–175*	*>175–275*	*>275–375*	*>375–475*	*>475*
APTT, *n*	425	1,002	68	132	568	125	88	21
>1.4×ULN or BSLN if >ULN	1 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
>2.5×ULN or BSLN if >ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PT, *n*	393	888	60	105	522	108	74	19
>1.2×ULN, or BSLN if >ULN	5 (1.3)[b]	15 (1.7)	0 (0.0)	0 (0.0)	13 (2.5)[c]	1 (0.9)[d]	1 (1.4)	0 (0.0)

[a]Subjects had to have received at least two doses of study drug. Incidence based on observations from the last measure collected 5 days or more after a dose and before the end of the treatment period (10 days post last dose). Data from the FXI ASO trials were excluded due to the known pharmacological effect on APTT [8].

[b]Five of five taking anticoagulants.

[c]Ten of 13 taking anticoagulants.

[d]One of one taking anticoagulants.

APTT, activated partial thromboplastin time; PT, prothrombin time; ULN, upper limit of normal.

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