Supplemental Online Content

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eTable1. Summary Statistics of Muvalaplin Dose Proportionality Analysis.

Part	Day	Dose Range	Parameter	Slope	Intercept	95% CI	
						Lower	Upper
SAD	1	30 mg to 800 mg	C_{max}	0.617	0.744	0.449	0.784
			AUC_{0-inf}	0.705	3.384	0.397	1.012
MAD	1	30mg to 800 mg QD	C_{max}	0.704	0.702	0.601	0.807
	14	30mg to 800 mg QD	C_{max}	0.628	1.144	0.534	0.722
			AUC_{0-tau}	0.640	3.826	0.540	0.740

eTable 1. Muvalaplin dose proportionality analysis. Power model: log(PK)=slope*log(dose) + intercept + error. Dose proportionality was concluded if the 95% CI for the slope was contained completely within 0.80 to 1.25 limits. If the 95% CI was completely outside of 0.80 to 1.25 limits, then “not proportional” was concluded. If the 95% CI was partly within the limits, “inconclusive” was concluded. AUC_{0-inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; AUC_{0-tau}, area under the plasma concentration-time curve during a dosing interval; CI, confidence interval; QD, once daily.

eTable2. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term* (SAD Part).

		Muvalaplin							
	Placebo	1 mg	10 mg	30 mg	100 mg	200 mg	400 mg	800 mg	Overall
	(N = 14)	(N = 6)	(N = 6)	(N = 6)	(N = 6)	(N = 5)	(N = 6)	(N = 6)	(N = 55)
	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)
Any treatment-emergent adverse event	19, 7 (50)	4, 3 (50)	9, 4 (67)	3, 2 (33)	8, 4 (67)	7, 4 (80)	5, 4 (67)	16, 6 (100)	71, 34 (62)
Nervous system disorders	9, 6 (43)	1, 1 (17)	2, 2 (33)	1, 1 (17)	3, 2 (33)	2, 2 (40)	2, 2 (33)	5, 4 (67)	25, 20 (36)
Headache	5, 5 (36)	1, 1 (17)	2, 2 (33)	0	2, 2 (33)	2, 2 (40)	2, 2 (33)	4, 4 (67)	18, 18 (33)
Dizziness	2, 2 (14)	0	0	0	1, 1 (17)	0	0	0	3, 3 (5)
Burning sensation	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Presyncope	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Restless legs syndrome	0	0	0	1, 1 (17)	0	0	0	0	1, 1 (2)
Syncope	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
General disorders and administration site conditions	5, 4 (29)	0	1, 1 (17)	1, 1 (17)	1, 1 (17)	1, 1 (20)	3, 3 (50)	1, 1 (17)	13, 12 (22)
Fatigue	3, 3 (21)	0	0	1, 1 (17)	0	1, 1 (20)	0	1, 1 (17)	6, 6 (11)
Catheter site pain	0	0	0	0	0	0	2, 2 (33)	0	2, 2 (4)
Asthenia	0	0	0	0	1, 1 (17)	0	0	0	1, 1 (2)
Catheter site swelling	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Medical device site pruritus	0	0	1, 1 (17)	0	0	0	0	0	1, 1 (2)
Vessel puncture site erythema	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Vessel puncture site pain	0	0	0	0	0	0	1, 1 (17)	0	1, 1 (2)
Musculoskeletal and connective tissue disorders	0	1, 1 (17)	2, 2 (33)	1, 1 (17)	3, 3 (50)	0	0	0	7, 7 (13)
Back pain	0	1, 1 (17)	2, 2 (33)	1, 1 (17)	3, 3 (50)	0	0	0	7, 7 (13)
Gastrointestinal disorders	0	0	1, 1 (17)	0	1, 1 (17)	3, 2 (40)	0	6, 2 (33)	11, 6 (11)
Diarrhea	0	0	0	0	0	2, 2 (40)	0	0	2, 2 (4)
Nausea	0	0	1, 1 (17)	0	0	0	0	2, 1 (17)	3, 2 (4)
Abdominal distension	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Abdominal pain	0	0	0	0	1, 1 (17)	0	0	0	1, 1 (2)
Gastrointestinal sounds abnormal	0	0	0	0	0	1, 1 (20)	0	0	1, 1 (2)
Vomiting	0	0	0	0	0	0	0	3, 1 (17)	3, 1 (2)
Injury, poisoning and procedural complications	2, 2 (14)	2, 2 (33)	0	0	0	0	0	3, 2 (33)	7, 6 (11)

Contusion	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Fall	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Hand fracture	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Joint dislocation	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Procedural dizziness	0	1, 1 (17)	0	0	0	0	0	0	1, 1 (2)
Procedural nausea	0	1, 1 (17)	0	0	0	0	0	0	1, 1 (2)
Traumatic hematoma	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Skin and subcutaneous tissue disorders	1, 1 (7)	0	0	0	0	1, 1 (20)	0	1, 1 (17)	3, 3 (5)
Dry skin	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Pruritus	0	0	0	0	0	1, 1 (20)	0	0	1, 1 (2)
Skin irritation	0	0	0	0	0	0	0	1, 1 (17)	1, 1 (2)
Infections and infestations	0	0	2, 2 (33)	0	0	0	0	0	2, 2 (4)
COVID-19	0	0	2, 2 (33)	0	0	0	0	0	2, 2 (4)
Cardiac disorders	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Palpitations	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Reproductive system and breast disorders	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Dysmenorrhea	1, 1 (7)	0	0	0	0	0	0	0	1, 1 (2)
Respiratory, thoracic and mediastinal disorders	0	0	1, 1 (17)	0	0	0	0	0	1, 1 (2)
Nasal congestion	0	0	1, 1 (17)	0	0	0	0	0	1, 1 (2)

eTable 2. Treatment-emergent adverse events by system organ class and preferred term in the single ascending dose (SAD) part.[*] AEs are coded using MedDRA Version 23.1. AE=adverse event; E=number of AEs; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects exposed; n=number of subjects who experienced the AEs; TEAE=treatment-emergent adverse event; %=number of subjects (n) as a percentage of number of subjects (N) per treatment.

eTable 3. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term* (MAD Part).

