# **Supplemental Online Content**

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This supplemental material has been provided by the authors to give readers additional information about their work.

#### eTable1. Summary Statistics of Muvalaplin Dose Proportionality Analysis.

						95%	6 CI
Part	Day	Dose Range	Parameter	Slope	Intercept	Lower	Upper
SAD	1	30 mg to 800 mg	C <sub>max</sub>	0.617	0.744	0.449	0.784
SAD	AD I 30 mg to 800 mg	AUC <sub>0-inf</sub>	0.705	3.384	0.397	1.012	
MAD	1	30mg to 800 mg QD	C <sub>max</sub>	0.704	0.702	0.601	0.807
			C <sub>max</sub>	0.628	1.144	0.534	0.722
	14 30mg to 800 mg QD	AUC <sub>0-tau</sub>	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<sub>0-inf</sub>, area under the concentration-time curve from time 0 extrapolated to infinite time; AUC<sub>0-tau</sub>, 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.<sup>\*</sup> 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 (%)								
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)			

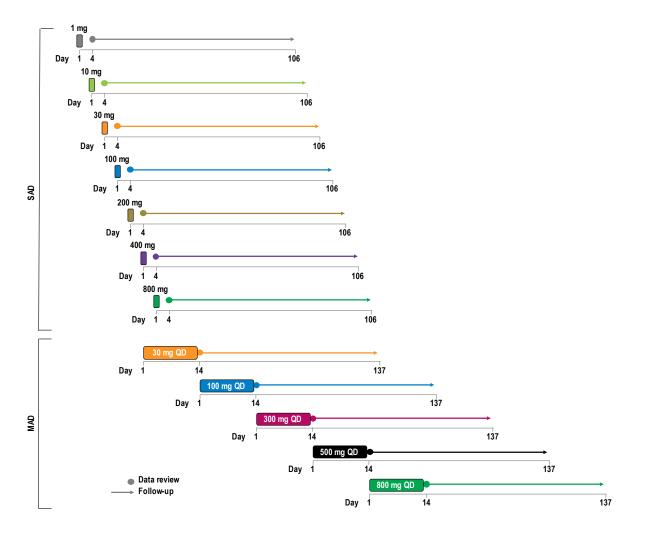
Catheter site bruise 1, 1 (9) 0 0, 1, 1(1) 0 0, 2, 2 (3)   Drug withdraval syndrome 0 2, 2 (2) 0 0 0, 2, 2 (3)   Vessel puncture site pain 0 1, 1(13) 0 0 0, 1, 1(7) 2, 2 (3)   Application site pruntus 0 0, 1, 1(13) 0 0, 1, 1(13) 0 1, 1(13) 0 1, 1(12)   Gatheter site swelling 0 1, 1(13) 0 0 0, 1, 1(2)   Influenza like illness 0 0 1, 1(13) 0 0 1, 1(2)   Vaccination site pain 1, 1(9) 0 0 0 1, 1(2)   Vessel puncture site erythema 0 0 0 0, 1, 1(2)   Vessel puncture site erythema 0 0 0 0, 1, 1(2)   Musculoskelotal and connective tissue 2, 2(18) 4, 4 (50) 3, 2 (22) 0 0 4, 4 (7)   Musculoskelotal chest pain 1, 1 (9) 1, 1 (13) 2, 2 (22) 0 0 4, 2 (2)	Catheter site pain	0	3, 2 (25)	2, 2 (25)	1, 1 (11)	0	0	6, 5 (8)
Drug withdrawai syndrome 0 2,2 (25) 0 0 0 2,2 (3)   Vessel puncture site pain 0 1,1 (13) 0 0 1,1 (2) 2,2 (3)   Application site punctures 0 0,1 (13) 0 0 1,1 (13) 0 1,1 (13)   Catheter site swelling 0 1,1 (13) 0 0 0 1,1 (2)   Feeling cold 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)   Vescination site pain 1,1 (9) 0 0 0 1,1 (2) 0 1,1 (2)   Musculoskeletal and connective tissue 2,2 (18) 4,4 (50) 3,2 (25) 4,2 (22) 1,1 (13) 0 4,4 (17)   Musculoskeletal and connective tissue 2,2 (18) 4,4 (50) 3,2 (25) 1,1 (13) 0 4,4 (17)   Musculoskeletal and connective tissue 1,1 (19) 0 1,1 (13) 0 0 2,2 (	Vessel puncture site bruise	2, 2 (18)	0	1, 1 (13)	3, 2 (22)	0	0	6, 5 (8)
Vessel puncture site pain 0 1,1(13) 0 0 1,1(7) 2,2(3)   Application site prutus 0 0 0 0,1,1(3) 0 0,1,1(2)   Catheter site swelling 0 1,1(13) 0 0 0,1,1(2)   Feeling cold 0 1,1(13) 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 0,1,1(2)   Vessel puncture site erythema 0 0 0 1,1(2) 0,1,1(2)   Vessel puncture site erythema 0 0 0 1,1(2) 0,1,1(2) 1,1(2)   Vessel puncture site erythema 0 0 1,1(13) 0,2,2(2) 1,1(13) 0,1,1(2)   Musculoskeletal and connective tissue 1,1(13) 0,1,1(13) 0,0 0,1,1(2) 1,1(2)   Mya	Catheter site bruise	1, 1 (9)	0	0	1, 1 (11)	0	0	2, 2 (3)
