

## Supplementary Online Content

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**eTable 1. Injection Site Assessment 2 Days After Injection Using the FDA Vaccine Product Injection Site Reaction Grading Scale**

	All Participants (n=29)*	200 mg Q4wk x2 (n=5)	300 mg Q8wk x2 (n=9)	450 m Q8wk x2 (n=9)	Placebo (n=6)
<b>Pain</b>					
None – grade 0	22 (76)	4 (80)	6 (67)	6 (67)	6 (100)
Mild – grade 1	7 (24)	1 (20)	3 (33)	3 (33)	0 (0)
Moderate – grade 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe – grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Tenderness</b>					
None – grade 0	17 (59)	3 (60)	6 (67)	2 (22)	6 (100)
Mild – grade 1	10 (35)	1 (20)	3 (33)	6 (67)	0 (0)
Moderate – grade 2	2 (7)	1 (20)	0 (0)	1 (11)	0 (0)
Severe – grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Erythema/redness †</b>					
None – grade 0	6 (21)	0 (0)	1 (11)	0 (0)	5 (83)
Mild – grade 1	5 (17)	0 (0)	1 (11)	3 (33)	1 (17)
Moderate – grade 2	7 (24)	3 (60)	4 (44)	0 (0)	0 (0)
Severe – grade 3	11 (38)	2 (40)	3 (33)	6 (67)	0 (0)
<b>Induration/swelling</b>					
None – grade 0	25 (86)	5 (100)	9 (100)	5 (56)	6 (100)
Mild – grade 1	2 (7)	0 (0)	0 (0)	2 (22)	0 (0)
Moderate – grade 2	1 (3)	0 (0)	0 (0)	1 (11)	0 (0)
Severe – grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

\*n represents number of participants with non-missing values

† Four patients at day 7 had moderate or severe erythema/redness (1 in 200 mg q4wk x2 dose, 2 in 300 mg q8wk x2 dose, and 1 in 450 mg q8wk x2 dose)

**eTable 2. Lipoprotein(a) Concentration Over Time During Extended Follow-Up in the Single-Dose Cohort**

Time from Baseline		300 mg (N=6)	600 mg (N=6)	Placebo (N=8)
		<b>Median Baseline Lipoprotein(a) in nmol/L (IQR)</b>		
		285 (195,338)	231 (179,276)	238 (203,308)
		<b>Median Level and Change from Baseline, nmol/L (IQR)</b>		
Day 7	<i>Value</i>	<i>121 (75,214)</i>	<i>115 (90,130)</i>	<i>227 (175,319)</i>
	<i>Absolute change</i>	<i>-145 (-182,-100)</i>	<i>-113 (-153,-90)</i>	<i>-12 (-33,13)</i>
	<i>Percent change</i>	<i>-52 (-62,-44)</i>	<i>-48 (-54,-45)</i>	<i>-3 (-14,5)</i>
Day 14	<i>Value</i>	<i>48 (24, 101)</i>	<i>42 (33, 55)</i>	<i>233 (177, 306)</i>
	<i>Absolute change</i>	<i>-235 (-261, -152)</i>	<i>-179 (-242, -149)</i>	<i>-14 (-52, 11)</i>
	<i>Percent change</i>	<i>-81 (-88, -75)</i>	<i>-78 (-83, -76)</i>	<i>-3 (-18, 5)</i>
Day 30	<i>Value</i>	<i>18 (5, 46)</i>	<i>10 (7, 13)</i>	<i>251 (176, 309)</i>
	<i>Absolute change</i>	<i>-268 (-292, -189)</i>	<i>-219 (-272, -172)</i>	<i>-10 (-45, 10)</i>
	<i>Percent change</i>	<i>-95 (-97, -91)</i>	<i>-95 (-96, -94)</i>	<i>-4 (-12, 5)</i>
Day 60	<i>Value</i>	<i>14 (4, 58)</i>	<i>6 (6, 9)</i>	<i>265 (168, 282)</i>
	<i>Absolute change</i>	<i>-254 (-267, -194)</i>	<i>-227 (-270, -174)</i>	<i>-20 (-61, 3)</i>
	<i>Percent change</i>	<i>-96 (-98, -82)</i>	<i>-98 (-98, -97)</i>	<i>-10 (-16, 1)</i>
Day 90	<i>Value</i>	<i>35 (9, 106)</i>	<i>17 (6, 25)</i>	<i>234 (177, 298)</i>
	<i>Absolute change</i>	<i>-199 (-248, -174)</i>	<i>-222 (-251, -174)</i>	<i>-11 (-58, 23)</i>
	<i>Percent change</i>	<i>-87 (-96, -66)</i>	<i>-95 (-97, -91)</i>	<i>1 (-24, 10)</i>
Day 120	<i>Value</i>	NA	NA	NA
	<i>Absolute change</i>	NA	NA	NA
	<i>Percent change</i>	NA	NA	NA
Day 150 <sup>a</sup>	<i>Value</i>	<i>86 (31, 153)</i>	<i>49 (21, 61)</i>	<i>244 (192, 319)</i>
	<i>Absolute change</i>	<i>-177 (-226, -78)</i>	<i>-173 (-222, -159)</i>	<i>-13 (-48, 16)</i>
	<i>Percent change</i>	<i>-71 (-87, -48)</i>	<i>-81 (-92, -67)</i>	<i>-5 (-16, 8)</i>
Day 180 <sup>a</sup>	<i>Value</i>	NA	NA	NA
	<i>Absolute change</i>	NA	NA	NA
	<i>Percent change</i>	NA	NA	NA
Day 210 <sup>a</sup>	<i>Value</i>	<i>160 (85, 249)</i>	<i>135 (84, 148)</i>	<i>284 (186, 297)</i>
	<i>Absolute change</i>	<i>-119 (-356, -38)</i>	<i>-117 (-129, -97)</i>	<i>38 (6, 74)</i>
	<i>Percent change</i>	<i>-51 (-73, -20)</i>	<i>-45 (-72, -42)</i>	<i>14 (3, 35)</i>
Day 270 <sup>a</sup>	<i>Value</i>	<i>178 (82, 277)</i>	<i>148 (141, 160)</i>	<i>237 (191, 297)</i>
	<i>Absolute change</i>	<i>-122 (-294, -76)</i>	<i>-128 (-145, -72)</i>	<i>26 (10, 38)</i>
	<i>Percent change</i>	<i>-59 (-60, -39)</i>	<i>-46 (-50, -31)</i>	<i>12 (5, 14)</i>
Day 330 <sup>a</sup>	<i>Value</i>	<i>213 (116, 296)</i>	<i>144 (134, 228)</i>	<i>237 (191, 269)</i>
	<i>Absolute change</i>	<i>-108 (-297, -19)</i>	<i>-79 (-135, -19)</i>	<i>10 (10, 27)</i>
	<i>Percent change</i>	<i>-35 (-63, -6)</i>	<i>-35 (-43, -12)</i>	<i>6 (4, 13)</i>
Day 365 <sup>a</sup>	<i>Value</i>	<i>236 (124, 335)</i>	<i>155 (142, 215)</i>	<i>240 (204, 298)</i>
	<i>Absolute change</i>	<i>-102 (-136, -28)</i>	<i>-68 (-134, -17)</i>	<i>29 (24, 39)</i>
	<i>Percent change</i>	<i>-30 (-51, -18)</i>	<i>-29 (-39, -7)</i>	<i>14 (13, 15)</i>

Italicized values represent data previously published in the first-in-human study. <sup>a</sup>After day 150, there were 5 participants in the 300 mg dose group, 6 in the 600 mg dose group and 3 in the placebo group.

