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GENERIC DRUG NAME AND COMPOUND NUMBER: Bococizumab / PF--04950615

PROTOCOL NO.: B1481015

PROTOCOL TITLE:

A Phase 2b Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Dose-Ranging Study to Assess the Efficacy, Safety, and Tolerability of PF-04950615 Following Monthly and Twice Monthly Subcutaneous Dosing for Six Months in Hypercholesterolemic Subjects on a Statin

Study Centers:

Fifty (50) centers in the United States of America took part in the study and randomized subjects.

Study Initiation Date and Final Completion Date:

25 July 2012 to 30 May 2013

Phase of Development:

Phase 2b

Study Objectives:

Primary Objective:

- The primary objective was to evaluate the low density lipoprotein cholesterol (LDL-C) lowering effect of bococizumab administered subcutaneously at monthly or twice monthly intervals, in hypercholesterolemic subjects whose LDL-C was ≥80 mg/dL (2.07 mmol/L) on background treatment with a statin.

Secondary Objectives:

- To evaluate the effect of bococizumab administered subcutaneously at monthly or twice monthly intervals, on other lipid parameters, including apolipoprotein B (ApoB), apolipoprotein A1 (ApoA1), apolipoprotein AII (ApoAII), and lipoprotein a (Lp[a]), in hypercholesterolemic subjects on a background of statins,

- To evaluate the safety, tolerability and immunogenicity of bococizumab administered subcutaneously at monthly or twice monthly intervals to hypercholesterolemic subjects on a background of statins,

- To assess injection site reaction and pain at the injection site following subcutaneous (SC) administration of bococizumab at monthly or twice monthly intervals to hypercholesterolemic subjects on a background of statins,

- To evaluate the lipid changes, safety and tolerability of bococizumab administered subcutaneously at monthly or twice monthly intervals, to hypercholesterolemic subjects on low dose statins,

- To evaluate the effect of bococizumab, administered subcutaneously at monthly or twice monthly intervals on total cholesterol, high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and non-high density lipoprotein cholesterol (non-HDL-C), in hypercholesterolemic subjects on a background of statins,

- To assess steady state pharmacokinetics (PK) of bococizumab following SC administration at monthly or twice monthly intervals to hypercholesterolemic subjects on a background of statins.

METHODS

Study Design:

This was a randomized, double-blind, placebo-controlled, parallel-group, dose ranging study of bococizumab administered subcutaneously, either every 14 days (Q14D) or every 28 days (Q28D) to hypercholesterolemic subjects. Subjects entered a screening phase of approximately 28 days duration, and those subjects who met the eligibility criteria were randomized in a 1:1:1:1:1:1:1 ratio to a total of 7 treatment groups (5 active dose groups and 2 placebos): placebo (1 x SC injection), bococizumab 50 mg (1 x 50 mg SC injection), 100 mg (1 x 100 mg SC injection) or 150 mg (1 x 150 mg SC injection) Q14D; or placebo (2 x SC injections), bococizumab 200 mg (2 x 100 mg SC injections) or 300 mg (2 x 150 mg SC injections) Q28D. Placebo or bococizumab was administered in a blinded fashion to the subjects.

The double-blind treatment phase stopped at Week 24 (Day 169) and subjects proceeded into a post-treatment follow-up phase for 36 weeks (225 days) if in the Q14D dose group, and 30 weeks (211 days) if in the Q28D dose group.

The study design allowed for downward dose adjustment (titration) of each bococizumab dose, to ensure that exposure to bococizumab was reduced in the event of an excessive LDL-C reduction. This was done by regular monitoring of fasting serum LDL-C values at all visits during the treatment period. If a subject had 2 consecutive LDL-C values ≤25 mg/dL (0.65 mmol/L) that subject's bococizumab dose was adjusted downwards at the following visit to a prespecified lower dose (eg, 150 mg to 100 mg). If subsequently the LDL-C value remained ≤25 mg/dL at any scheduled visit, the bococizumab dose was again adjusted downwards to the next prespecified dose (eg, for a subject whose original 150 mg dose had been initially reduced to 100 mg, the dose was decreased further to 50 mg). The last doses of study treatment were administered on Day 141 for the Q28D dose group and Day 155 for the Q14D dose group. Subjects then continued in a post-treatment follow-up period.

The schedule of assessments are provided in Table 1 and Table 2 for Q14D and Q28D dose groups respectively.

Table 1. Schedule of Assessments (Q14D Dose Group)

Study Phase	**Screening (Day)**		**Treatment Period (Day)**																	**Follow-Up (Day)**				
StudyActivity	**-28 to -8**	**-7**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**156[a]**	**158[a]**	**160[a]**	**162**	**169**	**176[a]**	**183**	**197**	**211**	**225**
Visit window (-)	**3**	**3**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Visit window (+)	**3**	**3**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Informed consent	X																							
General medical history	X																							
Physical exam	X																		X					
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X																		X					
Height	X																							
Waist circumference	X		X																X					
Blood for fasting lipid profile	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X	X
Hematology	X		X		X		X		X		X		X						X					
Biochemistry	X		X		X		X		X		X		X						X					
Urinalysis	X																		X					
Hepatitis screen	X																							
FSH[b]	X																							
Blood for ADA monitoring	X		X	X	X		X		X		X		X						X		X	X		X
HbA1c	X		X						X										X					
Hormone monitoring			X						X										X					
Blood for biomarkers			X						X										X					
12-lead ECG	X		X																X					
Pregnancy test[c]	X		X						X										X					
Randomization			X																					
Bococizumab/placebo dosing			X	X	X	X	X	X	X	X	X	X	X	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological panel[d]			X						X										X					
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for lipid particles			X						X										X					

Table 1. Schedule of Assessments (Q14D Dose Group)

Study Phase	**Screening (Day)**		**Treatment Period (Day)**																**Follow-Up (Day)**				
StudyActivity	**-28 to -8**	**-7**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**156[a]**	**158[a]**	**160[a]**	**162**	**169**	**176[a]**	**183**	**197**	**211**	**225**
Visit window (-)	**3**	**3**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Visit window (+)	**3**	**3**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Blood for Bococizumab PK			X	X	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X	X
Blood for PCSK9			X	X	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X	X
Blood for sparse fasting lipid profile[a]															X	X	X			X				
Blood for sparse bococizumab PK[a]															X	X	X			X				
Blood for sparse PSCK9[a]															X	X	X			X				
Blood for vitamin E			X																X					
Pharmacogenomics			X																					

ADA = anti-drug (bococizumab) antibody, ECG = electrocardiogram, FSH = follicle stimulating hormone, HbA1c = glycosylated hemoglobin, IRB = Institutional Review Board; PK = pharmacokinetic, PSCK9 = proprotein convertase subtilisin/kexin type 9, Q14D = dosing every 14 days.

a. A sparse sampling approach was used on Days 156, 158, 160 and 176. Each subject only needed to return once to have blood drawn on 1 of the 4 sparse sampling days. They were assigned to 1 of these particular days based on their randomization number.
b. FSH in appropriate subjects.
c. Pregnancy tests were repeated as per request of IRBs or if required by local regulations.
d. Neurological tests included tests of the cranial nerves and peripheral reflexes.

Table 2. Schedule of Assessments (Q28D Dose Group)

Study Phase	**Screening (Day)**		**Treatment Period (Day)**																		**Follow-Up (Day)**		
StudyActivity	**-28 to -8**	**-7**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**142**[a]	**144**[a]	**146**[a]	**148**	**155**	**162**[a]	**169**	**183**	**197**	**211**
Visit window (-)	**3**	**3**	**0**	**1**	**3**	**1**	**3**	**1**	**3**	**1**	**3**	**1**	**3**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Visit window (+)	**3**	**3**	**0**	**2**	**3**	**2**	**3**	**2**	**3**	**2**	**3**	**2**	**3**	**3**	**3**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**
Informed consent	X																						
General medical history	X																						
Physical exam	X																			X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X																			X			
Height	X																						
Waist circumference	X		X																	X			
Blood for fasting lipid profile	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X	X
Hematology	X		X		X		X		X		X		X							X			
Biochemistry	X		X		X		X		X		X		X							X			
Urinalysis	X																			X			
Hepatitis screen	X																						
FSH[b]	X																						
Blood for ADA monitoring	X		X	X	X		X		X		X		X							X	X		X
HbA1c	X		X						X											X			
Hormone monitoring			X						X											X			
Blood for biomarkers			X						X											X			
12-lead ECG	X		X																	X			
Pregnancy test[c]	X		X						X											X			
Randomization			X																				
Bococizumab / placebo dosing			X		X		X		X		X		X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological panel[d]			X						X											X			

Table 2. Schedule of Assessments (Q28D Dose Group)

Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for lipid particles			X						X											X			
Blood for bococizumab PK			X	X	X		X		X		X		X				X	X		X	X	X	X
Blood for PSCK9			X	X	X		X		X		X		X				X	X		X	X	X	X
Blood for sparse fasting lipid profile[a]														X	X	X			X				
Blood for sparse bococizumab PK[a]														X	X	X			X				
Blood for sparse PSCK9[a]														X	X	X			X				
Blood for vitamin E			X																	X			
Pharmacogenomics			X																				

ADA = antidrug (bococizumab) antibody, ECG = electrocardiogram, FSH = follicle stimulating hormone; HbA1c = glycosylated hemoglobin, IRB = Institutional Review Board; PK = pharmacokinetic, PSCK9 = proprotein convertase subtilisin/kexin type 9, Q28D = dosing every 28 days.

a. A sparse sampling approach was used on Days 142,144,146 and 162. Each subject only needed to return once to have blood drawn on 1 of the 4 sparse sampling days. They were assigned to 1 of these particular days based on their randomization number.
b. FSH in appropriate subjects.
c. Pregnancy tests were repeated as per request of IRBs or if required by local regulations.
d. Neurological tests included tests of the cranial nerves and peripheral reflexes.

Number of Subjects (Planned and Analyzed):

A total of 350 subjects were planned to be enrolled in the study; 354 subjects were randomized (50 each in Q14D placebo, Q14D bococizumab 50 mg, Q14D bococizumab 150 mg, and Q28D bococizumab; 51 each in Q28D placebo and Q28D bococizumab 300 mg; 52 in Q14D bococizumab 100 mg).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Male and female subjects aged ≥18 years who were receiving a stable dose (at least 6 weeks prior to Screening) of any statin and continued on same dose of statin for the duration of this study, whose fasting TG was ≤400 mg/dL (4.5 mmol/L) at the 2 Screening Visits, and fasting LDL-cholesterol (LDL-C) was ≥80 mg/dL (2.07 mmol/L) at the initial Screening Visit, and the value at the second visit within 7 days of randomization was not <20% of the initial value were included in the study.

Exclusion Criteria: Subjects with a history of a cardiovascular or cerebrovascular event, poorly controlled type 1 or type 2 diabetes mellitus (defined as glycated hemoglobin >9%), and poorly controlled hypertension were excluded from the study. Subjects who were on lipid-lowering herbs or supplements within 6 weeks of screening, those who were on systemic corticosteroids and on investigational or marketed monoclonal antibody within 6 months or 5 half-lives were excluded from the study.

Study Treatment:

Bococizumab and placebo were provided as 100 mg/mL sterile solution for SC injection. Each bococizumab vial contained 200 mg in 2 mL of aqueous buffered solution and was sealed with a coated stopper and an aluminium overseal. All subjects were randomly assigned to receive 1 of the placebos or 1 of the 5 doses of bococizumab for the duration of the study.

Efficacy, Pharmacokinetic and Safety Endpoints:

Primary Efficacy Endpoint:

- Absolute change from Baseline in LDL-C at the end of Week 12 following randomization.

Secondary Efficacy Endpoints:

- Change from Baseline in LDL-C at Week 24,
- Percent change from Baseline in LDL-C at Weeks 12 and 24,
- Change and percent change from Baseline at Weeks 12 and 24 in: HDL-C, very low density lipoprotein-triglycerides (VLDL-TG), total cholesterol, TG, ApoB, ApoA1, ApoAII, Lipoptotein (Lp) (a), and non-HDL-C,
- Proportion of subjects at Weeks 12 and 24 satisfying the criteria of LDL-C <100, <70, <40, and <25 mg/dL.

Secondary Pharmacokinetic Endpoints:

- Plasma steady-state bococizumab PK parameters.

Secondary Safety Endpoints:

- Incidence of ADA and injection site reaction.

Safety Evaluations:

Safety was assessed by physical and neurological examinations, waist circumference, vital signs, electrocardiograms (ECGs), clinical laboratory results, and the spontaneous reporting of adverse events (AEs) in all subjects who received at least 1 dose of study drug. Additionally, blood samples were collected for assessment of anti-drug (bococizumab) antibodies (ADAs) and neutralizing antibodies.

Statistical Methods:

The analysis set used in the study were:

Full Analysis Set: The full analysis set (FAS) was the primary analysis set for the analysis of efficacy data in this study. The FAS included all subjects who were randomized and subjects were analyzed according to their randomized dose regardless of any subsequent titrations or what treatment they actually took.

'Per Protocol' Analysis Set: This was subset of FAS and included subjects who were compliant with the study procedures. Subjects were compliant with their statins (80-120% compliance), took all the scheduled doses of study drug, and had their Day 85 low density lipoprotein (LDL) drawn within the appropriate clinical window.

Subjects with inappropriate dose adjustment were excluded from this set, which included:

- Subject who met criteria for dose adjustment, but whose dose was not adjusted,
- Subject who met criteria for dose adjustment, but whose dose was incorrectly adjusted (eg, wrong dose),
- Subject who did not meet criteria for dose adjustment, but whose dose was adjusted.

Safety Analysis Set: The safety analysis set included all subjects who received at least 1 dose of study treatment.

Other Analysis Set: The sensitivity analysis set included subjects from the FAS, and included all efficacy data up to the first dosing titration. The PK/pharmacodynamic (PD) analysis set included subjects from the FAS who had at least 1 PK or PD sample.

For efficacy data a mixed model repeated measures (MMRM) analysis was used as the primary method of analysis in which the dependent variable was the change from Baseline (or percent change from Baseline) in the endpoint of interest at all post baseline windowed

visits. Each dose schedule (Q14D or Q28D) was analyzed separately. The model-adjusted mean change from Baseline (or percent change from Baseline) for each treatment group at each time point was presented along with their 95% confidence intervals (CIs). Placebo-adjusted (bococizumab minus placebo) mean changes (or percent changes) from Baseline were presented at each time point along with p-values and 95% CIs (both unadjusted for multiplicity).

Continuous endpoints were summarized using the following statistics: number of subjects, arithmetic mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum values. These statistics were shown by treatment group and for each visit for the observed, change from Baseline, and percent change from Baseline data. Ordinal data were summarized using the total number of subjects and number and percent of subjects in each response category by treatment group and visit. Binary response endpoints (eg, subjects with LDL-C <100 mg/dL) were analyzed using a logistic regression model for binary data with the model terms treatment group (as a categorical variable) and baseline LDL-C (as a continuous variable). Summary measures from the analysis included the odds ratio, the 95% CI on the odds ratio, and 2-sided p-value for each treatment group comparison.

Safety data that were specifically summarized included:

- The incidence and severity of treatment-emergent adverse events (TEAEs) for all causalities and treatment-related TEAEs were tabulated by treatment group using Medical Dictionary for Regulatory Activities Version 16.0.

- A 3-tier approach was used to summarize AEs:

    - Tier 1 AEs, which were clinically important events arising from a Targeted Medical Event list or any other important clinical consideration Tier 2 AEs were more common AEs, and included events that occurred in ≥5% of subjects in any treatment group,

    - Tier 3 AEs were those AEs that were neither Tier 1 nor Tier 2. However, to facilitate the reporting process, all AEs (Tiers 1, 2 and 3) were included in the standard AE tables; that is, Tier 3 events were not specifically identified,

    - For both Tier 1 and 2 AEs, the percentage of subjects with incident AE, the risk difference versus placebo, and its 95% CI were produced. In addition, p-values were produced for the Tier 1 AEs, but for limited descriptive purposes only,

- Safety events that triggered withdrawal of a subject,

- Safety laboratory tests according to Sponsor standards,

- Summary statistics for changes from Baseline in vital signs (diastolic blood pressure, systolic blood pressure , pulse rate and body temperature) and the incidence of vital sign values of clinical concern observed at any time during the study and any time relative to dosing were tabulated,

- Clinical findings on any physical examination during the study and the number and percent of subjects with abnormalities identified on any neurological test,

- The incidence of significant changes from Baseline in 12-lead ECG measurements and descriptive summaries of the data.

Summary statistics of bococizumab and proprotein convertase subtilisin/kexin type 9 plasma concentrations by treatment group and visit were produced as well as summary statistics for the accumulation ratio of bococizumab: Concentration Day 169/Concentration Day 15 for the Q14D dose group and Concentration Day 169/Concentration Day 29 for the Q28D dose group. These data were also summarized by ADA status (ADA positive subjects, ADA negative subjects).

RESULTS

Subject Disposition and Demography:

A total of 354 subjects were randomized to study treatment and included in the FAS (Table 3 and Table 4). The distribution between the treatment groups was similar. Three (3) subjects in the Q14D dose group were excluded from the safety analysis set because they were discontinued from the study prior to receiving study treatment.

Table 3. Number of Subjects Randomized to Each Treatment Group

N=354			
Q14D Dose Group	**n**	**Q28D Dose Group**	**n**
Q14D placebo SC:	50	Q28D placebo SC:	51
Q14D bococizumab 50 mg SC	50	Q28D bococizumab 200 mg SC	50
Q14D bococizumab 100 mg SC	52	Q28D bococizumab 300 mg SC	51
Q14D bococizumab 150 mg SC	50		
Total	202	Total	152

N = total number of randomized subjects, n = number of subjects per treatment group, SC = subcutaneous, Q14D = dosing every 14 days, Q28D = dosing every 28 days.

Table 4. Summary of Subject Evaluation Groups – Q14D and Q28D All Randomized Subjects

	Number (%) of Subjects				
	Q14D				
Analysis Sets	Placebo (n=50)	Bococizumab 50 mg (n=50)	Bococizumab 100 mg (n=52)	Bococizumab 150 mg (n=50)	Total (N=202)
Full analysis set	50 (100.0)	50 (100.0)	52 (100.0)	50 (100.0)	202 (100.0)
Per protocol analysis set[a]	33 (66.0)	24 (48.0)	28 (53.8)	26 (52.0)	111 (55.0)
Safety analysis set	49 (98.0)	50 (100.0)	51 (98.1)	49 (98.0)	199 (98.5)
PK/PD analysis set	49 (98.0)	50 (100.0)	51 (98.1)	49 (98.0)	199 (98.5)
Completers–treatment[b]	45 (90.0)	42 (84.0)	41 (78.8)	42 (84.0)	170 (84.2)
Completers–study[a]	47 (94.0)	39 (78.0)	45 (86.5)	47 (94.0)	178 (88.1)

	Number (%) of Subjects			
	Q28D			
Analysis Sets	Placebo (n=51)	Bococizumab 200 mg (n=50)	Bococizumab 300 mg (n=51)	Total (N=152)
Full analysis set	51 (100.0)	50 (100.0)	51 (100.0)	152 (100.0)
Per protocol analysis set[a]	31 (60.8)	36 (72.0)	29 (56.9)	96 (63.2)
Safety analysis set	51 (100.0)	50 (100.0)	51 (100.0)	152 (100.0)
PK/PD analysis set	51 (100.0)	50 (100.0)	51 (100.0)	152 (100.0)
Completers–treatment[a]	41 (80.4)	44 (88.0)	44 (86.3)	129 (84.9)
Completers–study[b]	44 (86.3)	47 (94.0)	48 (94.1)	139 (91.4)

N = total number of subjects, n = number of subjects per treatment group, PD = pharmacodynamic, PK = pharmacokinetic, Q14D = dosing every 14 days, Q28D = dosing every 28 days.

a. All subjects who were deemed to have completed the study.

b. All subjects who were deemed to have completed the study treatment.