Application site pruritus 0 0 0 0 1,1(13) 0 1,1(2)   Catheer site swelling 0 1,1(13) 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)   Vaccination site pain 1,1(9) 0 0 0 0 1,1(2)   Vasculoskeletal and connective site erythema 0 0 0 0 0 1,1(13) 0 1,1(13)   Vasculoskeletal and connective site erythema 0 0 1,1(13) 0 1,1(13) 0 1,1(13)   Vasculoskeletal heats pain 1,1(9) 0,1,1(13) 0,2,2(22) 0 0 4,4(7)   Arthraigia 1,1(9) 1,1(13) 0 2,2(23) 0 0 1,1(2)   Musculoskeletal chest pan 0 0 2,1(13) 0 0 1,1(2)	Drug withdrawal syndrome	0	2, 2 (25)	0	0	0	0	2, 2 (3)
Catheter site swelling 0 1, 1(13) 0 0 0 1, 1(2)   Feeling cold 0 1, 1(13) 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 1, 1(2)   Musculoskeletal and connective tissue 2, 2(18) 4, 4(50) 3, 2(25) 4, 2(22) 1, 1(13) 0 4, 4(7)   Arthralgia 1, 1(9) 1, 1(13) 0 2, 1(11) 0 4, 4(7)   Musculoskeletal chest pain 0 0 0 0 1, 1(13) 0 2, 2(23) 0 0 2, 2(23)   Musculoskeletal chest pain 0 0 0 1, 1(13) 0 0 2, 2(23)   Majaja 0 0 0 0, 1, 1(13) 0, 0 0, 1, 1(2)	Vessel puncture site pain	0	1, 1 (13)	0	0	0	1, 1 (7)	2, 2 (3)
Feeling cold 0 1,1(13) 0 0 0 1,1(2)   Influenza like illness 0 0 1,1(13) 0 0 0,1,1(2)   Madical device site erythema 0 0 1,1(13) 0 0 0,1,1(2)   Vaccination site pain 1,1(9) 0 0 0 1,1(13) 0 1,1(2)   Vessel purchar site erythema 0 0 0 0 1,1(13) 0 1,1(2)   Vessel purchar site erythema 0 0 0 1,1(13) 0 1,1(13) 0 1,1(13)   Musculoskeletal and connective tissue 2,2(18) 4,4(50) 3,2(25) 4,2(22) 0 0 4,4(7)   Arthralgia 1,1(13) 0 2,1(11) 0 0 4,2(23) 0 0 1,1(2)   Musculoskeletal chest pain 0 0,2(2(25) 0 0 0,1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2) <	Application site pruritus	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Influenza like illness001, 1(13)0001, 1(2)Medical device site erythema001, 1(13)0001, 1(2)Vaccination site pain1, 1(9)000001, 1(2)Vessel puncture site erythema00000, 1, 1(3)01, 1(2)Musculoskeletal and connective tissue2, 2(18)4, 4(50)3, 2(25)4, 2(22)1, 1(13)04, 4(7)Back pain1, 1(9)01, 1(13)2, 2(22)004, 4(7)Arthralgia1, 1(9)01, 1(13)02, 1(11)02, 2(3)Musculoskeletal chest pain000004, 1(2)Musculoskeletal chest pain00001, 1(2)Majaja000001, 1(2)Pain in extremity002, 2(25)1, 1(11)002, 1(2)Skin and subcutaneous tissue disorders3, 3(27)1, 1(13)6, 3(3)3, 3(33)001, 1(2)Pain in extremity002, 2(25)1, 1(11)005, 5(8)Dry skin00001, 1(2)1, 1(2)1, 1(2)1, 1(2)Hyperhidrosis1, 1(9)0001, 1(2)1, 1(2)1, 1(2)Night sweats0000001, 1(2)Injury, poisoning and procedural complica	Catheter site swelling	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Medical device site erythema 0 1,1(13) 0 0 1,1(2)   Vaccination site pain 1,1(9) 0 0 0 0 1,1(13) 0 1,1(2)   Vaccination site pain 1,1(9) 0 0 0 1,1(13) 0 1,1(2)   Vasculoskeletal and connective tissue 2,2(18) 4,4(50) 3,2(25) 4,2(22) 1,1(13) 0 4,4(7)   Arthraigia 1,1(9) 0 1,1(13) 0 2,2(22) 0 0 4,3(5)   Musculoskeletal chest pain 0 2,2(25) 0 0 0 4,3(5)   Musculoskeletal chest pain 0 0 0 0 0 1,1(2)   Myalgia 0 1,1(13) 0 0 0 1,1(2)   Pain in extremity 0 0 0 0 0 1,1(2)   Skin and subcutaneous tissue disorders 3,3(27) 1,1(13) 2,2(25) 1,1(11) 0 0 3,3(5)   Pryskin	Feeling cold	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Vaccination site pain 1, 1(9) 0 0 0 0 1, 1(2)   Vessel puncture site erythema 0 0 0 0 1, 1(3) 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 (1   Back pain 1, 1(9) 0 1, 1(13) 0 2, 1(11) 0 4, 3 (5)   Muscule spasms 0 2, 2 (25) 0 0 0 4, 3 (5)   Muscule spasms 0 0 0 0 0, 1, 1 (13) 0 0 2, 2 (3)   Muscule spasms 0 0 0 0 0, 1, 1 (2) 1, 