**eTable 3. Lipoprotein (a) Concentration Over Time in Multiple-Dose Cohort**

Time From baseline		Dose Group			
		200 mg Q4wk x2 (N=9)	300 mg Q8wk x2 (N=8)	450 mg Q8wk x2 (N=9)	Placebo (N=9)
		<b>Median Baseline, nmol/L (IQR)</b>			
		266 (194,295)	316 (276, 377)	247 (183, 350)	292 (217, 389)
		<b>Median Level and Change from Baseline, nmol/L (IQR)</b>			
Day 7	Value	162 (129,173)	170 (119, 237)	136 (80,154)	329 (208,369)
	Absolute change	-100 (-115, -72)	-153 (-178, -113)	-137 (-155,-111)	-0.9 (-9, 15)
	Percent change	-39 (-42,-35)	-45 (-53, -39)	-48 (-59, -45)	-0.5 (-2, 5)
Day 14	Value	71 (63, 79)	50 (38, 120)	58 (30, 64)	321 (224, 364)
	Absolute change	-149 (-217, -141)	-254 (-295, -211)	-209 (-275, -154)	2 (-22, 7)
	Percent change	-73 (-75, -67)	-79 (-87, -72)	-83 (-84, -78)	0.5 (-12, 3)
Day 30	Value	19 (16, 31)	18 (7, 36)	10 (7, 13)	355 (235, 385)
	Absolute change	-235 (-276, -176)	-300 (-339, -268)	-234 (-329, -180)	-0.7 (-24, 57)
	Percent change	-93 (-94, -88)	-95 (-97, -91)	-95 (-97, -95)	-0.4 (-6, 17)
Day 60	Value	8 (6, 9)	18 (7, 36)	10 (3, 20)	370 (227, 379)
	Absolute change	-258 (-289, -188)	-300 (-341, -268)	-236 (-278, -180)	10 (-16, 53)
	Percent change	-97 (-98, -95)	-94 (-97, -91)	-95 (-98, -94)	2 (-4, 14)
Day 90	Value	20 (8, 24)	5 (1, 11)	4 (1, 5)	348 (225, 394)
	Absolute change	-251 (-288, -183)	-310 (-368, -274)	-242 (-343, -182)	0.6 (-9, 24)
	Percent change	-94 (-97, -88)	-98 (-99, -97)	-99 (-99, -98)	1 (-3, 8)
Day 120	Value	39 (26, 53)	8 (4, 20)	6 (1, 7)	356 (216, 365)
	Absolute change	-220 (-270, -168)	-304 (-360, -273)	-240 (-348, -182)	-1 (-25, 9)
	Percent change	-82 (-91, -80)	-98 (-99, -94)	-98 (-99, -96)	-0.6 (-9, 5)
Day 150	Value	68 (60, 91)	14 (9, 35)	12 (5, 15)	342 (232, 370)
	Absolute change	-216 (-243, -136)	-295 (-344, -267)	-233 (-306, -180)	19 (-17, 28)
	Percent change	-70 (-77, -65)	-96 (-97, -90)	-96 (-97, -92)	7 (-4, 21)
Day 180	Value	88 (76, 115)	36 (21, 55)	23 (10, 29)	319 (215, 401)
	Absolute change	-178 (-209, -126)	-276 (-309, -248)	-194 (-266, -157)	7 (-2, 27)
	Percent change	-61 (-73, -55)	-90 (-93, -82)	-92 (-94, -84)	2 (-0.7, 7)
Day 201	Value	117 (82, 140)	35 (27, 83)	30 (20, 47)	368 (240, 417)
	Absolute change	-146 (-206, -126)	-263 (-286, -221)	-164 (-262, -155)	0.4 (-6, 41)
	Percent change	-60 (-71, -40)	-90 (-91, -74)	-89 (-91, -76)	0.3 (-2, 21)

**eTable 4. Change in LDL-C During Multidose Phase of the Trial**

Time from Baseline		(n=9) 200mg Q4W	(n=8) 300mg Q8W	(n=9) 450mg Q8W	Placebo (n=9)
		<b>Median Baseline LDL Cholesterol in mg/dL (Q1, Q3)</b>			
		68 (45, 77)	59 (45, 69)	65 (55, 85)	58 (51, 89)
<b>Median change from baseline in LDL Cholesterol, mg/dL (Q1, Q3)</b>					
7 days	Absolute Change	-6 (-19, 11)	4 (-13, 15)	-11 (-13, -6)	1 (-6, 2)
	Percentage Change	-9 (-16, 17)	6 (-23, 33)	-15 (-16, -11)	3 (-11, 3)
14 days	Absolute Change	-7 (-23, -2)	-15 (-38, -6)	-17 (-19, -11)	1 (-2, 5)
	Percentage Change	-13 (-22, -2)	-45 (-60, -11)	-21 (-30, -17)	2 (-5, 7)
30 days	Absolute Change	-22 (-32, -3)	-25 (-40, -8)	-13 (-35, -11)	-2 (-9, -1)
	Percentage Change	-27 (-43, -8)	-47 (-64, -12)	-20 (-25, -14)	-3 (-15, -1)
36 days*	Absolute Change	-22 (-40, -4)	NA	NA	8 (-4, 13)
	Percentage Change	-29 (-50, -9)	NA	NA	13 (-8, 22)
43 days*	Absolute Change	-29 (-47, -8)	NA	NA	-6 (-9, -6)
	Percentage Change	-31 (-61, -19)	NA	NA	-12 (-15, -10)
60 days	Absolute Change	-28 (-39, -17)	-17 (-35, 5)	-14 (-30, -12)	1 (-3, 7)
	Percentage Change	-35 (-45, -26)	-31 (-58, 13)	-22 (-38, -18)	2 (-5, 14)
66 days**	Absolute Change	NA	-22 (-31, -1)	-17 (-25, -14)	-5 (-7, 0)
	Percentage Change	NA	-34 (-52, -2)	-26 (-35, -9)	-8 (-10, 0)
73 days**	Absolute Change	NA	-19 (-34, -7)	-18 (-25, -11)	-3 (-19, 6)
	Percentage Change	NA	-31 (-57, -11)	-26 (-34, -12)	-6 (-17, 13)
90 days	Absolute Change	-20 (-39, -1)	-23 (-32, -13)	-30 (-38, -11)	-4 (-4, 8)
	Percentage Change	-26 (-45, 0)	-35 (-50, -21)	-28 (-38, -26)	-4 (-6, 14)
120 days	Absolute Change	-24 (-30, -2)	-9 (-19, -1)	-10 (-43, -8)	1 (-2, 9)
	Percentage Change	-26 (-37, -3)	-13 (-40, -2)	-25 (-46, -12)	2 (-4, 16)
150 days	Absolute Change	-22 (-31, -4)	-11 (-17, -5)	-19 (-31, -4)	7 (-1, 17)
	Percentage Change	-31 (-42, -9)	-24 (-36, -7)	-17 (-33, -8)	17 (-2, 29)
180 days	Absolute Change	11 (-15, 28)	-12 (-14, -9)	-11 (-13, -6)	1 (0, 7)
	Percentage Change	9 (-19, 55)	-18 (-25, -12)	-14 (-20, -8)	2 (0, 12)
201 days	Absolute Change	-2 (-31, 7)	-8 (-14, -2)	-9 (-22, -1)	4 (3, 6)
	Percentage Change	-2 (-34, 22)	-13 (-34, -2)	-11 (-28, 0)	7 (6, 10)

