PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: B1481036

PROTOCOL TITLE:

A Phase 2 Double Blind, Parallel Group, Placebo Controlled, Randomized, Dose Ranging Study to Assess the Efficacy, Safety and Tolerability of PF-04950615 Following Twice Monthly Subcutaneous Doses in Hypercholesterolemic Japanese Subjects Who Are Receiving a Stable Dose of Atorvastatin or Treatment Naïve

Study Centers:

A total of 9 centers in Japan took part in the study and randomized subjects.

Study Initiation and Final Completion Dates:

31 March 2014 to 08 January 2015

Phase of Development:

Phase 2

Study Objectives:

Primary Objectives:

- To evaluate the low density lipoprotein-cholesterol (LDL-C) lowering effect of PF-04950615 (bococizumab) administered subcutaneously (SC) once every 14 days (Q14D) in hypercholesterolemic Japanese subjects whose fasting LDL-C was not controlled and was ≥100 mg/dL on background treatment with a stable dose of atorvastatin (Population A);

- To evaluate the LDL-C lowering effect of bococizumab administered SC Q14D in hypercholesterolemic Japanese subjects who were naïve for a treatment by lipid lowering drug and whose fasting LDL-C was ≥130 mg/dL (Population B).

Secondary Objectives:

- To evaluate the effect of bococizumab administered SC on lipid parameters other than LDL-C;

- To evaluate the safety including injection site reaction, tolerability and immunogenicity (anti-drug antibody [ADA]) against bococizumab administered SC;

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) following administration of bococizumab;

- To evaluate the effect of atorvastatin on PK and PD of bococizumab.

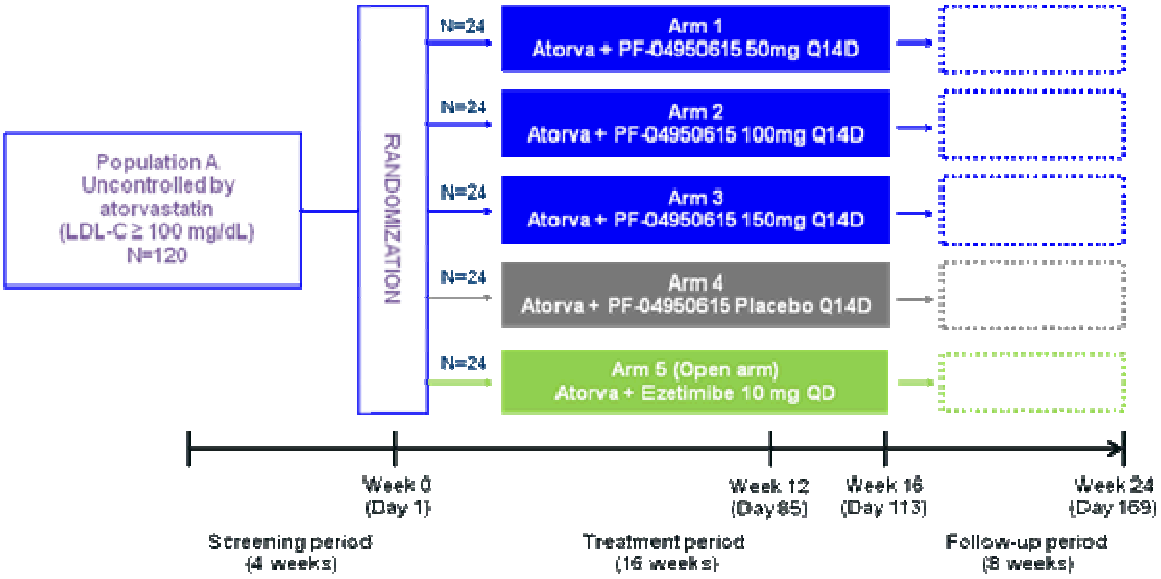
METHODS

Study Design:

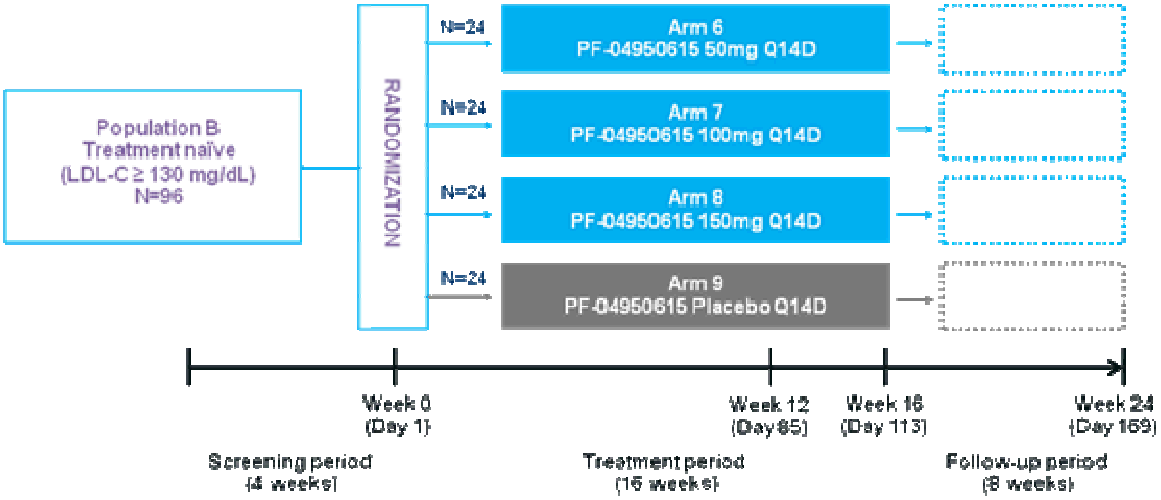
This study was a double-blind, parallel-group, placebo-controlled, randomized, dose-ranging study for 2 populations (Population A and Population B) with a treatment duration of 16 weeks (4 months). Population A comprised hypercholesterolemic subjects whose fasting LDL-cholesterol was not controlled and was ≥100 mg/dL on background treatment with a stable dose of atorvastatin. Population B consisted of hypercholesterolemic subjects who were naïve for a treatment by lipid lowering drug and whose fasting LDL-C was ≥130 mg/dL. A total of 9 arms in 2 populations, with 24 subjects per arm were planned. A schematic of the study design is shown in Figure 1.

Figure 1. A Schematic of the Study Design

Population A:



Population B:



Atorva=atorvastatin; LDL-C=low density lipoprotein-cholesterol; PF-04950615=bococizumab; Q14D=once every 14 days.

In Population A, a subject who was receiving a stable dose of atorvastatin was randomized into 1 out of 5 arms which consisted of;

- Arm 1: Atorvastatin plus bococizumab 50 mg Q14D SC;
- Arm 2: Atorvastatin plus bococizumab 100 mg Q14D SC;

- Arm 3: Atorvastatin plus bococizumab 150 mg Q14D SC;
- Arm 4: Atorvastatin plus bococizumab Placebo Q14D SC;
- Arm 5: Atorvastatin plus Ezetimibe 10 mg once a day (QD) per os (PO).

Subjects were on stable dosage of atorvastatin for at least 6 weeks prior to screening and throughout the duration of this study. Atorvastatin plus Ezetimibe 10 mg arm (Arm 5) was the only open arm because the purposes of this arm were to estimate the effect size of ezetimibe 10 mg on LDL-C reduction and to evaluate the effect on other lipid parameters and biomarkers.

In Population B, a subject who was treatment naïve was randomly assigned to 1 of 4 arms which comprised;

- Arm 6: Bococizumab 50 mg Q14D SC;
- Arm 7: Bococizumab 100 mg Q14D SC;
- Arm 8: Bococizumab 150 mg Q14D SC;
- Arm 9: Bococizumab Placebo Q14D SC.

Subjects, except those in Arm 5, received bococizumab active dose or bococizumab placebo by SC administration on Days 1, 15, 29, 43, 57, 71, 85 and 99. For the first 12 weeks, the assigned bococizumab active dose was administered. On or after Week 12 (Day 85), if subjects met the dose adjustment criteria, a reduced dose was administered. Subjects in Arm 5 took ezetimibe 10 mg tablet after food QD during treatment period (i.e., from Day 1 to 112).

Subjects were seen periodically at the study site for safety assessment, collection of blood for safety labs, lipid profiles, PK, PD, immunogenicity samples and to receive their dose of study drug (bococizumab active or bococizumab placebo).

The co-primary efficacy endpoints were 1) the percent change of LDL-C from baseline at Week 12 (Day 85) and 2) the percent change of LDL-C from baseline at Week 16 (Day 113).

Subjects who received at least 1 dose of study treatment (bococizumab active dose, bococizumab placebo, or ezetimibe 10 mg) and withdrew from the study were not replaced and were asked to remain in the study for safety follow-up and complete all scheduled visits without receiving study treatment (bococizumab active dose, bococizumab placebo, or ezetimibe 10 mg).

All evaluations and procedures are shown in Table 1, Table 2 and Table 3.

Table 1. Subjects With Full Blood Collection for PK (Arm 1 to 4 in Population A, and Arm 6 to 9 in Population B)

Study Phase	Screening		Treatment																							Follow-Up				
Week	−4 to −2	−1	0	-	-	-	-	-	-	1	2	3	4	5	6	7	8	10	12	14	-	-	-	15	16	17	18	20	22	24
Day	−28 to −8	−7	1	2	3	4	5	6	7	8	15	22	29	36	43	50	57	71	85	99	100	102	104	106	113 EOT	120	127	141	155	169 EOS
Visit Window	±3	−3/+0	±0	±0	±0	±0	±0	±0	±0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2[a]	±2[a]	±2[a]	±2[a]	±2	±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	X	X	X	X	X	X
Weight	X		X																						X					
Height	X																													
Waist circumference	X		X																						X					
Randomization			X																											
Bococizumab/Placebo administration			X								X		X		X		X	X	X	X										
Blood for bococizumab PK[b]			X	X	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 PCSK9[b]			X	X	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 atorvastatin PK[c]			X				X			X	X	X	X	X	X	X	X	X	X	X					X		X	X		
Concomitant medication	X	X	X	X	X	X	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 fasting lipid profile	X	X	X				X			X	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X	X
Blood for LDL composition			X										X						X						X					
Blood for Lp-PLA2			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	X	X	X	X
Hematology, biochemistry	X		X							X	X	X	X		X		X	X	X	X					X			X		X
Urinalysis	X										X		X		X		X	X	X	X					X			X		X
12-Lead ECG	X		X																						X					
Blood for ADA			X										X		X		X	X	X	X					X			X		X[d]
HbA1c	X		X																X						X					
Hormone monitoring			X														X		X						X					
Neurological panel			X																						X					
Pregnancy test[e]	X		X																						X					
Hepatitis screen	X																													
TSH	X																													
FSH[f]	X																													
Banked biospecimen (PGx)			X																											

Table 1. Subjects With Full Blood Collection for PK (Arm 1 to 4 in Population A, and Arm 6 to 9 in Population B)

ADA=anti-drug antibody; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; HbA1c=glycosylated hemoglobin; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LDL=low density lipoprotein; Lp-PLA2=lipoprotein-associated phospholipase A2; PGx=pharmacogenomics; PCSK9=proprotein convertase subtilisin/kexin type 9; PK=pharmacokinetics; TSH=thyroid stimulating hormone.

a. Subjects visited the study site 1, 3, 5, 7 days after injection at Day 99.
b. About a half of subjects in each treatment arm (n=12) were allocated to full PK sampling group.
c. Only Population A.
d. Subjects found to have ADA still present at EOS were requested to return to the study site at up to 90 days intervals until antibody was not detected.
e. Pregnancy tests were also repeated as per request of IRB/IECs or if required by local regulations.
f. FSH to be done in postmenopausal females only.