1 (2)   Myagia 0 0 0, 2, 1 (13) 0 0 2, 2 (3)   Skin and subcutaneous tissue disorders 3, 3 (27) 1, 1 (13) 6, 3 (38) 3, 3 (33) 0 0 1, 1 (2)   Pain in extremity 0 0 0, 1, 1 (1) 0 0, 3, 3 (5) 1, 1	Influenza like illness	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Vessel puncture site erythema 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(1)   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)   Musculoskeletal chest pain 0 2,2(25) 0 0 0 2,2 (3)   Myagia 0 1,1(13) 0 0 0 1,1 (2)   Pain in extremity 0 0 2,2 (25) 1,1 (11) 0 0 2,1 (2)   Skin and subcutaneous tissue disorders 3,3 (27) 1,1 (13) 6,3 (3) 3,3 (33) 0 0 1,1 (2)   Dry skin 0 0 0 1,1 (3) 0 0 0,1 (12)   Hyperhidrosis 1,1 (9) 0 0 0 0 1,1 (2)	Medical device site erythema	0	0	1, 1 (13)	0	0	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 (1 4, 11 (1)   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, 4 (7)   Musculoskeletal chest pain 0 2, 2 (25) 0 0 0 2, 2 (3)   Musculoskeletal chest pain 0 0 0 0 1, 1 (3) 0 1, 1 (2)   Pain in extremity 0 0 2, 1 (13) 0 0 0 1, 1 (2)   Skin and subcutaneous tissue disorders 3, 3 (27) 1, 1 (13) 6, 3 (38) 3, 3 (33) 0 0 13, 10 (1   Acne 1, 1 (9) 1, 1 (13) 2, 2 (25) 1, 1 (11) 0 0 3, 3 (57)   Pry skin 0 0 1, 1 (13) 0 0 1, 1 (2) 1, 1 (2) 1, 1 (2) 1, 1 (2) 1, 1 (2) 1, 1	Vaccination site pain	1, 1 (9)	0	0	0	0	0	1, 1 (2)
disorders 2, 2 (18) 4, 4 (50) 3, 2 (25) 4, 2 (22) 1, 1 (13) 0 14, 1 (14)   Back pain 1, 1 (9) 0 1, 1 (13) 0 2, 2 (22) 0 0 4, 4 (7)   Arthralgia 1, 1 (9) 1, 1 (13) 0 2, 1 (11) 0 0 4, 4 (7)   Muscules 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)   Myagia 0 1, 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 (1)   Acne 1, 1 (9) 1, 1 (13) 2, 2 (25) 1, 1 (11) 0 0, 3, 3 (5)   Erythema 0 0 1, 1 (3) 0 0 1, 1 (2)   Njelt sweats 0 0 0 0 0 1, 1 (2)   Ra	Vessel puncture site erythema	0	0	0	0	1, 1 (13)	0	1, 1 (2)
disorders 1,1(9) 0 1,1(13) 2,2(22) 0 0 4,4(7)   Arthralgia 1,1(9) 1,1(3) 0 2,1(11) 0 0 4,3(5)   Muscle spasms 0 2,2(25) 0 0 0 2,2(3)   Muscloskeletal chest pain 0 0 0 0 1,1(13) 0 0 1,1(2)   Pain in extremity 0 0 0,1,1(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(1   Acne 1,1(9) 1,1(13) 2,2(25) 1,1(11) 0 0 5,68)   Dry skin 0 0 0 1,1(2) 1,1(2) 1,1(2) 1,1(2) 1,1(2)   Hyperhidrosis 1,1(9) 0 0 0 1,1(2) 1,1(2) 1,1(2)   Night sweats 0 0 1,1(13) 0 0 1,1(2)	Musculoskeletal and connective tissue	2 2 (10)	4 4 (50)	2 2 (25)	4 2 (22)	1 1 (12)	0	14 11 (10)
Arthralgia1, 1(9)1, 1(13)02, 1(11)004, 3 (5)Muscle spasms02, 2 (25)00002, 2 (3)Musclo skeletal chest pain00001, 1 (13)01, 1 (2)Myalgia01, 1 (13)00001, 1 (2)Pain in extremity002, 1 (13)0002, 1 (2)Skin and subcutaneous tissue disorders3, 3 (27)1, 1 (13)6, 3 (38)3, 3 (33)0013, 10 (1)Acne1, 1 (9)1, 1 (13)2, 2 (25)1, 1 (11)005, 5 (8)Dry skin002, 2 (25)1, 1 (11)003, 3 (5)Erythema001, 1 (13)001, 1 (2)Night sweats0001, 1 (2)1, 1 (2)Night sweats1, 1 (9)00001, 1 (2)Skin fissures1, 1 (9)00001, 1 (2)Injury, poisoning and procedural complications1, 1 (9)0001, 1 (2)Injury0001, 1 (13)1, 1 (11)001, 1 (2)Injury000001, 1 (2)1, 1 (2)1, 1 (2)Injury, poisoning and procedural complications1, 1 (9)0001, 1 (2)Injury00001, 1 (2)1, 1 (2)1, 1 (2) <td>disorders</td> <td>2, 2 (10)</td> <td>4, 4 (50)</td> <td>3, 2 (23)</td> <td>4, 2 (22)</td> <td>1, 1 (13)</td> <td>0</td> <td>14, 11 (19)</td>	disorders	2, 2 (10)	4, 4 (50)	3, 2 (23)	4, 2 (22)	1, 1 (13)	0	14, 11 (19)