The number (%) of subjects in the FAS who discontinued treatment is summarized by dose group and treatment groups in Table 5. All 354 randomized subjects (202 subjects Q14D dose groups and 152 subjects Q28D dose groups) were included in the FAS while 351 subjects (199 subjects Q14D dose groups and 152 subjects Q28D dose groups) were included in the safety analysis set. Thus 3 randomized subjects were excluded from the safety analysis set of the Q14D dose groups, which was because these subjects were discontinued from the study prior to receiving study treatment.

Table 5. Summary of Subjects Who Discontinued the Study – Q14D and Q28D Full Analysis Sets

	Number (%) of Subjects				
	Q14D				
	Placebo (n=50)	Bococizumab			Total (N=202)
		50 mg (n=50)	100 mg (n=52)	150 mg (n=50)	
Discontinued study	3 (6.0)	11 (22.0)	7 (13.5)	3 (6.0)	24 (11.9)
Reason[a]					
Adverse event	1 (2.0)	0	0	1 (2.0)	2 (1.0)
Subject died	0	1 (2.0)	0	0	1 (0.5)
Lost to follow-up	1 (2.0)	3 (6.0)	1 (1.9)	0	5 (2.5)
Subjects did not meet entrance criteria	1 (2.0)[b]	0	1 (1.9)[b]	0	2 (1.0)
Subjects no longer willing to participate in study	0	4 (8.0)	4 (7.7)	1 (2.0)	9 (4.5)
Other	0	3 (6.0)	1 (1.9)	1 (2.0)	5 (2.5)
Scheduling EOS visit	0	3 (6.0)	0	0	3 (1.5)
Moved to a different state			1 (1.9)		1 (0.5)
Randomization full				1 (2.0)[b]	1 (0.5)

	Number (%) of Subjects			
	Q28D			
	Placebo (n=51)	Bococizumab		Total (N=152)
		200 mg (n=50)	300 mg (n=51)	
Discontinued treatment	7 (13.7)	3 (6.0)	3 (5.9)	13 (8.6)
Reason[a]				
Adverse event	1 (2.0)	0	0	1 (0.7)
Protocol violation	0	1 (2.0)	0	1 (0.7)
Lost to follow-up	3 (5.9)	2 (4.0)	0	5 (3.3)
Does not meet entrance criteria	0	0	0	0
Subject no longer willing to participate in study	3 (5.9)	0	2 (3.9)	5 (3.3)
Other	0	0	1 (2.0)	1 (0.7)
Scheduling EOS visit	0	0	1 (2.0)	1 (0.7)

N = total number of subjects; n= number of subjects per treatment group; EOS = end of study; Q14D = dosing every 14 days; Q28D = dosing every 28 days.
a. Subjects have 1 reason for discontinuing study.
b. Subjects discontinued from study prior to receiving treatment.

Demographic and baseline characteristics are summarized for the FAS of the Q14D and Q28D dose groups in Table 6 and Table 7 respectively. In general the demographic and baseline characteristics of subjects in the Q14D and Q28D dose groups were similar.

Table 6. Summary of Demographic and Baseline Characteristics – Q14D Full Analysis Set

Criteria	Q14D				
	Placebo (N=50)	Bococizumab			Total (N=202)
		50 mg (N=50)	100 mg (N=52)	150 mg (N=50)	
Age, years					
Mean (SD)	60.5 (9.84)	59.1 (11.26)	61.9 (9.58)	61.4 (9.75)	60.7 (10.11)
Min, max	35, 82	36, 84	40, 82	40, 79	35, 84
Median	61.5	59.0	63.0	61.5	61.0
Age group, n (%)					
18 to 64 yrs	30 (60.0)	31 (62.0)	29 (55.8)	29 (58.0)	119 (58.9)
≥65 yrs	20 (40.0)	19 (38.0)	23 (44.2)	21 (42.0)	83 (41.1)
Sex, n (%)					
Male	25 (50.0)	24 (48.0)	26 (50.0)	21 (42.0)	96 (47.5)
Female	25 (50.0)	26 (52.0)	26 (50.0)	29 (58.0)	106 (52.5)
Race, n (%)					
White	39 (78.0)	33 (66.0)	37 (71.2)	36 (72.0)	145 (71.8)
Black	9 (18.0)	15 (30.0)	12 (23.1)	10 (20.0)	46 (22.8)
Asian	1 (2.0)	0	1 (1.9)	2 (4.0)	4 (2.0)
Other	1 (2.0)	2 (4.0)	2 (3.8)	2 (4.0)	7 (3.5)
Ethnic origin, n (%)					
Hispanic/Latino	2 (4.0)	8 (16.0)	6 (11.5)	7 (14.0)	23 (11.4)
Not Hispanic/Latino	48 (96.0)	42 (84.0)	46 (88.5)	43 (86.0)	179 (88.6)
Weight, kg					
Mean (SD)	91.1 (21.76)	91.4 (23.55)	90.2 (21.27)	90.4 (16.82)	90.8 (20.85)
Min, max	53, 133	90, 144	56, 155	63, 130	50, 155
Median	91.3	88.4	87.3	88.4	88.1
Height, cm					
Mean (SD)	167.9 (11.05)	169.0 (9.16)	168.3 (10.42)	168.5 (10.34)	168.4 (10.20)
Min, max	145, 186	148, 191	150, 190	152, 191	145, 191
Median	167.5	169.1	167.6	166.9	167.9
BMI, kg/m^2					
Mean (SD)	32.3 (7.4)	31.9 (7.5)	31.8 (7.1)	31.9 (5.7)	32.0 (6.9)
Min, max	20.5, 49.9	18.9, 48.7	21.7, 60.5	22.4, 50.6	18.9, 60.5
Median	31.7	30.4	29.7	31.2	30.6
Smoking classification					
Never smoked	25 (50.0)	28 (56.0)	30 (57.7)	32 (64.0)	115 (56.9)
Ex-smoker	17 (34.0)	13 (26.0)	18 (34.6)	11 (22.0)	59 (29.2)
Smoker	8 (16.0)	9 (18.0)	4 (7.7)	7 (14.0)	28 (13.9)
Use of alcohol in past 4 weeks					
Yes	27 (54.0)	24 (48.0)	19 (36.5)	21 (42.0)	91 (45.0)
No	21 (42.0)	26 (52.0)	32 (61.5)	26 (52.0)	105 (52.0)
Missing	2 (4.0)	0	1 (1.9)	3 (6.0)	6 (3.0)
Baseline statin, n (%)[a]					
Atorvastatin	11 (22.0)	9 (18.0)	17 (32.7)	12 (24.0)	49 (24.3)
Rosuvastatin	5 (10.0)	5 (10.0)	5 (9.6)	9 (18.0)	24 (11.9)
Simvastatin	18 (36.0)	21 (42.0)	14 (26.9)	16 (32.0)	69 (34.2)
Pravastatin	8 (16.0)	11 (22.0)	11 (21.2)	10 (20.0)	40 (19.8)
Lovastatin	8 (16.0)	4 (8.0)	5 (9.6)	2 (4.0)	19 (9.4)
Fluvastatin	0	0	0	1 (2.0)	1 (0.5)
Other	0	0	0	1 (2.0)	1 (0.5)

Table 6. Summary of Demographic and Baseline Characteristics – Q14D Full Analysis Set

Criteria	Q14D				
	Placebo (N=50)	Bococizumab			Total (N=202)
		50 mg (N=50)	100 mg (N=52)	150 mg (N=50)	
Baseline statin dose, n (%)[b]					
High	24 (48.0)	25 (50.0)	30 (57.7)	30 (60.0)	109 (54.0)
Low	26 (52.0)	25 (50.0)	22 (42.3)	20 (40)	93 (46.0)
Baseline LDL-C (mg/dL)					
Mean (SD)	108.7 (31.50)	107.9 (20.17)	113.4 (25.66)	105.8 (17.98)	109.0 (24.36)
Min, max	57, 224	75, 177	61, 185	63, 155	57, 224
Median	100.0	106.5	108.0	106.0	106.0
Baseline TG (mg/dL)					
Mean (SD)	139.0 (68.88)	140.3 (120.83)	154.4 (98.85)	152.1 (77.00)	146.5 (93.36)
Min, max	53, 345	35, 628	18, 645	57, 461	18, 545
Median	124.0	109.0	135.0	138.0	128.0
Time since first hypercholesterolemia diagnosis (years)					
Mean (SD)	11.5 (10.04)	9.6 (9.01)	11.7 (7.88)	10.2 (7.61)	10.8 (8.66)
Min, max	0.3, 42.6	0.1, 42.6	0, 32.8	0.1, 32.8	0, 42.6
Median	9.2	6.7	10.2	8.7	8.7

BMI = body mass index, max = maximum, Min = minimum, LDL-C = low density lipoprotein-cholesterol, N = number of subjects per treatment group, n = number of subjects in prespecified criteria, Q14D = dosing every 14 days, SD = standard deviation, TG = triglycerides.

c. Subjects taking vytorin were classified under simvastatin.

d. One subject taking itavastatin 4 mg was classified as low.

Table 7. Summary of Demographic and Characteristics – Q28D Full Analysis Set

Criteria		Q28D			
		Placebo (N=51)	Bococizumab 200 mg (N=50)	Bococizumab 300 mg (N=51)	Total (N=152)
Age, years	Mean (SD)	58.4 (11.62)	60.3 (9.64)	60.2 (8.17)	59.6 (9.89)
	Min, max	24, 78	41, 77	38, 82	24, 82
	Median	59.0	61.0	61.0	60.0
Age group, n (%)	18 to 64 years	37 (72.5)	35 (70.0)	37 (72.5)	109 (71.7)
	≥65 years	14 (27.5)	15 (30.0)	14 (27.5)	43 (28.3)
Sex, n (%)	Male	29 (56.9)	19 (38.0)	25 (49.0)	73 (48.0)
	Female	22 (43.1)	31 (62.0)	26 (51.0)	79 (52.0)
Race, n (%)	White	35 (68.6)	39 (78.0)	41 (80.4)	115 (75.7)
	Black	14 (27.5)	9 (18.0)	8 (15.7)	31 (20.4)
	Asian	0	0	1 (2.0)	1 (0.7)
	Other	2 (3.9)	2 (4.0)	1 (2.0)	5 (3.3)
Ethnic origin, n (%)					
Hispanic/Latino		7 (13.7)	6 (12.0)	2 (3.9)	15 (9.9)
Not Hispanic/Latino		44 (86.3)	44 (88.0)	49 (96.1)	137 (90.1)
Weight, kg	Mean (SD)	90.5 (21.27)	88.3 (23.89)	88.5 (19.22)	89.1 (21.41)
	Min, max	58, 160	54, 166	53, 136	53, 166
	Median	85.8	82.3	88.5	85.3
Height, cm	Mean (SD)	171.6 (10.20)	167.4 (10.32)	169.6 (10.41)	169.6 (10.38)
	Min, max	153, 188	142, 193	147, 188	142, 193
	Median	170.2	166.9	171.6	170.0
BMI, kg/m^2	Mean (SD)	30.7 (6.4)	31.3 (6.7)	30.7 (6.4)	30.9 (6.4)
	Min, max	21.6, 48.9	18.6, 50.5	20.3, 49.2	18.6, 50.5
	Median	29.4	29.8	29.4	29.5
Smoking classification					
Never smoked		23 (45.1)	26 (52.0)	25 (49.0)	74 (48.7)
Ex-smoker		13 (25.5)	18 (36.0)	21 (41.2)	52 (34.2)
Smoker		15 (29.4)	6 (12.0)	5 (9.8)	26 (17.1)
Use of alcohol in past 4 week					
Yes		25 (49.0)	24 (48.0)	31 (60.8)	80 (52.6)
No		25 (49.0)	24 (48.0)	19 (37.3)	68 (44.7)
Missing		1 (2.0)	2 (4.0)	1 (2.0)	4 (2.6)
Baseline statin, n (%)[a]					
Atorvastatin		9 (17.6)	7 (14.0)	7 (13.7)	23 (15.1)
Rosuvastatin		7 (13.7)	9 (18.0)	6 (11.8)	22 (14.5)
Simvastatin		17 (33.3)	20 (40.0)	27 (52.9)	64 (42.1)
Pravastatin		14 (27.5)	12 (24.0)	7 (13.7)	33 (21.7)
Lovastatin		4 (7.8)	2 (4.0)	4 (7.8)	10 (6.6)
Fluvastatin		0	0	0	0
Other		0	0	0	0
Baseline statin dose, n (%)					
High		23 (45.1)	26 (52.0)	28 (54.9)	77 (50.7)
Low		28 (54.9)	23 (46.0)	22 (43.1)	73 (48.0)
Missing		0	1 (2.0)	1 (2.0)	2 (1.3)
Baseline LDL-C (mg/dL)					
Mean (SD)		118.8 (44.77)	105.7 (23.21)	104.7 (22.09)	109.8 (32.27)
Min, max		70, 281	58, 166	57, 168	57, 281
Median		102.0	104.0	99.0	102.0
Baseline TG (mg/dL)					
Mean (SD)		135.0 (69.74)	139.2 (69.60)	128.7 (81.63)	134.3 (73.53)
Min, max		47, 342	43, 405	43, 600	43, 600
Median		109.0	122.5	113.0	114.5

Table 7. Summary of Demographic and Characteristics – Q28D Full Analysis Set

Criteria	Q28D			
	Placebo (N=51)	Bococizumab		Total (N=152)
		200 mg (N=50)	300 mg (N=51)	
Time since first hypercholesterolemia diagnosis (years)				
Mean (SD)	9.9 (8.47)	10.6 (9.33)	10.3 (10.32)	10.3 (9.34)
Min, max	0.2, 38.6	0.2, 52.8	0.3, 67.7	0.2, 67.7
Median	8.7	7.7	8.7	8.6

BMI = body mass index, LDL-C = low density lipoprotein-cholesterol, max = maximum, min = minimum, N = number of subjects per treatment group, n = number of subjects in prespecified criteria, Q28D = dosing every 28 days, SD = standard deviation, TG = triglycerides.
e. Subjects taking vytorin were classified under simvastatin.

Efficacy Results:

The summary of observed and change from Baseline in LDL-C (mg/dL) at Week 12 and Week 24 for Q14D and Q28D dosing regimens is presented in Table 8.

For the Q14D dose group, at Week 12, the observed mean changes (SD) from Baseline in LDL-C (mg/dL) demonstrated a decrease from Baseline of at least 50% in the highest Q14D dose groups, and a clear dose response. For the Q28D dose group at Week 12, the observed mean (SD) changes from Baseline in LDL-C (mg/dL) in the bococizumab 200 mg and 300 mg Q28D groups were -21.3 (28.03) and -38.3 (41.26) mg/dL, respectively. There were no changes from Baseline in mean observed LDL-C at Week 12 in subjects in either dose groups receiving placebo.

The dosing algorithm in the Q14D dosing regimen dictated 1 or more downward dose adjustments when the serum LDL-C was ≤25 mg/dL (0.65 mmol/L) on or at any time after Day 43. Similarly, the dosing algorithm in the Q28D dosing regimen forced downward adjustment of dose upon the occurrence of LDL-C ≤25 mg/dL 1 or more times after Day 57. Despite this forced downward dose reduction, the primary endpoint was met for all bococizumab Q14D and Q28D dose groups.

The decreases in LDL-C concentrations at Weeks 12 and 24 were statistically significant ($P<0.001$) for all the treatment groups in both dosing regimens, as determined from the adjusted mean differences from placebo on the changes from Baseline in the MMRM analysis of observed case data. The comparison of change from Baseline to Weeks 12 and Week 24 in LDL-C (mg/dL) using MMRM for both dosing regimens is provided in Table 9.

Table 8. Summary of Observed and Change From Baseline in LDL-C (mg/dL) at Weeks 12 and 24 – Q14D and Q28D Full Analysis Sets

LDL-C (mg/dL)	Q14D				Q28D		
	Placebo	Bococizumab			Placebo	Bococizumab	
Mean (SD)	N=50	50 mg N=50	100 mg N=52	150 mg N=50	N=51	200 mg N=50	300 mg N=51
Observed value at Baseline	108.7 (31.50)	107.9 (20.17)	113.4 (25.66)	105.8 (17.98)	118.8 (44.77)	105.7 (23.21)	104.7 (22.09)
n	49	50	51	49	51	50	51
Observed value at Week 12	105.7 (28.20)	71.3 (31.99)	59.9 (24.94)	50.1 (27.65)	117.3 (40.54)	84.4 (32.14)	66.5 (31.78)
n	47	44	42	46	46	48	50
Change from Baseline to Week 12	-2.8 (29.24)	-35.4 (26.58)	-52.3 (31.26)	-54.2 (26.98)	-1.3 (37.16)	-21.3 (28.03)	-38.3 (41.26)
n	47	44	42	46	46	48	50
Dose adjustment at Week 12 n/N (%)	0	0	7/41 (17.1)	14/43 (32.6)	0	16/47 (34.0)	14/42 (33.3)
Observed value at Week 24	102.7 (23.48)	75.6 (26.44)	62.6 (34.34)	63.0 (25.24)	112.0 (33.48)	83.0 (23.56)	75.3 (28.40)
n	47	43	45	47	43	47	48
Change from Baseline to Week 24	-4.4 (26.11)	-31.3 (20.18)	-51.4 (37.69)	-42.5 (28.81)	-4.4 (31.17)	-22.5 (20.99)	-29.6 (31.78)
n	47	43	45	47	43	47	48
Dose adjustment at Week 20/Week 22[a] n/N (%)	0	0	8/41 (19.5)	16/41 (39.0)	0	20/44 (45.5)	20/44 (45.5)

LDL-C = low density lipoprotein - cholesterol, N = total number of subjects, n = number of subjects with pre-specified criteria, N = number of subjects per treatment group, n = number of subjects in prespecified criteria, Q14D = dosing every 14 days; Q28D = dosing every 28 days, SD = standard deviation.

a. Week 20 for Q28D and Week 22 for Q14D.

Table 9. Comparison of Change From Baseline to Weeks 12 and 24 in LDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis Based on Observed Case Data – Q14D and Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Week 12/Day 85	Q14D:					
	Bococizumab 50 mg	44	-35.4	-36.9 (-44.55, -29.17)	-34.28 (-45.06, -23.50)	<0.001
	Bococizumab 100 mg	42	-52.3	-47.6 (-55.45, -39.85)	-45.07 (-55.93, -34.21)	<0.001
	Bococizumab 150 mg	46	-54.2	-56.0 (-63.60, -48.40)	-53.42 (-64.14, -42.70)	<0.001
	Placebo	47	-2.8	-2.6 (-10.14, 4.98)		
Week 24/Day 169	Q14D					
	Bococizumab 50 mg	43	-31.3	-32.0 (-39.72, -24.37)	-28.41 (-39.15, -17.67)	<0.001
	Bococizumab 100 mg	45	-51.4	-46.8 (-54.44, -39.25)	-43.21 (-53.90, -32.51)	<0.001
	Bococizumab 150 mg	47	-42.5	-44.7 (-52.19, -37.16)	-41.03 (-51.66, -30.41)	<0.001
	Placebo	47	-4.4	-3.6 (-11.16, 3.88)		
Week 12/Day 85	Q28D					
	Bococizumab 200 mg	48	-21.3	-23.0 (-32.00, -14.02)	-27.58 (-40.49, -14.67)	<0.001
	Bococizumab 300 mg	50	-38.3	-40.3 (-49.09, -31.48)	-44.85 (-57.65, -32.05)	<0.001
	Placebo	46	-1.3	4.6 (-4.59, 13.73)		
Week 24/Day 169	Q28D					
	Bococizumab 200 mg	47	-22.5	-24.3 (-31.21, -17.49)	-23.77 (-33.70, -13.84)	<0.001
	Bococizumab 300 mg	48	-29.6	-30.9 (-37.71, -24.18)	-30.36 (-40.24, -20.49)	<0.001
	Placebo	43	-4.4	-0.6 (-7.69, 6.54)		

Change = LDL-C (mg/dL) at Week 12 or Week 24 – LDL-C (mg/dL) at Baseline.
CI = confidence interval; LDL-C = low density lipoprotein-cholesterol; n = subjects with non-missing values in the analysis set; Q14D = dosing every 14 days; Q28D = dosing every 28 days, vs = versus.
a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

The summary of observed and percent change from Baseline in average LDL-C (mg/dL) at Weeks 12 and 24 for Q14D and Q28D dosing regimens are provided in Table 10 and Table 11 respectively.