Table 2. Subjects Without Full Blood Collection for PK (Arm 1 to 4 in Population A, and Arm 6 to 9 in Population B)

Study Phase	Screening		Treatment															Follow-Up			
Week	−4 to −2	−1	0	-	1	2	3	4	5	6	7	8	10	12	14	15	16	18	20	22	24
Day	−28 to −8	−7	1	5	8	15	22	29	36	43	50	57	71	85	99	106	113 EOT	127	141	155	169 EOS
Visit Window	±3	-3/+0	±0	±0	±0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2[a]	±2	±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
Weight	X		X														X				
Height	X																				
Waist circumference	X		X														X				
Randomization			X																		
Bococizumab/placebo administration			X			X		X		X		X	X	X	X						
Blood for bococizumab PK			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		
Blood for atorvastatin PK[b]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X
Blood for LDL composition			X					X						X			X				
Blood for Lp-PLA2			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
Hematology, biochemistry	X		X		X	X	X	X		X		X	X	X	X		X		X		X
Urinalysis	X					X		X		X		X	X	X	X		X		X		X
12-Lead ECG	X		X														X				
Blood for ADA			X					X		X		X	X	X	X		X		X		X[c]
HbA1c	X		X											X			X				
Hormone monitoring			X									X		X			X				
Neurological panel			X														X				
Pregnancy test[d]	X		X														X				
Hepatitis screen	X																				
TSH	X																				
FSH[e]	X																				
Banked biospecimen (PGx)			X																		

ADA=anti-drug antibody; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; HbA1c=glycosylated hemoglobin; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LDL=low density lipoprotein; Lp-PLA2=lipoprotein-associated phospholipase A2; PGx=pharmacogenomics; PCSK9=proprotein convertase subtilisin/kexin type 9; PK=pharmacokinetics; TSH=thyroid stimulating hormone.

Table 2. Subjects Without Full Blood Collection for PK (Arm 1 to 4 in Population A, and Arm 6 to 9 in Population B)

a. Subjects visited the study site 7 days after injection at Day 99.
b. Only Population A.
c. Subjects found to have ADA still present at EOS were requested to return to the study site at up to 90 days intervals until antibody was not detected.
d. Pregnancy tests were also repeated as per request of IRB/IECs or if required by local regulations.
e. FSH to be done in postmenopausal females only.

Table 3. Open-Label Ezetimibe Arm (Arm 5 in Population A)

Study Phase	**Screening**		**Treatment**															**Follow-Up**			
Week	**−4 to −2**	**−1**	**0**	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**15**	**16**	**18**	**20**	**22**	**24**
Day	**−28 to −8**	**−7**	**1**	**5**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**71**	**85**	**99**	**106**	**113 EOT**	**127**	**141**	**155**	**169 EOS**
Visit Window	**±3**	**-3/+0**	**±0**	**±0**	**±0**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±1**	**±2**	**±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
Weight	X		X														X				
Height	X																				
Waist circumference	X		X														X				
Randomization			X																		
Ezetimibe 10 mg (only open ezetimibe arm)			←	—	—	—	—	—	—	—	—	—	→								
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X
Blood for LDL composition			X					X						X			X				
Blood for Lp-PLA2			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
Hematology, biochemistry	X		X		X	X	X	X		X		X	X	X	X		X		X		X
Urinalysis	X					X		X		X		X	X	X	X		X		X		X
12-Lead ECG	X		X														X				
HbA1c	X		X											X			X				
Pregnancy test[a]	X		X														X				
Hepatitis screen	X																				
TSH	X																				
FSH[b]	X																				
Banked biospecimen (PGx)			X																		

ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; FSH=follicle stimulating hormone; HbA1c=glycosylated hemoglobin; IEC=Independent Ethics Committee; IRB=Institutional Review Board; LDL=low density lipoprotein; Lp-PLA2=lipoprotein-associated phospholipase A2; PGx=pharmacogenomics; TSH=thyroid stimulating hormone.

a. Pregnancy tests were also repeated as per request of IRB/IECs or if required by local regulations.
b. FSH to be done in postmenopausal females only.

Number of Subjects (Planned and Analyzed):

Initially a total of 9 arms in 2 populations, with 24 subjects per arm were planned. Out of which a total of 121 subjects were randomized to either bococizumab 50 mg arm (25 subjects), bococizumab 100 mg arm (24 subjects), bococizumab 150 mg arm (24 subjects), placebo arm (26 subjects), or ezetimibe arm (22 subjects), and all of them were administered at least 1 dose of study treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Main Inclusion Criteria for Population A: Subjects whose LDL-C was not controlled by a stable dose of atorvastatin were included in this study.

Main Inclusion Criteria for Population B: Subjects who were naïve to a treatment by lipid lowering drug and whose LDL-C was not controlled were included in this study.

Main Exclusion Criteria: Severe acute or chronic medical or psychiatric condition or laboratory abnormality; pregnant females; breastfeeding females; males and females of childbearing potential who were unwilling or unable to use a highly effective method of contraception; subjects who were administered or prior exposed to bococizumab and/or anti-body targeting proprotein convertase subtilisin/kexin Type 9 (PCSK9) were excluded from this study.

Study Treatment:

In Population A, a subject was administered bococizumab 50 mg Q14D SC (Arm 1), bococizumab 100 mg Q14D SC (Arm 2), bococizumab 150 mg Q14D SC (Arm 3), bococizumab placebo Q14D SC (Arm 4), and ezetimibe 10 mg QD PO (Arm 5), adding on the stable dose of atorvastatin. All subjects in Population A kept the same dose of atorvastatin as background treatment throughout the study. For Arm 1 to Arm 4, all subjects were SC administered the same bococizumab or placebo dose as assigned for the first 12 weeks. On or after Week 12 (Day 85), if a subject met the dose adjustment criteria illustrated below, the dose was reduced. A subject in Arm 5 took ezetimibe 10 mg tablet after food QD during treatment period (i.e., from Day 1 to 112).

In Population B, a subject was administered bococizumab 50 mg Q14D SC (Arm 6), bococizumab 100 mg Q14D SC (Arm 7), bococizumab 150 mg Q14D SC (Arm 8), and bococizumab placebo Q14D SC (Arm 9). For Arm 6 to Arm 9, all subjects were SC administered the same bococizumab or placebo dose as assigned for the first 12 weeks. On or after Week 12 (Day 85), if a subject met the dose adjustment criteria illustrated below, the dose was reduced.

Study drug administration including the following dose reduction was performed by the designated unblind pharmacist at the study site.

Efficacy and Pharmacokinetic Endpoints:

Primary Endpoints:

The co-primary efficacy endpoints were

- Percent change from baseline (CFB) in fasting LDL-C at Week 12 (Day 85) following randomization;
- Percent CFB in fasting LDL-C at Week 16 (Day 113) following randomization.

Secondary Endpoints:

- LDL-C (actual value and CFB);
- Actual value, CFB and percent CFB in
  - Total cholesterol;
  - Apolipoprotein B (ApoB), Apolipoprotein A-1 (ApoA1), Apolipoprotein A-2 (ApoA2);
  - Lipoprotein (a) (Lp[a]);
  - High density lipoprotein–cholesterol (HDL-C);
  - Very low density lipoprotein (VLDL)-cholesterol;
  - Triglycerides (TG);
  - Non-HDL-cholesterol;
  - TC/HDL-C ratio;
  - ApoB/ApoA1 ratio;
- Proportion of subjects having LDL-C less than particular limits (<100 mg/dL, <70 mg/dL, <40 mg/dL, <25 mg/dL, <10 mg/dL);
- Adverse events (AEs) (including injection site reaction) and clinical laboratory abnormalities;
- ADA;
- Plasma bococizumab PK parameters;
- Plasma concentration of PCSK9.

Safety Evaluations:

Safety was assessed by physical examinations, neurological examinations, vital signs, electrocardiograms (ECGs), clinical laboratory results, and the spontaneous reporting of AEs in all subjects who received at least 1 dose of study drug. Additionally, blood samples were collected to assay the development of ADAs.

Statistical Methods:

The full analysis set (FAS) which included all subjects who were randomized and were administered at least 1 dose of study treatment, was the primary analysis set for efficacy analysis. Subjects were analyzed according to their randomized dose. The per-protocol analysis set (PPS) was a subset of the FAS and consisted of subjects who were compliant with the protocol. The safety analysis set included all randomized subjects who were administered at least 1 dose of study treatment. The PK concentration population was defined as subjects in the FAS who had at least 1 concentration of bococizumab, PCSK9 or atorvastatin and its active metabolites. The PK parameter analysis population was defined as subjects with full PK sampling in the FAS who had at least 1 of the bococizumab PK parameters of interest calculated. The PD analysis population was defined as subjects in the FAS who had at least 1 PD measurement.

In statistical inferences for Population A, data from Arm 5 were not used. Data from Arm 5 were only summarized descriptively.

For each population (Population A and Population B) separately, each bococizumab dose arm was compared with placebo. For the statistical test of the co-primary endpoints in each population, the following sequence testing was performed (type I error at α=0.025 1-sided, Bonferroni correction):

- Superiority of each bococizumab dose arm over placebo at Week 12 was tested at α=0.025/3.

- If superiority of a bococizumab dose arm over placebo at Week 12 was demonstrated, superiority of the bococizumab dose arm over placebo at Week 16 was tested at the 1-sided α=0.025/3.