		Muvalaplin					
	Placebo QD	30 mg QD	100 mg QD	300 mg QD	500 mg QD	800 mg QD	Overall
	(N = 11)	(N = 8)	(N = 8)	(N = 9)	(N = 8)	(N = 15)	(N = 59)
	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)	E, n (%)
Any treatment-emergent adverse event	36, 9 (82)	30, 7 (88)	24, 5 (63)	48, 7 (78)	17, 7 (88)	20, 12 (80)	175, 47 (80)
Gastrointestinal disorders	12, 4 (36)	6, 4 (50)	7, 2 (25)	12, 7 (78)	2, 2 (25)	6, 5 (33)	45, 24 (41)
Diarrhea	1, 1 (9)	1, 1 (13)	3, 2 (25)	4, 4 (44)	1, 1 (13)	3, 3 (20)	13, 12 (20)
Abdominal pain	4, 2 (18)	3, 3 (38)	0	4, 4 (44)	0	0	11, 9 (15)
Nausea	2, 2 (18)	1, 1 (13)	1, 1 (13)	2, 2 (22)	0	0	6, 6 (10)
Gastrointestinal sounds abnormal	0	0	0	1, 1 (11)	1, 1 (13)	1, 1 (7)	3, 3 (5)
Abdominal discomfort	2, 2 (18)	0	0	0	0	0	2, 2 (3)
Abdominal distension	0	0	1, 1 (13)	1, 1 (11)	0	0	2, 2 (3)
Abdominal pain upper	1, 1 (9)	0	0	0	0	1, 1 (7)	2, 2 (3)
Change of bowel habit	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Dyspepsia	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Flatulence	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Gastric disorder	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Lip dry	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Toothache	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Nervous system disorders	7, 5 (45)	8, 5 (63)	1, 1 (13)	8, 5 (56)	5, 3 (38)	7, 5 (33)	36, 24 (41)
Headache	4, 4 (36)	5, 4 (50)	1, 1 (13)	7, 4 (44)	3, 2 (25)	4, 3 (20)	24, 18 (31)
Dizziness	0	0	0	1, 1 (11)	1, 1 (13)	1, 1 (7)	3, 3 (5)
Paraesthesia	0	3, 3 (38)	0	0	0	0	3, 3 (5)
Poor quality sleep	0	0	0	0	0	2, 2 (13)	2, 2 (3)
Lethargy	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Presyncope	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Sleep paralysis	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Tremor	1, 1 (9)	0	0	0	0	0	1, 1 (2)
General disorders and administration site conditions	4, 3 (27)	8, 5 (63)	5, 3 (38)	9, 5 (56)	4, 3 (38)	2, 2 (13)	32, 21 (36)
Fatigue	0	0	0	4, 3 (33)	2, 2 (25)	1, 1 (7)	7, 6 (10)

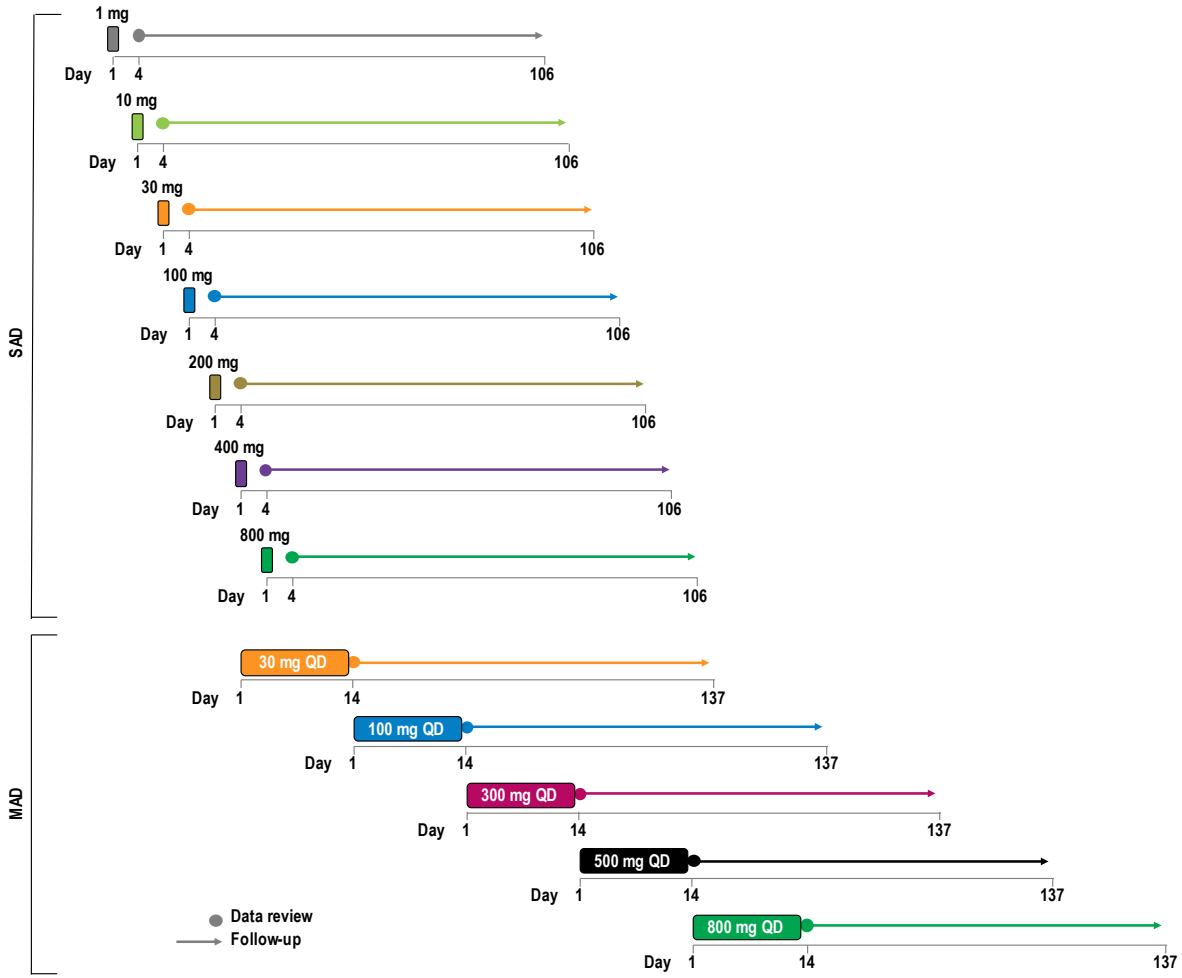
Catheter site pain	0	3, 2 (25)	2, 2 (25)	1, 1 (11)	0	0	6, 5 (8)
Vessel puncture site bruise	2, 2 (18)	0	1, 1 (13)	3, 2 (22)	0	0	6, 5 (8)
Catheter site bruise	1, 1 (9)	0	0	1, 1 (11)	0	0	2, 2 (3)
Drug withdrawal syndrome	0	2, 2 (25)	0	0	0	0	2, 2 (3)
Vessel puncture site pain	0	1, 1 (13)	0	0	0	1, 1 (7)	2, 2 (3)
Application site pruritus	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Catheter site swelling	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Feeling cold	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Influenza like illness	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Medical device site erythema	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Vaccination site pain	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Vessel puncture site erythema	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Musculoskeletal and connective tissue disorders	2, 2 (18)	4, 4 (50)	3, 2 (25)	4, 2 (22)	1, 1 (13)	0	14, 11 (19)
Back pain	1, 1 (9)	0	1, 1 (13)	2, 2 (22)	0	0	4, 4 (7)
Arthralgia	1, 1 (9)	1, 1 (13)	0	2, 1 (11)	0	0	4, 3 (5)
Muscle spasms	0	2, 2 (25)	0	0	0	0	2, 2 (3)
Musculoskeletal chest pain	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Myalgia	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Pain in extremity	0	0	2, 1 (13)	0	0	0	2, 1 (2)
Skin and subcutaneous tissue disorders	3, 3 (27)	1, 1 (13)	6, 3 (38)	3, 3 (33)	0	0	13, 10 (17)
Acne	1, 1 (9)	1, 1 (13)	2, 2 (25)	1, 1 (11)	0	0	5, 5 (8)
Dry skin	0	0	2, 2 (25)	1, 1 (11)	0	0	3, 3 (5)
Erythema	0	0	1, 1 (3)	0	0	0	1, 1 (2)
Hyperhidrosis	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Night sweats	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Rash	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Skin fissures	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Injury, poisoning and procedural complications	1, 1 (9)	1, 1 (13)	1, 1 (13)	1, 1 (11)	0	2, 2 (13)	6, 6 (10)
Contusion	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Injury	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Procedural dizziness	1, 1 (9)	0	0	0	0	0	1, 1 (2)