Muscle spasms02,2 (25)0002,2 (25)Musculoskeletal chest pain0001,1 (13)01,1 (2)Myalgia01,1 (13)00001,1 (2)Pain in extremity002,1 (13)0002,1 (2)Skin and subcutaneous tissue disorders3,3 (27)1,1 (13)6,3 (38)3,3 (33)0013,1 0 (1)Acne1,1 (9)1,1 (13)2,2 (25)1,1 (11)005,5 (8)Dry skin002,2 (25)1,1 (11)003,3 (5)Erythema001,1 (3)0001,1 (2)Night sweats0001,1 (13)001,1 (2)Skin fissures1,1 (9)00001,1 (2)Injury, poisoning and procedural complications1,1 (9)1,1 (13)1,1 (11)02,2 (13)6,6 (10)Injury0001,1 (13)1,1 (11)001,1 (2)Injury0001,1 (13)1,1 (11)001,1 (2)Injury0001,1 (13)1,1 (13)001,1 (2)Injury0001,1 (13)001,1 (2)1,1 (2)Injury0001,1 (13)0001,1 (2)Injury00001,1 (2)00<	Back pain	1, 1 (9)	0	1, 1 (13)	2, 2 (22)	0	0	4, 4 (7)
Musculoskeletal chest pain0001,1(13)01,1(2)Myalgia01,1(13)0001,1(2)Pain in extremity002,1(13)0002,1(2)Skin and subcutaneous tissue disorders3,3(27)1,1(13)6,3(38)3,3(33)0013,10(1)Acne1,1(9)1,1(13)2,2(25)1,1(11)005,5(8)Dry skin002,2(25)1,1(11)003,3(5)Erythema001,1(3)001,1(2)Myperhidrosis1,1(9)00001,1(2)Night sweats001,1(13)001,1(2)Skin fissures1,1(9)00001,1(2)Injury, poisoning and procedural complications1,1(9)1,1(13)1,1(11)02,2(13)6,6 (10)Injury0001,1(13)1,1(11)001,1(2)Injury0001,1(13)1,1(11)01,1(2)Injury0001,1(13)1,1(11)001,1(2)Injury0001,1(13)1,1(11)001,1(2)Injury0001,1(13)001,1(2)1,1(2)Injury0001,1(13)0001,1(2)Injury0001,1(13	Arthralgia	1, 1 (9)	1, 1 (13)	0	2, 1 (11)	0	0	4, 3 (5)
Myalgia01,1(13)0001,1(2)Pain in extremity002,1(13)002,1(2)Skin and subcutaneous tissue disorders3,3(27)1,1(13)6,3(38)3,3(33)0013,10(1)Acne1,1(9)1,1(13)2,2(25)1,1(11)005,5(8)Dry skin002,2(25)1,1(11)003,3(5)Erythema001,1(3)000,1,1(2)Hyperhidrosis1,1(9)00001,1(2)Night sweats0001,1(13)001,1(2)Skin fissures1,1(9)00000,1,1(2)Injury, poisoning and procedural complications1,1(9)1,1(13)1,1(13)1,1(11)02,2(13)6,6 (10)Injury0001,1(13)1,1(11)001,1(2)Injury0001,1(13)1,1(11)01,1(2)Injury00001,1(2)1,1(2)Injury0001,1(13)1,1(11)01,1(2)Injury00001,1(2)1,1(2)Injury00001,1(2)1,1(2)Injury00001,1(2)1,1(2)Injury00001,1(2)1,1(2)Injury000<	Muscle spasms	0	2, 2 (25)	0	0	0	0	2, 2 (3)
Pain in extremity002,1(13)0002,1(2)Skin and subcutaneous tissue disorders3,3(27)1,1(13)6,3(38)3,3(33)0013,10(1Acne1,1(9)1,1(13)2,2(25)1,1(11)005,5(8)Dry skin002,2(25)1,1(11)003,3(5)Erythema001,1(3)0001,1(2)Hyperhidrosis1,1(9)00001,1(2)Night sweats0001,1(11)001,1(2)Rash000001,1(2)Injury, poisoning and procedural complications1,1(9)1,1(13)1,1(11)02,2(13)6,6(10)Injury0001,1(13)1,1(11)001,1(2)Injury0001,1(13)1,1(11)001,1(2)	Musculoskeletal chest pain	0	0	0	0	1, 1 (13)	0	1, 1 (2)
Skin and subcutaneous tissue disorders 3, 3 (27) 1, 1 (13) 6, 3 (38) 3, 3 (33) 0 0 13, 10 (1   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 1, 1 (2)   Night sweats 0 0 0 1, 1 (13) 0 0 1, 1 (2)   Skin fissures 1, 1 (9) 0 0 0 0 1, 1 (2)   Injury, poisoning and procedural complications 1, 1 (9) 0 0 0 0 1, 1 (2)   Injury 0 0 0 0 0 0 1, 1 (2)   Injury 0 0 0 0 0 0 1, 1 (2)   Injury 0 <	Myalgia	0	1, 1 (13)	0	0	0	0	1, 1 (2)