The primary endpoint of percent CFB in LDL-C at Week 12 and Week 16, was analyzed using a mixed-effects model for repeated measures (MMRM) analysis using all observed measures. The least squares means with their 95% confidence intervals (CIs) were plotted by treatment arm. There was no imputation for missing data.

The analyses of secondary endpoints were conducted using only the FAS. For each population separately, the following lipid endpoints of absolute and percent CFB were analyzed in a MMRM. The respective baseline value of the endpoint was used in the model as a continuous covariate.

- Absolute and percent CFB in LDL-C other than the co-primary endpoints (percent CFB in LDL-C at Week 12 and Week 16)

- Absolute and percent CFB in the following endpoints: total cholesterol, ApoB, ApoA1, ApoA2, Lp(a), HDL-C, VLDL-C, TG, non-HDL-C, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio

Descriptive statistics summaries were provided by treatment and dosing day for the PK parameters, plasma concentrations of PCSK9 were summarized and the mean percent change from baseline of PCSK9 concentration were plotted by treatment arm and visit.

A 3-tier approach was used to summarize AEs.

- Tier 1 events were pre-specified events of clinical importance and were maintained in a list in the product's Safety Review Plan. For tier 1 events, the percentage of subjects with treatment-emergent adverse event, the risk difference and/or risk ratio versus placebo, its 95% CI, and p-value were provided. The CIs and p-values were not adjusted for multiplicity and were provided for screening purposes only.

- Tier 2 events were defined as common (≥5%) events. For tier 2 events, the percentage of subjects with incident AE, the risk difference and/or risk ratio versus placebo, its 95% CI were provided. The CIs were for estimation purposes only.

- Tier 3 events were all other AEs. For tier 3 events, the percentage of subjects with incident AE was provided.

The number and percentage of subjects with detectable ADAs were summarized by treatment arm and visit and also any post-baseline visit during the entire study. Subjects in Arm 5 were not included in this summary because blood for ADA was not collected in Arm 5.

The number and percentage of subjects with laboratory test abnormalities observed at any time during the study were tabulated by treatment arm following the Sponsor's data standards. Absolute values and CFB in continuous laboratory parameters were summarized by treatment arm.

Absolute values and CFB in vital sign parameters were summarized by treatment arm and visit following the sponsor's data standards.

RESULTS

Subject Disposition and Demography:

Population A:

A total of 121 subjects were randomized to either bococizumab 50 mg arm (25 subjects), bococizumab 100 mg arm (24 subjects), bococizumab 150 mg arm (24 subjects), placebo arm (26 subjects), or ezetimibe arm (22 subjects), and all of them were administered at least 1 dose of study treatment. Of the 121 treated subjects, 117 subjects (25, 23, 22, 25, and 22 subjects in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively) completed study treatment, and 4 subjects (1, 2, and 1 subject in the bococizumab 100 mg and 150 mg, and placebo arms, respectively) permanently discontinued study treatment.

The reasons for discontinuation from the study are summarized in Table 4.

Table 4. Reasons for Discontinuation From Study (Population A)

Number (%) of Subjects	Placebo	Atorvastatin + Bococizumab			Ezetimibe 10 mg	Total
		50 mg	100 mg	150 mg		
	(N=26)	(N=25)	(N=24)	(N=24)	(N=22)	(N=121)
Discontinuations						
Relation to study drug not defined	1 (3.8)	0	0	1 (4.2)	0	2 (1.7)
Other	0	0	0	1[a] (4.2)	0	1 (0.8)
Does not meet inclusion/exclusion criteria	0	0	0	0	0	0
Lost to follow-up	1 (3.8)	0	0	0	0	1 (0.8)
Not related to study drug	0	0	0	0	0	0
Adverse event	0	0	0	0	0	0
Total	1 (3.8)	0	0	1 (4.2)	0	2 (1.7)

N=number of subjects.
a. One (1) subject discontinued the study because the subject could no longer visit the study center due to the subject's parent care.

Population B:

A total of 97 subjects were randomized to bococizumab 50 mg arm (25 subjects), bococizumab 100 mg arm (25 subjects), bococizumab 150 mg arm (24 subjects), or placebo arm (23 subjects), and all of them were administered at least 1 dose of study treatment. Of the 97 treated subjects, 92 subjects (23, 22, 24, and 23 subjects in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively) completed study treatment, and 5 subjects (2 and 3 subjects in the bococizumab 50 mg and 100 mg arms, respectively) permanently discontinued the study treatment.

The reasons for discontinuation from the study are summarized in Table 5.

In Population A, the mean age ranged from 55.9 to 59.6 years across the treatment arms, and minimum and maximum ages were 31 and 80 years, respectively. Across treatment arms, the total number of male and female subjects were 68 and 53, respectively.

Table 5. Reasons for Discontinuation From Study (Population B)

Number (%) of Subjects	Placebo	Bococizumab			Total
		50 mg	100 mg	150 mg	
	(N=23)	(N=25)	(N=25)	(N=24)	(N=97)
Discontinuations					
Relation to study drug not defined	0	0	1 (4.0)	0	1 (1.0)
Other	0	0	0	0	0
Does not meet inclusion/exclusion criteria	0	0	1 (4.0)	0	1 (1.0)
Lost to follow-up	0	0	0	0	0
Not related to study drug	0	1 (4.0)	1 (4.0)	0	2 (2.1)
Adverse event	0	1 (4.0)	1 (4.0)	0	2 (2.1)
Total	0	1 (4.0)	2 (8.0)	0	3 (3.1)

N=number of subjects.

In Population B, the mean age ranged from 53.3 to 60.1 years across the treatment arms, and minimum and maximum ages were 26 and 76 years, respectively. Across treatment arms, the total number of male and female subjects were 50 and 47, respectively.

Efficacy and Pharmacokinetic Results:

Population A:

The results showed that bococizumab significantly reduced the LDL-C for all bococizumab dose arms ($p<0.001$) at Weeks 12 and 16 compared to placebo (Table 6). The adjusted mean differences from placebo in percent CFB at Week 12 in LDL-C in the FAS were −49.838%, −66.754% and −71.534% in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. The corresponding values at Week 16 were −42.293%, −56.262%, and −61.384% in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. Dose response is evident as the treatment arm differences from placebo become more pronounced as dose increases in Population A.

Additionally, the mean percent change (standard deviation [SD]) from baseline in LDL-C was −18.56% (15.968) and −20.55% (18.682) in the ezetimibe arm at Week 12 and Week 16, respectively.

Table 6. Comparison of Percent Change From Baseline at Weeks 12 and 16 in LDL-C (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population A) – FAS

Time Point	Treatment arm (Atorvastatin +)	N	Raw Mean Percent Change	Adjusted Mean Percent Change (95% CI)	Adjusted Mean Difference vs. Placebo (95% CI)	p-value[a]	
						Unadjusted for Multiplicity	Adjusted for Multiplicity
Week 12	Placebo	26	−5.91	−5.18 (−10.453, 0.102)	-	-	-
	Bococizumab 50 mg	25	−55.65	−55.01 (−60.388, −49.639)	−49.838 (−57.335, −42.340)	<0.001	<0.001
	Bococizumab 100 mg	23	−70.76	−71.93 (−77.547, −66.313)	−66.754 (−74.523, −58.986)	<0.001	<0.001
	Bococizumab 150 mg	22	−75.99	−76.71 (−82.354, −71.066)	−71.534 (−79.284, −63.784)	<0.001	<0.001
Week 16	Placebo	25	−12.10	−11.77 (−16.783, −6.749)	-	-	-
	Bococizumab 50 mg	24	−54.41	−54.06 (−59.168, −48.949)	−42.293 (−49.417, −35.168)	<0.001	<0.001
	Bococizumab 100 mg	23	−67.51	−68.03 (−73.305, −62.751)	−56.262 (−63.603, −48.921)	<0.001	<0.001
	Bococizumab 150 mg	22	−72.78	−73.15 (−78.487, −67.813)	−61.384 (−68.733, −54.035)	<0.001	<0.001

% change=100% × [LDL-C (mg/dL) − LDL-C (mg/dL) at baseline] / LDL-C (mg/dL) at baseline.
CI=confidence interval; FAS=full analysis set; LDL-C=low density lipoprotein-cholesterol; MMRM=mixed-effects model for repeated measures; N=number of subjects with non-missing values collected except the off-drug follow-up period; vs=versus.
a. p-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure=unstructured, Newton-Raphson algorithm). Unadjusted for multiplicity: 1-sided, 0.025/3 significance level. Adjusted for multiplicity: 1-sided, 0.025 significance level.

Population B

The results showed that bococizumab significantly reduced the LDL-C for all bococizumab dose arms (p<0.001) at Weeks 12 and 16 compared to placebo (Table 7). The adjusted mean differences from placebo in percent CFB at Week 12 in LDL-C in the FAS were −47.531%, −62.624%, and −64.268% in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. The corresponding values at Week 16 were −47.578%, −63.346%, and −66.691% in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At both Weeks 12 and 16, the treatment arm differences from placebo were larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm.

Table 7. Comparison of Percent Change From Baseline at Weeks 12 and 16 in LDL-C (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population B) – FAS

Time Point	Treatment arm	N	Raw Mean Percent Change	Adjusted Mean Percent Change (95% CI)	Adjusted Mean Difference vs. Placebo (95% CI)	p-value[a]	
						Unadjusted for Multiplicity	Adjusted for Multiplicity
Week 12	Placebo	23	−1.21	−1.62 (−7.246, 4.014)	-	-	-
	Bococizumab 50 mg	23	−49.37	−49.15 (−54.729, −43.565)	−47.531 (−55.511, −39.551)	<0.001	<0.001
	Bococizumab 100 mg	22	−64.64	−64.24 (−69.845, −58.635)	−62.624 (−70.557, −54.691)	<0.001	<0.001
	Bococizumab 150 mg	24	−65.89	−65.88 (−71.367, −60.401)	−64.268 (−72.128, −56.409)	<0.001	<0.001
Week 16	Placebo	23	0.39	−0.13 (−6.119, 5.868)	-	-	-
	Bococizumab 50 mg	23	−47.96	−47.70 (−53.637, −41.770)	−47.578 (−56.067, −39.088)	<0.001	<0.001
	Bococizumab 100 mg	22	−63.97	−63.47 (−69.419, −57.524)	−63.346 (−71.776, −54.915)	<0.001	<0.001
	Bococizumab 150 mg	23	−66.98	−66.82 (−72.692, −60.942)	−66.691 (−75.088, −58.295)	<0.001	<0.001

% change=100% × [LDL-C (mg/dL) − LDL-C (mg/dL) at baseline] / LDL-C (mg/dL) at baseline.
CI=confidence interval; FAS=full analysis set; LDL-C=low density lipoprotein-cholesterol; MMRM=mixed-effects model for repeated measures; N=number of subjects with non-missing values collected except the off-drug follow-up period; vs=versus.
a. p-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment × visit + baseline value × visit (covariance structure=unstructured, Newton-Raphson algorithm). Unadjusted for multiplicity: 1-sided, 0.025/3 significance level. Adjusted for multiplicity: 1-sided, 0.025 significance level.