Traumatic hematoma	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Ulnar nerve injury	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Wrist fracture	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Respiratory, thoracic and mediastinal disorders	0	0	1, 1 (13)	4, 3 (33)	0	1, 1 (7)	6, 5 (8)
Epistaxis	0	0	1, 1 (13)	3, 2 (22)	0	0	4, 3 (5)
Nasal dryness	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Oropharyngeal pain	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Infections and infestations	1, 1 (9)	1, 1 (13)	0	0	0	2, 2 (13)	4, 4 (7)
Asymptomatic COVID-19	0	1, 1 (13)	0	0	0	0	1, 1 (2)
COVID-19	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Gingivitis	0	0	0	0	0	1, 1 (7)	1, 1 (2)
Nasopharyngitis	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Ear and labyrinth disorders	0	1, 1 (13)	0	0	2, 2 (25)	0	3, 3 (5)
Ear pain	0	1, 1 (13)	0	0	1, 1 (13)	0	2, 2 (3)
External ear inflammation	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Renal and urinary disorders	2, 1 (9)	0	0	1, 1 (11)	1, 1 (13)	0	4, 3 (5)
Pollakiuria	1, 1 (9)	0	0	1, 1 (11)	1, 1 (13)	0	3, 3 (5)
Chromaturia	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Reproductive system and breast disorders	1, 1 (9)	0	0	2, 2 (22)	0	0	3, 3 (5)
Dysmenorrhea	1, 1 (9)	0	0	2, 2 (22)	0	0	3, 3 (5)
Metabolism and nutrition disorders	0	0	0	2, 2 (22)	0	0	2, 2 (3)
Decreased appetite	0	0	0	2, 2 (22)	0	0	2, 2 (3)
Psychiatric disorders	2, 2 (18)	0	0	0	0	0	2, 2 (3)
Insomnia	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Nightmare	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Vascular disorders	0	0	0	1, 1 (11)	1, 1 (13)	0	2, 2 (3)
Hot flush	0	0	0	1, 1 (11)	1, 1 (13)	0	2, 2 (3)
Cardiac disorders	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Cardiac discomfort	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Eye disorders	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Dry eye	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Social circumstances	0	0	0	0	1, 1 (13)	0	1, 1 (2)

Exercise lack of	0	0	0	0	1, 1 (13)	0	1, 1 (2)

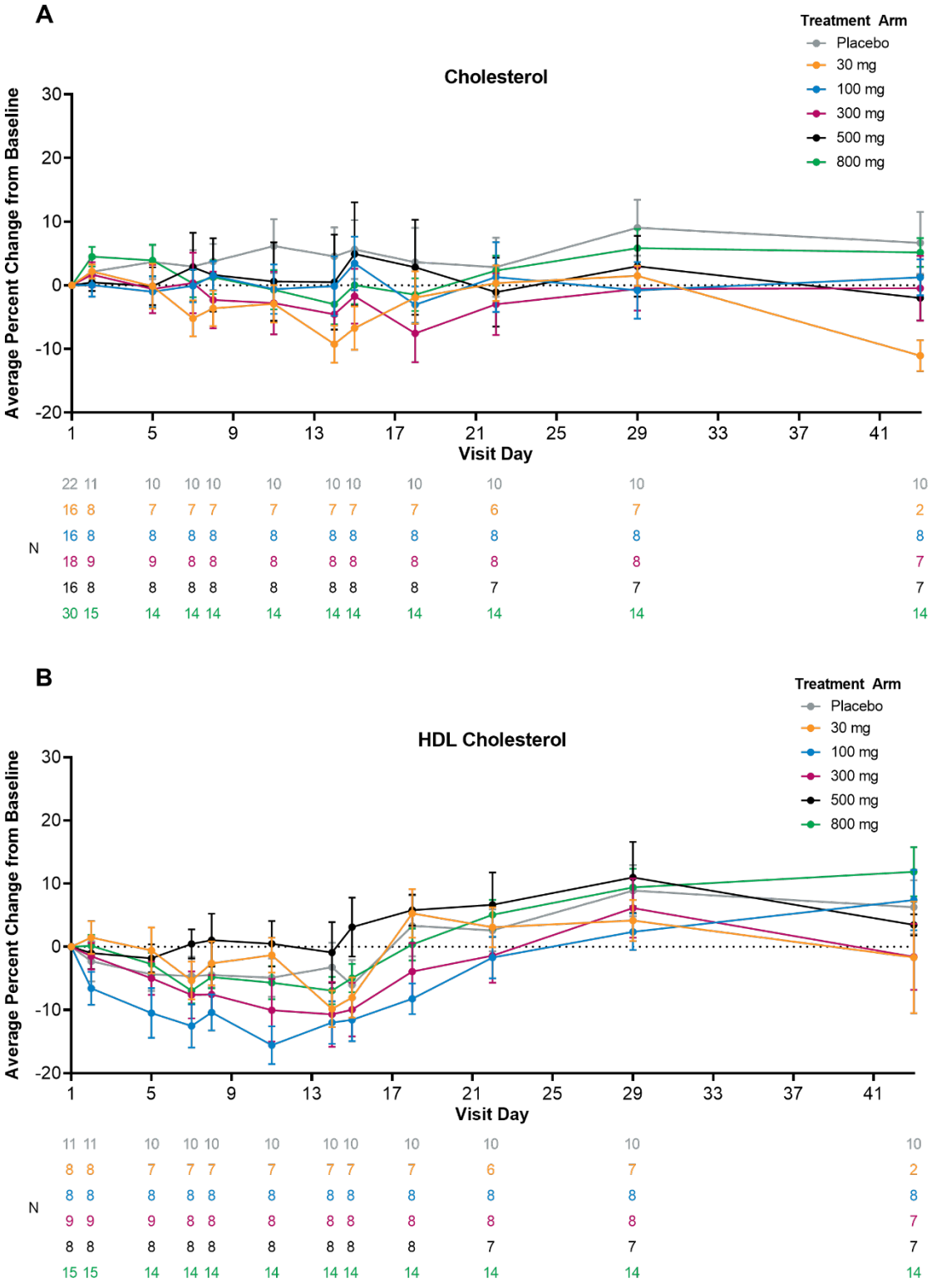
Supplementary Table 3. Treatment-emergent adverse events by system organ class and preferred term in the multiple ascending dose (MAD) part. *AEs are coded using MedDRA Version 23.1. AE=adverse event; E=number of AEs; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects exposed; n=number of subjects who experienced the AEs; QD=once daily; TEAE=treatment-emergent adverse event; %=number of subjects (n) as a percentage of number of subjects (N) per treatment.