Acne1, 1 (9)1, 1 (13)2, 2 (25)1, 1 (11)005, 5 (8)Dry skin002, 2 (25)1, 1 (11)003, 3 (5)Erythema001, 1 (3)0001, 1 (2)Hyperhidrosis1, 1 (9)00001, 1 (2)Night sweats0001, 1 (11)001, 1 (2)Rash001, 1 (13)001, 1 (2)Skin fissures1, 1 (9)00001, 1 (2)Injury, poisoning and procedural complications1, 1 (9)1, 1 (13)1, 1 (11)02, 2 (13)6, 6 (10)Contusion0001, 1 (13)1, 1 (11)001, 1 (2)Injury0001, 1 (13)0001, 1 (2)Injury00001, 1 (2)1, 1 (2)1, 1 (2)Injury00001, 1 (2)1, 1 (2)1, 1 (2)Injury00001, 1 (2)001, 1 (2)Injury000001, 1 (2)1, 1 (2)Injury000001, 1 (2)Injury000001, 1 (2)Injury00001, 1 (2)1, 1 (2)Injury0000001, 1 (2)	Pain in extremity	0	0	2, 1 (13)	0	0	0	2, 1 (2)
Dry skin002, 2 (25)1, 1 (1)003, 3 (5)Erythema001, 1 (3)0001, 1 (2)Hyperhidrosis1, 1 (9)00001, 1 (2)Night sweats0001, 1 (1)001, 1 (2)Rash001, 1 (13)001, 1 (2)Skin fissures1, 1 (9)00001, 1 (2)Injury, poisoning and procedural complications1, 1 (9)1, 1 (13)1, 1 (11)02, 2 (13)6, 6 (10)Contusion0001, 1 (13)1, 1 (11)001, 1 (2)Injury001, 1 (13)1, 1 (13)001, 1 (2)Injury001, 1 (13)0001, 1 (2)Injury00 <td>Skin and subcutaneous tissue disorders</td> <td>3, 3 (27)</td> <td>1, 1 (13)</td> <td>6, 3 (38)</td> <td>3, 3 (33)</td> <td>0</td> <td>0</td> <td>13, 10 (17)</td>	Skin and subcutaneous tissue disorders	3, 3 (27)	1, 1 (13)	6, 3 (38)	3, 3 (33)	0	0	13, 10 (17)
Erythema001, 1 (3)0001, 1 (2)Hyperhidrosis1, 1 (9)000001, 1 (2)Night sweats0001, 1 (1)001, 1 (2)Rash001, 1 (13)0001, 1 (2)Skin fissures1, 1 (9)00001, 1 (2)Injury, poisoning and procedural complications1, 1 (9)1, 1 (13)1, 1 (11)02, 2 (13)6, 6 (10)Contusion0001, 1 (13)1, 1 (11)001, 1 (2)Injury001, 1 (13)1, 1 (13)001, 1 (2)Injury001, 1 (13)0001, 1 (2)Injury001, 1 (13)0000Injury00	Acne	1, 1 (9)	1, 1 (13)	2, 2 (25)	1, 1 (11)	0	0	5, 5 (8)
Hyperhidrosis 1, 1 (9) 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 1, 1 (13) 0 0 1, 1 (2)   Injury, poisoning and procedural complications 1, 1 (9) 1, 1 (13) 1, 1 (11) 0 2, 2 (13) 6, 6 (10)   Contusion 0 0 0 1, 1 (13) 1, 1 (11) 0 2, 2 (13) 6, 6 (10)   Injury 0 0 0 1, 1 (13) 1, 1 (11) 0 0 1, 1 (2)   Injury 0 0 0 1, 1 (13) 0 0 1, 1 (2)	Dry skin	0	0	2, 2 (25)	1, 1 (11)	0	0	3, 3 (5)
Night sweats 0 0 0 1, 1(1) 0 0 1, 1(2)   Rash 0 0 1, 1(13) 0 0 1, 1(2)   Skin fissures 1, 1(9) 0 0 0 0 1, 1(2)   Injury, poisoning and procedural complications 1, 1(9) 1, 1(13) 1, 1(11) 0 2, 2(13) 6, 6 (10)   Contusion 0 0 0 1, 1(13) 1, 1(11) 0 0, 1, 1(2)   Injury 0 0 1, 1(13) 1, 1(13) 0, 0 1, 1(2)	Erythema	0	0	1, 1 (3)	0	0	0	1, 1 (2)
Rash001, 1 (13)0001, 1 (2)Skin fissures1, 1 (9)000001, 1 (2)Injury, poisoning and procedural complications1, 1 (9)1, 1 (13)1, 1 (13)1, 1 (11)02, 2 (13)6, 6 (10)Contusion00001, 1 (11)001, 1 (2)Injury001, 1 (13)001, 1 (2)	Hyperhidrosis	1, 1 (9)	0	0	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 (13) 1, 1 (11) 0 2, 2 (13) 6, 6 (10)   Injury 0 0 0 1, 1 (13) 0 0 1, 1 (2)	Night sweats	0	0	0	1, 1 (11)	0	0	1, 1 (2)
Injury, poisoning and procedural complications 1, 1 (9) 1, 1 (13) 1, 1 (11) 0 2, 2 (13) 6, 6 (10   Contusion 0 0 0 1, 1 (11) 0 2, 2 (13) 6, 6 (10   Injury 0 0 0 1, 1 (11) 0 0 1, 1 (2)   Injury 0 0 1, 1 (13) 0 0 1, 1 (2)	Rash	0	0	1, 1 (13)	0	0	0	1, 1 (2)
Contusion 0 0 0 1, 1 (11) 0 0 1, 1 (2)   Injury 0 0 1, 1 (13) 0 0 1, 1 (2)	Skin fissures	1, 1 (9)	0	0	0	0	0	1, 1 (2)
Injury 0 0 1, 1 (13) 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)
Procedural dizziness 1, 1 (9) 0 0 0 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)