Secondary Endpoints:

Low Density Lipoprotein-Cholesterol: The summary of observed value and change from Baseline in LDL-C (mg/dL) at Weeks 12 and 16 in Population A and Population B in FAS is summarized in Table 8 and Table 9 respectively.

Table 8. Summary of Observed Value and Change From Baseline in LDL-C (mg/dL) at Weeks 12 and 16 (Population A) – FAS

LDL-C (mg/dL) Mean (SD)	Atorvastatin +				
	Placebo	Bococizumab			Ezetimibe 10 mg
		50 mg	100 mg	150 mg	
Observed value at baseline	135.90 (24.697)	135.36 (23.652)	123.85 (20.585)	129.19 (17.769)	135.36 (24.745)
N	26	25	24	24	22
Observed value at Week 12	126.38 (21.478)	58.96 (19.650)	38.00 (19.077)	33.91 (19.400)	110.64 (33.530)
N	26	25	24	23	22
Change from baseline at Week 12	−9.52 (21.041)	−76.40 (26.447)	−85.85 (28.977)	−95.11 (21.145)	−24.73 (23.125)
N	26	25	24	23	22
Observed value at Week 16	118.88 (22.883)	62.17 (20.417)	42.88 (19.427)	38.48 (24.346)	107.32 (30.459)
N	25	24	24	23	22
Change from baseline at Week 16	−17.48 (20.767)	−73.33 (18.047)	−80.98 (28.902)	−90.54 (28.496)	−28.05 (23.663)
N	25	24	24	23	22

Baseline was defined as the mean of the last 2 non-missing measurements collected within 10 days prior to randomization. If only 1 measurement was available 10 days prior to randomization, that measurement served.
FAS=full analysis set; LDL-C=low density lipoprotein-cholesterol; N=number of subjects with non-missing values collected including the off-drug follow-up period in the analysis set; SD=standard deviation.

Table 9. Summary of Observed Value and Change From Baseline in LDL-C (mg/dL) at Weeks 12 and 16 (Population B) – FAS

LDL-C (mg/dL) Mean (SD)	Placebo	Bococizumab		
		50 mg	100 mg	150 mg
Observed value at baseline	155.22 (23.096)	164.22 (25.839)	158.00 (20.004)	159.90 (19.800)
N	23	25	25	24
Observed value at Week 12	151.30 (21.137)	86.64 (30.447)	59.83 (27.495)	54.71 (18.388)
N	23	25	23	24
Change from baseline at Week 12	−3.91 (23.632)	−77.58 (29.943)	−99.28 (32.550)	−105.19 (19.833)
N	23	25	23	24
Observed value at Week 16	153.30 (16.255)	89.44 (29.798)	61.48 (28.511)	53.39 (20.954)
N	23	25	23	23
Change from baseline at Week 16	−1.91 (20.147)	−74.78 (34.970)	−97.63 (25.545)	−107.57 (21.765)
N	23	25	23	23

Baseline was defined as the mean of the last 2 non-missing measurements collected within 10 days prior to randomization. If only 1 measurement was available 10 days prior to randomization, that measurement served.
FAS=full analysis set; LDL-C=low density lipoprotein-cholesterol; N=number of subjects with non-missing values collected including the off-drug follow-up period in the analysis set; SD=standard deviation.

Total Cholesterol:

Population A: The comparison of percent change from Baseline at Weeks 12 and 16 in total cholesterol (mg/dL) using MMRM for Population A is summarized in (Table 10).

The mean (SD) baseline total cholesterol values were 214.16 (30.658), 210.29 (21.594), 211.71 (23.065), 222.44 (31.317) and 222.84 (25.395) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −78.64 (28.525), −90.71 (31.705), −101.43 (25.436), −13.56 (22.346) and −24.02 (26.166) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −73.44 (21.242), −85.71 (30.263), −95.83 (27.765), −21.68 (23.686) and −31.11 (24.992) mg/dL. Dose-related decreases over time were observed in the bococizumab dose arms.

Table 10. Comparison of Percent Change From Baseline at Weeks 12 and 16 in Total Cholesterol (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population A) – FAS

Time Point	Treatment arm (Atorvastatin +)	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	26	−5.47	−4.70 (−8.496, −0.909)	-	-
	Bococizumab 50 mg	25	−36.26	−36.34 (−40.174, −32.515)	−31.642 (−37.039, −26.246)	<0.001
	Bococizumab 100 mg	23	−44.27	−44.58 (−48.557, −40.608)	−39.880 (−45.403, −34.358)	<0.001
	Bococizumab 150 mg	22	−49.77	−50.59 (−54.619, −46.564)	−45.889 (−51.450, −40.329)	<0.001
Week 16	Placebo	25	−9.18	−8.95 (−12.705, −5.192)	-	-
	Bococizumab 50 mg	24	−34.28	−34.32 (−38.112, −30.533)	−25.374 (−30.717, −20.032)	<0.001
	Bococizumab 100 mg	23	−42.35	−42.44 (−46.340, −38.537)	−33.490 (−38.934, −28.047)	<0.001
	Bococizumab 150 mg	22	−47.30	−47.71 (−51.687, −43.730)	−38.760 (−44.262, −33.258)	<0.001

% change=100% x [total cholesterol (mg/dL) − total cholesterol (mg/dL) at baseline] / total cholesterol (mg/dL) at baseline. MMRM=mixed-effects model for repeated measures; FAS=full analysis set; N=number of subjects with non-missing values collected except the off-drug follow-up period; CI=confidence interval.

a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment•visit + baseline value •visit (covariance structure=unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

Population B: The comparison of percent change from Baseline at Weeks 12 and 16 in total cholesterol (mg/dL) using MMRM for Population B is summarized in (Table 11).

The mean (SD) baseline total cholesterol values were 245.94 (30.425), 243.26 (21.967), 244.19 (29.987) and 242.04 (22.956) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −80.50 (31.851), −102.80 (34.603), −110.02 (24.119) and −10.52 (26.111) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −76.22 (36.301), −97.89 (29.274), −111.96 (24.871) and −5.22 (20.333) mg/dL. In all

bococizumab dose arms, total cholesterol values decreased after start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no observable CFB in the placebo arm.

Table 11. Comparison of Percent Change From Baseline at Weeks 12 and 16 in Total Cholesterol (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population B) – FAS

Time Point	Treatment Arm	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	23	−3.82	−3.92 (−8.153, 0.322)	-	-
	Bococizumab 50 mg	23	−33.99	−34.05 (−38.249, −29.855)	−30.137 (−36.110, −24.164)	<0.001
	Bococizumab 100 mg	22	−43.58	−43.44 (−47.685, −39.197)	−39.525 (−45.520, −33.531)	<0.001
	Bococizumab 150 mg	24	−45.28	−45.29 (−49.431, −41.143)	−41.372 (−47.299, −35.445)	<0.001
Week 16	Placebo	23	−1.62	−1.72 (−5.778, 2.345)	-	-
	Bococizumab 50 mg	23	−32.52	−32.56 (−36.580, −28.548)	−30.847 (−36.568, −25.127)	<0.001
	Bococizumab 100 mg	22	−41.94	−41.74 (−45.788, −37.684)	−40.019 (−45.754, −34.285)	<0.001
	Bococizumab 150 mg	23	−45.71	−45.66 (−49.662, −41.666)	−43.947 (−49.647, −38.247)	<0.001

% change = 100% x [total cholesterol (mg/dL) − total cholesterol (mg/dL) at baseline] / total cholesterol (mg/dL) at baseline.
MMRM = mixed-effects model for repeated measures; FAS = full analysis set; N = number of subjects with non-missing values collected except the off-drug follow-up period; CI = confidence interval.
a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline = treatment + visit + baseline value + treatment*visit + baseline value *visit (covariance structure = unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

ApoB

Population A:

The mean (SD) baseline ApoB values were 92.76 (14.383), 92.54 (12.362), 90.40 (12.732), 95.65 (13.229) and 96.70 (13.382) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −41.44 (16.385), −53.33 (19.097), −56.43 (17.650), −2.19 (10.703) and −9.93 (14.350) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −39.56 (12.011), −49.71 (18.699), −53.61 (16.526), −7.70 (12.436) and −13.93 (12.650) mg/dL. In all bococizumab dose arms, ApoB values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no observable CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoB were −43.265% (−50.347%, −36.183%), −57.962% (−65.167%, −50.758%) and −64.729%

(−72.039%, −57.419%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −35.288% (−42.059%, −28.516%), −48.845% (−55.709%, −41.982%) and −55.114% (−62.116%, −48.112%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline ApoB values were 106.54 (15.800), 104.02 (14.652), 101.88 (11.494) and 103.13 (13.608) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, mean (SD) CFB were −37.86 (18.125), −54.33 (21.080), −56.75 (14.506) and −1.04 (13.020) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −37.46 (18.504), −51.15 (16.855), −56.83 (15.501) and 2.48 (11.107) mg/dL. In all bococizumab dose arms, ApoB values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no observable CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoB were −36.428% (−43.451%, −29.405%), −53.296% (−60.325%, −46.267%) and −55.489% (−62.436%, −48.542%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −40.045% (−47.118%, −32.971%), −53.810% (−60.883%, −46.737%) and −58.620% (−65.640%, −51.600%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

ApoA1

Population A:

The mean (SD) baseline ApoA1 values were 137.02 (13.235), 142.60 (16.507), 140.31 (18.813), 145.65 (21.908) and 145.34 (16.171) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were 1.02 (9.479), 5.56 (10.575), 3.63 (11.155), −9.65 (9.495) and −1.11 (11.118) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were 2.52 (9.226), 6.56 (12.310), 3.72 (11.977), −7.86 (13.052) and −0.34 (10.783) mg/dL. No meaningful CFB were found in all treatment arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA1 were 6.079% (2.296%, 9.863%), 10.786% (6.976%, 14.597%) and 9.069% (5.206%, 12.932%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA1 were 5.936% (1.435%, 10.437%), 10.213% (5.702%, 14.724%) and 8.056% (3.484%, 12.629%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline ApoA1 values were 138.90 (21.808), 145.38 (19.260), 146.75 (25.587) and 150.13 (16.834) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −6.02 (11.069), −2.09 (12.040), −0.17 (11.897) and −13.83 (10.602) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −0.50 (9.512), 1.87 (9.328), −3.54 (8.982) and −10.09 (11.236) mg/dL. No meaningful CFB were found in all treatment arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA1 were 4.859% (0.541%, 9.178%), 7.331% (3.037%, 11.624%) and 9.075% (4.856%, 13.293%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA1 were 5.846% (2.312%, 9.380%), 6.910% (3.400%, 10.421%) and 4.168% (0.693%, 7.642%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