**eTable 5. Change in Apo B During Multiple-Dose Phase of the Trial**

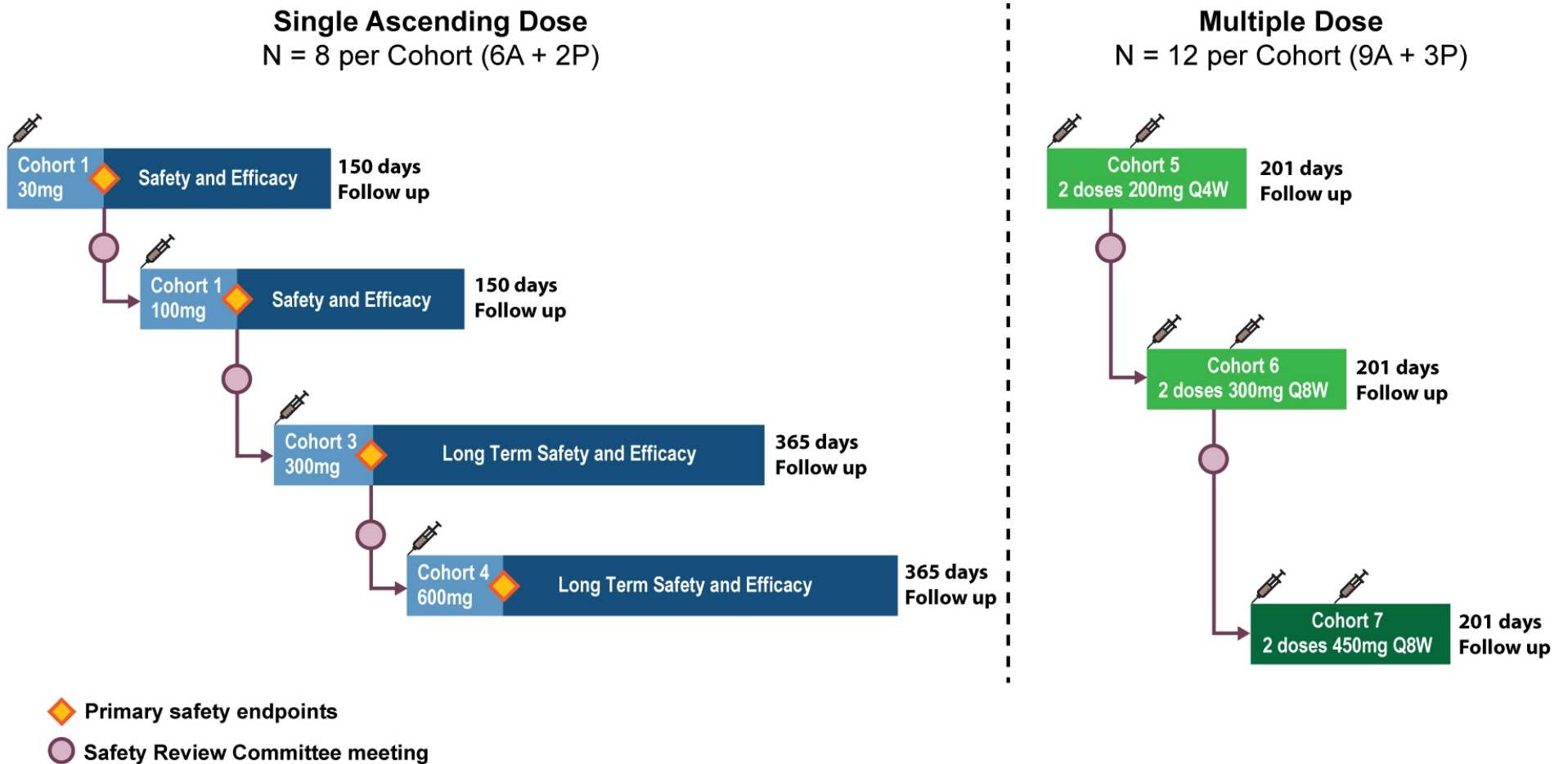
Time from Baseline		(n=9)	(n=8)	(n=9)	Placebo
		200mg Q4W	300mg Q8W	450mg Q8W	(n=9)
		Median Baseline Apolipoprotein B in mg/dL (Q1, Q3)			
		63 (45, 72)	58 (52, 67)	65 (58, 70)	63 (61, 81)
		Median Change from Baseline in Apolipoprotein B, mg/dL (Q1, Q3)			
7 days	Absolute Change	-2 (-11, 5)	0 (-6, 5)	-7 (-10, -2)	2 (-2, 3)
	Percentage Change	-3 (-9, 11)	0 (-10, 7)	-11 (-11, -4)	4 (-3, 5)
14 days	Absolute Change	-6 (-18, 2)	-12 (-17, -4)	-7 (-14, -6)	3 (0, 5)
	Percentage Change	-17 (-21, 3)	-22 (-35, -5)	-15 (-17, -10)	3 (0, 11)
30 days	Absolute Change	-10 (-28, -2)	-18 (-20, -11)	-11 (-30, -9)	-2 (-9, 0)
	Percentage Change	-25 (-28, -4)	-25 (-39, -19)	-17 (-26, -13)	-3 (-10, 0)
36 days*	Absolute Change	-11 (-36, -6)	NA	NA	1 (0, 4)
	Percentage Change	-23 (-37, -10)	NA	NA	2 (0, 9)
43 days*	Absolute Change	-13 (-26, -4)	NA	NA	-4 (-7, 1)
	Percentage Change	-26 (-35, -8)	NA	NA	-6 (-11, 2)
60	Absolute Change	-13 (-21, -4)	-14 (-23, -3)	-12 (-17, -10)	2 (-5, 11)
	Percentage Change	-20 (-29, -9)	-24 (-41, -6)	-21 (-22, -17)	5 (-8, 10)
66 days**	Absolute Change	NA	-12 (-19, 0)	-16 (-21, -8)	-3 (-7, 0)
	Percentage Change	NA	-21 (-29, 0)	-19 (-23, -17)	-3 (-7, 0)
73 days**	Absolute Change	NA	-17 (-26, -10)	-15 (-18, -9)	-5 (-7, 2)
	Percentage Change	NA	-28 (-44, -16)	-19 (-24, -15)	-4 (-11, 3)
90 days	Absolute Change	-5 (-23, 2)	-17 (-23, -12)	-14 (-30, -10)	-2 (-7, 7)
	Percentage Change	-11 (-31, 3)	-28 (-37, -21)	-23 (-34, -22)	-3 (-9, 10)
120 days	Absolute Change	-9 (-18, -6)	-14 (-18, -8)	-16 (-27, -8)	0 (-7, 2)
	Percentage Change	-15 (-19, -12)	-23 (-29, -11)	-22 (-36, -13)	0 (-11, 2)
150 days	Absolute Change	-8 (-19, -1)	-12 (-19, -6)	-9 (-23, -4)	7 (2, 10)
	Percentage Change	-14 (-23, -1)	-21 (-30, -10)	-14 (-22, -7)	12 (2, 17)
180 days	Absolute Change	12 (-6, 28)	-9 (-19, -4)	-5 (-18, 0)	5 (-5, 10)
	Percentage Change	21 (-8, 51)	-14 (-28, -6)	-8 (-16, 0)	11 (-5, 19)
201 days	Absolute Change	-2 (-7, 10)	-3 (-11, 6)	-12 (-23, 0)	8 (4, 11)
	Percentage Change	-4 (-20, 24)	-5 (-20, 8)	-10 (-35, 0)	9 (6, 17)