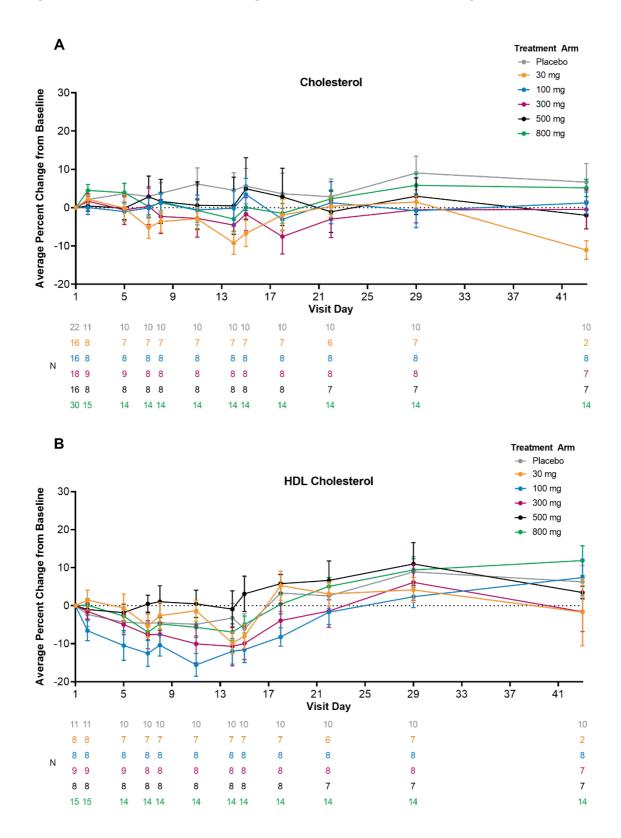
Exercise lack of	0	0	0	0	1, 1 (13)	0	1, 1 (2)
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Supplementary Table 3. Treatment-emergent adverse events by system organ class and preferred term in the multiple ascending dose (MAD) part. \*AEs are coded using MedDRA Version 23.1. AE=adverse event; 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.