ApoA2

Population A:

The mean (SD) baseline ApoA2 values were 30.700 (3.6817), 30.223 (2.8992), 30.471 (2.8918), 31.515 (3.8373) and 32.189 (3.2855) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −0.216 (2.2274), 0.073 (2.6605), −0.450 (2.3906), −0.938 (1.8339) and 0.907 (2.6785) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −0.073 (2.0937), 0.090 (2.3882), −0.637 (2.2412), −1.104 (4.0438) and 0.370 (2.2388) mg/dL. No meaningful CFB were found in all treatment arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA2 were 2.0813% (−1.9730%, 6.1356%), 3.2608% (−0.9035%, 7.4250%) and 0.8224% (−3.3733%, 5.0182%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA2 were 2.1827% (−2.6334%, 6.9988%), 2.1376% (−2.7718%, 7.0469%) and 0.3113% (−4.6358%, 5.2584%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline ApoA2 values were 29.940 (3.3630), 31.232 (3.9681), 30.294 (3.0541) and 31.354 (3.9552) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −0.904 (2.3894), 0.354 (3.3769), 0.240 (3.1812) and −1.698 (2.9589) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −0.640 (2.0394), 0.759 (2.2739), 0.002 (2.8256) and −1.228 (3.4404) mg/dL. No meaningful CFB were found in all treatment arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA2 were 2.3254% (−3.1801%, 7.8310%), 6.1048% (0.5833%, 11.6263%) and 5.2393% (−0.2058%, 10.6845%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoA2 were 0.6078% (−4.0274%, 5.2431%), 5.7096% (1.0659%, 10.3532%) and 2.4558% (−2.1608%, 7.0724%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Lp(a)

Population A:

The mean (SD) baseline Lp(a) values were 18.452 (13.1792), 20.998 (17.2111), 18.840 (16.7289), 19.265 (14.3646) and 19.468 (18.4181) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, mean (SD) CFB were −7.492 (5.1400), −10.119 (5.4374), −10.239 (8.2471), −2.746 (3.1292) and −1.859 (3.0759) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −6.815 (4.6182), −9.815 (5.0568), −9.913 (6.6763), −3.574 (4.0251) and −2.655 (3.1725) mg/dL. In all bococizumab dose arms, Lp(a) values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. Small decreases from baseline were also found in the placebo arm, but the magnitude of the change was larger in all bococizumab dose arms compared with the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in Lp(a) were −27.4492% (−47.7872%, −7.1112%), −40.5908% (−61.3577%, −19.8240%) and −27.1630% (−48.0927%, −6.2332%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −18.3898% (−28.6698%, −8.1097%), −36.7882% (−47.2423%, −26.3341%) and −36.8453% (−47.3864%, −26.3041%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline Lp(a) values were 14.080 (11.9369), 15.458 (12.6296), 13.400 (9.0719) and 16.239 (10.1883) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −5.272 (5.1528), −7.100 (5.9402), −6.763 (5.3474) and −3.513 (3.6550) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −6.060 (4.5477), −8.074 (6.0886), −7.098 (4.5025) and −3.326 (3.4975) mg/dL. In all bococizumab dose arms, Lp(a) values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was similar among the 3 dose arms. A small decrease from baseline was also found in the placebo arm, but the magnitude of the change was larger in all bococizumab dose arms compared with the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in Lp(a) were −24.1677% (−41.8023%, −6.5332%), −19.2255% (−36.9471%, −1.5038%) and

−26.5155% (−44.0795%, −8.9515%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −32.9411% (−48.5748%, −17.3075%), −31.3176% (−47.0238%, −15.6114%) and −32.8470% (−48.4650%, −17.2289%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

HDL-C

Population A: The comparison of percent change from Baseline at Weeks 12 and 16 in HDL-C (mg/dL) using MMRM for population A is summarized in (Table 12).

The mean (SD) baseline HDL-C values were 54.58 (9.048), 54.75 (11.789), 57.00 (12.858), 58.54 (14.683) and 56.98 (9.607) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were 3.66 (6.216), 4.79 (5.568), 2.63 (5.394), −4.58 (4.573) and 2.80 (6.223) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were 3.90 (6.437), 6.29 (7.003), 2.33 (8.053), −3.28 (7.264) and 3.34 (5.702) mg/dL. In all bococizumab dose arms and ezetimibe arms, small increases in HDL-C values were observed after the start of study treatment. HDL-C values in the placebo arm slightly decreased.

Table 12. Comparison of Percent Change From Baseline at Weeks 12 and 16 in HDL-C (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population A) – FAS

Time Point	Treatment arm (Atorvastatin +)	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	26	−7.31	−6.64 (−10.142, −3.135)	-	-
	Bococizumab 50 mg	25	7.26	6.75 (3.185, 10.317)	13.389 (8.373, 18.405)	<0.001
	Bococizumab 100 mg	23	10.39	9.91 (6.197, 13.619)	16.546 (11.430, 21.663)	<0.001
	Bococizumab 150 mg	22	6.40	6.65 (2.861, 10.438)	13.288 (8.137, 18.438)	<0.001
Week 16	Placebo	25	−4.83	−3.99 (−8.599, 0.623)	-	-
	Bococizumab 50 mg	24	7.39	6.02 (1.316, 10.715)	10.004 (3.395, 16.612)	0.002
	Bococizumab 100 mg	23	12.75	12.26 (7.438, 17.089)	16.252 (9.560, 22.943)	<0.001
	Bococizumab 150 mg	22	5.42	5.58 (0.672, 10.493)	9.571 (2.847, 16.295)	0.003

% change=100% x [HDL-C (mg/dL) − HDL-C (mg/dL) at baseline]/ HDL-C (mg/dL) at baseline.
HDL-C=high density lipoprotein-cholesterol; MMRM=mixed-effects model for repeated measures; FAS=full analysis set; N=number of subjects with non-missing values collected except the off-drug follow-up period; CI=confidence interval.
a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment*visit + baseline value *visit (covariance structure=unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

Population B: The comparison of percent change from Baseline at Weeks 12 and 16 in HDL-C (mg/dL) using MMRM for population B is summarized in (Table 13).

The mean (SD) baseline HDL-C values were 57.22 (14.146), 60.40 (13.228), 62.02 (21.455) and 60.87 (10.606) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −2.18 (6.065), 1.46 (7.408), −0.02 (7.575) and −4.52 (5.191) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were 0.70 (6.489), 1.37 (7.799), −0.63 (6.995) and −4.70 (5.045) mg/dL. In all bococizumab dose arms, small increases in HDL-C values were observed except some evaluation points after the start of study treatment. HDL-C values in the placebo arm slightly decreased.

Table 13. Comparison of Percent Change From Baseline at Weeks 12 and 16 in HDL-C (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population B) – FAS

Time Point	Treatment arm	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	23	−7.16	−7.04 (−11.132, −2.956)	-	-
	Bococizumab 50 mg	23	−2.05	-2.93 (−7.017, 1.152)	4.112 (−1.671, 9.895)	0.081
	Bococizumab 100 mg	22	2.90	2.52 (−1.624, 6.656)	9.560 (3.743, 15.377)	<0.001
	Bococizumab 150 mg	24	2.35	2.78 (−1.226, 6.789)	9.826 (4.103, 15.548)	<0.001
Week 16	Placebo	23	−7.53	-7.44 (−11.450, −3.427)	-	-
	Bococizumab 50 mg	23	2.25	1.59 (−2.426, 5.607)	9.029 (3.348, 14.710)	0.001
	Bococizumab 100 mg	22	1.44	1.10 (−2.969, 5.179)	8.543 (2.827, 14.260)	0.002
	Bococizumab 150 mg	23	1.05	1.46 (−2.517, 5.436)	8.898 (3.252, 14.544)	0.001

% change=100% x [HDL-C (mg/dL) − HDL-C (mg/dL) at baseline] / HDL-C (mg/dL) at baseline.
HDL-C=high density lipoprotein-cholesterol; MMRM=mixed-effects model for repeated measures; FAS=full analysis set; N=number of subjects with non-missing values collected except the off-drug follow-up period; CI=confidence interval.
a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment•visit + baseline value•visit (covariance structure=unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

VLDL-C

Population A:

The mean (SD) baseline VLDL-C values were 19.92 (9.312), 23.79 (11.286), 20.92 (7.651), 21.42 (6.858) and 22.48 (7.869) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −5.68 (6.973), −6.17 (7.171), −6.57 (6.726), 1.15 (4.841) and −2.70 (7.069) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −4.29 (8.538), −7.25 (9.067), −5.35 (6.619), 0.34 (10.957) and −3.98 (8.873) mg/dL. In all bococizumab dose arms, decreases in VLDL-

C values were observed except some evaluation points after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was similar among the 3 dose arms. There was no meaningful CFB in the placebo and ezetimibe arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in VLDL-C were −31.880% (−45.925%, −17.836%), −29.187% (−43.571%, −14.803%) and −39.657% (−54.136%, −25.178%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −12.911% (−33.411%, 7.589%), −23.119% (−43.923%, −2.315%) and −17.159% (−38.108%, 3.789%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline VLDL-C values were 17.44 (7.509), 17.66 (9.090), 16.63 (6.273) and 17.50 (8.549) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −0.76 (5.114), −2.63 (9.497), −2.58 (7.290) and −1.07 (4.989) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −1.52 (5.771), −0.76 (9.276), −2.98 (6.998) and 1.89 (5.762) mg/dL. No meaningful CFB were found in all treatment arms.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in VLDL-C were −4.681% (−31.713%, 22.350%), 10.227% (−16.774%, 37.228%) and −2.646% (−29.206%, 23.915%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB in VLDL-C were −24.416% (−49.696%, 0.865%), −6.287% (−31.541%, 18.968%) and −32.443% (−57.400%, −7.485%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

TG

Population A: The comparison of percent change from Baseline at Weeks 12 and 16 in TG (mg/dL) Using MMRM for Population A is summarized in (Table 14).