Table 10. Summary of Observed and Percent Change From Baseline in LDL-C (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50		Bococizumab 50 mg N=50		Bococizumab 100 mg N=52		Bococizumab 150 mg N=50	
	Observed Value	% Change From Baseline	Observed Value	% Change From Baseline	Observed Value	% Change From Baseline	Observed Value	% Change From Baseline
Baseline								
n	49	-	50	-	51	-	49	-
Mean	108.7	-	107.9	-	113.4	-	105.8	-
SD	31.50	-	20.17	-	25.66	-	17.98	-
Minimum	57	-	75	-	61	-	63	-
1st Quartile	90.0	-	93.0	-	96.0	-	95.0	-
Median	100.0	-	106.5	-	108.0	-	106.0	-
3rd Quartile	119.0	-	118.0	-	129.0	-	116.0	-
Maximum	224	-	177	-	185	-	155	-
Day 85								
n	47	47	44	44	42	42	46	46
Mean	105.7	0.57	71.3	-33.65	59.9	-44.87	50.1	-52.02
SD	28.20	25.445	31.99	23.314	24.94	23.431	27.65	24.652
Minimum	49	-56.1	0	-100.0	16	-83.4	11	-88.7
1st Quartile	85.0	-14.04	59.0	-47.17	42.0	-60.17	29.0	-71.74
Median	106.0	-1.11	69.5	-33.66	56.5	-48.12	40.0	-59.65
3rd Quartile	117.0	8.33	78.5	-22.38	74.0	-33.33	60.0	-37.89
Maximum	187	106.0	207	16.9	127	9.8	122	3.4
Day 169								
n	47	47	43	43	45	45	47	47
Mean	102.7	-1.11	75.6	-29.58	62.6	-43.81	63.0	-38.98
SD	23.48	22.224	26.44	18.133	34.34	27.069	25.24	24.712
Minimum	55	-46.7	30	-60.7	22	-86.0	22	-77.6
1st Quartile	87.0	-15.38	59.0	-44.64	41.0	-61.25	46.0	-59.84
Median	105.0	1.11	66.0	-32.18	56.0	-50.81	57.0	-43.75
3rd Quartile	116.0	7.02	84.0	-15.79	72.0	-34.12	73.0	-20.88
Maximum	162	65.1	152	14.4	198	35.6	128	21.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = number of subjects per treatment group, n = number of subjects in pre-specified criteria, Q14D = dosing every 14 days, SD = standard deviation.

Table 11. Summary of Observed and Percent Change From Baseline in LDL-C (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N=51		Bococizumab 200 mg N=50		Bococizumab 300 mg N=51	
	Observed	% Change From Baseline	Observed	% Change From Baseline	Observed	% Change From Baseline
Baseline						
n	51	-	50	-	51	-
Mean	118.8	-	105.7	-	104.7	-
SD	44.77	-	23.21	-	22.09	-
Minimum	70	-	58	-	57	-
1st Quartile	87.0	-	89.0	-	88.0	-
Median	102.0	-	104.0	-	99.0	-
3rd Quartile	137.0	-	121.0	-	114.0	-
Maximum	281	-	166	-	168	-
Day 85						
n	46	46	48	48	50	50
Mean	117.3	3.34	84.4	-19.48	66.5	-33.26
SD	40.54	25.044	32.14	26.604	31.78	35.179
Minimum	72	-59.9	24	-72.3	10	-93.3
1st Quartile	89.0	-8.79	65.5	-33.41	36.0	-61.70
Median	109.5	1.64	85.0	-17.58	65.5	-34.86
3rd Quartile	128.0	25.00	102.0	-4.73	96.0	-5.95
Maximum	288	66.7	196	35.6	122	46.8
Day 169						
n	43	43	47	47	48	48
Mean	112.0	0.54	83.0	-20.40	75.3	-26.45
SD	33.48	20.921	23.56	19.676	28.40	27.719
Minimum	67	-53.3	29	-68.8	11	-88.9
1st Quartile	92.0	-14.02	71.0	-31.33	50.0	-44.91
Median	104.0	2.54	84.0	-19.23	74.0	-21.95
3rd Quartile	124.0	12.64	97.0	-8.13	93.5	-9.23
Maximum	231	53.5	133	31.7	138	76.9

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = number of subjects per treatment group, n = number of subjects in pre-specified criteria, Q28D = dosing every 28 days, SD = standard deviation.

The summary of the MMRM analysis on the adjusted mean percent changes from Baseline are presented in Table 12. The results were comparable to the analyses of the absolute values and showed that within the 2 bococizumab dosing groups the adjusted mean differences from placebo to Weeks 12 and 24 were statistically significant (P<0.001) despite a slightly diminished response over time. The dose reduction, particularly sequential reductions (eg, 300 mg to 200 mg to 100 mg to 50 mg) resulted in reducing the individual LDL-C response and overall dose group percent mean LDL-C observed at Week 24.

Table 12. Comparison of Percent Change From Baseline to Weeks 12 and 24 in LDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis Based on Observed Case Data – Q14D and Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Week 12/Day 85	Q14D:					
	Bococizumab 50 mg	44	-33.6	-34.4 (-41.47, -27.34)	-35.00 (-44.91, -25.10)	<0.001
	Bococizumab 100 mg	42	-44.9	-41.7 (-48.90, -34.54)	-42.32 (-52.30, -32.33)	<0.001
	Bococizumab 150 mg	46	-52.0	-52.5 (-59.51, -45.54)	-53.12 (-62.97, -43.27)	<0.001
	Placebo	47	0.6	0.6 (-6.34, 7.54)	-	-
Week 24/Day 169	Q14D					
	Bococizumab 50 mg	43	-29.6	-30.0 (-36.64, -23.29)	-29.09 (-38.42, -19.77)	<0.001
	Bococizumab 100 mg	45	-43.8	-41.0 (-47.62, -34.42)	-40.14 (-49.43, -30.86)	<0.001
	Bococizumab 150 mg	47	-39.0	-40.0 (-46.55, -33.51)	-39.16 (-48.37, -29.94)	<0.001
	Placebo	47	-1.1	-0.9 (-7.39, 5.64)	-	-
Week 12/Day 85	Q28D					
	Bococizumab 200 mg	48	-19.5	-20.2 (-28.10, -12.39)	-26.96 (-38.25, -15.67)	<0.001
	Bococizumab 300 mg	50	-33.3	-34.4 (-42.11, -26.72)	-41.13 (-52.32, -29.94)	<0.001
	Placebo	46	3.3	6.7 (-1.30, 14.73)	-	-
Week 24/Day 169	Q28D					
	Bococizumab 200 mg	47	-20.4	-21.3 (-27.63, -15.07)	-23.79 (-32.88, -14.70)	<0.001
	Bococizumab 300 mg	48	-26.4	-26.6 (-32.84, -20.45)	-29.08 (-38.13, -20.04)	<0.001
	Placebo	43	0.5	2.4 (-4.08, 8.96)	-	-

Percent change = 100% x [LDL-C (mg/dL) - LDL-C (mg/dL) at Baseline]/LDL-C (mg/dL) at Baseline.
CI = confidence interval, LDL-C = low density lipoprotein cholesterol, n = subjects with non-missing values in the analysis set, Q14D = dosing with placebo or bococizumab every 14 days, Q28D = dosing with placebo or bococizumab every 28 days, vs = versus.

a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Pharmacodynamic Results: In this study, biomarkers representing different pathways were assessed in an attempt to understand the mechanisms by which bococizumab exerts its PD effects. The results from the analyses of the PD parameters are described below:

Total Serum Cholesterol: Generally, dose-related reductions in total serum cholesterol were observed for the bococizumab Q14D and Q28D dose groups as presented in Table 13 and Table 14 respectively. As seen with the LDL-C endpoints, there was a decrease in the response over time for which a contributory factor was the forced downward dose adjustment.

Table 13. Summary of Observed, Change, and Percent Change From Baseline in Total Cholesterol (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	188.8	-	-	186.0	-	-	194.5	-	-	188.9	-	-
SD	35.12	-	-	34.85	-	-	33.72	-	-	25.30	-	-
Minimum	140	-	-	136	-	-	145	-	-	135	-	-
1st Quartile	169.0	-	-	169.0	-	-	171.0	-	-	171.0	-	-
Median	180.0	-	-	183.5	-	-	189.0	-	-	187.0	-	-
3rd Quartile	201.0	-	-	198.0	-	-	211.0	-	-	201.0	-	-
Maximum	304	-	-	368	-	-	287	-	-	273	-	-
Day 85												
n	47	47	47	43	43	43	43	43	43	46	46	46
Mean	183.6	-5.6	-2.35	150.3	-35.8	-18.96	140.5	-52.7	-26.45	128.2	-58.6	-31.64
SD	37.79	29.58	14.406	35.49	24.73	12.299	29.85	32.67	14.943	38.48	32.90	18.012
Minimum	129	-90	-31.9	102	-87	-45.5	90	-138	-50.2	63	-107	-61.6
1st Quartile	152.0	-19.0	-10.71	129.0	-49.0	-28.67	116.0	-76.0	-39.64	99.0	-84.0	-45.41
Median	181.0	-8.0	-4.23	144.0	-34.0	-17.98	139.0	-50.0	-27.37	120.0	-69.5	-36.94
3rd Quartile	201.0	8.0	4.44	159.0	-19.0	-11.06	160.0	-33.0	-15.71	157.0	-33.0	-18.33
Maximum	293	96	48.7	304	24	12.2	229	25	17.0	224	13	7.9
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	181.6	-5.5	-2.31	151.4	-31.7	-16.70	139.9	-55.0	-27.77	141.6	-46.9	-24.31
SD	32.96	28.04	13.481	34.77	32.53	15.860	40.96	38.67	16.993	31.99	33.83	16.491
Minimum	127	-80	-33.0	94	-127	-38.5	78	-141	-58.1	90	-119	-47.8
1st Quartile	152.0	-18.0	-10.59	125.0	-52.0	-30.06	120.0	-80.0	-40.68	122.0	-73.0	-38.83
Median	177.0	-3.0	-1.75	144.0	-39.0	-19.52	135.0	-55.0	-30.77	136.0	-47.0	-24.32
3rd Quartile	206.0	16.0	7.96	167.0	-14.0	-8.24	152.0	-33.0	-18.93	161.0	-18.0	-10.00
Maximum	252	53	26.9	241	59	33.0	322	72	28.8	239	28	16.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing every 14 days, SD = standard deviation.

Table 14. Summary of Observed, Change, and Percent Change From Baseline in Total Cholesterol (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline
Baseline									
n	51	-	-	50	-	-	51	-	-
Mean	198.4	-	-	185.1	-	-	178.9	-	-
SD	45.28	-	-	29.56	-	-	29.92	-	-
Minimum	145	-	-	117	-	-	110	-	-
1st Quartile	171.0	-	-	164.0	-	-	158.0	-	-
Median	187.0	-	-	191.0	-	-	175.0	-	-
3rd Quartile	210.0	-	-	202.0	-	-	202.0	-	-
Maximum	354	-	-	256	-	-	252	-	-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	199.1	-0.4	1.24	165.7	-19.5	-10.51	141.4	-37.6	-19.44
SD	47.64	40.00	16.624	39.17	27.39	15.318	35.59	43.58	22.054
Minimum	140	-154	-48.7	89	-88	-43.6	72	-150	-60.5
1st Quartile	166.0	-11.0	-5.23	135.0	-36.0	-17.64	114.0	-64.0	-35.83
Median	188.0	-1.0	-0.47	168.5	-19.0	-10.35	146.5	-36.5	-19.89
3rd Quartile	210.0	24.0	13.41	194.0	1.5	0.78	172.0	-4.0	-2.82
Maximum	374	77	27.0	283	27	15.4	211	45	31.0
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	189.0	-6.4	-1.35	160.4	-24.5	-12.83	151.4	-28.6	-14.61
SD	34.57	33.98	14.426	31.99	25.86	13.365	29.77	33.61	17.302
Minimum	140	-140	-44.3	96	-87	-41.4	102	-131	-55.3
1st Quartile	164.0	-18.0	-9.63	136.0	-47.0	-22.75	130.0	-41.0	-22.44
Median	184.0	2.0	1.16	162.0	-24.0	-13.11	149.0	-23.0	-15.27
3rd Quartile	199.0	14.0	7.35	181.0	-6.0	-3.13	173.0	-11.0	-5.38
Maximum	304	37	22.0	227	31	16.0	216	71	49.0

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing every 28 days, SD = standard deviation.

ApoB, ApoA1 and ApoAII: The summary of observed, change, and percent change from Baseline in ApoB (mg/dL) in Q14D and Q28D dosing regimen is provided in Table 15 and Table 16 respectively. In general, dose-related decreases over time were observed in the bococizumab dose groups relative to placebo.

Table 15. Summary of Observed, Change, and Percent Change From Baseline in ApoB (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	92.3	-	-	89.3	-	-	96.6	-	-	89.6	-	-
SD	20.40	-	-	22.30	-	-	17.32	-	-	15.99	-	-
Minimum	65	-	-	63	-	-	68	-	-	35	-	-
1st Quartile	78.0	-	-	75.0	-	-	83.0	-	-	81.0	-	-
Median	87.0	-	-	86.0	-	-	98.0	-	-	88.0	-	-
3rd Quartile	102.0	-	-	101.0	-	-	107.0	-	-	96.0	-	-
Maximum	159	-	-	203	-	-	138	-	-	147	-	-
Day 85												
n	47	47	47	45	45	45	44	44	44	46	46	46
Mean	89.5	-3.2	-2.11	67.9	-20.4	-23.22	62.5	-33.7	-34.91	54.4	-33.4	-37.41
SD	19.59	16.90	17.703	22.63	12.88	14.214	21.67	19.17	17.995	21.09	19.92	23.459
Minimum	50	-61	-38.4	35	-45	-46.2	35	-87	-68.0	35	-64	-64.6
1st Quartile	75.0	-12.0	-14.78	54.0	-30.0	-34.18	45.5	-44.5	-46.11	36.0	-50.0	-55.13
Median	87.0	-3.0	-2.94	63.0	-20.0	-22.86	61.0	-32.0	-33.56	47.5	-37.5	-46.28
3rd Quartile	99.0	6.0	6.67	72.0	-13.0	-15.76	79.0	-22.0	-22.64	65.0	-20.0	-23.53
Maximum	144	45	65.2	171	7	8.9	131	12	16.0	120	12	34.3
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	88.5	-3.1	-1.88	68.0	-20.8	-22.98	62.6	-34.1	-34.86	62.6	-26.5	-27.79
SD	17.82	17.19	17.058	20.98	17.87	16.958	22.97	22.71	20.407	20.25	21.70	26.725
Minimum	59	-55	-38.3	35	-82	-50.0	35	-91	-71.1	35	-63	-63.6
1st Quartile	74.0	-10.0	-13.51	52.0	-29.0	-37.78	47.0	-46.0	-44.19	45.0	-46.0	-50.00
Median	85.0	-4.0	-5.63	64.0	-24.0	-25.68	61.0	-34.0	-39.25	62.0	-26.0	-31.03
3rd Quartile	101.0	10.0	12.33	77.0	-6.0	-8.00	74.0	-21.0	-25.00	73.0	-11.0	-13.16
Maximum	128	32	46.4	122	20	20.8	139	25	23.1	119	30	85.7

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
ApoB = apolipoprotein B, N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing every 14 days, SD = standard deviation.

Table 16. Summary of Observed, Change, and Percent Change From Baseline in ApoB (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo			Bococizumab					
				200 mg N=50			300 mg N=51		
	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline
Baseline									
n	51	-	-	50	-	-	51	-	-
Mean	97.4	-	-	91.3	-	-	87.4	-	-
SD	28.09	-	-	16.49	-	-	16.14	-	-
Minimum	63	-	-	59	-	-	53	-	-
1st Quartile	78.0	-	-	79.0	-	-	78.0	-	-
Median	91.0	-	-	88.0	-	-	87.0	-	-
3rd Quartile	112.0	-	-	101.0	-	-	98.0	-	-
Maximum	180	-	-	140	-	-	132	-	-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	97.6	-0.5	1.50	78.9	-12.2	-13.55	62.7	-24.7	-25.97
SD	27.71	21.94	17.093	23.66	17.40	20.165	21.31	26.21	28.150
Minimum	62	-99	-55.0	35	-60	-59.4	35	-97	-73.5
1st Quartile	82.0	-8.0	-8.33	66.0	-22.0	-22.52	44.0	-45.0	-50.47
Median	93.0	0.0	0.00	80.0	-9.0	-9.35	61.5	-28.5	-29.63
3rd Quartile	107.0	12.0	12.99	91.0	0.0	0.00	81.0	-1.0	-1.27
Maximum	201	45	40.6	145	35	42.2	104	31	58.5
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	90.6	-5.1	-2.93	75.5	-15.3	-16.63	69.1	-18.7	-20.11
SD	22.03	19.18	15.885	19.03	14.88	17.392	19.84	19.60	22.894
Minimum	53	-80	-44.4	35	-48	-56.5	35	-63	-62.4
1st Quartile	77.0	-9.0	-12.50	63.0	-26.0	-27.59	55.0	-27.0	-32.58
Median	87.0	-2.0	-2.53	73.0	-16.0	-17.02	71.0	-14.0	-16.67
3rd Quartile	100.0	9.0	9.09	91.0	-6.0	-5.61	85.0	-7.0	-9.23
Maximum	159	19	29.7	113	28	33.7	110	35	66.0

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
ApoB = apolipoprotein B, N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing every 28 days, SD = standard deviation.

For Q14D and Q28D dose groups, in the MMRM analysis the adjusted mean differences from placebo were statistically significant (P<0.001) at all timepoints despite the reduction in response of which a contributory factor was the forced downward dose adjustment as provided in Table 17 and Table 19 respectively. Also, the results of the corresponding analyses of the percent change from Baseline were comparable to the absolute changes as shown in Table 18 and Table 20 for Q14D and Q28D dose groups respectively.