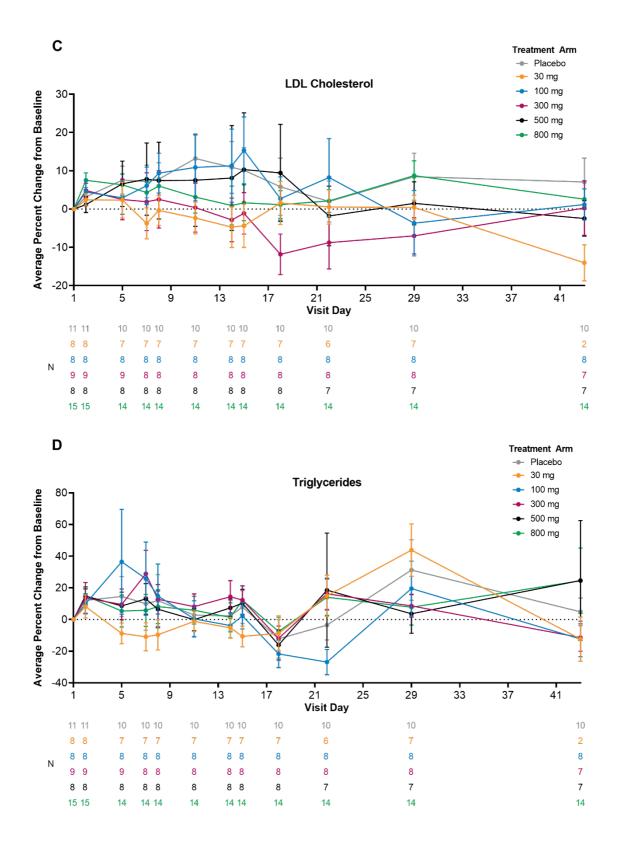


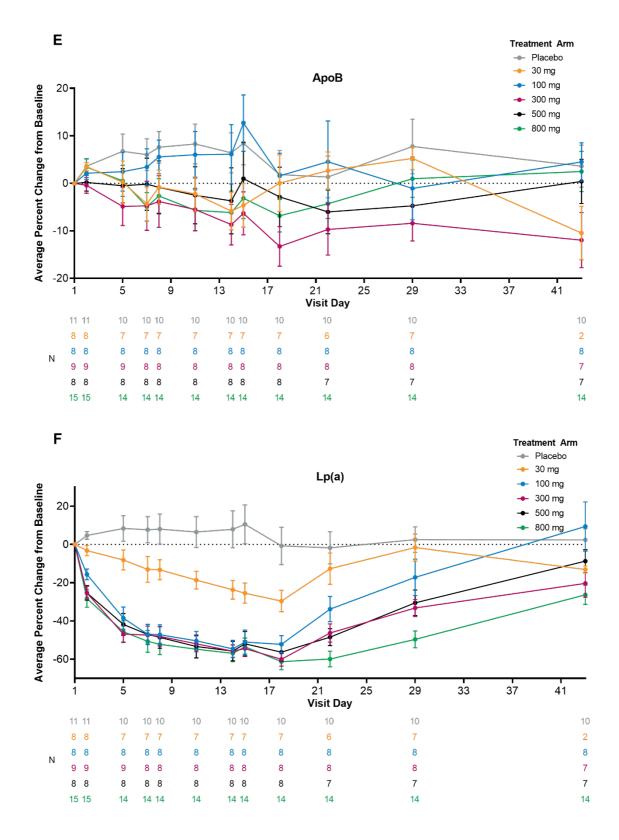


Supplementary Figure 1. Study design. MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose.

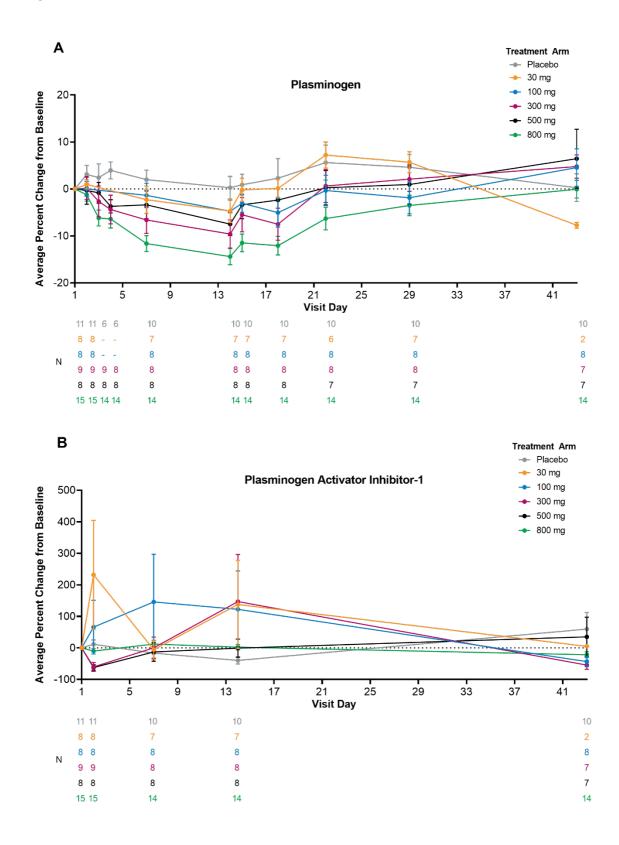


eFigure 2. Lipoprotein Panel Change vs. Time (Multiple Ascending Dose Part).