The mean (SD) baseline TG values were 121.04 (56.152), 158.21 (71.477),127.65 (59.878), 140.23 (51.283) and 152.59 (50.105) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, mean (SD) CFB were −28.68 (41.898), −27.96 (49.754), −29.52 (40.669), 2.58 (35.796) and −10.14 (43.129) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −20.02 (41.197), −45.33 (53.285), −30.13 (48.592), −0.58 (63.896) and −23.45 (51.443) mg/dL. In all bococizumab dose arms, decreases in TG values were observed except some evaluation points after the start of study treatment. There was no meaningful CFB in the placebo arm.

Table 14. Comparison of Percent Change From Baseline at Weeks 12 and 16 in TG (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population A) – FAS

Time Point	Treatment arm (Atorvastatin +)	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	26	3.74	4.03 (−6.580, 14.633)	-	-
	Bococizumab 50 mg	25	−21.00	−21.95 (−32.842, −11.052)	−25.974 (−41.217, −10.731)	<0.001
	Bococizumab 100 mg	23	−18.52	−17.08 (−28.536, −5.630)	−21.110 (−36.665, −5.555)	0.004
	Bococizumab 150 mg	22	−26.26	−27.01 (−38.573, −15.441)	−31.034 (−46.758, −15.310)	<0.001
Week 16	Placebo	25	−3.82	−3.22 (−15.390, 8.946)	-	-
	Bococizumab 50 mg	24	−14.44	−13.28 (−25.767, −0.788)	−10.056 (−27.549, 7.437)	0.128
	Bococizumab 100 mg	23	−28.77	−27.57 (−40.486, −14.662)	−24.352 (−42.008, −6.695)	0.004
	Bococizumab 150 mg	22	−17.55	−18.22 (−31.229, −5.203)	−14.994 (−32.858, 2.870)	0.049

% change=100% x [TG (mg/dL) − TG (mg/dL) at baseline] / TG (mg/dL) at baseline.
TG=triglyceride; MMRM = mixed-effects model for repeated measures; FAS=full analysis set; N=number of subjects with non-missing values collected except the off-drug follow-up period; CI=confidence interval.
a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment•visit + baseline value•visit (covariance structure=unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

Population B: The comparison of percent change from Baseline at Weeks 12 and 16 in TG (mg/dL) Using MMRM for Population B is summarized in (Table 15).

The mean (SD) baseline TG values were 122.40 (50.578), 124.40 (59.717), 111.58 (42.354) and 130.39 (49.826) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −3.76 (37.502), −15.87 (48.341), −11.67 (42.519) and −11.22 (23.797) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −10.68 (27.488), 0.35 (48.858), −12.46 (44.128) and 6.22 (32.888) mg/dL. No meaningful CFB were found in all treatment arms.

Table 15. Comparison of Percent Change From Baseline at Weeks 12 and 16 in TG (mg/dL) Using MMRM Analysis Based on Observed Case Data (Population B) – FAS

Time Point	Treatment arm	N	Raw Mean Percent Change (%)	Adjusted Mean Percent Change (95% CI) (%)	Adjusted Mean Difference vs. Placebo (95% CI) (%)	p-Value[a]
Week 12	Placebo	23	−9.33	−7.43 (−20.958, 6.106)	-	-
	Bococizumab 50 mg	23	−0.27	0.61 (−12.777, 13.991)	8.034 (−10.948, 27.015)	0.799
	Bococizumab 100 mg	22	−8.65	−9.94 (−23.565, 3.691)	−2.511 (−21.748, 16.727)	0.398
	Bococizumab 150 mg	24	−5.21	−7.06 (−20.303, 6.188)	0.369 (−18.668, 19.407)	0.515
Week 16	Placebo	23	4.57	4.96 (−8.221, 18.145)	-	-
	Bococizumab 50 mg	23	−8.98	−8.87 (−21.976, 4.240)	−13.830 (−32.368, 4.709)	0.071
	Bococizumab 100 mg	22	1.99	1.58 (−11.796, 14.963)	−3.378 (−22.191, 15.435)	0.361
	Bococizumab 150 mg	23	−8.47	−10.07 (−23.168, 3.022)	−15.035 (−33.698, 3.629)	23

% change=100% x [TG (mg/dL) − TG (mg/dL) at baseline] / TG (mg/dL) at baseline.
TG=triglyceride; MMRM=mixed-effects model for repeated measures; FAS=full analysis set; N=number of subjects with non-missing values collected except the off-drug follow-up period; CI=confidence interval.
a. Unadjusted for multiplicity. P-value obtained from mixed model: % change from baseline=treatment + visit + baseline value + treatment•visit + baseline value•visit (covariance structure=unstructured, Newton-Raphson algorithm). 1-sided, 0.025/3 significance level.

Non-HDL-C

Population A:

The mean (SD) baseline non-HDL-C values were 159.58 (29.033), 155.54 (20.706), 154.71 (22.511), 163.90 (25.271) and 165.86 (26.655) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −82.30 (30.323), −95.50 (32.345), −104.07 (27.573), −8.98 (20.888) and −26.82 (28.796) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −77.33 (22.371), −92.00 (32.099), −98.15 (28.798), −18.40 (22.784) and −34.45 (26.242) mg/dL. In all bococizumab dose arms, non-HDL-C values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no meaningful CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in non-HDL-C were −46.772% (−53.671%, −39.874%), −59.200% (−66.257%, −52.143%) and −66.868% (−74.007%, −59.730%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −37.991% (−44.721%, −31.260%), −50.856% (−57.709%, −44.002%) and −56.354% (−63.315%, −49.393%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline non-HDL-C values were 188.72 (30.222), 182.86 (22.842), 182.17 (21.217) and 181.17 (23.577) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, the mean (SD) CFB were −78.32 (33.436), −104.26 (34.056), −110.00 (24.274) and −6.00 (24.009) mg/dL in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −76.92 (35.588), −99.26 (27.347), −111.33 (24.646) and −0.52 (20.267) mg/dL. In all bococizumab dose arms, non-HDL-C values decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no meaningful CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in non-HDL-C were −40.051% (−47.195%, −32.908%), −56.009% (−63.135%, −48.882%) and −57.576% (−64.618%, −50.533%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −43.172% (−50.417%, −35.926%), −56.698% (−63.916%, −49.480%) and −61.305% (−68.477%, −54.134%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Total Cholesterol/HDL-C ratio

Population A

The mean (SD) baseline total cholesterol/HDL-C ratio were 4.0118 (0.82813), 4.0154 (0.92478), 3.8500 (0.72414), 3.9629 (0.77435) and 4.0223 (0.81145) in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −1.6394 (0.69058), −1.9433 (0.90358), −1.9835 (0.78766), 0.0879 (0.43755) and −0.6236 (0.66072) in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −1.5671 (0.65875), −1.9113 (0.93385), −1.8704 (0.73630), −0.1560 (0.53286) and −0.7864 (0.60966). In all bococizumab dose arms, total cholesterol/HDL-C ratio decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50-mg arm. There was no meaningful CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in total cholesterol/HDL-C ratio were −41.92915% (−47.55052%, −36.30778%), −51.08604% (−56.81235%, −45.35973%) and −55.51600% (−61.29424%, −49.73777%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −33.52920% (−39.42015%, −27.63826%), −43.85680% (−49.82617%, −37.88744%) and −46.36865% (−52.40589%, −40.33142%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B

The mean (SD) baseline total cholesterol/HDL-C ratio were 4.5408 (1.11809), 4.2558 (1.15512), 4.2610 (1.08481) and 4.1076 (0.88524) in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, mean (SD) CFB were −1.4204 (0.91892), −1.8407 (0.85260), −2.0469 (0.96230) and 0.1537 (0.47755) in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −1.4648 (0.83864), −1.7563 (0.74752), −2.0461 (0.92038) and 0.2493 (0.43772). In all bococizumab dose arms, total cholesterol/HDL-C ratio decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no meaningful CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in total cholesterol/HDL-C ratio were −33.30375% (−39.41376%, −27.19373%), −47.85210% (−53.92668%, −41.77751%) and −48.65686% (−54.66060%, −42.65313%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −38.06019% (−44.29176%, −31.82863%), −48.57807% (−54.76397%, −42.39217%) and −51.87214% (−58.01968%, −45.72460%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

ApoB/ApoA1 ratio

Population A:

The mean (SD) baseline ApoB/ApoA1 ratio were 0.6846 (0.14145), 0.6606 (0.13665), 0.6567 (0.12772), 0.6687 (0.12269) and 0.6775 (0.14076) in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively. At Week 12, the mean (SD) CFB were −0.3078 (0.13144), −0.3910 (0.15635), −0.4211 (0.16147), 0.0337 (0.09054) and −0.0643 (0.11318) in the bococizumab 50 mg, 100 mg and 150 mg, placebo, and ezetimibe arms, respectively; the corresponding values at Week 16 were −0.2998 (0.12105), −0.3698 (0.16194), −0.3998 (0.15163), −0.0170 (0.10303) and −0.0998 (0.09487). In all bococizumab dose arms, ApoB/ApoA1 ratio decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was slightly larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no meaningful CFB in the placebo and ezetimibe arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoB/ApoA1 ratio were −49.42411% (−56.83019%, −42.01803%), −66.63383% (−74.16086%, −59.10681%) and −71.72901% (−79.30431%, −64.15371%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −40.52435% (−47.81299%, −33.23571%), −56.14495% (−63.52668%, −48.76322%) and −61.56370% (−69.02510%, −54.10230%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Population B:

The mean (SD) baseline ApoB/ApoA1 ratio were 0.7890 (0.17841), 0.7324 (0.16556), 0.7167 (0.16058) and 0.6980 (0.13867) in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively. At Week 12, mean (SD) CFB were −0.2626 (0.16341), −0.3748 (0.17224), −0.4042 (0.14894) and 0.0685 (0.10818) in the bococizumab 50 mg, 100 mg and 150 mg, and placebo arms, respectively; the corresponding values at Week 16 were −0.2750 (0.15604), −0.3626 (0.14553), −0.3965 (0.15431) and 0.0702 (0.09306). In all bococizumab dose arms, ApoB/ApoA1 ratio decreased after the start of study treatment. The magnitude of the changes at Weeks 12 and 16 was slightly larger in the bococizumab 100 mg and 150 mg arms compared with the bococizumab 50 mg arm. There was no meaningful CFB in the placebo arm.