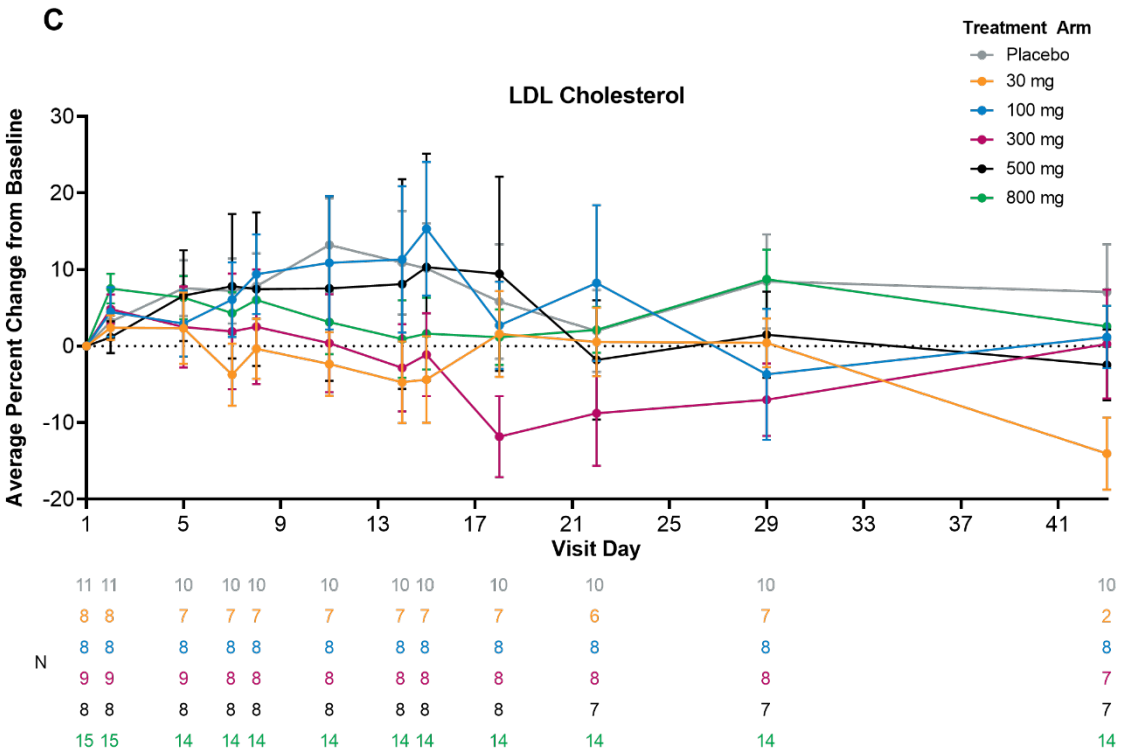
eFigure 1. Study Design.