Table 17. Comparison of Change From Baseline to Week 24 in ApoB (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85	Q14D					
	Bococizumab 50 mg	45	-20.4	-21.4 (-26.26, -16.48)	-18.55 (-25.44, -11.67)	<0.001
	Bococizumab 100 mg	44	-33.7	-30.5 (-35.40, -25.57)	-27.67 (-34.55, -20.79)	<0.001
	Bococizumab 150 mg	46	-33.4	-34.9 (-39.77, -30.04)	-32.09 (-38.95, -25.22)	<0.001
	Placebo	47	-3.2	-2.8 (-7.65, 2.02)	-	-
Day 169	Q14D					
	Bococizumab 50 mg	43	-20.8	-22.2 (-27.46, -16.89)	-19.67 (-27.07, -12.27)	<0.001
	Bococizumab 100 mg	45	-34.1	-30.7 (-35.92, -25.44)	-28.17 (-35.52, -20.82)	<0.001
	Bococizumab 150 mg	47	-26.5	-27.9 (-33.09, -22.75)	-25.41 (-32.73, -18.09)	<0.001
	Placebo	47	-3.1	-2.5 (-7.68, 2.66)	-	-

Change = ApoB (mg/dL) - ApoB (mg/dL) at Baseline.
ApoB = apolipoprotein B, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q14D = dosing with placebo or Bococizumab every 14 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 18. Comparison of Percent Change From Baseline to Week 24 in ApoB (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85	Q14D					
	Bococizumab 50 mg	45	-23.2	-23.5 (-28.94, -18.07)	-21.58 (-29.23, -13.92)	<0.001
	Bococizumab 100 mg	44	-34.9	-32.5 (-37.93, -27.01)	-30.54 (-38.19, -22.89)	<0.001
	Bococizumab 150 mg,	46	-37.4	-37.9 (-43.29, -32.47)	-35.95 (-43.59, -28.31)	<0.001
	Placebo,	47	-2.1	-1.9 (-7.31, 3.45)	-	-
Day 169	Q14D					
	Bococizumab 50 mg	43	-23.0	-23.6 (-29.48, -17.72)	-22.09 (-30.32, -13.86)	<0.001
	Bococizumab 100 mg	45	-34.9	-32.5 (-38.29, -26.64)	-30.95 (-39.13, -22.77)	<0.001
	Bococizumab 150 mg	47	-27.8	-28.7 (-34.50, -22.99)	-27.23 (-35.38, -19.09)	<0.001
	Placebo	47	-1.9	-1.5 (-7.27, 4.25)	-	-

Percent change = 100% × [ApoB (mg/dL) - ApoB (mg/dL) at Baseline]/ApoB (mg/dL) at Baseline
ApoB = apolipoprotein B, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q14D = dosing every 14 days, vs = versus.

a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 19. Comparison of Change From Baseline to Week 24 in ApoB (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	-12.2	-12.2 (-18.08, -6.40)	-14.56 (-22.89, -6.24)	<0.001
	Bococizumab 300 mg	50	-24.7	-26.2 (-31.92, -20.42)	-28.50 (-36.83, -20.16)	<0.001
	Placebo	47	-0.5	2.3 (-3.59, 8.24)	-	<0.001
Day 169						
	Bococizumab 200 mg	47	-15.3	-15.7 (-20.26, -11.06)	-12.72 (-19.35, -6.09)	<0.001
	Bococizumab 300 mg	49	-18.7	-19.8 (-24.32, -15.26)	16.85 (-23.47, -10.23)	<0.001
	Placebo	43	-5.1	-2.9 (-7.70, 1.83)	-	<0.001

Change = ApoB (mg/dL) – ApoB (mg/dL) at Baseline.
ApoB = apolipoprotein B, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q28D = dosing every 28 days, vs = versus.

a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 20. Comparison of Percent Change From Baseline to Week 24 in ApoB (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	-13.5	-13.5 (-19.60, -7.37)	-17.14 (-25.87, -8.41)	<0.001
	Bococizumab 300 mg	50	-26.0	-27.1 (-33.09, -21.04)	-30.72 (-39.45, -21.98)	<0.001
	Placebo	47	1.5	3.7 (-2.55, 9.86)	-	<0.001
Day 169						
	Bococizumab 200 mg	47	-16.6	-16.8 (-22.04, -11.54)	-15.34 (-22.90, -7.78)	<0.001
	Bococizumab 300 mg	49	-20.1	-20.6 (-25.76, -15.42)	-19.15 (-26.70, -11.59)	<0.001
	Placebo	43	-2.9	-1.4 (-6.88, 3.98)	-	<0.001

Percent change = 100% × [Apo-B (mg/dL) – Apo-B (mg/dL) at Baseline]/Apo B (mg/dL) at Baseline.
Apo B = apolipoprotein B, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q28D = dosing every 28 days, vs = versus.

a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

The mean change from Baseline showed a trend of an increase from Baseline in ApoA1 in both the bococizumab Q14D and Q28D dose groups as shown in Table 21 and Table 22 respectively. However, the adjusted mean differences from placebo were only statistically significant at a number of isolated time points for Q14D regimen (Table 23) and Q28D regimen (Table 24). The results of the corresponding analyses of the percent change from Baseline were similar to the absolute changes in the Q14D and Q28D dose groups as provided in Table 25 and Table 26 respectively.

Table 21. Summary of Observed, Change, and Percent Change From Baseline in ApoA1 (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	151.3	-	-	148.4	-	-	149.0	-	-	151.4	-	-
SD	25.19	-	-	24.35	-	-	25.39	-	-	29.65	-	-
Minimum	92	-	-	102	-	-	108	-	-	39	-	-
1st Quartile	134.0	-	-	132.0	-	-	128.0	-	-	133.0	-	-
Median	150.0	-	-	144.0	-	-	150.0	-	-	152.0	-	-
3rd Quartile	165.0	-	-	165.0	-	-	165.0	-	-	163.0	-	-
Maximum	221	-	-	202	-	-	214	-	-	214	-	-
Day 85												
n	47	47	47	45	45	45	44	44	44	46	46	46
Mean	152.9	1.5	1.80	152.6	4.7	2.91	158.9	8.7	5.85	158.4	6.7	9.86
SD	25.33	18.48	12.860	33.92	18.96	13.029	32.45	17.54	11.542	26.30	24.92	45.813
Minimum	115	-29	-18.8	68	-47	-40.9	110	-29	-20.6	118	-47	-27.2
1st Quartile	135.0	-13.0	-8.11	133.0	-4.0	-2.42	138.5	-3.5	-1.99	140.0	-3.0	-2.14
Median	144.0	4.0	2.42	150.0	6.0	3.51	151.0	9.0	6.12	155.0	5.5	3.48
3rd Quartile	169.0	12.0	9.09	174.0	15.0	10.61	175.5	18.0	12.06	172.0	17.0	11.84
Maximum	247	54	42.9	249	47	25.2	257	65	33.9	239	119	305.1
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	151.9	0.4	0.89	146.3	1.6	1.16	150.7	1.2	0.44	156.7	5.2	7.30
SD	27.33	19.40	12.367	29.95	19.25	13.195	33.42	18.10	11.670	23.72	19.23	31.172
Minimum	110	-41	-25.0	102	-41	-26.1	94	-36	-27.7	112	-42	-22.0
1st Quartile	135.0	-10.0	-7.09	118.0	-15.0	-9.94	128.0	-9.0	-5.88	145.0	-2.0	-1.25
Median	149.0	2.0	1.23	146.0	7.0	4.61	141.0	-1.0	-0.82	157.0	3.0	2.75
3rd Quartile	165.0	13.0	9.46	163.0	15.0	10.14	172.0	15.0	7.85	165.0	14.0	9.92
Maximum	252	57	29.2	235	37	26.6	239	47	24.5	229	80	205.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
ApoA1 =apolipoprotein A1, N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing every 14 days, SD = standard deviation.

Table 22. Summary of Observed, Change, and Percent Change From Baseline in ApoA1 (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N=51			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline	Observed	Change From Baseline	% Change From Baseline
Baseline									
n	51	-	-	50	-	-	51	-	-
Mean	150.4	-	-	151.1	-	-	145.4	-	-
SD	22.23	-	-	25.60	-	-	25.02	-	-
Minimum	112	-	-	105	-	-	89	-	-
1st Quartile	135.0	-	-	132.0	-	-	124.0	-	-
Median	147.0	-	-	152.0	-	-	143.0	-	-
3rd Quartile	168.0	-	-	169.0	-	-	165.0	-	-
Maximum	211	-	-	209	-	-	193	-	-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	154.2	2.1	2.11	158.4	7.7	5.55	152.7	7.7	5.68
SD	20.38	15.86	10.284	28.76	16.82	11.121	28.65	16.38	11.556
Minimum	120	-50	-29.2	107	-24	-13.2	90	-17	-11.8
1st Quartile	138.0	-6.0	-4.38	139.5	-2.5	-1.74	130.0	-2.0	-1.60
Median	153.0	3.0	2.00	158.0	5.5	3.99	154.5	3.0	1.85
3rd Quartile	168.0	11.0	7.25	173.5	16.0	9.96	173.0	15.0	11.38
Maximum	195	42	29.8	254	45	32.0	247	61	37.0
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	151.2	1.9	1.72	150.8	-0.2	0.46	146.2	0.7	0.88
SD	24.70	18.71	12.484	30.46	22.37	13.718	27.90	17.68	12.080
Minimum	102	-71	-40.6	106	-61	-36.1	81	-50	-33.3
1st Quartile	132.0	-8.0	-4.49	136.0	-10.0	-6.90	126.0	-10.0	-8.03
Median	152.0	3.0	2.33	149.0	-1.0	-0.63	144.0	0.0	0.00
3rd Quartile	170.0	11.0	7.63	170.0	11.0	7.91	168.0	13.0	9.68
Maximum	214	43	32.3	268	59	28.2	205	32	23.4

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
ApoA1 =apolipoprotein A1, N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing every 28 days, SD = standard deviation.

Table 23. Comparison of Change From Baseline to Week 24 in ApoA1 (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	45	4.7	3.9 (-1.83, 9.67)	1.77 (-6.33, 9.88)	0.667
	Bococizumab 100 mg,	44	8.7	7.6 (1.84, 13.33)	5.44 (-2.66, 13.54)	0.187
	Bococizumab 150 mg	46	6.7	6.0 (0.25, 11.68)	3.82 (-4.25, 11.90)	0.352
	Placebo	47	1.5	2.1 (-3.56, 7.85)	-	-
Day 169						
	Bococizumab 50 mg	43	1.6	1.4 (-4.14, 6.86)	0.59 (-7.09, 8.28)	0.879
	Bococizumab 100 mg	45	1.2	1.2 (-4.19, 6.58)	0.43 (-7.17, 8.02)	0.911
	Bococizumab 150 mg	47	5.2	4.9 (-0.45, 10.23)	4.12 (-3.44, 11.69)	0.283
	Placebo	47	0.4	0.8 (-4.59, 6.12)	-	-

Change = ApoA1 (mg/dL) – ApoA1 (mg/dL) at Baseline.
ApoA1 = apolipoprotein A1, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q14D = dosing every 14 days, vs = versus.
a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 24. Comparison of Change From Baseline to Week 24 in ApoA1 (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	7.7	7.8 (3.24, 12.43)	5.60 (-0.89, 12.09)	0.090
	Bococizumab 300 mg	50	7.7	6.6 (2.09, 11.11)	4.36 (-2.10, 10.82)	0.184
	Placebo	47	2.1	2.2 (-2.37, 6.84)	-	-
Day 169						
	Bococizumab 200 mg	47	-0.2	0.6 (-5.01, 6.15)	-1.41 (-9.41, 6.59)	0.728
	Bococizumab 300 mg	49	0.7	-0.2 (-5.68, 5.26)	-2.19 (-10.13, 5.75)	0.587
	Placebo	43	1.9	2.0 (-3.76, 7.72)	-	-

Change = ApoA1 (mg/dL) – ApoA1 (mg/dL) at Baseline.
ApoA1 = apolipoprotein A1, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q28 = dosing every 28 days, vs = versus.
a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 25. Comparison of Percent Change From Baseline to Week 24 in ApoA1 (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	45	2.9	2.0 (-4.65, 8.55)	-0.66 (-10.05, 8.74)	0.890
	Bococizumab 100 mg	44	5.9	4.9 (-1.63, 11.48)	2.32 (-7.04, 11.68)	0.625
	Bococizumab 150 mg	46	9.9	9.1 (2.52, 15.77)	6.54 (-2.86, 15.94)	0.172
	Placebo	47	1.8	2.6 (-4.06, 9.28)	-	-
Day 169						
	Bococizumab 50 mg	43	1.2	0.5 (-4.53, 5.59)	-0.86 (-8.01, 6.29)	0.812
	Bococizumab 100 mg	45	0.4	0.2 (-4.73, 5.22)	-1.15 (-8.24, 5.94)	0.749
	Bococizumab 150 mg	47	7.3	7.2 (2.20, 12.22)	5.82 (-1.29, 12.93)	0.108
	Placebo	47	0.9	1.4 (-3.65, 6.44)	-	-

Percent change = [ApoA1 (mg/dL) – ApoA1 (mg/dL) at Baseline]/ApoA1 (mg/dL) at Baseline.
ApoA1 = apolipoprotein A1, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q14D = dosing with placebo or bococizumab every 14 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 26. Comparison of Percent Change From Baseline to Week 24 in ApoA1 (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	5.6	5.7 (2.67, 8.74)	3.50 (-0.79, 7.80)	0.109
	Bococizumab 300 mg	50	5.7	4.9 (1.90, 7.85)	2.67 (-1.60, 6.94)	0.218
	Placebo	47	2.1	2.2 (-0.84, 5.24)	-	-
Day 169						
	Bococizumab 200 mg	47	0.5	1.0 (-2.58, 4.62)	-0.83 (-5.99, 4.34)	0.752
	Bococizumab 300 mg	49	0.9	0.3 (-3.23, 3.83)	-1.55 (-6.68, 3.57)	0.550
	Placebo	43	1.7	1.9 (-1.86, 5.56)	-	-

Percent change = [ApoA1 (mg/dL) – ApoA1 (mg/dL) at Baseline]/ApoA1 (mg/dL) at Baseline.
ApoA1 = apolipoprotein A1, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q28D = dosing with placebo or bococizumab every 28 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Small increases ApoAII from Baseline were observed in the bococizumab Q14D and Q28D dose groups as shown in Table 27 and Table 28 respectively. However, statistically significant differences relative to placebo in the bococizumab Q14D groups were sporadic (Table 29) and no statistically significant differences were seen relative to placebo in the bococizumab Q28D dose groups (Table 30). There were no statistically significant differences relative to placebo in the analyses of the percent changes from Baseline as provided in Table 31 and Table 32 respectively.

Table 27. Summary of Observed, Change, and Percent Change From Baseline in ApoAII (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline	Observed Value	Change From Baseline	% Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	39.4	-	-	38.7	-	-	40.6	-	-	41.5	-	-
SD	7.94	-	-	7.40	-	-	6.67	-	-	7.44	-	-
Minimum	6	-	-	3	-	-	31	-	-	30	-	-
1st Quartile	35.0	-	-	35.0	-	-	37.0	-	-	37.0	-	-
Median	40.0	-	-	39.0	-	-	39.0	-	-	41.0	-	-
3rd Quartile	45.0	-	-	43.0	-	-	44.0	-	-	45.0	-	-
Maximum	55	-	-	54	-	-	61	-	-	76	-	-
Day 85												
n	47	47	47	45	45	45	44	44	44	46	46	46
Mean	40.7	1.0	10.60	40.0	1.8	28.56	42.8	2.3	6.03	41.4	-0.2	0.70
SD	9.00	7.73	64.861	7.66	7.60	174.232	8.58	6.70	16.534	7.52	7.59	15.859
Minimum	29	-12	-26.7	14	-16	-53.3	28	-10	-22.7	27	-33	-43.4
1st Quartile	35.0	-3.0	-7.69	37.0	-2.0	-5.13	36.0	-2.0	-4.65	38.0	-3.0	-8.33
Median	38.0	0.0	0.00	39.0	1.0	2.50	41.5	0.5	1.61	40.5	-1.0	-2.30
3rd Quartile	45.0	4.0	11.76	45.0	3.0	8.57	49.0	5.0	13.17	45.0	3.0	7.89
Maximum	69	26	433.3	63	35	1166.7	62	19	51.4	70	19	59.4
Day 169												
n	47	47	47	43	43	43	45	45	45	46	46	46
Mean	38.9	-0.6	8.13	39.4	1.5	26.43	40.5	0.0	0.30	41.4	-0.3	0.54
SD	7.69	7.57	77.061	7.33	7.45	157.943	8.18	5.59	13.700	6.53	6.90	15.110
Minimum	25	-12	-24.4	28	-11	-26.2	25	-11	-25.0	30	-24	-31.6
1st Quartile	33.0	-4.0	-12.50	34.0	-3.0	-7.32	35.0	-4.0	-8.20	37.0	-3.0	-6.82
Median	38.0	-2.0	-4.26	38.0	0.0	0.00	38.0	0.0	0.00	41.0	-1.0	-2.35
3rd Quartile	44.0	1.0	3.13	44.0	4.0	11.76	43.0	2.0	6.25	44.0	3.0	7.89
Maximum	67	31	516.7	61	31	1033.3	65	20	45.5	60	17	53.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
ApoAII = apolipoprotein AII, N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing every 14 days, SD = standard deviation.

Table 28. Summary of Observed, Change, and Percent Change From Baseline in ApoAII (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N=51			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline
Baseline									
n	51		-	50		-	51		-
Mean	41.2		-	40.0		-	38.4		-
SD	7.78		-	6.20		-	6.00		-
Minimum	31		-	28		-	27		-
1st Quartile	35.0		-	35.0		-	34.0		-
Median	40.0		-	40.0		-	38.0		-
3rd Quartile	44.0		-	43.0		-	42.0		-
Maximum	65		-	58		-	55		-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	43.0	1.4	4.51	41.2	1.1	3.48	41.1	2.7	7.94
SD	9.51	8.33	19.135	7.46	6.33	15.658	7.23	6.19	17.065
Minimum	31	-21	-35.6	29	-15	-25.9	27	-9	-23.1
1st Quartile	36.0	-4.0	-10.00	36.0	-3.0	-7.66	36.0	-1.0	-2.86
Median	40.0	1.0	2.78	40.0	0.0	0.00	40.0	1.5	3.94
3rd Quartile	49.0	5.0	15.63	45.0	4.0	11.03	46.0	5.0	14.29
Maximum	78	20	52.9	64	19	50.0	59	22	59.5
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	40.4	0.0	0.72	39.3	-0.8	-1.37	38.3	-0.1	-0.07
SD	7.01	5.67	12.501	6.58	5.33	11.034	6.58	4.09	11.079
Minimum	28	-21	-35.6	27	-25	-43.1	23	-8	-25.0
1st Quartile	37.0	-3.0	-8.33	35.0	-3.0	-7.50	34.0	-3.0	-7.14
Median	39.0	0.0	0.00	38.0	0.0	0.00	39.0	0.0	0.00
3rd Quartile	43.0	4.0	9.52	43.0	2.0	6.00	43.0	3.0	7.32
Maximum	67	14	26.4	59	12	25.5	52	8	21.9

ApoAII = apolipoprotein AII, N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing every 28 days, SD = standard deviation.

Table 29. Comparison of Change From Baseline to Week 24 in ApoAII (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	45	1.8	1.2 (-0.84, 3.18)	0.19 (-2.62, 3.00)	0.893
	Bococizumab 100 mg	44	2.3	2.3 (0.29, 4.32)	1.33 (-1.49, 4.15)	0.355
	Bococizumab 150 mg	46	-0.2	0.3 (-1.65, 2.33)	-0.64 (-3.45, 2.17)	0.655
	Placebo	47	1.0	1.0 (-0.99, 2.95)	-	-
Day 169						
	Bococizumab 50 mg	43	1.5	0.9 (-0.94, 2.72)	1.66 (-0.88, 4.20)	0.199
	Bococizumab 100 mg	45	0.0	0.1 (-1.66, 1.91)	0.90 (-1.62, 3.41)	0.483
	Bococizumab 150 mg	46	-0.3	0.3 (-1.53, 2.05)	1.03 (-1.49, 3.56)	0.420
	Placebo	47	-0.6	-0.8 (-2.54, 1.00)	-	-

Change = ApoAII (mg/dL) – ApoAII (mg/dL) at Baseline.
ApoAII = apolipoprotein AII, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q14D = dosing every 14 days, vs -= versus.
a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured [UN]).