At Week 12, the adjusted mean differences (95% CI) from placebo in percent CFB in ApoB/ApoA1 ratio were −43.56596% (−51.35899%, −35.77293%), −62.34926% (−70.02607%, −54.67245%) and −65.06617% (−72.65818%, −57.47415%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively. At Week 16, the adjusted mean differences (95% CI) from placebo in percent CFB were −46.34109% (−54.61427%, −38.06792%), −61.37890% (−69.52338%, −53.23443%) and −64.67274% (−72.75728%, −56.58820%) in the bococizumab 50 mg, 100 mg and 150 mg arms, respectively.

Low Density Lipoprotein-Cholesterol Proportion Analysis

The proportion of subjects reaching LDL-C of <100, <70, <40, <25 and <10 mg/dL during the treatment period in the FAS is shown in Table 16 for Population A and Table 17 for Population B.

Population A:

Table 16. Proportion of Subjects Reaching LDL-C of <100, <70, <40, <25 and <10 mg/dL During Treatment Period (Population A) – FAS

LDL-C	Percentage Responders, n/N (%)			
		Atorvastatin +		
	Placebo	Bococizumab		
		50 mg	100 mg	150 mg
<100 mg/dL	6/26 (23.1)	25/25 (100.0)	24/24 (100.0)	24/24 (100.0)
<70 mg/dL	0/26 (0.0)	24/25 (96.0)	24/24 (100.0)	24/24 (100.0)
<40 mg/dL	0/26 (0.0)	21/25 (84.0)	22/24 (91.7)	23/24 (95.8)
<25 mg/dL	0/26 (0.0)	3/25 (12.0)	16/24 (66.7)	14/24 (58.3)
<10 mg/dL	0/26 (0.0)	0/25 (0.0)	1/24 (4.2)	0/24 (0.0)

FAS=full analysis set; LDL-C=low density lipoprotein-cholesterol; n=number of responders; N=number of subjects in study population with at least 1 non-missing data at any visit during treatment period.

Population B:

Table 17. Proportion of Subjects Reaching LDL-C of <100, <70, <40, <25 and <10 mg/dL During Treatment Period (Population B) – FAS

LDL-C	Percentage Responders, n/N (%)			
	Placebo	PF-04950615		
		50 mg	100 mg	150 mg
<100 mg/dL	1/23 (4.3)	23/25 (92.0)	25/25 (100.0)	24/24 (100.0)
<70 mg/dL	0/23 (0.0)	16/25 (64.0)	23/25 (92.0)	21/24 (87.5)
<40 mg/dL	0/23 (0.0)	3/25 (12.0)	9/25 (36.0)	10/24 (41.7)
<25 mg/dL	0/23 (0.0)	0/25 (0.0)	0/25 (0.0)	5/24 (20.8)
<10 mg/dL	0/23 (0.0)	0/25 (0.0)	0/25 (0.0)	0/24 (0.0)

FAS = full analysis set; LDL-C=low density lipoprotein-cholesterol; n=number of responders; N=number of subjects in study population with at least 1 non-missing data at any visit during treatment period.

Population A and Population B:

To assess the robustness of the primary analysis, the same analysis was conducted in the PPS which was a subset of the FAS and consisted of subjects who were compliant with the protocol. The analysis revealed consistent results with those in the FAS, in which comparison of percent CFB at Weeks 12 and 16 in LDL-C showed statistically significant differences from placebo in all bococizumab dose arms in both populations.

Additionally, the study showed that subjects receiving bococizumab 100 mg or 150 mg had the high proportion of subjects obtaining LDL-C levels less than the specified limit values. In Population A, including subjects whose fasting LDL-C was ≥100 mg/dL at screening, >90% of subjects receiving bococizumab 100 mg and 150 mg had LDL-C of <40 mg/dL during the treatment period (91.7% and 95.8%, respectively), and approximately 60% of subjects had LDL-C of <25 mg/dL (66.7% and 58.3%, respectively) during the treatment period. In Population B, including subjects whose fasting LDL-C was ≥130 mg/dL at screening, approximately 90% of subjects had LDL-C of <70 mg/dL (92.0% and 87.5%, respectively), and approximately 40% of subjects had LDL-C of <40 mg/dL (36.0% and 41.7%, respectively) during the treatment period.

Consistent with LDL-C lowering, other lipids (including, total cholesterol, ApoB, Lp(a), and non-HDL-C) were also lowered in both populations. LDL-C particles were decreased across all estimated size categories (small LDL-C and large LDL-C) in both populations. In Population A, there was a trend towards increases in HDL-C.

Pharmacokinetic Results:

Pharmacokinetic parameters for Days 1 and 99 are summarized descriptively in Table 18 and Table 19 for Populations A and B respectively.

Table 18. Summary of Plasma Bococizumab Pharmacokinetic Parameters Following Single and Multiple SC Doses (Population A)

Parameter (Units)	Parameter Summary Statistics[a] by Dose and Treatment		
	Atorvastatin + Bococizumab 50 mg	Atorvastatin + Bococizumab 100 mg	Atorvastatin + Bococizumab 150 mg
Day 1 (Single dose)			
N	12	12	13
AUC_{tau} (µg•day/mL)	32.98 (57)	52.33 (49)	77.11 (43)
AUC_{tau} (dn) (µg•day/mL/mg)	0.6595 (57)	0.5233 (49)	0.5139 (43)
C_{max} (µg/mL)	3.173 (61)	5.074 (50)	7.382 (45)
C_{max} (dn) (µg/mL/mg)	0.06344 (61)	0.05074 (50)	0.04921 (45)
T_{max} (Day)	4.01 (3.00-5.96)	4.97 (3.94-7.00)	5.94 (1.94-7.00)
Day 99 (multiple dose)			
N, n	10,10	8,7	8,8
AUC_{tau} (µg•day/mL)	63.54 (40)	92.46 (127)	242.5 (81)
AUC_{tau} (dn) (µg•day/mL/mg)	1.270 (40)	0.9246 (127)	1.617 (81)
AUC_{last} (µg•day/mL)	87.86 (49)	140.3 (145)	434.2 (91)
AUC_{last} (dn) (µg•day/mL/mg)	1.759 (49)	1.403 (145)	2.892 (91)
AUC_{inf} (µg•day/mL)	94.83 (46)	176.9 (144)	469.5 (90)
C_{max} (µg/mL)	6.197(36)	8.343 (119)	21.91 (76)
C_{max} (dn) (µg/mL/mg)	0.1239 (36)	0.08343 (119)	0.1461 (76)
C_{min} (µg/mL)	2.176 (65)	4.041 (147)	12.95 (94)
T_{max} (day)	3.03 (2.92-6.98)	2.98 (1.00-4.97)	2.97 (0.964-4.99)
$t_{½}$ (day)	7.716±1.759	9.471±2.289	10.56±1.593
PTR	2.847 (42)	2.063 (25)	1.692 (16)
R_{ac}	2.027 (47)	1.889 (60)	3.176 (56)
R_{ac}, C_{max}	2.057 (46)	1.794 (64)	2.998 (49)
CL/F (L/day)	0.7870 (40)	1.082 (127)	0.6184 (81)
V_z/F (L)	8.552 (48)	12.48 (107)	9.330 (94)

AUC_{tau}=area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau=14 days; AUC_{last}=area under the concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}); AUC_{inf}=area under the concentration-time profile from time 0 extrapolated to infinite time; %CV=percent coefficient of variation; C_{max}=maximum plasma concentration; C_{min}=lowest concentration observed during the dosing interval; CL/F=apparent clearance; dn=dose normalized; PTR=peak-to-trough ratio; SC=subcutaneously; SD=standard deviation; T_{max}=time for C_{max}; $t_{½}$=terminal half-life; N=number of subjects in the treatment group and contributing to the mean; n= number of subjects where $t_{½}$, AUC_{inf} and V_z/F, were reported; R_{ac}= observed accumulation ratio; V_z/F= volume of distribution.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

Table 19. Summary of Plasma Bococizumab Pharmacokinetic Parameters Following Single and Multiple SC Doses (Population B)

Parameter (Units)	Parameter Summary Statistics[a] by Dose and Treatment		
	Bococizumab 50 mg	Bococizumab 100 mg	Bococizumab 150 mg
Day 1 (single dose)			
N	11	12	12
AUC_{tau}, (µg•day/mL)	32.97 (42)	51.49 (46)	82.05 (45)
AUC_{tau} (dn) (µg•day/mL/mg)	0.6595 (42)	0.5149 (46)	0.5472 (45)
C_{max} (µg/mL)	2.994 (44)	4.744 (47)	7.726 (42)
C_{max} (dn) (µg/mL/mg)	0.05983 (44)	0.04744 (47)	0.05156 (42)
T_{max} (day)	5.94 (3.94-6.95)	5.45 (2.95-6.94)	6.94 (2.96-14.0)
Day 99 (multiple dose)			
N, n	10,9	11, 11	12,7
AUC_{tau} (µg•day/mL)	63.74 (57)	136.6 (32)	273.5 (100)
AUC_{tau} (dn) (µg•day/mL/mg)	1.275 (57)	1.366 (32)	1.822 (100)
AUC_{last} (µg•day/mL)	96.32 (65)	220.9 (39)	486.7 (143)
AUC_{last} (dn) (µg•day/mL/mg)	1.927 (65)	2.209 (39)	3.246 (143)
AUC_{inf} (µg•day/mL)	111.7 (63)	237.4 (41)	248.4 (76)
C_{max} (µg/mL)	5.874 (55)	12.22 (29)	23.64 (88)
C_{max} (dn) (µg/mL/mg)	0.1174 (55)	0.1222 (29)	0.1575 (88)
C_{min} (µg/mL)	2.858 (64)	6.571 (40)	13.47 (139)
T_{max} (day)	2.99 (0.985-7.06)	2.98 (0.988-4.98)	4.98 (2.97-7.00)
t½ (day)	9.404±2.145	9.570±2.234	9.333±2.754
PTR	2.054 (32)	1.858 (22)	1.755 (35)
R_{ac}	1.920 (35)	2.665 (46)	3.330 (57)
R_{ac}, C_{max}	1.961 (41)	2.557 (44)	3.057 (56)
CL/F (L/day)	0.7845 (57)	0.7317 (32)	0.5490 (100)
V_z/F (L)	9.866 (65)	9.881 (39)	12.77 (45)

AUC_{tau}=area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau=14 days; AUC_{last}=area under the concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}); AUC_{inf}=area under the concentration-time profile from time 0 extrapolated to infinite time; C_{max}=maximum plasma concentration; C_{min}=lowest concentration observed during the dosing interval; CL/F=apparent clearance; dn=dose normalized; PTR=peak-to-trough ratio; %CV=percent coefficient of variation; T_{max}=time for C_{max}; $t_{½}$=terminal half-life; N=number of subjects in the treatment group and contributing to the mean; n=number of subjects where $t_{½}$, AUC_{inf} and V_z/F, were reported; R_{ac}=observed accumulation ratio; SC=subcutaneously; SD=standard deviation; V_z/F= volume of distribution.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean±SD for $t_{½}$.