**eTable 6. Absolute and Percent Change in Oxidized LDL-C During Multiple-Dose Phase of the Trial**

Time from Baseline		(n=9) 200mg Q4W	(n=8) 300mg Q8W	(n=9) 450mg Q8W	Placebo (n=9)
		Mean Baseline Oxidized LDL Cholesterol in U/L* (SD)			
		48 (25)	42 (13)	57 (41)	49 (17)
<b>Mean Change from Baseline in Oxidized LDL Cholesterol in U/L* (SD)</b>					
7 days	Absolute Change	-2 (8)	1 (9)	-15 (25)	1.5 (10)
	Percentage Change	-2 (19)	7 (24)	-16 (19)	6 (19)
14 days	Absolute Change	-7 (10)	-7 (10)	-18 (27)	-2 (10)
	Percentage Change	-10 (20)	-17 (19)	-22 (18)	-0.6 (19)
30 days	Absolute Change	-7 (9)	-6 (16)	-20 (28)	-3 (7)
	Percentage Change	-13 (12)	-7 (50)	-26 (23)	-5 (13)
36 days	Absolute Change	-9 (9)	NA	NA	-1 (4)
	Percentage Change	-18 (14)	NA	NA	-2 (10)
43 days	Absolute Change	-9 (9)	NA	NA	-1 (8)
	Percentage Change	-19 (13)	NA	NA	-1 (19)
60	Absolute Change	-5 (11)	-5 (12)	-19 (27)	14 (43)
	Percentage Change	-11 (20)	-13 (26)	-24 (19)	32 (84)
66 days	Absolute Change	NA	-4 (13)	-17 (26)	-5 (11)
	Percentage Change	NA	-4 (36)	-21 (26)	-7 (19)
73 days	Absolute Change	NA	-10 (11)	-20 (28)	-5 (11)
	Percentage Change	NA	-23 (25)	-23 (20)	-4 (21)
90 days	Absolute Change	-3 (14)	-8 (12)	-18 (25)	-2 (12)
	Percentage Change	-5 (25)	-15 (33)	-23 (28)	1 (22)
120 days	Absolute Change	-2 (9)	-5 (7)	-18 (24)	0.6 (14)
	Percentage Change	-2 (15)	-14 (22)	-25 (26)	9 (32)
150 days	Absolute Change	-0.7 (15)	-5 (8)	-19 (26)	6 (13)
	Percentage Change	4 (27)	-11 (22)	-24 (22)	18 (31)
180 days	Absolute Change	17 (14)	-4 (6)	-14 (28)	5 (10)
	Percentage Change	35 (31)	-9 (15)	-14 (26)	13 (22)
201 days	Absolute Change	10 (19)	-2 (7)	-16 (27)	2 (10)
	Percentage Change	25 (37)	-5 (22)	-19 (32)	9 (24)