Table 30. Comparison of Change From Baseline to Week 24 in ApoAII (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	1.1	1.2 (-0.67, 3.13)	-0.49 (-3.20, 2.21)	0.719
	Bococizumab 300 mg	50	2.7	2.1 (0.25, 4.01)	0.41 (-2.31, 3.12)	0.768
	Placebo	47	1.4	1.7 (-0.20, 3.65)	-	-
Day 169						
	Bococizumab 200 mg	47	-0.8	-0.8 (-2.14, 0.60)	-0.69 (-2.67, 1.28)	0.488
	Bococizumab 300 mg	49	-0.1	-0.5 (-1.82, 0.88)	-0.39 (-2.36, 1.58)	0.694
	Placebo	43	0.0	-0.1 (-1.50, 1.35)	-	-

Change = ApoAII (mg/dL) – ApoAII (mg/dL) at Baseline.
ApoAII = apolipoprotein AII, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q28D = dosing every 28 days, vs = versus.
a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Table 31. Comparison of Percent Change From Baseline to Week 24 in ApoAII (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Percent Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	45	28.6	18.4 (-4.09, 40.90)	10.29 (-21.73, 42.30)	0.527
	Bococizumab 100 mg	44	6.0	8.5 (-13.70, 30.72)	0.39 (-31.49, 32.26)	0.981
	Bococizumab 150 mg	46	0.7	8.7 (-14.06, 31.38)	0.54 (-31.72, 32.80)	0.974
	Placebo	47	10.6	8.1 (-14.72, 30.96)	-	-
Day 169						
	Bococizumab 50 mg	43	26.4	15.3 (-5.26, 35.81)	9.80 (-19.41, 39.01)	0.509
	Bococizumab 100 mg	45	0.3	2.8 (-17.47, 23.03)	-2.69 (-31.76, 26.38)	0.855
	Bococizumab 150 mg	46	0.5	8.5 (-12.22, 29.23)	3.04 (-26.39, 32.47)	0.839
	Placebo	47	8.1	5.5 (-15.36, 26.30)	-	-

Pecent change = 100% × [ApoAII (mg/dL) – ApoAII (mg/dL) at Baseline/ApoAII (mg/dL) at Baseline.
ApoAII = apolipoprotein AII, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q14D = dosing with placebo or bococizumab every 14 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Table 32. Comparison of Percent Change From Baseline to Week 24 in ApoAII (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Percent Change	Adjusted Mean Percent Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Week 12/Day 85						
	Bococizumab 200 mg	48	3.5	3.8 (-0.91, 8.48)	-1.58 (-8.25, 5.09)	0.640
	Bococizumab 300 mg	50	7.9	6.4 (1.82, 11.08)	1.08 (-5.61, 7.77)	0.750
	Placebo	47	4.5	5.4 (0.61, 10.12)	-	-
Week 24/Day 169						
	Bococizumab 200 mg	47	-1.4	-1.4 (-4.59, 1.78)	-1.99 (-6.57, 2.59)	0.392
	Bococizumab 300 mg	49	-0.1	-0.7 (-3.89, 2.39)	-1.33 (-5.91, 3.24)	0.565
	Placebo	43	0.7	0.6 (-2.72, 3.89)	-	-

Percent change = 100% × [ApoAII (mg/dL) – ApoAII (mg/dL) at Baseline/ApoAII (mg/dL) at Baseline.
ApoAII = apolipoprotein AII, CI = confidence interval, n = subjects with non-missing values in the analysis set,
Q28D = dosing with placebo or bococizumab every 28 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Lp(a): The reduction of Lp(a) by bococizumab represents an additional beneficial mechanism of action that complements LDL-C lowering. Decreases in Lp(a) were observed particularly at the higher doses in the bococizumab Q14D and Q28D dose groups as shown in Table 33 and Table 34. The magnitude of decrease might have been impacted by dose reductions occurring in all but the smallest (50 mg) dose bococizumab groups.

Table 33. Summary of Observed, Change, and Percent Change From Baseline in Lp(a) (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	42.997	-	-	44.506	-	-	40.214	-	-	47.850	-	-
SD	51.0432	-	-	47.5045	-	-	45.2397	-	-	50.2969	-	-
Minimum	4.00	-	-	4.00	-	-	4.00	-	-	4.00	-	-
1st Quartile	5.180	-	-	7.520	-	-	5.580	-	-	7.460	-	-
Median	17.000	-	-	24.950	-	-	18.200	-	-	22.400	-	-
3rd Quartile	61.700	-	-	64.300	-	-	65.600	-	-	85.800	-	-
Maximum	243.00	-	-	204.00	-	-	203.00	-	-	155.00	-	-
Day 85												
n	47	47	47	45	45	45	44	44	44	46	46	46
Mean	41.119	1.654	6.11	45.643	-0.515	40.43	36.823	-2.956	-11.89	43.083	-4.334	-9.01
SD	50.2222	9.8020	30.573	48.9265	17.6889	333.949	43.1010	9.9368	22.517	49.9594	14.3377	35.644
Minimum	4.00	-18.00	-53.8	4.00	-28.30	-86.1	4.00	-27.00	-60.6	4.00	-47.30	-73.8
1st Quartile	5.590	-4.400	-11.96	5.480	-4.700	-18.32	4.070	-7.550	-24.70	4.210	-8.820	-26.89
Median	16.500	0.000	0.00	26.000	-1.720	-7.93	13.250	-1.600	-6.29	17.950	-2.186	-8.95
3rd Quartile	74.500	3.560	19.82	70.400	0.580	5.12	53.650	0.000	0.00	68.800	0.131	3.28
Maximum	238.00	34.00	114.6	183.00	89.00	2225.6	180.00	26.30	35.5	201.00	46.00	174.8
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	42.798	1.065	8.78	44.278	-1.893	43.97	34.488	-3.945	-10.18	46.097	-3.205	0.03
SD	51.2585	13.2025	43.596	45.0724	18.8951	330.964	40.7911	16.2841	26.612	47.1719	11.6380	50.256
Minimum	4.00	-38.00	-69.3	4.00	-57.00	-42.9	4.00	-64.00	-59.7	4.00	-35.00	-53.4
1st Quartile	6.000	-3.500	-13.71	7.080	-7.000	-16.64	3.999	-8.800	-31.30	5.170	-8.800	-18.18
Median	13.700	0.000	0.00	33.300	-1.500	-7.97	11.000	-0.540	-6.62	21.900	-0.870	-5.15
3rd Quartile	72.100	5.600	14.17	67.100	1.900	6.61	55.300	0.000	0.00	77.100	0.100	0.57
Maximum	205.00	54.90	148.6	163.00	86.40	2160.6	159.00	56.00	62.3	148.00	35.20	306.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
Lp(a) = lipoprotein (a), N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing with placebo or bococizumab every 14 days, SD = standard deviation.

Table 34. Summary of Observed, Change, and Percent Change From Baseline in Lp(a) (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo			Bococizumab					
				200 mg N=50			300 mg N=51		
	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline
Baseline									
n	51		-	50	-	-	51	-	-
Mean	33.138	-	-	42.962	-	-	46.522	-	-
SD	31.1512		-	61.0938	-	-	51.5609	-	-
Minimum	4.00		-	4.00	-	-	4.00	-	-
1st Quartile	8.130		-	4.870	-	-	7.330	-	-
Median	18.100		-	15.250	-	-	31.000	-	-
3rd Quartile	48.100		-	60.300	-	-	59.800	-	-
Maximum	106.00		-	290.00	-	-	235.00	-	-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	34.288	1.547	9.28	44.495	0.502	-0.91	41.062	-5.195	-11.93
SD	33.2231	12.0489	33.809	69.1797	15.1527	26.271	46.1367	12.9577	23.893
Minimum	4.00	-48.50	-74.3	4.00	-28.00	-59.3	4.00	-44.00	-68.3
1st Quartile	7.260	-1.920	-11.07	3.999	-4.440	-9.59	5.090	-8.500	-27.11
Median	23.400	0.800	3.47	13.750	0.000	0.00	27.550	-1.945	-10.74
3rd Quartile	49.800	5.310	24.87	63.000	0.480	5.02	54.800	0.000	0.00
Maximum	122.00	31.20	129.3	380.00	90.00	97.6	204.00	31.10	36.2
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	32.482	2.718	10.18	45.553	2.191	-0.79	43.836	-3.281	-5.42
SD	34.0805	12.9153	32.604	79.5585	26.1574	25.066	46.1753	16.9586	22.451
Minimum	4.00	-43.40	-66.5	4.00	-38.90	-59.3	4.00	-68.00	-57.1
1st Quartile	9.330	-0.900	-5.43	4.010	-2.400	-15.42	7.940	-4.400	-18.69
Median	16.500	0.080	0.30	14.000	0.000	0.00	28.500	-0.730	-2.65
3rd Quartile	42.900	5.100	21.25	59.700	1.000	4.55	53.000	1.230	5.56
Maximum	136.00	47.20	104.3	451.00	161.00	77.7	173.00	38.10	53.8

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
Lp(a) = lipoprotein (a), N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing with placebo or bococizumab every 28 days, SD = standard deviation.

No discernible post-baseline changes in VLDL-TG were observed, and there were no consistent dose-dependent changes in either the Bococizumab Q14D and/or Q28D dose groups as shown in Table 35 and Table 36 respectively.

Table 35. Summary of Observed, Change, and Percent Change From Baseline in VLDL Triglycerides (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline
Baseline												
n	49	-	-	48	-	-	49	-	-	47	-	-
Mean	92.2	-	-	86.7	-	-	95.2	-	-	103.4	-	-
SD	61.70	-	-	83.43	-	-	61.56	-	-	71.52	-	-
Minimum	12	-	-	10	-	-	9	-	-	15	-	-
1st Quartile	41.0	-	-	34.0	-	-	50.0	-	-	61.0	-	-
Median	76.0	-	-	65.0	-	-	89.0	-	-	90.0	-	-
3rd Quartile	128.0	-	-	108.5	-	-	119.0	-	-	126.0	-	-
Maximum	273	-	-	401	-	-	346	-	-	349	-	-
Day 85												
n	47	47	47	42	42	42	41	41	41	42	42	42
Mean	82.7	-12.3	9.62	75.3	-11.8	2.81	82.8	-6.0	-3.77	78.9	-20.3	-15.61
SD	55.98	50.98	71.415	72.52	35.82	54.888	71.91	46.43	54.845	57.18	43.27	36.099
Minimum	15	-118	-69.1	8	-120	-57.6	7	-128	-64.0	5	-151	-70.0
1st Quartile	45.0	-48.0	-44.74	37.0	-29.0	-30.56	39.0	-26.0	-39.25	46.0	-35.0	-43.21
Median	64.0	-10.0	-26.92	50.5	-7.0	-17.41	62.0	-14.0	-16.75	65.5	-16.5	-25.83
3rd Quartile	113.0	26.0	44.86	100.0	7.0	9.62	91.0	7.0	12.70	93.0	8.0	13.11
Maximum	277	116	185.7	403	82	195.2	353	165	243.8	272	57	65.2
Day 169												
n	47	47	47	41	41	41	42	42	42	43	43	43
Mean	88.0	-4.8	20.26	70.9	-11.5	5.34	79.0	-12.4	-9.78	78.6	-24.3	-13.28
SD	57.68	46.55	101.188	51.61	49.20	59.092	57.25	38.58	39.626	49.85	57.43	44.197
Minimum	14	-127	-69.5	4	-210	-71.8	8	-85	-70.1	9	-223	-70.4
1st Quartile	47.0	-27.0	-33.33	33.0	-31.0	-40.78	40.0	-37.0	-41.84	49.0	-50.0	-46.83
Median	75.0	-9.0	-11.03	61.0	-3.0	-10.53	63.5	-13.5	-16.91	74.0	-14.0	-17.43
3rd Quartile	122.0	14.0	21.64	89.0	20.0	41.18	112.0	8.0	17.33	97.0	1.0	1.11
Maximum	287	129	487.0	216	72	204.0	270	112	89.8	231	75	106.1

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing with placebo or bococizumab every 14 days, SD = standard deviation, VLDL = very low density lipoprotein.

Table 36. Summary of Observed, Change, and Percent Change From Baseline in VLDL Triglycerides (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N = 51			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline
Baseline									
n	50	-	-	50	-	-	51	-	-
Mean	90.6	-	-	91.0	-	-	85.4	-	-
SD	59.44	-	-	59.37	-	-	73.88	-	-
Minimum	14	-	-	1	-	-	7	-	-
1st Quartile	50.0	-	-	43.0	-	-	44.0	-	-
Median	71.0	-	-	79.0	-	-	70.0	-	-
3rd Quartile	116.0	-	-	118.0	-	-	106.0	-	-
Maximum	243	-	-	301	-	-	501	-	-
Day 85									
n	45	45	45	48	48	48	49	49	49
Mean	92.4	2.5	17.58	85.3	-5.8	17.32	76.1	-12.1	2.16
SD	54.34	39.66	54.707	52.28	38.21	94.238	52.99	51.36	80.419
Minimum	25	-108	-55.4	7	-106	-50.6	10	-240	-65.9
1st Quartile	50.0	-11.0	-18.52	49.0	-29.5	-21.15	40.0	-43.0	-46.24
Median	84.0	2.0	1.37	81.5	-2.5	-4.08	59.0	-5.0	-12.68
3rd Quartile	111.0	22.0	45.28	103.0	12.5	34.76	115.0	9.0	20.83
Maximum	285	140	200.0	275	70	600.0	261	94	447.6
Day 169									
n	42	42	42	46	46	46	48	48	48
Mean	78.4	12.1	-3.60	75.2	-15.3	15.72	87.6	2.8	33.89
SD	50.76	40.35	40.646	49.70	47.53	142.996	66.95	41.81	131.723
Minimum	16	-151	-77.4	10	-126	-75.0	15	-92	-67.2
1st Quartile	43.0	-28.0	-34.98	44.0	-37.0	-40.15	45.5	-22.5	-24.72
Median	66.0	-8.0	-15.72	59.5	-9.0	-12.96	68.5	-5.0	-9.95
3rd Quartile	107.0	16.0	23.08	93.0	10.0	18.52	114.5	29.5	42.17
Maximum	272	59	91.9	222	106	900.0	409	105	785.7

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing with placebo or bococizumab every 28 days, SD = standard deviation, VLDL = very low density lipoprotein.

The mean changes from Baseline indicated a modest increase in HDL-C at most timepoints in the Bococizumab Q14D and Q28D dose groups as provided in Table 37 and Table 38. However the adjusted mean differences from placebo were only statistically significant at a number of isolated timepoints (Table 39 and Table 40). The same was observed for the percent changes from Baseline as shown in Table 41 and Table 42.

Table 37. Summary of Observed, Change, and Percent Change From Baseline in HDL-C (mg/dL) - Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline
Baseline												
n	49	-	-	50	-	-	51	-	-	49	-	-
Mean	52.3	-	-	52.1	-	-	51.2	-	-	52.9	-	-
SD	14.09	-	-	15.90	-	-	13.67	-	-	14.05	-	-
Minimum	32	-	-	23	-	-	32	-	-	31	-	-
1st Quartile	44.0	-	-	42.0	-	-	42.0	-	-	44.0	-	-
Median	50.0	-	-	51.5	-	-	50.0	-	-	49.0	-	-
3rd Quartile	57.0	-	-	62.0	-	-	57.0	-	-	56.0	-	-
Maximum	107	-	-	105	-	-	94	-	-	89	-	-
Day 85												
n	47	47	47	43	43	43	44	44	44	46	46	46
Mean	52.4	0.1	0.82	54.5	1.7	3.89	54.6	2.1	3.85	54.4	1.0	2.65
SD	14.67	6.99	14.569	18.03	7.08	14.983	16.41	7.45	13.221	14.11	7.47	12.741
Minimum	34	-15	-30.0	26	-11	-17.3	29	-10	-17.2	32	-18	-25.4
1st Quartile	43.0	-5.0	-10.00	43.0	-3.0	-7.14	42.5	-3.0	-5.59	46.0	-2.0	-4.08
Median	49.0	0.0	0.00	54.0	0.0	0.00	49.5	0.5	1.14	50.0	0.5	1.25
3rd Quartile	59.0	5.0	8.93	62.0	7.0	12.73	64.0	7.0	11.03	61.0	8.0	13.04
Maximum	108	19	51.4	121	23	60.9	101	28	42.4	98	14	26.9
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	52.1	-0.1	-0.16	52.3	1.4	3.47	52.2	0.9	0.94	53.5	0.4	2.21
SD	15.25	6.42	12.855	17.78	7.15	16.098	15.89	7.08	12.414	11.41	6.46	11.679
Minimum	30	-13	-25.0	28	-10	-24.4	29	-13	-22.4	34	-18	-25.7
1st Quartile	41.0	-4.0	-10.00	39.0	-3.0	-9.68	42.0	-3.0	-5.66	46.0	-3.0	-6.12
Median	48.0	-1.0	-2.17	52.0	2.0	4.84	49.0	0.0	0.00	53.0	1.0	2.04
3rd Quartile	62.0	5.0	8.00	64.0	6.0	9.38	56.0	3.0	4.69	57.0	6.0	9.38
Maximum	105	14	27.3	113	17	65.2	94	28	42.4	85	13	29.5

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
HDL-C = high density lipoprotein-cholesterol, N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing with placebo or bococizumab every 14 days, SD = standard deviation.

Table 38. Summary of Observed, Change, and Percent Change From Baseline in HDL-C (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N = 51			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline
Baseline									
n	51	-	-	50	-	-	51	-	-
Mean	52.6	-	-	51.9	-	-	49.2	-	-
SD	11.57	-	-	14.36	-	-	13.20	-	-
Minimum	34	-	-	28	-	-	24	-	-
1st Quartile	45.0	-	-	41.0	-	-	39.0	-	-
Median	50.0	-	-	51.0	-	-	47.0	-	-
3rd Quartile	61.0	-	-	60.0	-	-	58.0	-	-
Maximum	78	-	-	93	-	-	87	-	-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	52.2	-1.0	-0.41	55.4	3.4	7.06	52.1	3.1	6.90
SD	10.02	7.43	14.000	17.56	9.15	17.079	15.62	7.71	16.879
Minimum	34	-20	-29.9	30	-15	-24.6	25	-13	-23.6
1st Quartile	44.0	-4.0	-7.04	42.5	-1.5	-3.61	41.0	-1.0	-2.56
Median	52.0	-1.0	-2.56	54.0	2.0	4.21	49.5	1.0	2.70
3rd Quartile	62.0	2.0	3.64	63.0	7.0	13.18	62.0	6.0	12.77
Maximum	74	22	51.2	126	33	60.0	108	27	63.6
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	52.6	0.3	1.88	53.9	1.8	3.93	49.7	0.3	1.34
SD	11.08	7.94	15.166	18.84	11.29	17.974	13.16	6.26	12.361
Minimum	31	-16	-23.2	29	-20	-32.8	26	-20	-24.4
1st Quartile	44.0	-4.0	-8.89	43.0	-5.0	-8.05	39.0	-4.0	-9.09
Median	53.0	0.0	0.00	50.0	2.0	3.28	49.0	1.0	1.79
3rd Quartile	60.0	5.0	10.67	60.0	5.0	11.11	59.0	3.0	6.52
Maximum	83	21	46.7	141	48	62.7	83	16	35.6

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
HDL-C = high density lipoprotein-cholesterol, N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing with placebo or bococizumab every 28 days, SD = standard deviation.