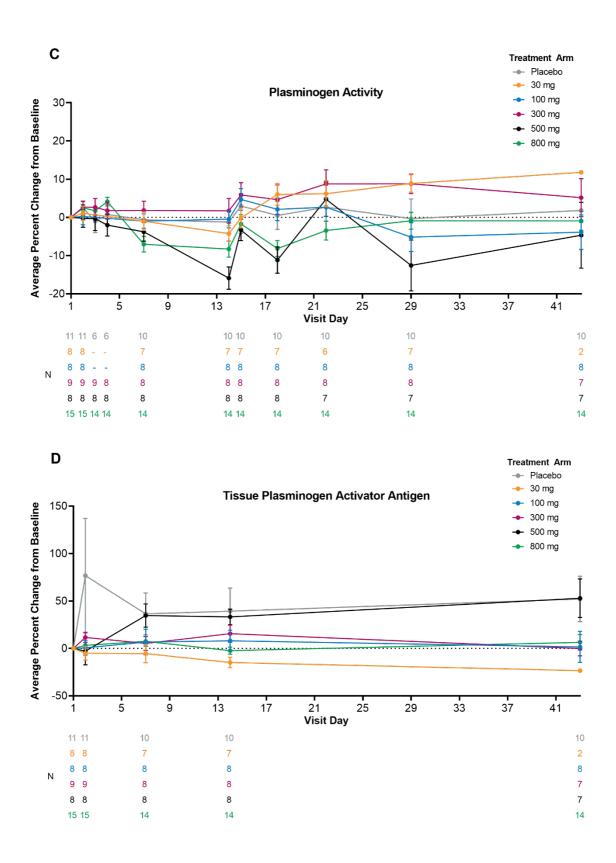


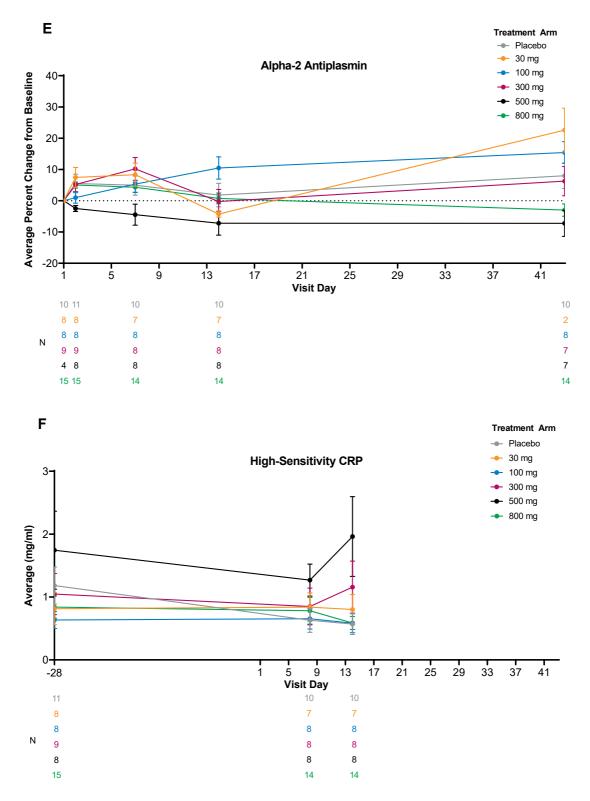


Supplementary Figure 2. Changes in lipid parameters during the multiple ascending dose study. HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoB, apolipoprotein B; Lp(a), lipoprotein(a).



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

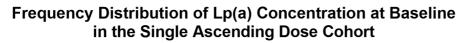


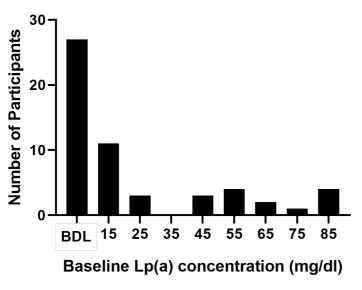


Supplementary Figure 3. Changes in non-lipid biomarkers during the multiple ascending dose study. CRP, C-reactive protein.

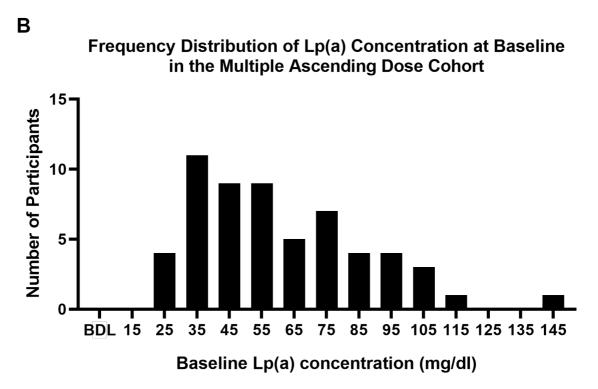
eFigure 4. Frequency Distribution of Lp(a) Concentration at Baseline

## Α





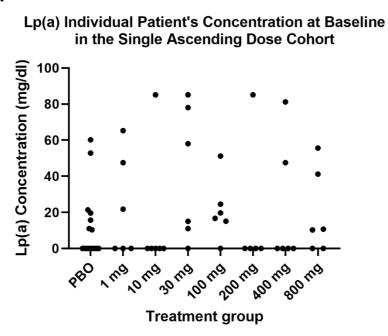
BDL=below detection limit (detection limit =10 mg/dl)



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

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

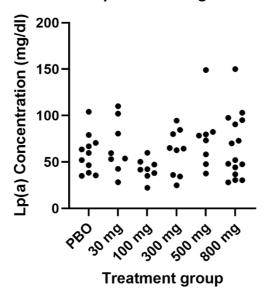
Α



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).

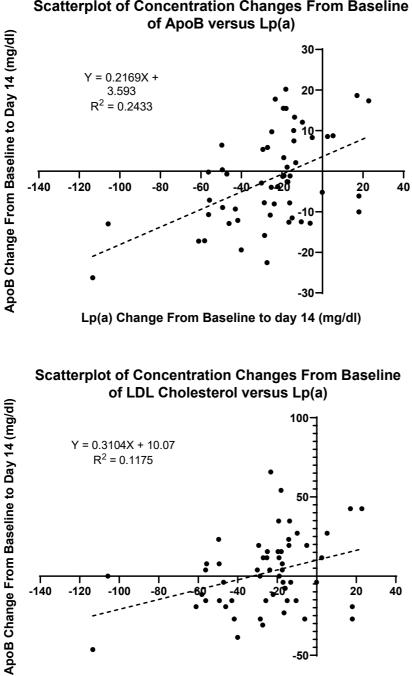
В

Lp(a) Individual Patient's Concentration at Baseline in the Multiple Ascending Dose Cohort



Each dot represents a single participant





**Scatterplot of Concentration Changes From Baseline** 

Lp(a) Change From Baseline to day 14 (mg/dl)