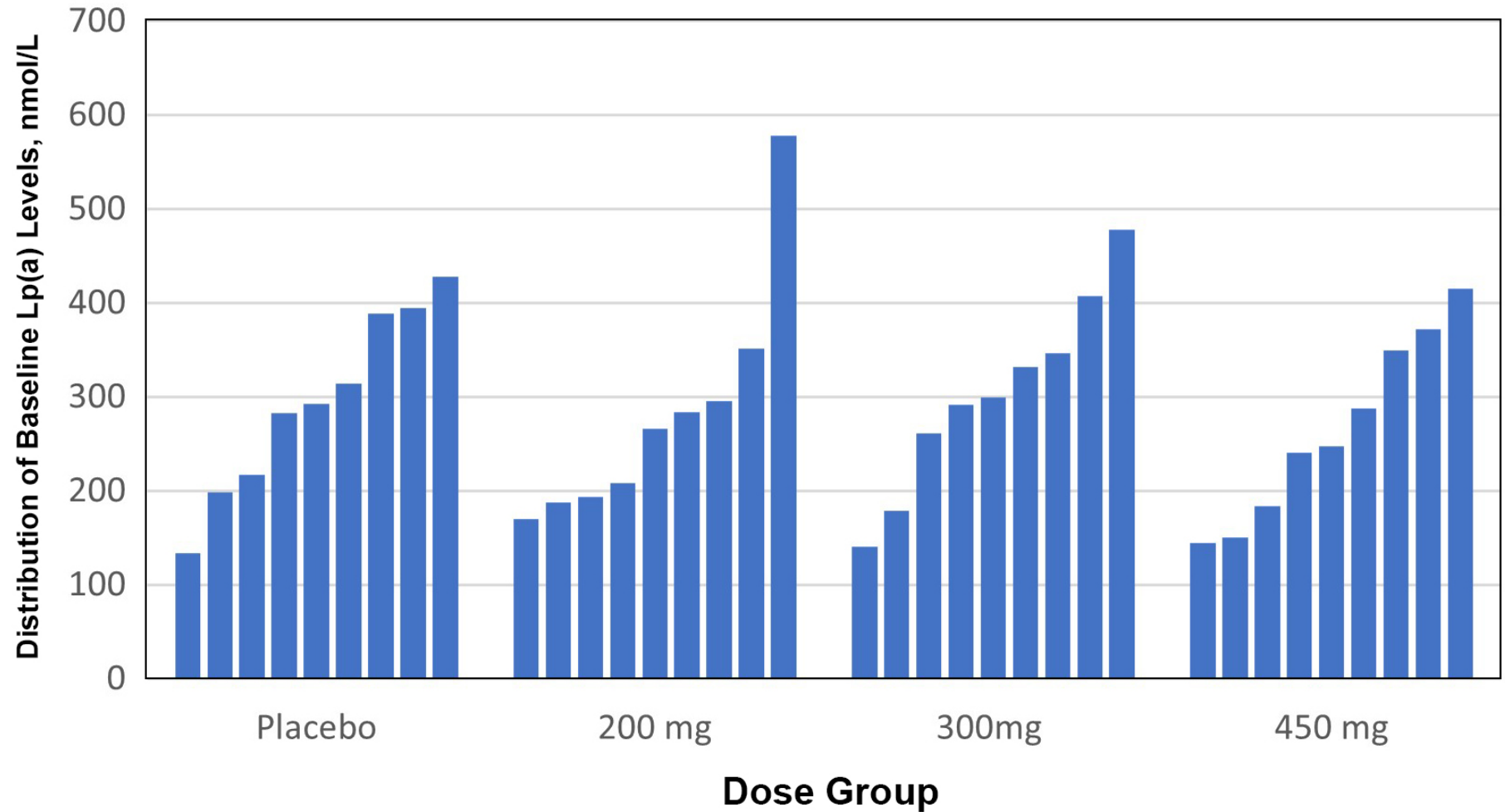
eFigure 1. Schematic of the Phase 1 Trial Showing the Ascending-Dose Approach for Single and Multiple Doses.



A - Zelarisan

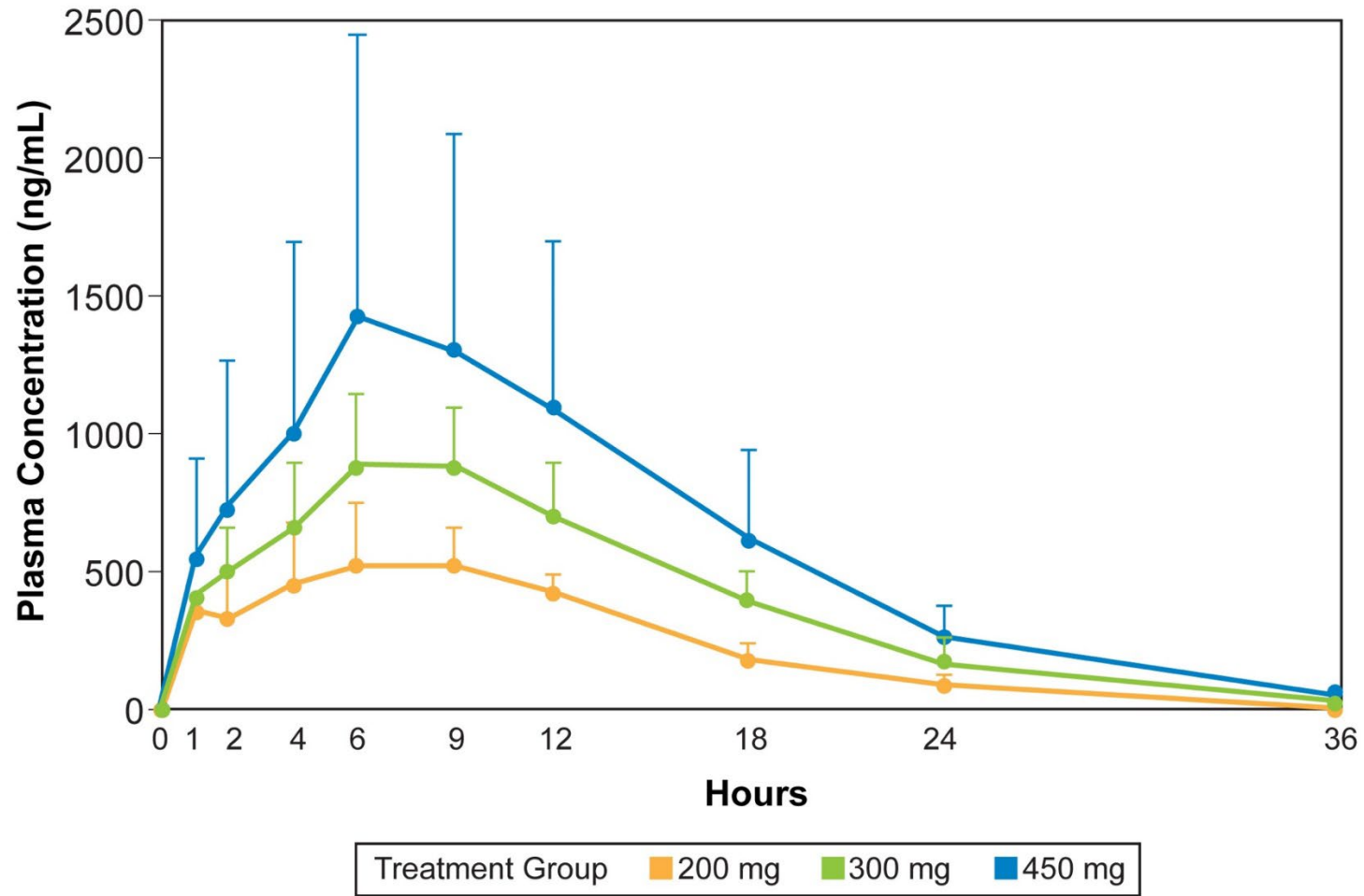
P - Placebo (sodium chloride solution for injection)

A safety review committee evaluated each of the ascending dose groups and recommended escalation to the next higher dose levels based on initial safety and efficacy findings. At the recommendation of the committee, the two highest doses, 300 mg and 600 mg, had extended follow up to 365 days.