Table 39. Comparison of Change From Baseline to Week 24 in HDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	43	1.7	1.9 (-0.20, 4.06)	1.64 (-1.35, 4.63)	0.281
	Bococizumab 100 mg	44	2.1	2.0 (-0.08, 4.13)	1.73 (-1.24, 4.71)	0.251
	Bococizumab 150 mg	46	1.0	0.8 (-1.28, 2.92)	0.53 (-2.43, 3.50)	0.724
	Placebo	47	0.1	0.3 (-1.80, 2.39)	-	-
Day 169						
	Bococizumab 50 mg	43	1.4	1.6 (-0.44, 3.57)	1.72 (-1.07, 4.51)	0.225
	Bococizumab 100 mg	45	0.9	0.6 (-1.32, 2.61)	0.79 (-1.97, 3.56)	0.571
	Bococizumab 150 mg	47	0.4	0.3 (-1.60, 2.28)	0.49 (-2.25, 3.24)	0.725
	Placebo	47	-0.1	-0.2 (-2.09, 1.79)	-	-

Change = HDL-C (mg/dL) - HDL-C (mg/dL) at Baseline.
HDL-C = high density lipoprotein-cholesterol, CI = confidence interval, n = subjects with non-missing values in the analysis set, Q14D = dosing with placebo or bococizumab every 14 days, vs = versus.

a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Table 40. Comparison of Change From Baseline to Week 24 in HDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Timepoint	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	3.4	3.4 (1.12, 5.72)	4.45 (1.21, 7.70)	0.007
	Bococizumab 300 mg	50	3.1	2.8 (0.58, 5.08)	3.86 (0.63, 7.09)	0.019
	Placebo	47	-1.0	-1.0 (-3.33, 1.27)		
/Day 169						
	Bococizumab 200 mg	47	1.8	2.2 (-0.32, 4.66)	2.01 (-1.56, 5.57)	0.268
	Bococizumab 300 mg	49	0.3	0.2 (-2.28, 2.60)	-0.01 (-3.55, 3.54)	0.996
	Placebo	43	0.3	0.2 (-2.39, 2.72)		

Change = HDL-C (mg/dL) - HDL-C (mg/dL) at Baseline.
CI = confidence interval, HDL-C = high density lipoprotein cholesterol, n = subjects with non-missing values in the analysis set, Q28D = dosing with placebo or bococizumab every 28 days.

a. The p-value obtained from mixed model: change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Table 41. Comparison of Percent Change From Baseline to Week 24 in HDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q14D Full Analysis Sets

Time point	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 50 mg	43	3.9	4.6 (0.48, 8.74)	3.41 (-2.38, 9.21)	0.246
	Bococizumab 100 mg	44	3.9	3.8 (-0.27, 7.89)	2.62 (-3.14, 8.38)	0.371
	Bococizumab 150 mg	46	2.7	2.5 (-1.52, 6.61)	1.35 (-4.40, 7.10)	0.643
	Placebo	47	0.8	1.2 (-2.87, 5.25)	-	-
Day 169						
	Bococizumab 50 mg	43	3.5	3.6 (-0.27, 7.55)	3.90 (-1.56, 9.36)	0.160
	Bococizumab 100 mg	45	0.9	0.6 (-3.26, 4.43)	0.85 (-4.56, 6.25)	0.758
	Bococizumab 150 mg	47	2.2	2.3 (-1.49, 6.11)	2.57 (-2.81, 7.95)	0.347
	Placebo	47	-0.2	-0.3 (-4.07, 3.55)	-	-

Percent change = 100% × [HDL-C (mg/dL) - HDL-C (mg/dL) at Baseline]/HDL-C (mg/dL) at Baseline.
CI = confidence interval, HDL-C = high density lipoprotein-cholesterol, n = subjects with non-missing values in the analysis set, Q14D = dosing with placebo or bococizumab every 14 days.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

Table 42. Comparison of Percent Change From Baseline to Week 24 in HDL-C (mg/dL) Using Mixed-Effects Model for Repeated Measures Analysis (MMRM) Based on Observed Case Data – Q28D Full Analysis Sets

Time point	Treatment Groups	n	Raw Mean Change	Adjusted Mean Change (95% CI)	Adjusted Mean Difference vs Placebo (95% CI)	p-Value[a]
Day 85						
	Bococizumab 200 mg	48	7.1	7.2 (2.76, 11.72)	7.66 (1.33, 13.99)	0.018
	Bococizumab 300 mg	50	6.9	6.1 (1.71, 10.50)	6.52 (0.22, 12.83)	0.043
	Placebo	47	-0.4	-0.4 (-4.91, 4.06)	-	-
Day 169						
	Bococizumab 200 mg	47	3.9	4.7 (0.34, 8.99)	2.99 (-3.22, 9.21)	0.343
	Bococizumab 300 mg	49	1.3	1.0 (-3.27, 5.22)	-0.70 (-6.87, 5.48)	0.824
	Placebo	43	1.9	1.7 (-2.79, 6.14)	-	-

Percent Change = 100% × [HDL-C (mg/dL) - HDL-C (mg/dL) at Baseline]/HDL-C (mg/dL) at Baseline.
CI = confidence interval, HDL-C = high density lipoprotein-cholesterol, n = subjects with non-missing values in the analysis set, Q28D = dosing with placebo or bococizumab every 28 days, vs = versus.
a. The p-value obtained from mixed model: percent change from Baseline = treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure = unstructured).

The summaries of observed, absolute change and percent change from Baseline in non-HDL-C are presented in Table 43 for the Q14D dose groups and in Table 44 for the Q28D dose groups. In common with LDL-C results for this study, dose-related decreases from Baseline were observed in the Bococizumab dose groups relative to placebo.

Table 43. Summary of Observed, Change, and Percent Change From Baseline in Non-HDL-C (mg/dL) – Q14D Full Analysis Set

Timepoint	Placebo N=50			Bococizumab 50 mg N=50			Bococizumab 100 mg N=52			Bococizumab 150 mg N=50		
	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline	Observed Value	Change From Baseline	Percent Change From Baseline
Baseline												
n	49		-	50		-	51		-	49		-
Mean	136.5		-	134.0		-	143.4		-	136.0		-
SD	33.79		-	35.90		-	31.26		-	23.44		-
Minimum	81		-	82		-	103		-	96		-
1st Quartile	116.0		-	112.0		-	119.0		-	123.0		-
Median	129.0		-	130.0		-	136.0		-	130.0		-
3rd Quartile	149.0		-	147.0		-	162.0		-	141.0		-
Maximum	250		-	326		-	249		-	233		-
Day 85												
n	47	47	47	43	43	43	43	43	43	46	46	46
Mean	131.2	-5.7	-2.28	95.8	-37.5	-28.34	85.5	-55.0	-38.52	73.7	-59.6	-44.86
SD	30.39	26.92	20.234	36.28	22.40	15.836	31.58	32.75	21.362	35.32	33.23	24.258
Minimum	65	-85	-37.0	42	-84	-53.5	36	-135	-72.2	27	-107	-79.1
1st Quartile	106.0	-18.0	-14.12	77.0	-48.0	-39.34	57.0	-79.0	-54.76	47.0	-85.0	-62.10
Median	127.0	-5.0	-3.85	89.0	-39.0	-30.00	88.0	-52.0	-38.66	62.0	-68.0	-52.80
3rd Quartile	152.0	8.0	6.71	107.0	-27.0	-21.48	109.0	-36.0	-24.60	94.0	-37.0	-24.80
Maximum	208	90	88.2	265	30	22.4	156	26	23.2	183	20	12.3
Day 169												
n	47	47	47	43	43	43	45	45	45	47	47	47
Mean	129.5	-5.4	-2.02	99.1	-33.2	-24.89	87.7	-55.9	-38.02	88.1	-47.3	-34.02
SD	26.64	26.84	18.694	34.97	29.21	18.938	37.50	38.79	23.039	31.16	33.71	22.788
Minimum	74	-78	-39.4	36	-126	-56.1	40	-142	-75.9	42	-115	-67.3
1st Quartile	108.0	-19.0	-13.71	77.0	-47.0	-39.42	64.0	-79.0	-52.88	63.0	-75.0	-56.06
Median	128.0	-6.0	-5.43	91.0	-38.0	-26.92	83.0	-55.0	-41.83	83.0	-47.0	-35.16
3rd Quartile	149.0	10.0	7.97	111.0	-18.0	-15.53	103.0	-33.0	-29.20	104.0	-25.0	-20.00
Maximum	183	52	54.7	200	52	35.4	232	67	40.6	184	21	15.7

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
HDL-C = high density lipoprotein-cholesterol, N = total number of subjects, n = number of subjects per prespecified criteria, Q14D = dosing with placebo or bococizumab every 14 days, SD = standard deviation.

Table 44. Summary of Observed, Change, and Percent Change From Baseline in Non-HDL-C (mg/dL) – Q28D Full Analysis Set

Timepoint	Placebo N = 51			Bococizumab 200 mg N=50			Bococizumab 300 mg N=51		
	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline	Observed	Change From Baseline	Percent Change From Baseline
Baseline									
n	51		-	50		-	51		-
Mean	145.8		-	133.2		-	129.8		-
SD	45.26		-	26.61		-	28.56		-
Minimum	95		-	76		-	72		-
1st Quartile	112.0		-	114.0		-	111.0		-
Median	137.0		-	131.0		-	123.0		-
3rd Quartile	165.0		-	149.0		-	148.0		-
Maximum	302		-	205		-	219		-
Day 85									
n	47	47	47	48	48	48	50	50	50
Mean	146.9	0.6	2.76	110.3	-22.9	-17.30	89.3	-40.7	-28.68
SD	47.11	38.04	20.337	38.34	29.05	22.324	35.24	44.91	30.857
Minimum	94	-150	-56.8	40	-98	-66.1	30	-159	-75.0
1st Quartile	114.0	-12.0	-6.14	83.5	-39.5	-30.22	55.0	-69.0	-51.92
Median	141.0	2.0	1.44	108.5	-21.5	-16.40	87.0	-46.5	-34.23
3rd Quartile	162.0	22.0	17.65	131.0	-4.0	-3.23	119.0	-5.0	-4.10
Maximum	315	77	38.7	237	42	29.3	156	29	31.9
Day 169									
n	43	43	43	47	47	47	49	49	49
Mean	136.3	-6.8	-1.78	106.5	-26.3	-19.39	101.8	-28.9	-19.99
SD	34.94	31.49	17.145	28.77	22.98	17.304	30.58	34.50	24.887
Minimum	90	-134	-50.8	45	-76	-56.7	46	-125	-68.7
1st Quartile	114.0	-12.0	-8.76	88.0	-44.0	-29.73	81.0	-47.0	-30.21
Median	129.0	0.0	0.00	105.0	-26.0	-19.40	99.0	-22.0	-19.51
3rd Quartile	148.0	13.0	7.88	122.0	-8.0	-7.92	125.0	-9.0	-7.50
Maximum	248	41	28.9	175	30	24.4	171	64	70.3

Baseline was defined as the last non-missing assessment collected prior to the first dose of study drug.
HDL-C = high density lipoprotein-cholesterol, N = total number of subjects, n = number of subjects per prespecified criteria, Q28D = dosing with placebo or bococizumab every 28 days, SD = standard deviation.

The logistic regression analyses of subjects with <100 mg/dL, <70 mg/dL, <40 mg/dL or <25 mg/dL LDL-C at Weeks 12 and 24 are summarized for the Q14D and Q28D FAS in Table 45 and Table 46 respectively.

Table 45. Analysis of Proportion of Subjects Reaching LDL-C <100, <70, <40 and <25 mg/dL at Weeks 12 and 24 – Q14D Full Analysis Set

Q14D Treatment Groups		Responders n/N (%)	Adjusted Odds Ratio	Wald 95% CI Adjusted Odds Ratio	p-Value
Week 12					
LDL-C	Bococizumab 50 mg	40/44 (90.9)	14.964	(3.997, 56.020)	<0.001
<100 mg/dL	Bococizumab 100 mg	40/42 (95.2)	49.615	(7.984, 308.328)	<0.001
	Bococizumab 150 mg	42/46 (91.3)	12.842	(3.674, 44.892)	<0.001
	Placebo	23/47 (48.9)			
LDL-C	Bococizumab 50 mg	22/44 (50.0)	27.703	(5.752, 133.423)	<0.001
<70 mg/dL	Bococizumab 100 mg	28/42 (66.7)	71.177	(13.783, 367.564)	<0.001
	Bococizumab 150 mg	36/46 (78.3)	100.667	(19.855, 510.387)	<0.001
	Placebo	2/47 (4.3)			
LDL-C	Bococizumab 50 mg	3/44 (6.8)	5.587E+10	(1.509E+10, 2.069E+11)	<0.001
<40 mg/dL	Bococizumab 100 mg	7/42 (16.7)	1.602E+11	(5.873E+10, 4.372E+11)	<0.001
	Bococizumab 150 mg	22/46 (47.8)	6.950E+11	(6.950E+11, 6.950E+11)	
	Placebo	0/47 (0.0)			
LDL-C	Bococizumab 50 mg	2/44 (4.5)	3.844E+10	(6.918E+09, 2.136E+11)	<0.001
<25 mg/dL	Bococizumab 100 mg	2/42 (4.8)	4.354E+10	(7.767E+09, 2.440E+11)	<0.001
	Bococizumab 150 mg	5/46 (10.9)	9.759E+10	(9.759E+10, 9.759E+10)	
	Placebo	0/47 (0.0)			
Week 24					
LDL-C	Bococizumab 50 mg	37/43 (86.0)	12.773	(3.932, 41.495)	<0.001
<100 mg/dL	Bococizumab 100 mg	41/45 (91.1)	36.886	(8.330, 163.335)	<0.001
	Bococizumab 150 mg	43/47 (91.5)	20.750	(5.741, 75.006)	<0.001
	Placebo	20/47 (42.6)			
LDL-C	Bococizumab 50 mg	24/43 (55.8)	24.941	(6.336, 98.169)	<0.001
<70 mg/dL	Bococizumab 100 mg	33/45 (73.3)	80.004	(18.094, 353.742)	<0.001
	Bococizumab 150 mg	32/47 (68.1)	42.101	(10.621, 166.894)	<0.001
	Placebo	3/47 (6.4)			
LDL-C	Bococizumab 50 mg	2/43 (4.7)	3.767E+10	(7.515E+09, 1.888E+11)	<0.001
<40 mg/dL	Bococizumab 100 mg	10/45 (22.2)	2.360E+11	(8.248E+10, 6.750E+11)	<0.001
	Bococizumab 150 mg	8/47 (17.0)	1.574E+11	(1.574E+11, 1.574E+11)	-
	Placebo	0/47 (0.0)			
LDL-C	Bococizumab 50 mg	0/43 (0.0)	1.587	(0.000, NA)	1.000
<25 mg/dL	Bococizumab 100 mg	2/45 (4.4)	2.947E+11	(2.176E+10, 3.990E+12)	<0.001
	Bococizumab 150 mg	1/47 (2.1)	2.147E+11	(2.147E+11, 2.147E+11)	-
	Placebo	0/47 (0.0)			

Logistic regression using response (0/1) as a response variable and treatment as a factor and the baseline LDL-C mg/dL as a covariate.
CI = confidence interval, LDL-C = low density lipoprotein-cholesterol, N = number of subjects in study population with non-missing data at Weeks 12 and 24, n = number of responders, NA = not applicable, Q14D = dosing with placebo or bococizumab every 14 days.

Table 46. Analysis of Proportion of Subjects Reaching LDL-C <100, <70, <40 and <25 mg/dL at Weeks 12 and 24 – Q28D Full Analysis Set

Q28D Treatment Groups		Responders n/N (%)	Adjusted Odds Ratio	Wald 95% CI Adjusted Odds Ratio	p-Value
Week 12					
LDL-C	Bococizumab 200 mg	31/48 (64.6)	3.107	(1.304, 7.401)	0.010
<100 mg/dL	Bococizumab 300 mg	39/50 (78.0)	6.048	(2.402, 15.225)	<0.001
	Placebo	16/46 (34.8)			
LDL-C	Bococizumab 200 mg	16/48 (33.3)	3.551E+11	(1.554E+11, 8.114E+11)	<0.001
<70 mg/dL	Bococizumab 300 mg	29/50 (58.0)	9.817E+11	(9.817E+11, 9.817E+11)	-
	Placebo	0/46 (0.0)			
LDL-C	Bococizumab 200 mg	4/48 (8.3)	7.797E+10	(2.380E+10, 2.554E+11)	<0.001
<40 mg/dL	Bococizumab 300 mg	16/50 (32.0)	4.082E+11	(4.082E+11, 4.082E+11)	-
	Placebo	0/46 (0.0)			
LDL-C	Bococizumab 200 mg	1/48 (2.1)	4.783E+10	(4.796E+09, 4.771E+11)	<0.001
<25 mg/dL	Bococizumab 300 mg	3/50 (6.0)	1.443E+11	(1.443E+11, 1.443E+11)	-
	Placebo	0/46 (0.0)			
Week 24					
LDL-C	Bococizumab 200 mg	37/47 (78.7)	6.219	(2.061, 18.764)	0.001
<100 mg/dL	Bococizumab 300 mg	38/48 (79.2)	6.205	(2.060, 18.693)	0.001
	Placebo	19/43 (44.2)			-
LDL-C	Bococizumab 200 mg	10/47 (21.3)	11.700	(1.396, 98.075)	0.023
<70 mg/dL	Bococizumab 300 mg	21/48 (43.8)	36.841	(4.527, 299.817)	<0.001
	Placebo	1/43 (2.3)			-
LDL-C	Bococizumab 200 mg	1/47 (2.1)	6.409E+10	(6.391E+09, 6.426E+11)	<0.001
<40 mg/dL	Bococizumab 300 mg	3/48 (6.3)	1.994E+11	(1.994E+11, 1.994E+11)	-
	Placebo				
LDL-C	Bococizumab 200 mg	0/47 (0.0)	0.925	(0.000, NA)	1.000
<25 mg/dL	Bococizumab 300 mg	1/48 (2.1)	2.990E+11	(2.990E+11, 2.990E+11)	-
	Placebo	0/43 (0.0)			

Logistic regression using response (0/1) as a response variable and treatment as a factor and the baseline LDL-C mg/dL as a covariate.
CI = confidence interval; LDL-C = low density lipoprotein cholesterol; N = number of subjects in study population with non-missing data at Weeks 12 and 24; n = number of responders; NA = not applicable; Q28D = dosing with placebo or bococizumab every 28 days.

Safety Results:

Table 47 and Table 48 presents the treatment-emergent serious AEs by system organ class and preferred term for the Q14D and Q28D treatment regimens, respectively.