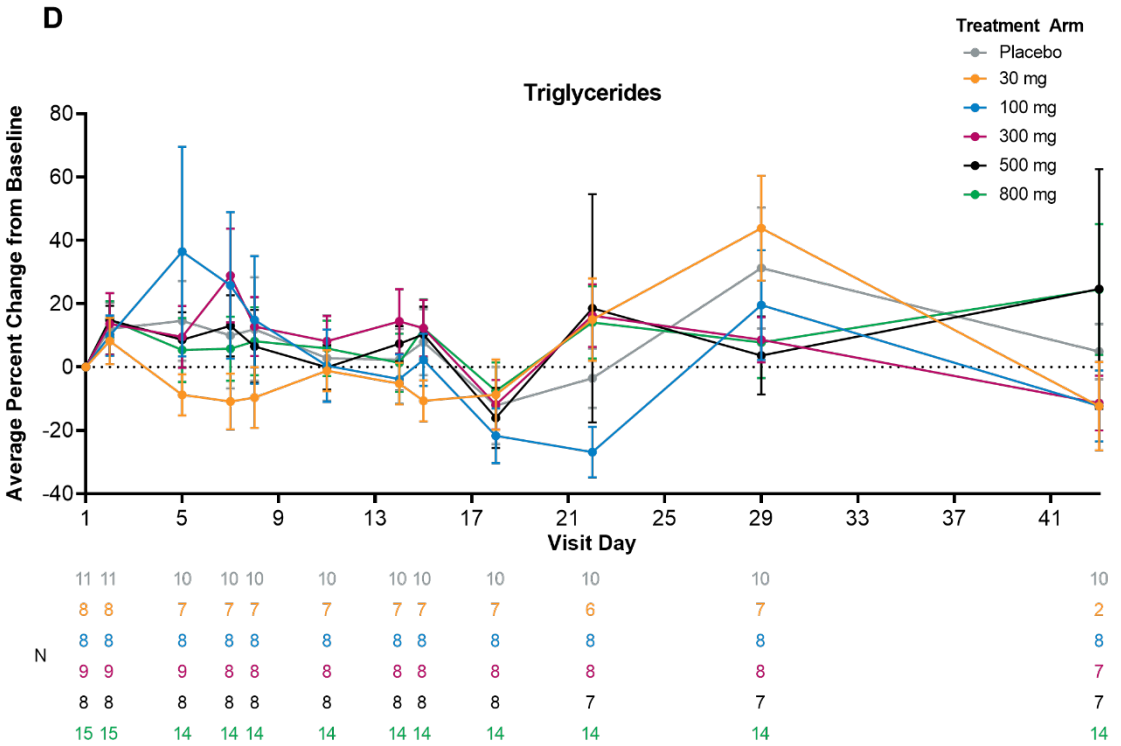


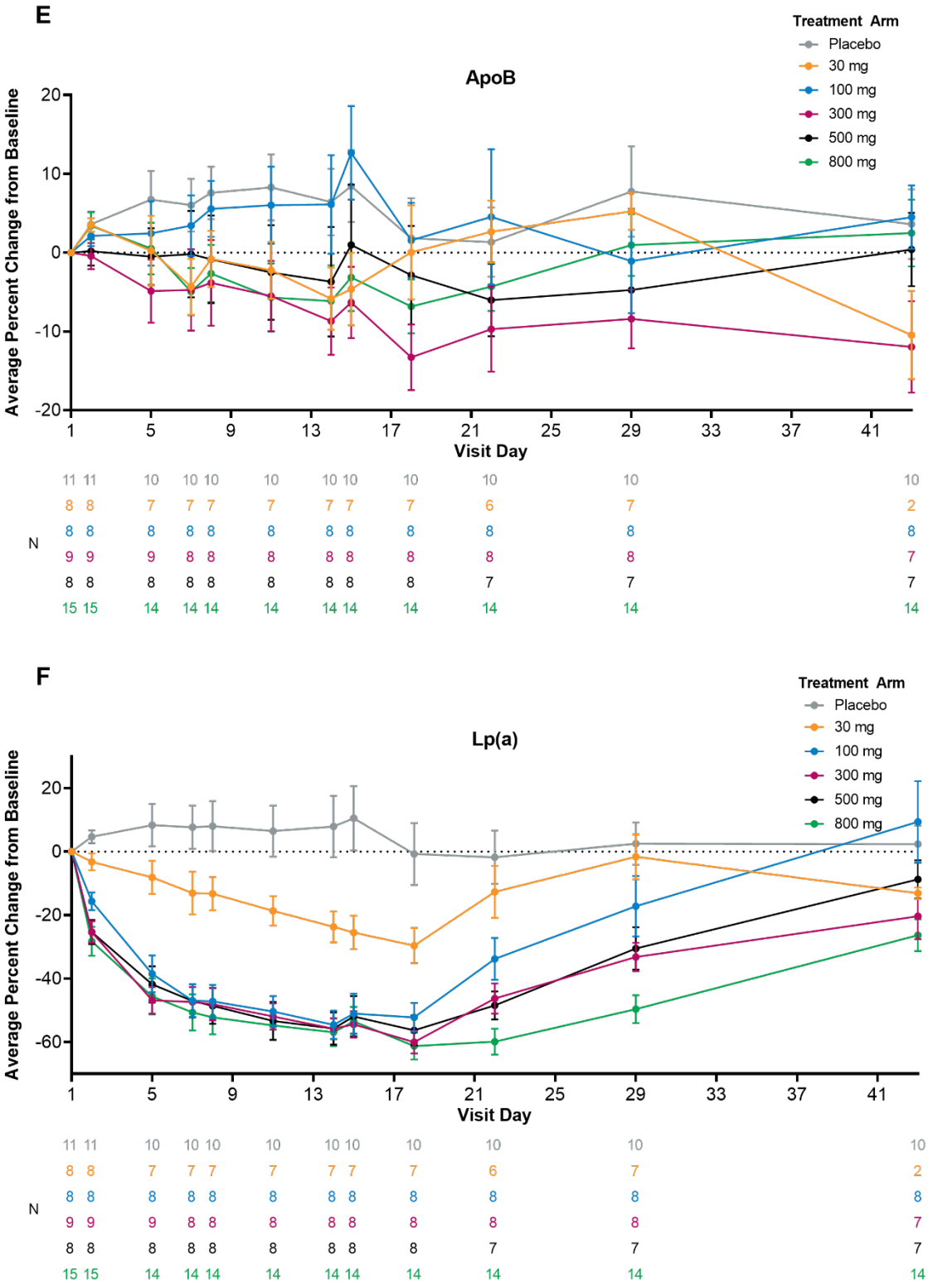
Supplementary Figure 1. Study design. MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose.

eFigure 2. Lipoprotein Panel Change vs. Time (Multiple Ascending Dose Part).