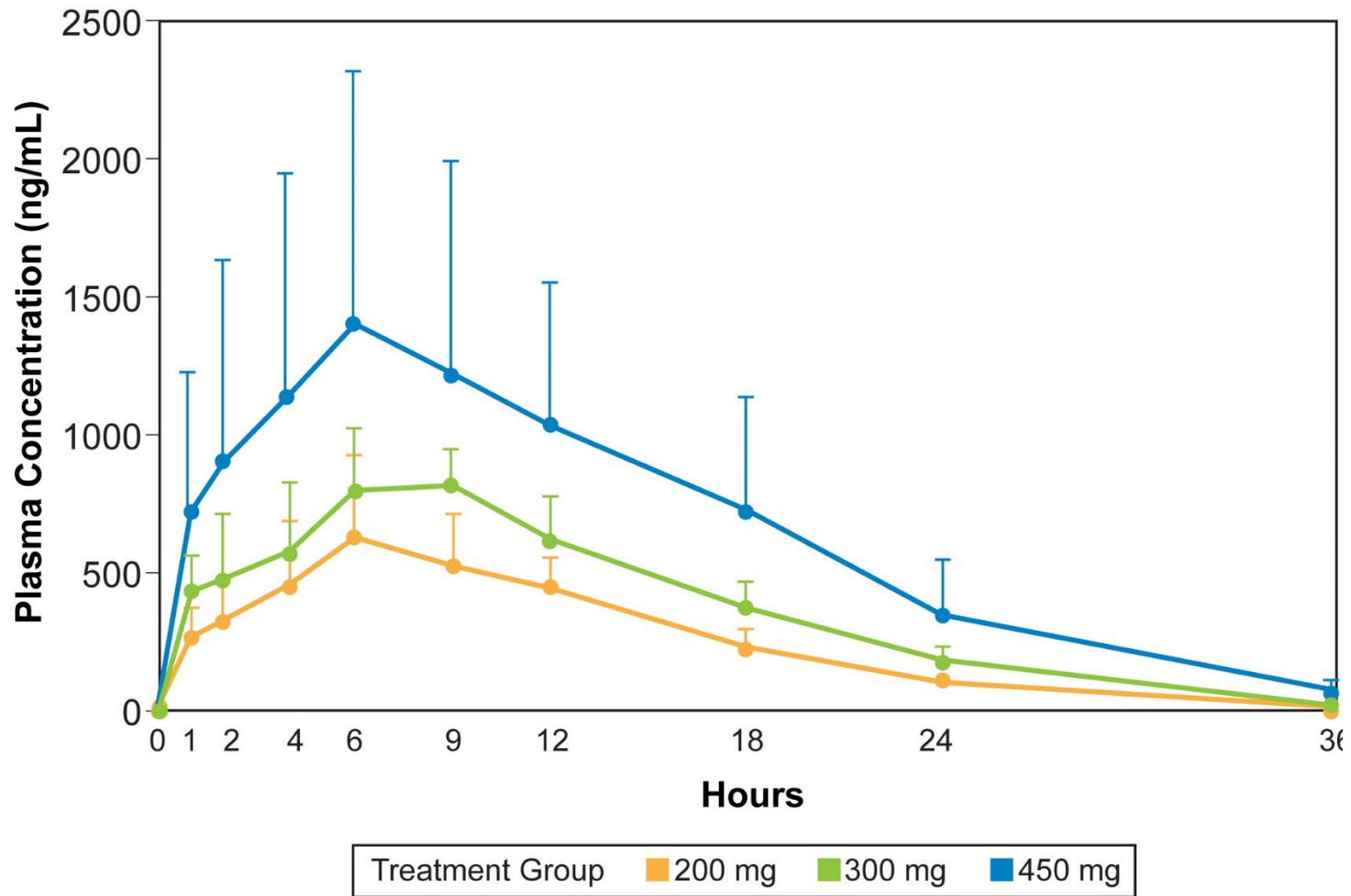
**eFigure 2. Distribution of Baseline Lipoprotein (a) Levels**

Baseline values for lipoprotein(a) in patients randomized in the multiple dose phase of the trial. Each bar represents the baseline Lp(a) value for a single patient.

eFigure 3A. Plasma Concentrations of Zerlasiran After the First Administered Dose

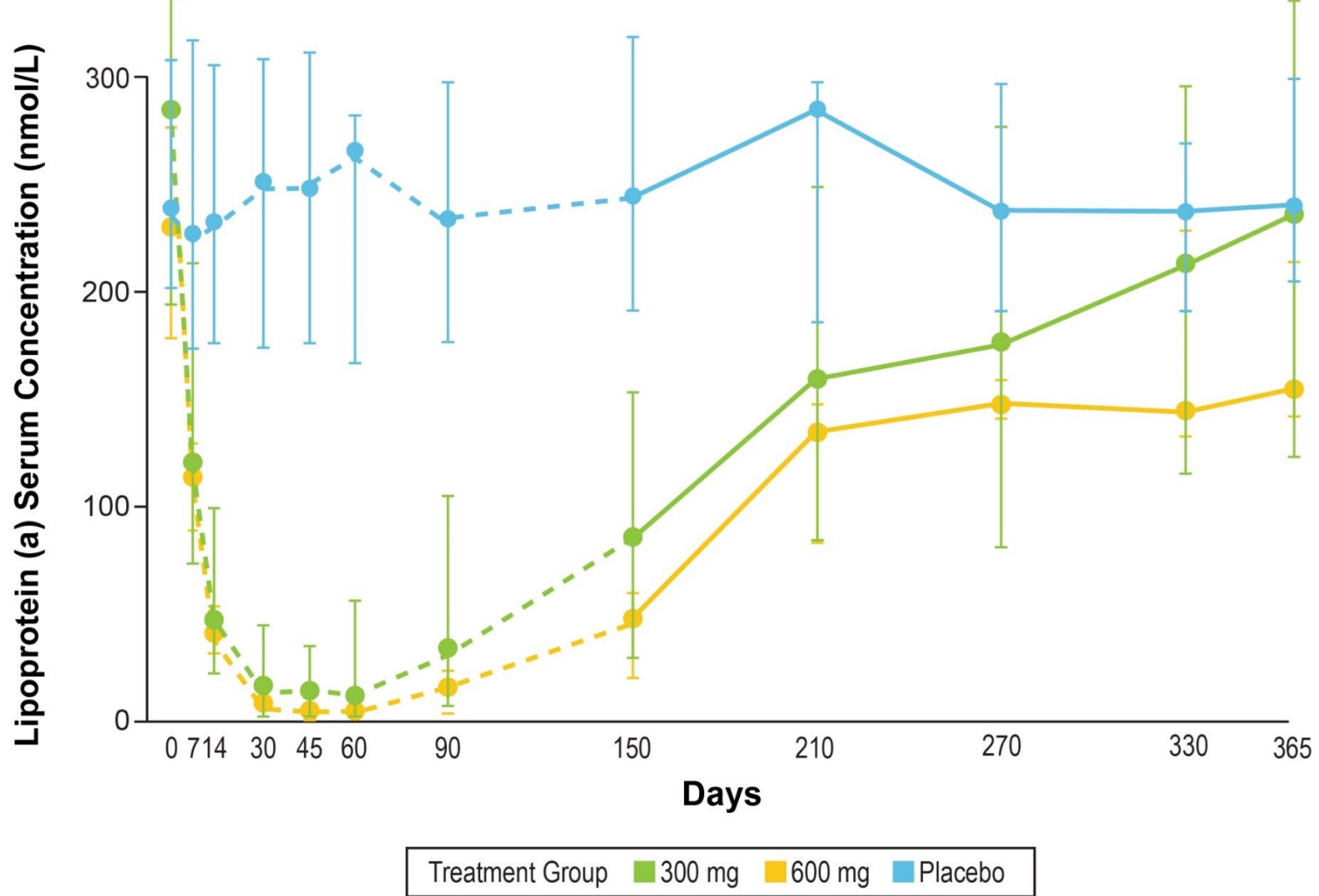


eFigure 3B. Plasma Concentrations of Zerlasiran after the Second Administered Dose