Table 47. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Placebo Q14D			Bococizumab 50 mg Q14D			Bococizumab 100 mg Q14D			Bococizumab 150 mg Q14D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:												
Evaluable for adverse events	49			50			51			49		
With adverse events	7 (14.3)			4 (8.0)			2 (3.9)			4 (8.2)		
Number (%) of subjects with adverse events by:												
System organ class												
MedDRA (v17.0) preferred term												
Cardiac Disorders	0	0	0	0	0	0	0	0	0	2 (4.1)	4	0
Angina pectoris	0	0	0	0	0	0	0	0	0	0	0	0
Angina unstable	0	0	0	0	0	0	0	0	0	1 (2.0)	1	0
Aortic valve stenosis	0	0	0	0	0	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac failure chronic	0	0	0	0	0	0	0	0	0	1 (2.0)	3	0
Cardiac failure congestive	0	0	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Intestinal obstruction	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	0	0	0	0	0	0	0	0	0
Chest pain	0	0	0	0	0	0	0	0	0	0	0	0
Infections and infestations	1 (2.0)	1	0	0	0	0	1 (2.0)	3	0	1 (2.0)	1	1
Bronchitis viral	0	0	0	0	0	0	0	0	0	0	0	0
Cellulitis	0	0	0	0	0	0	1 (2.0)	1	0	0	0	0
Localised infection	0	0	0	0	0	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (2.0)	1	0	0	0	0
Urinary tract infection	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Viral upper respiratory tract infection	0	0	0	0	0	0	0	0	0	1 (2.0)	1	1
Wound infection	0	0	0	0	0	0	1 (2.0)	1	0	0	0	0
Injury, poisoning and procedural complications	1 (2.0)	3	0	1 (2.0)	1	0	1 (2.0)	1	0	0	0	0
Chest injury	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Exposure via father	0	0	0	0	0	0	0	0	0	0	0	0
Fall	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Head injury	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Rib fracture	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Thermal burn	0	0	0	0	0	0	1 (2.0)0	1	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	0	0	0	0	0	0	0	0	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	0	0	0	0	0	0

Table 47. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Placebo Q14D			Bococizumab 50 mg Q14D			Bococizumab 100 mg Q14D			Bococizumab 150 mg Q14D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Hypovolaemia	0	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Osteoarthritis	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (4.1)	2	0	0	0	0	0	0	0	0	0	0
Endometrial cancer stage II	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Malignant melanoma	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	1 (2.0)	1	0	0	0	0	1 (2.0)	1	0
Cerebrovascular accident	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Presyncope	0	0	0	0	0	0	0	0	0	0	0	0
Transient ischaemic attack	0	0	0	0	0	0	0	0	0	1 (2.0)	1	0
Psychiatric disorders	0	0	0	0	0	0	0	0	0	0	0	0
Alcoholism	0	0	0	0	0	0	0	0	0	0	0	0
Bipolar disorder	0	0	0	0	0	0	0	0	0	0	0	0
Drug dependence	0	0	0	0	0	0	0	0	0	0	0	0
Reproductive system and breast disorders	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Prostatic dysplasia	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.0)	1	0	1 (2.0)	2	0	1 (2.0)	1	0	2 (4.1)	2	1
Asthma	0	0	0	0	0	0	0	0	0	1 (2.0)	1	0
Chronic obstructive pulmonary disease	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Dyspnoea	0	0	0	0	0	0	0	0	0	1 (2.0)	1	1
Hypercapnia	0	0	0	0	0	0	1 (2.0)	1	0	0	0	0
Hypoxia	0	0	0	0	0	0	0	0	0	0	0	0
Pneumothorax	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Respiratory failure	0	0	0	1 (2.0)	1	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (2.0)	1	0	0	0	0	1 (2.0)	1	0	0	0	0
Angioedema	0	0	0	0	0	0	1 (2.0)	1	0	0	0	0
Dermal cyst	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Vascular disorders	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0
Aortic aneurysm	1 (2.0)	1	0	0	0	0	0	0	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities.
n1: The number of occurrences of treatment-emergent all-causalities adverse events.
n2 (optional): The number of occurrences of treatment-emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA (v17.0) coding dictionary applied.
MedDRA = Medical Dictionary of Regulatory Activities, Q14D = dosing with placebo or bococizumab every 14 days, v = version.

Table 48. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Placebo, Q28D			Bococizumab 200 mg, Q28D			Bococizumab 300 mg, Q28D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	51			50			51		
With adverse events	2 (3.9)			5 (10.0)			4 (7.8)		
Number (%) of subjects with adverse events by:									
System organ class and MedDRA (v17.0) preferred term									
Cardiac disorders	0	0	0	0	0	0	2 (3.9)	5	0
Angina pectoris	0	0	0	0	0	0	1 (2.0)	1	0
Angina unstable	0	0	0	0	0	0	0	0	0
Aortic valve stenosis	0	0	0	0	0	0	1 (2.0)	1	0
Atrial fibrillation	0	0	0	0	0	0	1 (2.0)	1	0
Cardiac failure chronic	0	0	0	0	0	0	0	0	0
Cardiac failure congestive	0	0	0	0	0	0	1 (2.0)	1	0
Myocardial infarction	0	0	0	0	0	0	1 (2.0)	1	0
Gastrointestinal disorders	1 (2.0)	1	0	0	0	0	0	0	0
Intestinal obstruction	0	0	0	0	0	0	0	0	0
Vomiting	1 (2.0)	1	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	1 (2.0)	1	0	0	0	0
Chest pain	0	0	0	1 (2.0)	1	0	0	0	0
Infections and infestations	0	0	0	2 (4.0)	3	0	1 (2.0)	1	0
Bronchitis viral	0	0	0	1 (2.0)	1	0	0	0	0
Cellulitis	0	0	0	0	0	0	0	0	0
Localised infection	0	0	0	0	0	0	1 (2.0)	1	0
Pneumonia	0	0	0	1 (2.0)	2	0	0	0	0
Urinary tract infection	0	0	0	0	0	0	0	0	0
Viral upper respiratory tract infection	0	0	0	0	0	0	0	0	0
Wound infection	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	1 (2.0)	1	0	0	0	0	0	0	0
Chest injury	0	0	0	0	0	0	0	0	0
Exposure via father	1 (2.0)	1	0	0	0	0	0	0	0

Table 48. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Placebo, Q28D			Bococizumab 200 mg, Q28D			Bococizumab 300 mg, Q28D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Fall	0	0	0	0	0	0	0	0	0
Head injury	0	0	0	0	0	0	0	0	0
Rib fracture	0	0	0	0	0	0	0	0	0
Thermal burn	0	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (2.0)	1	0	0	0	0	1 (2.0)	2	0
Dehydration	1 (2.0)	1	0	0	0	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	1 (2.0)	1	0
Hypovolaemia	0	0	0	0	0	0	1 (2.0)	1	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	0	0	0
Osteoarthritis	0	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	0	0	0	0	0	0
Endometrial cancer stage II	0	0	0	0	0	0	0	0	0
Malignant melanoma	0	0	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	1 (2.0)	1	0	1 (2.0)	1	0
Cerebrovascular accident	0	0	0	0	0	0	0	0	0
Presyncope	0	0	0	0	0	0	1 (2.0)	1	0
Transient ischaemic attack	0	0	0	1 (2.0)	1	0	0	0	0
Psychiatric disorders	0	0	0	1 (2.0)	2	0	1 (2.0)	1	0
Alcoholism	0	0	0	1 (2.0)	1	0	0	0	0
Bipolar disorder	0	0	0	0	0	0	1 (2.0)	1	0
Drug dependence	0	0	0	1 (2.0)	1	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	0	0	0
Prostatic dysplasia	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (2.0)	2	0	0	0	0
Asthma	0	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease	0	0	0	1 (2.0)	1	0	0	0	0
Dyspnoea	0	0	0	0	0	0	0	0	0
Hypercapnia	0	0	0	0	0	0	0	0	0

Table 48. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

	Placebo, Q28D			Bococizumab 200 mg, Q28D			Bococizumab 300 mg, Q28D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Respiratory, thoracic and mediastinal disorder									
Hypoxia	0	0	0	1 (2.0)	1	0	0	0	0
Pneumothorax	0	0	0	0	0	0	0	0	0
Respiratory failure	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	0	0	0
Angioedema	0	0	0	0	0	0	0	0	0
Dermal cyst	0	0	0	0	0	0	0	0	0
Vascular disorders	0	0	0	0	0	0	0	0	0
Aortic aneurysm	0	0	0	0	0	0	0	0	0

Except for 'n1' and 'n2', subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities.
n1: The number of occurrences of treatment-emergent all-causalities adverse events.
n2 (optional): The number of occurrences of treatment-emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA (v17.0) coding dictionary applied.
MedDRA = Medical Dictionary of Regulatory Activities, Q28D = dosing with placebo or bococizumab every 28 days; v = version.

Treatment-emergent non-serious AEs reported by >5% subjects are presented in Table 49 and Table 50 by system organ class and preferred term for the Q14D and Q28D dose groups respectively.

Table 49. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) in ≥5% of Subjects (Q14D Dose Groups)

	Placebo Q14D			Bococizumab 50 mg Q14D			Bococizumab 100 mg Q14D			Bococizumab 150 mg Q14D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:												
Evaluable for adverse events	49			50			51			49		
With adverse events	35 (71.4)			27 (54.0)			38 (74.5)			36 (73.5)		
Number (%) of subjects with adverse events by:												
System organ class MedDRA (v17.0) preferred term												
Blood and lymphatic system disorders	1 (2.0)	1	1	0	0	0	5 (9.8)	5	0	2 (4.1)	2	0
Anaemia	1 (2.0)	1	1	0	0	0	5 (9.8)	5	0	2 (4.1)	2	0
Gastrointestinal disorders	9 (18.4)	11	0	4 (8.0)	5	0	10 (19.6)	14	3	10 (20.4)	16	4
Constipation	3 (6.1)	3	0	1 (2.0)	2	0	0	0	0	0	0	0
Diarrhoea	4 (8.2)	4	0	3 (6.0)	3	0	4 (7.8)	6	3	5 (10.2)	7	3
Gastrooesophageal reflux disease	1 (2.0)	1	0	0	0	0	5 (9.8)	5	0	2 (4.1)	2	0
Nausea	1 (2.0)	1	0	0	0	0	2 (3.9)	2	0	3 (6.1)	3	1
Vomiting	2 (4.1)	2	0	0	0	0	1 (2.0)	1	0	4 (8.2)	4	0
General disorders and administration site conditions	6 (12.2)	10	10	7 (14.0)	26	25	7 (13.7)	21	14	14 (28.6)	38	33
Fatigue	0	0	0	1 (2.0)	1	1	1 (2.0)	2	1	3 (6.1)	3	2
Injection site erythema	2 (4.1)	3	3	2 (4.0)	3	2	4 (7.8)	15	10	5 (10.2)	13	13
Injection site pain	4 (8.2)	5	5	4 (8.0)	12	12	1 (2.0)	3	3	1 (2.0)	2	2
Injection site pruritus	0	0	0	0	0	0	0	0	0	3 (6.1)	4	4
Injection site reaction	1 (2.0)	2	2	3 (6.0)	10	10	1 (2.0)	1	0	6 (12.2)	16	12
Immune system disorders	2 (4.1)	2	0	0	0	0	2 (3.9)	2	0	0	0	0
Seasonal allergy	2 (4.1)	2	0	0	0	0	2 (3.9)	2	0	0	0	0
Infections and infestations	22 (44.9)	30	1	15 (30.0)	20	0	24 (47.1)	35	0	20 (40.8)	22	1
Bronchitis	4 (8.2)	5	0	2 (4.0)	2	0	3 (5.9)	3	0	5 (10.2)	5	0
Influenza	1 (2.0)	1	0	0	0	0	2 (3.9)	2	0	1 (2.0)	1	0
Localised infection	1 (2.0)	1	0	0	0	0	3 (5.9)	4	0	0	0	0
Nasopharyngitis	6 (12.2)	9	0	8 (16.0)	9	0	7 (13.7)	7	0	5 (10.2)	6	0
Sinusitis	2 (4.1)	2	1	3 (6.0)	4	0	3 (5.9)	3	0	3 (6.1)	3	0
Upper respiratory tract infection	7 (14.3)	8	0	4 (8.0)	4	0	5 (9.8)	7	0	3 (6.1)	3	0

Table 49. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) in ≥5% of Subjects (Q14D Dose Groups)

	Placebo Q14D			Bococizumab 50 mg Q14D			Bococizumab 100 mg Q14D			Bococizumab 150 mg Q14D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Urinary tract infection	3 (6.1)	4	0	1 (2.0)	1	0	5 (9.8)	9	0	4 (8.2)	4	1
Injury, poisoning and procedural complications	0	0	0	3 (6.0)	3	0	5 (9.8)	7	0	2 (4.1)	2	0
Contusion	0	0	0	1 (2.0)	1	0	4 (7.8)	4	0	1 (2.0)	1	0
Fall	0	0	0	2 (4.0)	2	0	3 (5.9)	3	0	1 (2.0)	1	0
Ligament sprain	0	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	7 (14.3)	9	1	7 (14.0)	7	1	11 (21.6)	14	1	8 (16.3)	11	0
Arthralgia	2 (4.1)	3	0	0	0	0	6 (11.8)	6	1	4 (8.2)	4	0
Back pain	2 (4.1)	2	0	1 (2.0)	1	0	4 (7.8)	4	0	2 (4.1)	2	0
Muscle spasms	2 (4.1)	2	1	3 (6.0)	3	1	2 (3.9)	2	0	3 (6.1)	4	0
Musculoskeletal pain	1 (2.0)	1	0	0	0	0	1 (2.0)	1	0	1 (2.0)	1	0
Osteoarthritis	1 (2.0)	1	0	3 (6.0)	3	0	1 (2.0)	1	0	0	0	0
Nervous system disorders	3 (6.1)	3	2	2 (4.0)	2	0	6 (11.8)	7	1	2 (4.1)	5	1
Carpal tunnel syndrome	0	0	0	0	0	0	0	0	0	0	0	0
Dizziness	1 (2.0)	1	0	0	0	0	4 (7.8)	4	0	1 (2.0)	1	0
Headache	2 (4.1)	2	2	2 (4.0)	2	0	2 (3.9)	3	1	2 (4.1)	4	1
Respiratory, thoracic and mediastinal disorders	5 (10.2)	5	0	2 (4.0)	3	0	1 (2.0)	1	0	2 (4.1)	3	0
Cough	5 (10.2)	5	0	2 (4.0)	3	0	1 (2.0)	1	0	2 (4.1)	3	0
Vascular disorders	4 (8.2)	4	0	0	0	0	2 (3.9)	2	0	3 (6.1)	3	1
Hypertension	4 (8.2)	4	0	0	0	0	2 (3.9)	2	0	3 (6.1)	3	1

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities.
n1: The number of occurrences of treatment-emergent all-causalities adverse events.
n2 (optional): The number of occurrences of treatment-emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA (v17.0) coding dictionary applied.
MedDRA = Medical Dictionary of Regulatory Activities, Q14D = dosing with placebo or bococizumab every 14 days, v = version.

Table 50. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) in ≥5% of Subjects (Q28D Dose Group)

	Placebo Q28D			Bococizumab 200 mg Q28D			Bococizumab 300 mg Q28D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Number (%) of subjects:									
Evaluable for adverse events	51			50			51		
With adverse events	30 (58.8)			34 (68.0)			27 (52.9)		
Number (%) of subjects with adverse events by:									
System organ class MedDRA (v17.0) preferred term									
Blood and lymphatic system disorders	0	0	0	2 (4.0)	2	0	0	0	0
Anaemia	0	0	0	2 (4.0)	2	0	0	0	0
Gastrointestinal disorders	3 (5.9)	5	0	5 (10.0)	9	0	5 (9.8)	11	0
Constipation	0	0	0	1 (2.0)	1	0	0	0	0
Diarrhoea	2 (3.9)	2	0	2 (4.0)	2	0	4 (7.8)	6	0
Gastrooesophageal reflux disease	1 (2.0)	1	0	1 (2.0)	1	0	0	0	0
Nausea	1 (2.0)	1	0	1 (2.0)	1	0	3 (5.9)	3	0
Vomiting	1 (2.0)	1	0	3 (6.0)	4	0	1 (2.0)	2	0
General disorders and administration site conditions	5 (9.8)	6	4	8 (16.0)	26	25	12 (23.5)	20	18
Fatigue	2 (3.9)	3	2	2 (4.0)	2	1	1 (2.0)	1	1
Injection site erythema	0	0	0	4 (8.0)	12	12	5 (9.8)	5	4
Injection site pain	2 (3.9)	2	1	1 (2.0)	1	1	3 (5.9)	4	4
Injection site pruritus	0	0	0	3 (6.0)	6	6	2 (3.9)	2	2
Injection site reaction	1 (2.0)	1	1	1 (2.0)	5	5	5 (9.8)	8	7
Immune system disorders	3 (5.9)	3	0	3 (6.0)	3	0	2 (3.9)	2	0
Seasonal allergy	3 (5.9)	3	0	3 (6.0)	3	0	2 (3.9)	2	0
Infections and infestations	22 (43.1)	27	0	18 (36.0)	23	1	15 (29.4)	21	0
Bronchitis	3 (5.9)	3	0	3 (6.0)	3	0	2 (3.9)	2	0
Influenza	2 (3.9)	2	0	1 (2.0)	1	0	3 (5.9)	3	0
Localised infection	0	0	0	0	0	0	0	0	0
Nasopharyngitis	7 (13.7)	8	0	6 (12.0)	8	0	6 (11.8)	8	0
Sinusitis	2 (3.9)	2	0	2 (4.0)	2	0	1 (2.0)	1	0
Upper respiratory tract infection	9 (17.6)	11	0	5 (10.0)	7	1	3 (5.9)	5	0
Urinary tract infection	1 (2.0)	1	0	2 (4.0)	2	0	2 (3.9)	2	0
Injury, poisoning and procedural complications	0	0	0	4 (8.0)	4	0	3 (5.9)	3	0

Table 50. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities) in ≥5% of Subjects (Q28D Dose Group)

	Placebo Q28D			Bococizumab 200 mg Q28D			Bococizumab 300 mg Q28D		
	n (%)	n1	n2	n (%)	n1	n2	n (%)	n1	n2
Contusion	0	0	0	0	0	0	1 (2.0)	1	0
Fall	0	0	0	1 (2.0)	1	0	1 (2.0)	1	0
Ligament sprain	0	0	0	3 (6.0)	3	0	1 (2.0)	1	0
Musculoskeletal and connective tissue disorders	6 (11.8)	7	2	5 (10.0)	9	2	6 (11.8)	9	0
Arthralgia	3 (5.9)	3	0	0	0	0	2 (3.9)	2	0
Back pain	1 (2.0)	1	0	4 (8.0)	5	0	1 (2.0)	2	0
Muscle spasms	2 (3.9)	3	2	1 (2.0)	1	0	1 (2.0)	1	0
Musculoskeletal pain	0	0	0	1 (2.0)	3	2	3 (5.9)	3	0
Osteoarthritis	0	0	0	0	0	0	1 (2.0)	1	0
Nervous system disorders	3 (5.9)	3	0	9 (18.0)	10	3	5 (9.8)	6	1
Carpal tunnel syndrome	0	0	0	3 (6.0)	3	0	0	0	0
Dizziness	2 (3.9)	2	0	2 (4.0)	2	2	1 (2.0)	1	0
Headache	1 (2.0)	1	0	4 (8.0)	5	1	4 (7.8)	5	1
Respiratory, thoracic and mediastinal disorders	1 (2.0)	1	0	1 (2.0)	1	0	1 (2.0)	1	0
Cough	1 (2.0)	1	0	1 (2.0)	1	0	1 (2.0)	1	0
Vascular disorders	1 (2.0)	1	0	1 (2.0)	1	0	0	0	0
Hypertension	1 (2.0)	1	0	1 (2.0)	1	0	0	0	0

Except for 'n1' and 'n2' subjects were only counted once per treatment for each row.
n: The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities.
n1: The number of occurrences of treatment-emergent all-causalities adverse events.
n2 (optional): The number of occurrences of treatment-emergent causally related to treatment adverse events.
Includes data up to 999 days after last dose of study drug.
MedDRA (v17.0) coding dictionary applied.
MedDRA = Medical Dictionary of Regulatory Activities, Q28D = dosing with placebo or bococizumab every 28 days, v = version.

In total, 99 of 351 subjects (28.2%) had treatment-related TEAEs, 60 of 199 subjects (30.2%) in the groups of the Q14D dose regimen and 39 of 152 subjects (25.7%) in the groups of the Q28D dose regimen. The number (%) subjects with treatment-related TEAEs are presented in Table 51 for the Q14D dose groups, and Table 52 for the Q28D dose groups.