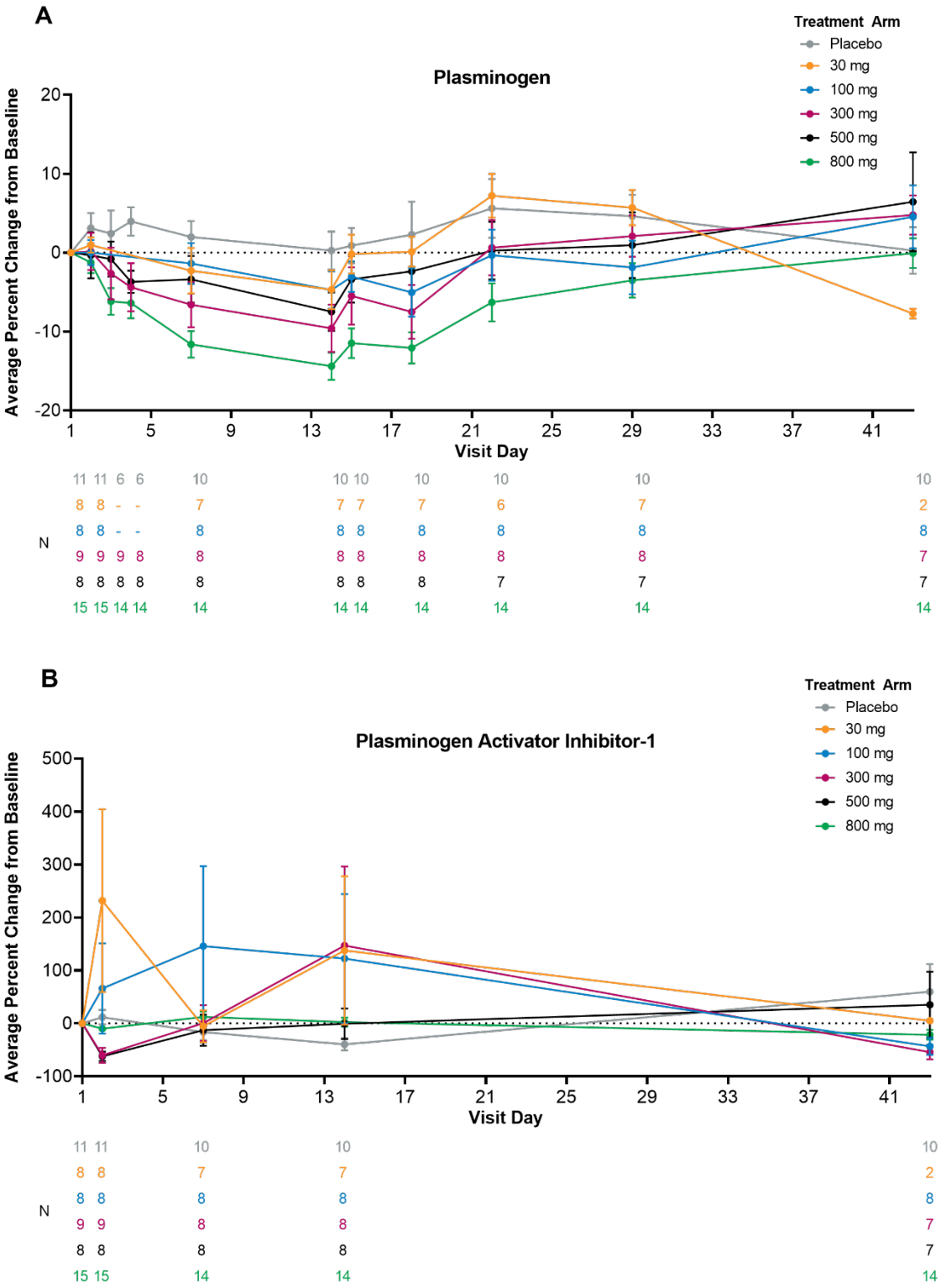


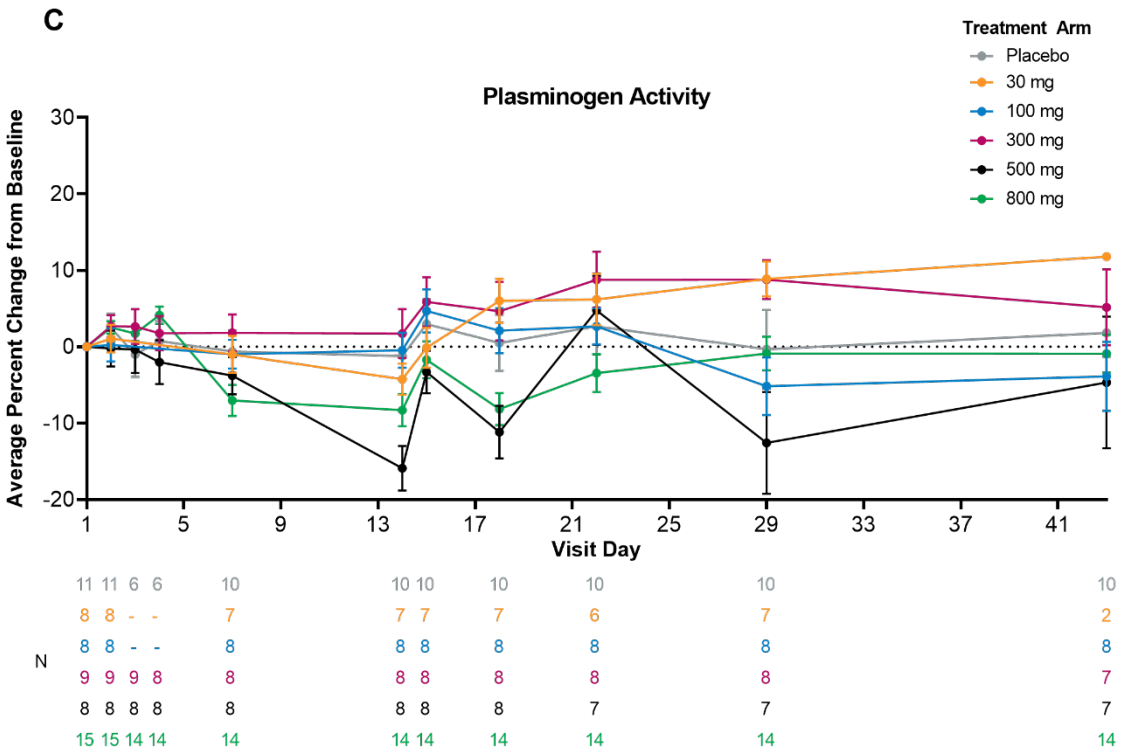


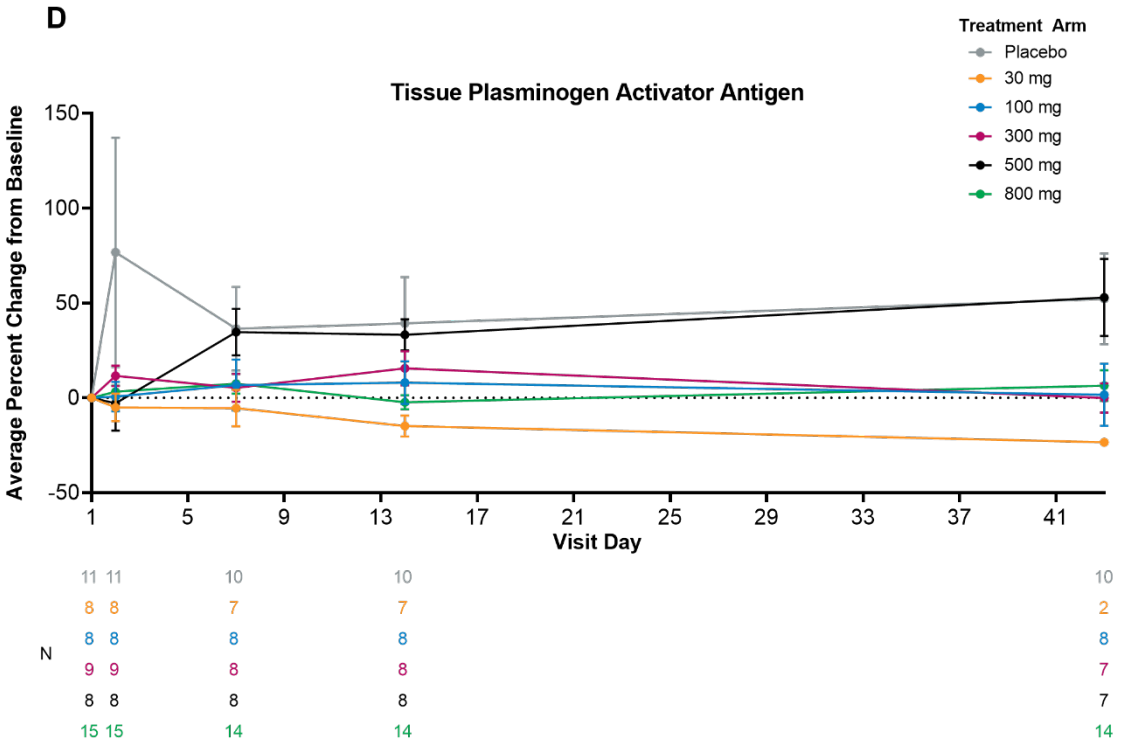


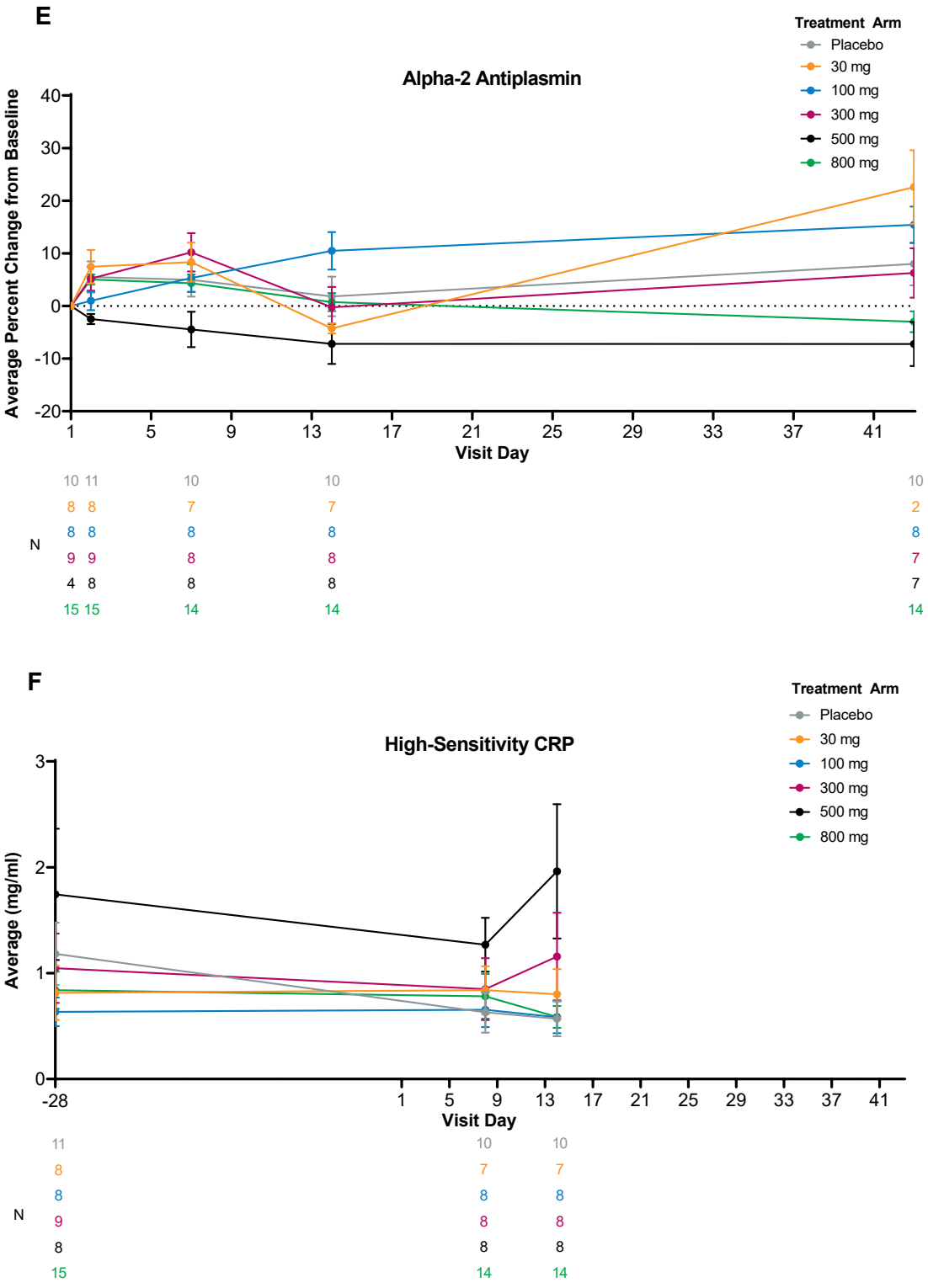
Supplementary Figure 2. Changes in lipid parameters during the multiple ascending dose study. HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoB, apolipoprotein B; Lp(a), lipoprotein(a).

eFigure 3. Other Biomarkers Panel Change vs. Time (Multiple Ascending Dose Part).