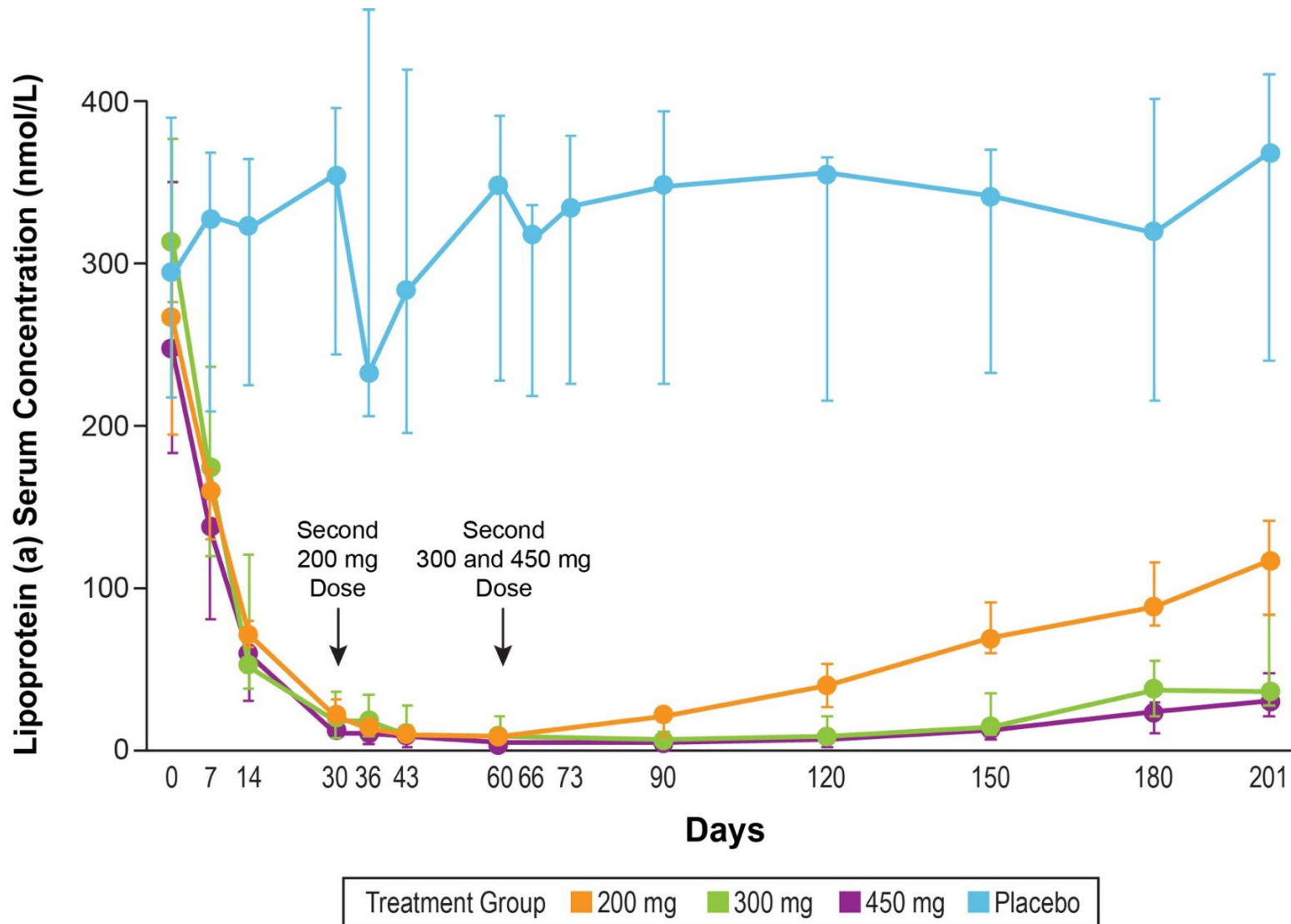
Plasma concentrations of zerlasiran during the first 36 hours following drug administration for the multiple dose cohort. Panel A. The solid circles indicate the mean values following the first injection, and the error bars show the standard deviations for plasma concentrations of zerlasiran at each time point. Panel B. Mean and standard deviations for plasma concentrations after the second injection.

eFigure 4. Observed Lipoprotein(a) Concentrations During 365 Days Follow-Up After a Single Dose