Table 51. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events - Q14D Safety Analysis Set

System Organ Class[a] Preferred Term	Placebo Q14D (N=49)	Bococizumab 50 mg Q14D (N=50)	Bococizumab 100 mg Q14D (N=51)	Bococizumab 150 mg Q14D (N=49)
Subject with any adverse event	14 (28.6)	12 (24.0)	16 (31.4)	18 (36.7)
Blood and lymphatic system disorders	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Hearing impaired	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (2.0)	1 (2.0)	3 (5.9)	3 (6.1)
Abdominal distension	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Diarrhoea	0 (0.0)	0 (0.0)	2 (3.9)	1 (2.0)
Dry mouth	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Lip swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Oral discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Steatorrhoea	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
General disorders and administration site conditions	6 (12.2)	6 (12.0)	10 (19.6)	12 (24.5)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Chills	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Fatigue	0 (0.0)	1 (2.0)	1 (2.0)	2 (4.1)
Injection site erythema	2 (4.1)	1 (2.0)	3 (5.9)	5 (10.2)
Injection site haemorrhage	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Injection site induration	0 (0.0)	1 (2.0)	1 (2.0)	0 (0.0)
Injection site inflammation	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Injection site pain	4 (8.2)	4 (8.0)	1 (2.0)	1 (2.0)
Injection site pruritus	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.1)
Injection site rash	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Injection site reaction	1 (2.0)	3 (6.0)	0 (0.0)	4 (8.2)
Injection site urticaria	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Infections and infestations	2 (4.1)	0 (0.0)	0 (0.0)	2 (4.1)
Gastroenteritis	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Overdose	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Investigations	2 (4.1)	1 (2.0)	2 (3.9)	1 (2.0)
Blood cortisol decreased	0 (0.0)	1 (2.0)	1 (2.0)	0 (0.0)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)
Blood creatinine increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood pressure increased	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	2 (4.1)	1 (2.0)	0 (0.0)	0 (0.0)
Hyperkalaemia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Hyponatraemia	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Type 2 diabetes mellitus	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)
Arthralgia	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Flank pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Muscle spasms	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)

Table 51. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events - Q14D Safety Analysis Set

System Organ Class[a] Preferred Term	Placebo Q14D (N=49)	Bococizumab 50 mg Q14D (N=50)	Bococizumab 100 mg Q14D (N=51)	Bococizumab 150 mg Q14D (N=49)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Nervous system disorders	3 (6.1)	1 (2.0)	4 (7.8)	3 (6.1)
Areflexia	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Decreased vibratory sense	0 (0.0)	1 (2.0)	1 (2.0)	1 (2.0)
Dysgeusia	1 (2.0)	0 (0.0)	1 (2.0)	1 (2.0)
Headache	2 (4.1)	0 (0.0)	1 (2.0)	1 (2.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Panic attack	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Skin and subcutaneous tissue disorders	1 (2.0)	2 (4.0)	2 (3.9)	1 (2.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Erythema	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	1 (2.0)	0 (0.0)	1 (2.0)
Rash erythematous	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Urticaria	1 (2.0)	1 (2.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

N = number of subjects; Q14D = once with placebo or bococizumab every 14 days.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report ≥2 different adverse events within the higher level category.

Table 52. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events (TEAEs) - Q28D Safety Analysis Set

System Organ Class[a] Preferred Term	Placebo Q28D (N=51)	Bococizumab 200 mg Q28D (N=50)	Bococizumab 300 mg Q28D (N=51)
Subject with any adverse event	8 (15.7)	14 (28.0)	17 (33.3)
Gastrointestinal disorders	3 (5.9)	0 (0.0)	2 (3.9)
Abdominal distension	0 (0.0)	0 (0.0)	1 (2.0)
Abdominal pain	0 (0.0)	0 (0.0)	1 (2.0)
Abdominal pain lower	1 (2.0)	0 (0.0)	0 (0.0)
Frequent bowel movements	1 (2.0)	0 (0.0)	0 (0.0)
Impaired gastric emptying	1 (2.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	4 (7.8)	8 (16.0)	11 (21.6)
Application site erythema	0 (0.0)	0 (0.0)	1 (2.0)
Application site pruritus	0 (0.0)	0 (0.0)	1 (2.0)
Fatigue	2 (3.9)	1 (2.0)	1 (2.0)
Injection site bruising	0 (0.0)	0 (0.0)	1 (2.0)
Injection site erythema	0 (0.0)	4 (8.0)	4 (7.8)
Injection site haemorrhage	0 (0.0)	1 (2.0)	0 (0.0)
Injection site pain	1 (2.0)	1 (2.0)	3 (5.9)
Injection site paraesthesia	0 (0.0)	1 (2.0)	0 (0.0)
Injection site pruritus	0 (0.0)	3 (6.0)	2 (3.9)
Injection site reaction	1 (2.0)	1 (2.0)	4 (7.8)
Infections and infestations	0 (0.0)	1 (2.0)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (2.0)	0 (0.0)
Investigations	2 (3.9)	0 (0.0)	1 (2.0)
Antinuclear antibody increased	1 (2.0)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	0 (0.0)	1 (2.0)
Heart rate increased	0 (0.0)	0 (0.0)	1 (2.0)
Weight increased	1 (2.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (2.0)	1 (2.0)	1 (2.0)
Decreased appetite	1 (2.0)	0 (0.0)	0 (0.0)
Impaired fasting glucose	0 (0.0)	0 (0.0)	1 (2.0)
Increased appetite	0 (0.0)	1 (2.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (3.9)	2 (4.0)	1 (2.0)
Exostosis	1 (2.0)	0 (0.0)	0 (0.0)
Muscle spasms	1 (2.0)	0 (0.0)	0 (0.0)
Musculoskeletal pain	0 (0.0)	1 (2.0)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	1 (2.0)
Pain in extremity	0 (0.0)	2 (4.0)	0 (0.0)
Nervous system disorders	0 (0.0)	4 (8.0)	3 (5.9)
Amnesia	0 (0.0)	0 (0.0)	1 (2.0)
Areflexia	0 (0.0)	0 (0.0)	1 (2.0)
Decreased vibratory sense	0 (0.0)	0 (0.0)	1 (2.0)
Dizziness	0 (0.0)	2 (4.0)	0 (0.0)
Headache	0 (0.0)	1 (2.0)	1 (2.0)
Hyporeflexia	0 (0.0)	0 (0.0)	1 (2.0)
Sensory disturbance	0 (0.0)	1 (2.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.0)
Nightmare	0 (0.0)	0 (0.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (2.0)	0 (0.0)
Dyspnoea	0 (0.0)	1 (2.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.0)	3 (5.9)
Dermatitis	0 (0.0)	0 (0.0)	1 (2.0)
Hair growth abnormal	0 (0.0)	0 (0.0)	1 (2.0)
Rash	0 (0.0)	0 (0.0)	1 (2.0)
Rash papular	0 (0.0)	1 (2.0)	0 (0.0)

Table 52. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events (TEAEs) - Q28D Safety Analysis Set

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.
N = number of subjects; Q28D = once with placebo or bococizumab every 28 days.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report ≥2 different adverse events within the higher level category.

The number (%) of subjects who discontinued treatment due to TEAEs in Q14D dose group and Q28D dose group are summarized in Table 53 and Table 54 respectively.

Table 53. Number (%) of Subjects Reporting Treatment Emergent Adverse Events (TEAEs) Which Lead to Treatment Discontinuation - Q14D Safety Analysis Set

System Organ Class[a] Preferred Term	Placebo N=49	Bococizumab 50 mg N=50	Bococizumab 50 mg N=51	Bococizumab 50 mg N=49
Subject with any adverse event	1 (2.0)	1 (2.0)	2 (3.9)	5 (10.2)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Lip swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Infections and infestations	1 (2.0)	0 (0.0)	1 (2.0)	1 (2.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Urinary tract infection	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.0)	1 (2.0)	0 (0.0)
Angioedema	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Urticaria	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities Version 16.0.
Treatment discontinuation refers to "Study treatment dose = permanently discontinued".
N = number of subjects; Q14D = dosing with placebo or bococizumab every 14 days.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different adverse events within the higher level category.

Table 54. Number (%) of Subjects Reporting Treatment Emergent Adverse Events (TEAEs) Which Lead to Treatment Discontinuation - Q28D Safety Analysis Set

System Organ Class Preferred Term	Placebo N=51	Bococizumab 200 mg N=50	Bococizumab 300 mg N=51
Subject with any adverse event	0 (0.0)	0 (0.0)	5 (9.8)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (2.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (2.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	2 (3.9)
Abdominal pain	0 (0.0)	0 (0.0)	1 (2.0)
Vomiting	0 (0.0)	0 (0.0)	1 (2.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (2.0)
Injection site reaction	0 (0.0)	0 (0.0)	1 (2.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (2.0)
Bipolar disorder	0 (0.0)	0 (0.0)	1 (2.0)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0. Treatment discontinuation refers to "Study treatment dose = permanently discontinued".
MedDRA = Medical Dictionary of Regulatory Activities, N = number of subjects; Q28D = dosing with placebo or bococizumab every 28 days, v = version.

The injection site TEAEs are summarized in Table 55. The events included injection site erythema (22 of 351 subjects), injection site reactions (18 of 351 subjects), injection site pain (16 of 351 subjects) and injection site pruritus (8 of 351 subjects).

Table 55. Injection Site Treatment-Emergent Adverse Events – Q14D and Q28D Safety Analysis Sets

Preferred Term n (%) of Subjects With	Q14D				Q28D		
	Placebo	Bococizumab			Placebo	Bococizumab	
	N=49	50 mg N=50	100 mg N=51	150 mg N=49	N=51	200 mg N=50	300 mg N=51
Injection site bruising	0	0	0	1 (2.0)	1 (2.0)	0	1 (2.0)
Injection site discomfort	0	0	1 (2.0)	0	0	0	0
Injection site erythema	2 (4.1)	2 (4.0)	4 (7.8)	5 (10.2)	0	4 (8.0)	5 (9.8)
Injection site hemorrhage	0	1 (2.0)	1 (2.0)	1 (2.0)	0	1 (2.0)	0
Injection site induration	0	1 (2.0)	1 (2.0)	1 (2.0)	0	0	0
Injection site inflammation	0	1 (2.0)	0	0	0	0	0
Injection site pain	4 (8.2)	4 (8.0)	1 (2.0)	1 (2.0)	2 (3.9)	1 (2.0)	3 (5.9)
Injection site paresthesia	0	0	0	3 (6.1)	0	1 (2.0)	0
Injection site pruritus	0	1 (2.0)	1 (2.0)	0	0	3 (6.0)	2 (3.9)
Injection site rash	1 (2.0)	3 (6.0)	1 (2.0)	6 (12.2)	0	0	0
Injection site reaction	0	0	1 (2.0)	0	1 (2.0)	1 (2.0)	5 (9.8)
Injection site urticaria	0	0	0	0	0	0	0
Injection site swelling	0	0	0	1 (2.0)	0	0	1 (2.0)

N = number of randomized subjects; n = number of subjects in the specified category with non-missing values; Q14D = dosing with placebo or bococizumab every 14 days; Q28D = dosing with placebo or bococizumab every 28 days.

No subject died while on study treatment. During the post-therapy follow-up period, a 74-year old male subject died 57 days after completing study treatment with bococizumab 50 mg Q14D SC. The cause of death was an accidental head trauma following a fall.

The Investigator reported that there was not a reasonable possibility that the fatal event was related to study treatment, concomitant drug or to a clinical trial procedure. The Sponsor concurred with this assessment.

The overall incidence of ADA in this study was 7%, with 18 out of 251 bococizumab treated subjects having positive ADA titers. All subjects in the bococizumab treatment groups tested negative for ADA at Baseline and through Day 57. Subsequently, 12 subjects in the bococizumab treatment groups (3 subjects in the 50 mg Q14D group and 2 subjects in the 150 mg Q14D group, and 2 subjects in the 200 mg Q28D group and 5 subjects in the 300 mg Q28D group) developed ADA at some point during treatment (Days 85 to 225). An additional 6 subjects in the bococizumab treatment groups developed ADA during follow-up (2 subjects in the 100 mg Q14D group and 3 subjects in the 150 mg Q14D group, and 1 subject in the 200 mg Q28D group. At the end of the study follow-up (Day 225 for the Q14D groups and Day 211 for the Q28D groups) 16 of these 18 subjects still had positive ADAs. One subject in the bococizumab 50 mg Q14D group had developed positive ADAs on Day 85 but subsequently became ADA negative on Day 169 (end of treatment) and remained negative throughout the remainder of the study. One subject in the bococizumab 300 mg Q28D group was discontinued from the study on Day 142 (no longer willing to participate) and the last available ADA sample was on Day 115. Of the 16 subjects who had positive ADAs at the end of study follow-up 1 subject had ADA titers that remained detectable at the last post-study monitoring reported for this subject, however, it was decreased over 50% from a peak of 12.10 on Day 169, to 5.56 at Month 9 post-study. One ADA subject was lost to follow-up after end of the study (Day 221). For other 14 subjects who had positive ADAs at the end of the study follow-up ADAs became non-detectable (negative) during post-study monitoring as described below:

- 4 subjects were negative by Month 3 (2 subjects in the 150 mg Q14D group and 2 subjects in the 300 mg Q28D group);
- 3 subjects by Month 6 (1 subject in the 50 mg Q14D group, 1 subject in the 150 mg Q14D group and 1 subject in the 200 mg Q28D group);
- 6 subjects by Month 9 (1 subject in the 50 mg Q14D group, 1 subject in the 100 mg Q14D group, 1 subject in the 150 mg Q14D group, 1 subject in the 200 mg Q28D group and 2 subjects in the 300 mg Q28D group);
- 1 subject was negative by Month 12 (100 mg Q14D group).

The number (%) of subjects with positive ADA titers are summarized in Table 56.

Table 56. Summary of Incidence of Positive Anti-Drug (Bococizumab) Antibodies - Q14D and Q28D Safety Analysis Sets

Visit	Q14D				Q28D		
	Placebo	Bococizumab			Placebo	Bococizumab	
	n/N (%)	50 mg n/N (%)	100 mg n/N (%)	150 mg n/N (%)	n/N (%)	200 mg n/N (%)	300 mg n/N (%)
Day 1	0/11	0/46	0/49	0/47	0/7	0/50	0/50
Day 15	0	0/44	0/50	0/47	0	0/46	0/50
Day 29	0	0/45	0/47	0/46	0	0/47	0/48
Day 57	0	0/44	0/48	0/43	0	0/47	0/47
Day 85	0	1/40 (2.5)	0/40	0/40	0	0/46	1/48 (2.1)
Day 113	0	1/42 (2.4)	0/44	1/41 (2.4)	0	0/45	4/47 (8.5)
Day 141	0	1/44 (2.3)	0/45	2/43 (4.7)	0	0/46	3/49 (6.1)
Day 169	0	2/42 (4.8)	0/43	2/45 (4.4)	0	2/47 (4.3)	3/49 (6.1)
Day 183	0	2/43 (4.7)	1/44 (2.3)	4/45 (8.9)	0	2/46 (4.3)	4/46 (8.7)
Day 197	0	2/40 (5.0)	2/43 (4.7)	5/42 (11.9)	0	-	-
Day 211	0	-	-	-	0	3/44 (6.8)	4/47 (8.5)
Day 225	0	2/38 (5.3)	2/44 (4.5)	5/45 (11.1)	0	-	-
Final on-treatment	0	2/50 (4.0)	0/51	2/49 (4.1)	0	2/50 (4.0)	4/51 (7.8)
At any time Post-Baseline	0	3/50 (6.0)	2/51 (3.9)	5/49 (10.2)	0	3/50 (6.0)	5/51 (9.8)

Positive: ADA titer ≥4.32. Negative: ADA titer <4.32. Percentages are based on the number (n) of subjects with a non-missing titer (N) at the indicated visit.
ADA = anti-drug antibody; N = total number of subjects; n = number of subjects in pre-specified criteria; Q14D = dosing with placebo or bococizumab every 14 days; Q28D = dosing with placebo or bococizumab every 28 days.

TEAEs were reported for 16 of the 18 subjects from start of study through post-study monitoring as shown in Table 57.

Table 57. Overview of Treatment-Emergent Adverse Events in Subjects With Positive Anti-Drug Antibodies During the Study

Visit	n (%)						
	Q14D				Q28D		
	Placebo	Bococizumab			Placebo	Bococizumab	
	N=0	50 mg N=3	100 mg N=2	150 mg N=5	N=0	200 mg N=3	300 mg N=5
Any TEAEs	0	2 (66.7)	2 (100.00)	5 (100.0)	0	3 (100.0)	4 (80.0)
Any SAEs	0	0	0	0	0	0	1 (20.0)
Any severe TEAEs	0	0	0	0	0	0	2 (40.0)
Deaths	0	0	0	0	0	0	0

Medical Dictionary for Regulatory Activities Version 17.0 coding dictionary applied.
N = number of randomized subjects; n = number of subjects in the specified category with non-missing values; Q14D = once with placebo or bococizumab every 14 days; Q28D = once with placebo or bococizumab every 28 days; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

One (1) serious adverse event, angina pectoris, was reported in 300 mg bococizumab Q28D treatment group on Day 138, 26 days after the subject's third dose of study treatment, when he was admitted to hospital for a stent placement. The Investigator assessed the causality of the angina pectoris as not related to study treatment and related to underlying coronary artery disease.

The most common TEAEs by preferred term were nasopharyngitis (5 subjects), headache (3 subjects), injection site reaction (3 subjects), nausea (3 subjects), vomiting (3 subjects), seasonal allergy (2 subjects), and uterine hemorrhage (2 subjects), and all were assessed by the Investigator as not related to study treatment.

No clinically significant changes or trends were observed for any of the other safety findings, including vital signs, physical and neurological findings, or ECGs. TG decreased relative to baseline levels but there were no consistent changes in relation to dose of bococizumab in either the Q14D or Q28D dose groups.

CONCLUSIONS:

The conclusions with respect to the objectives of the study were:

Primary objective:

- Bococizumab administered SC to hypercholesterolemic subjects on a background of statins produced a statistically significant reduction in LDL-C (Week 12 and 24) at all doses tested compared to placebo and the primary objective of the study was met.

- LDL-C lowering was maintained over the 24-week period, although the reduction in LDL-C measured as either absolute change or percent change from Baseline was not as great at Week 24 as it was at Week 12, which was not unexpected given the number of subjects that received downward dose adjustments, particularly in the higher dose groups.

Secondary objectives:

- The changes in serum levels of other lipoproteins and lipids (including ApoB, ApoA1 and Lp[a]) in subjects who received bococizumab on a back ground of statins were generally consistent with the effect of LDL-C lowering.

- Regarding immunogenicity, the overall incidence of ADA in this study was low.

- In general, the majority of occurrences of ADA was only detected after the end of the bococizumab treatment period, and there was no relationship with safety or tolerability of bococizumab.

- A dose response was noted for injection site reaction and injection site erythema, although the overall incidence of these events, including pain, was small.

- There were no apparent safety or tolerability findings in relation to lipid changes after treatment with bococizumab.

- Small increases in HDL-C, and decreases in non-HDL-C and TG, were observed that was generally consistent with effect of LDL-C lowering bococizumab plasma concentrations in subjects without dose adjustments increased in a less than dose-proportional manner with increasing dose.

- The overall occurrence of positive ADA titers in this study was low (18 of 251 [7%] subjects who received bococizumab). In 14 out of the 16 subjects followed post-study, ADA titers were negative within 9 months. No relationship between the occurrence of positive ADA titers and the occurrence of TEAEs was apparent, and no TEAEs reported were associated with any systemic reactions or change in vital signs.