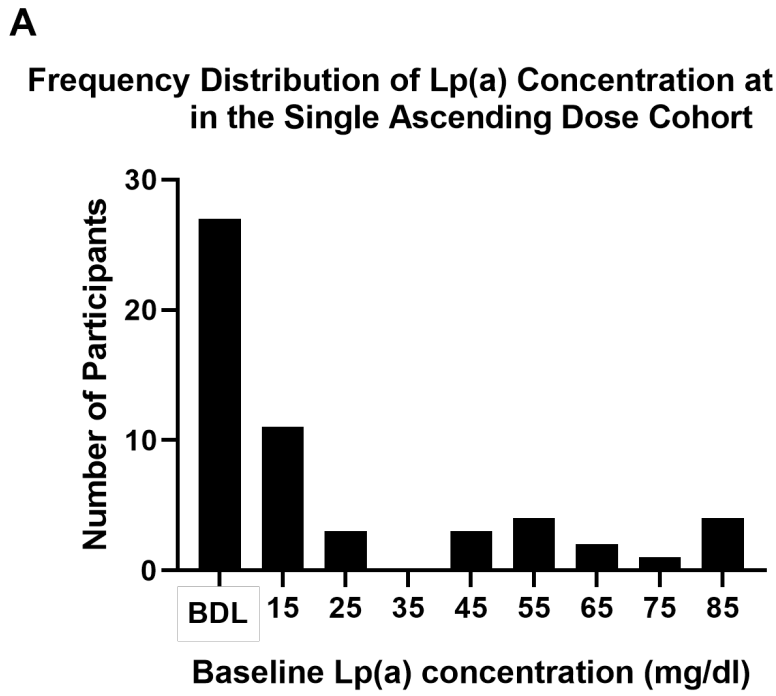




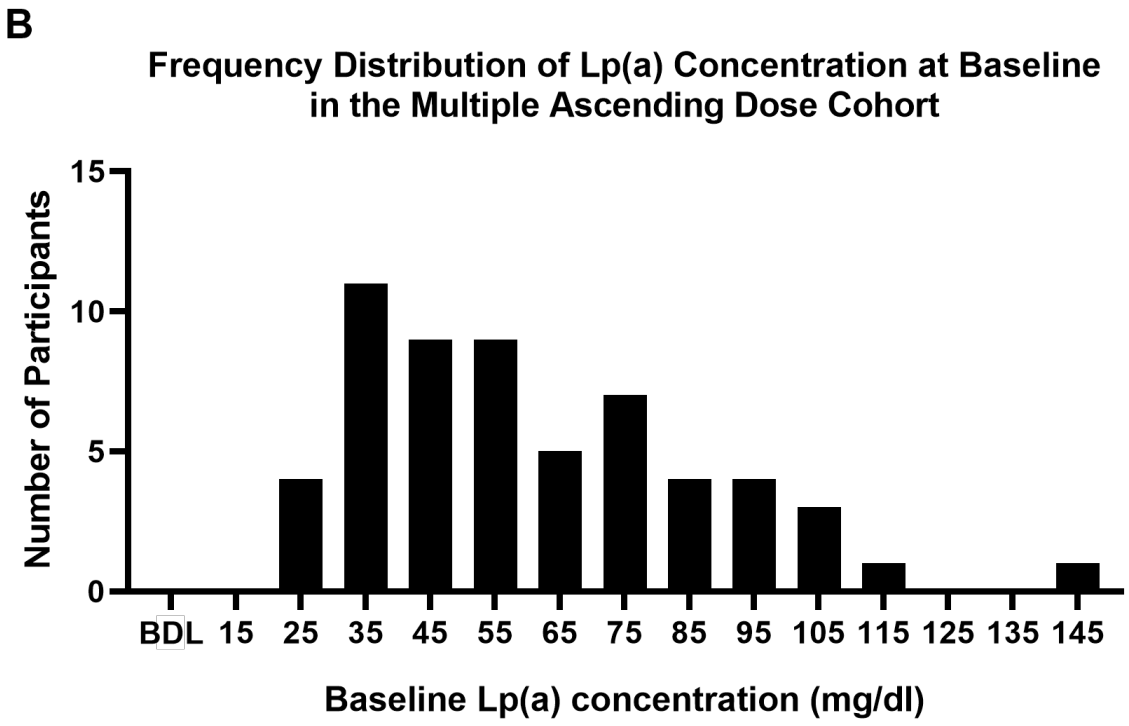


Supplementary Figure 3. Changes in non-lipid biomarkers during the multiple ascending dose study. CRP, C-reactive protein.

eFigure 4. Frequency Distribution of Lp(a) Concentration at Baseline



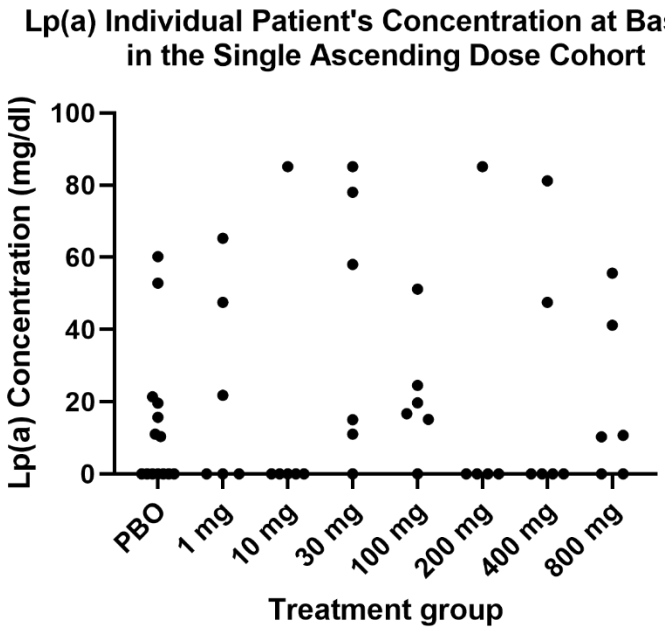
BDL=below detection limit (detection limit =10 mg/dl)



BDL=below detection limit (detection limit =10 mg/dl)

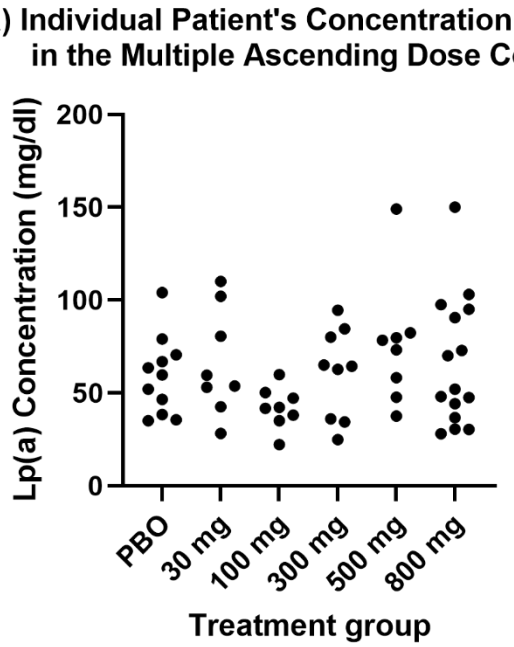
eFigure 5. Lp(a) Concentration at Baseline on a Per-Patient Basis

A



Each dot represents a single participant.
A value of zero was assigned to participants with Lp(a) concentration below the detection limit (10 mg/dl).

B



Each dot represents a single participant

eFigure 6. Scatterplot of Concentration Changes From Baseline