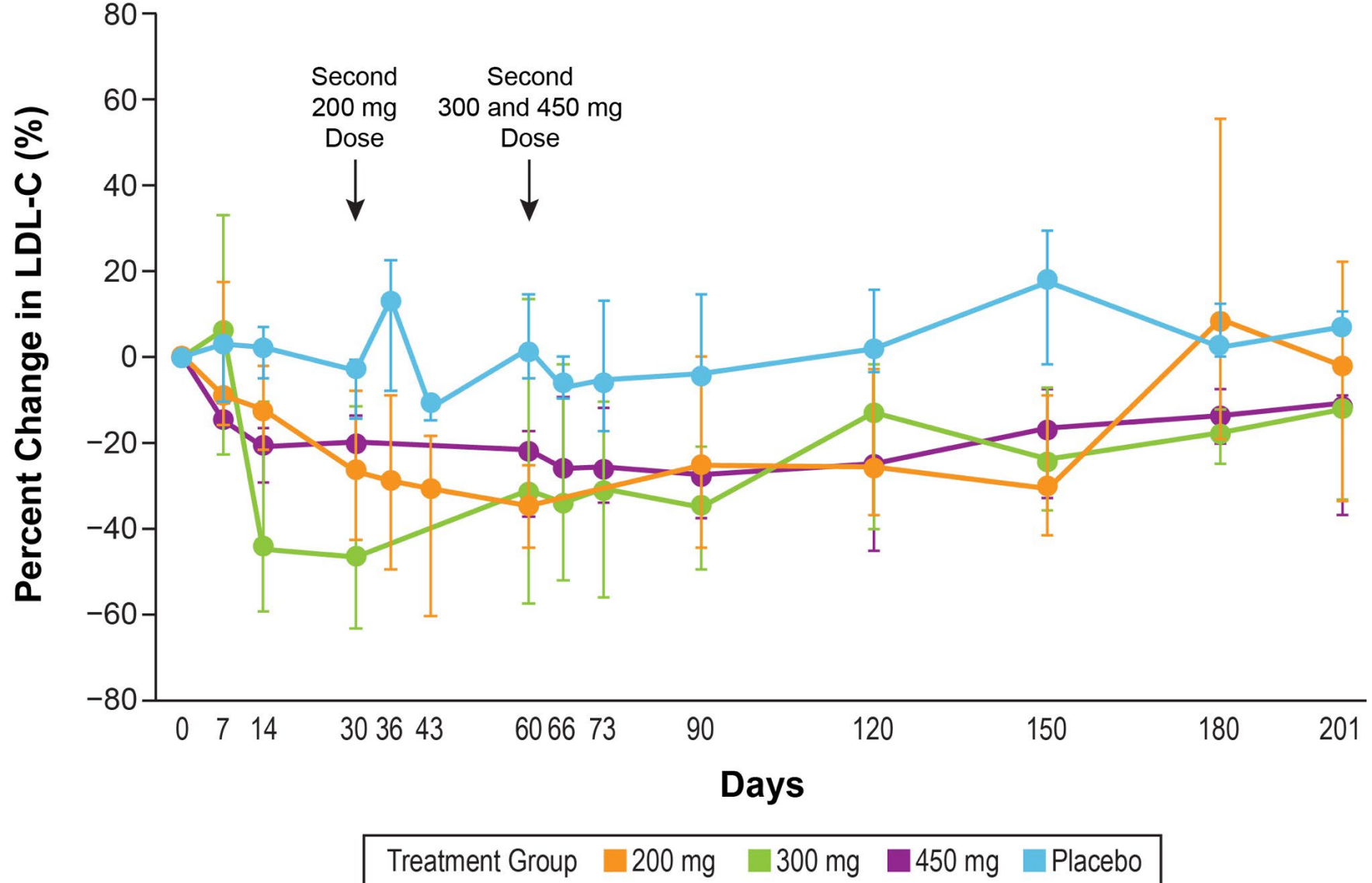
Observed Lipoprotein(a) concentrations during 365 days follow up after a single dose. The solid circles indicate median values and the error bars the IQR values after administration of single doses of zerlasiran. The dashed lines show previously reported data for Lp(a) concentrations during the first 150 days following administration.

eFigure 5. Observed Lipoprotein(a) Concentrations During 201 Days Follow-Up After Multiple Doses



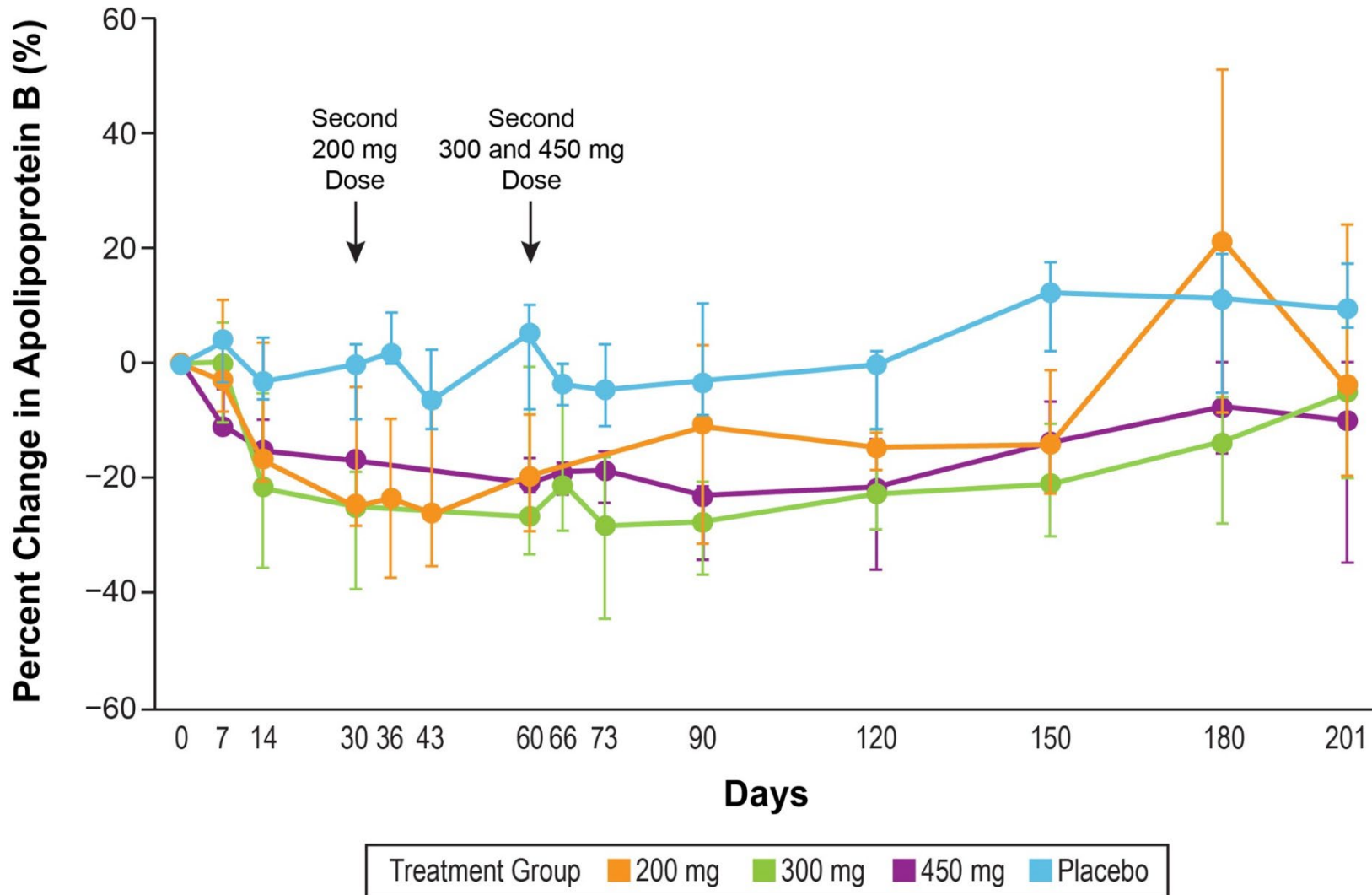
Median and IQR values for Lp(a) concentrations for the multiple dose cohort. The solid circles indicate median values and the error bars the IQR values for Lp(a) concentrations.

eFigure 6. Percent Change in LDL-C During 201 Days Follow-up After Multiple Doses



The solid circles indicate median values and the error bars the IQR values after administration of single and multiple doses of zelasiran.

**eFigure 7. Percent Change in Apo B During 201 Days Follow-Up After Multiple Doses**



The solid circles indicate median values and the error bars the IQR values after administration of single and multiple doses of zerlasiran.