Single Dose Administration (Day 1)

Following a single SC administration of bococizumab at doses of 50 mg, 100 mg, and 150 mg to hypercholesterolemic subjects, absorption of bococizumab into the systemic circulation was slow, with mean maximum plasma concentrations (C_{max}) achieved within a median T_{max} of 4-7 days postdose for both Population A and Population B across all dose levels.

There were no apparent differences in the PK profiles between Population A and Population B following a single SC dose of bococizumab. Exposure based on geometric mean area under the concentration-time profile from time 0 to time tau, the dosing interval (AUC_τ) and C_{max} values increased in a slightly less than dose proportional manner across the 50-150 mg doses. However, the dose related exposure was interpreted with caution since large variability in bococizumab was observed across all dose groups and populations.

Multiple Dose Administration (Day 99)

Following multiple SC administration of bococizumab at doses of 50 mg, 100 mg, and 150 mg Q14D for a period of 16 weeks, mean C_{max} was achieved within a median T_{max} of 3-5 days postdose across all dose levels for both Population A and Population B. Following the attainment of C_{max}, plasma concentrations appeared to decline in a mono-phasic manner, with mean terminal t½ values ranging between 8-11 days.

Bococizumab PK profiles for Population A and Population B were generally similar across all doses following multiple SC administration. An upward trend was observed in bococizumab exposure with an increase in dose with greater than dose proportional increases for both mean AUC_{τ} and C_{max} values across the 50-150 mg dose range in both subject populations. However, the dose related exposure should be interpreted with caution since large variability in bococizumab was observed across all dose groups and populations.

Exposure on Day 99 based on mean AUC_{τ} and C_{max} was higher compared to that observed on Day 1. Mean accumulation ratios on Day 99 based on mean AUC_{τ} (observed accumulation ratio [R_{ac}]) and C_{max} (R_{ac}, C_{max}) values ranged between 1.9 -3.3 and 1.8-3.1 respectively, with the higher values observed for the 150-mg dose indicating that there is some drug accumulation following multiple dosing every 2 weeks at higher doses.

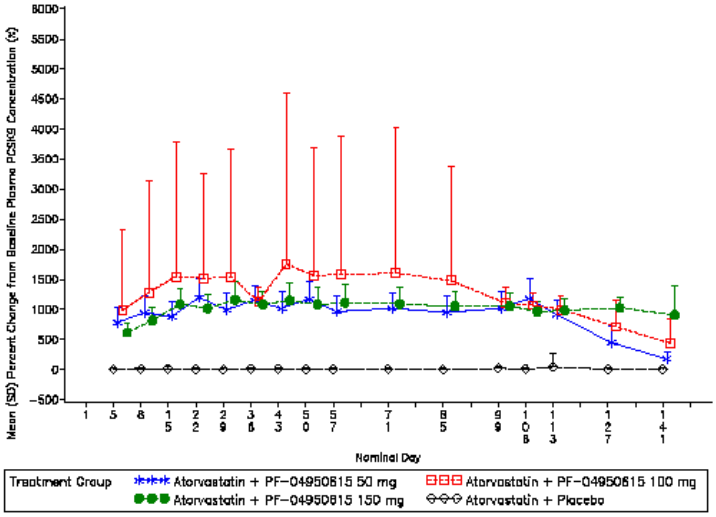
Apparent clearance (CL/F) and volume of distribution (Vz/F) geometric mean values on Day 99 were generally similar between the 2 populations, with mean CL/F and Vz/F values ranging between 0.549 -1.08 L/day and 8.6-12.8 L, respectively. The lower mean CL/F values were observed for the higher dose 150 mg.

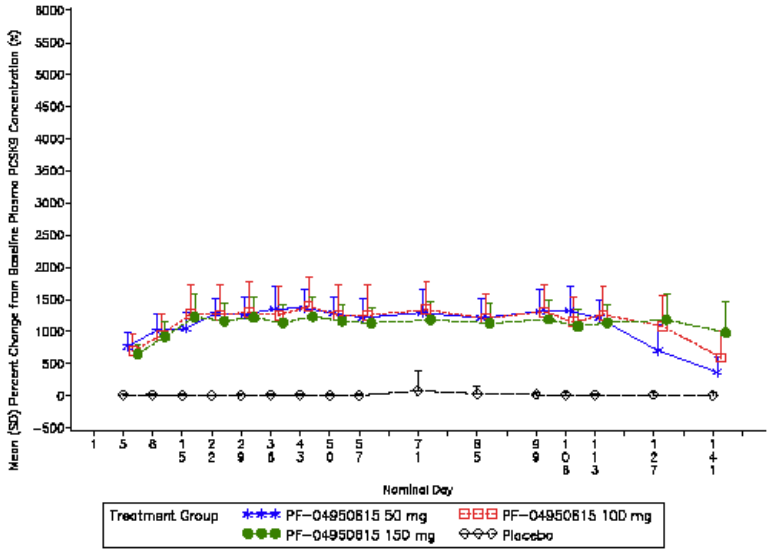
Based on median trough plasma bococizumab concentrations, steady state for the 50 mg and 100 mg doses appeared to have been reached by the third dose (Day 43) for both Population A and Population B, however, for the 150 mg dose steady state did not appear to have been reached by Day 113 (2 weeks after last dose on Day 99). However, due to the small sample size and large variability, this data was interpreted with caution.

Total Plasma PCSK9

The mean (SD) percent CFB in PCSK9 for Populations A and B, are shown in Figure 2. Similar mean (SD) total plasma PCSK9 concentrations were seen at baseline across placebo and bococizumab treatment groups with values ranging from 261.2 (72.4) to 286.0 (75.8) ng/mL in Population A and from 210.2 (48.6) to 234.4 (77.5) ng/mL in Population B. At Day 85, mean total plasma PCSK9 concentrations increased by 10- to 15-fold from baseline in Population A and by 11- to 13-fold from baseline in Population B. In both Population A and B, percent change in PCSK9 from baseline quickly reached steady state at Day 15 or Day 22 for all dose groups as shown in Figure 2. Total PCSK9 on Day 141 remained close to steady-state concentrations in the 150 mg dose group.

Figure 2. Mean (SD) Percent Change from Baseline (%CFB) in Plasma PCSK9 Concentration-Time Profiles (Upper panel: Population A; Lower panel: Population B)





CFB=change from baseline; PCSK= proprotein convertase subtilisin/kexin ; SD=standard deviation.

Safety Results:

Serious adverse events (SAEs): Treatment-emergent SAEs by system organ class (SOC) and preferred term (PT) are summarized in Table 20.

Deaths: There were no deaths reported during the study.

Discontinuations due to AEs:

Permanent Discontinuations due to AEs:

Population A

In total, 2 subjects in the bococizumab dose arms discontinued study treatment due to treatment-emergent AEs. These events included gastrointestinal disorder in 1 subject in the bococizumab 100 mg arm, and nausea and dizziness in 1 subject in the bococizumab 150 mg arm. All these events were considered by the investigator to be related to the study drug. These subjects continued and completed the study. No treatment-emergent AEs leading to treatment discontinuation were reported in the bococizumab 50 mg, placebo, and ezetimibe arms.

Population B

In total, 4 subjects in the bococizumab dose arms discontinued study treatment due to treatment-emergent AEs. These events included injection site erythema and myalgia in 1 subject each in the bococizumab 50 mg arm, and hepatic function abnormal and spinal compression fracture in 1 subject each in the bococizumab 100 mg arm. All these events were considered by the investigator to be related to the study drug, except for spinal compression fracture. No treatment-emergent AEs leading to treatment discontinuation were reported in the bococizumab 150 mg and placebo arms.

No treatment-emergent AEs which led to dose reductions or temporary discontinuation were reported in this study.

Table 20. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 17.1) Preferred Term	Population A					Population B			
	Atorvastatin +					Bococizumab			Placebo
	Bococizumab 50 mg n (%)	Bococizumab 100 mg n (%)	Bococizumab 150 mg n (%)	Placebo n (%)	Ezetimibe 10 mg n (%)	50 mg n (%)	100 mg n (%)	150 mg n (%)	n (%)
Number (%) of Subjects:									
Evaluable for Adverse Events	**25**	**24**	**24**	**26**	**22**	**25**	**25**	**24**	**23**
With Adverse Events	**1 (4.0)**	**0**	**0**	**1 (3.8)**	**0**	**0**	**1 (4.0)**	**0**	**0**
Cardiac disorders	0	0	0	1 (3.8)	0	0	0	0	0
Angina pectoris	0	0	0	1 (3.8)	0	0	0	0	0
Infections and infestations	1 (4.0)	0	0	0	0	0	0	0	0
Cellulitis	1 (4.0)	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (4.0)	0	0
Spinal compression fracture	0	0	0	0	0	0	1 (4.0)	0	0

Subjects were only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 17.1) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects.

Adverse events (AEs): Treatment-emergent nonserious AEs by SOC and PT are summarized in Table 21.

Table 21. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 17.1) Preferred Term	Population A					Population B			
	Atorvastatin +					Bococizumab			Placebo
	Bococizumab 50 mg n (%)	Bococizumab 100 mg n (%)	Bococizumab 150 mg n (%)	Placebo n (%)	Ezetimibe 10 mg n (%)	50 mg n (%)	100 mg n (%)	150 mg n (%)	n (%)
Number (%) of Subjects: Evaluable for Adverse Events With Adverse Events	**25 10 (40.0)**	**24 12 (50.0)**	**24 12 (50.0)**	**26 10 (38.5)**	**22 2 (9.1)**	**25 11 (44.0)**	**25 11 (44.0)**	**24 11 (45.8)**	**23 9 (39.1)**
General disorders and administration site conditions	2 (8.0)	6 (25.0)	9 (37.5)	2 (7.7)	0	5 (20.0)	7 (28.0)	7 (29.2)	1 (4.3)
Injection site erythema	2 (8.0)	6 (25.0)	8 (33.3)	0	0	4 (16.0)	7 (28.0)	6 (25.0)	1 (4.3)
Injection site haemorrhage	0	0	1 (4.2)	2 (7.7)	0	1 (4.0)	1 (4.0)	0	0
Injection site pain	0	1 (4.2)	0	0	0	0	0	3 (12.5)	0
Injection site pruritus	2 (8.0)	4 (16.7)	7 (29.2)	0	0	4 (16.0)	6 (24.0)	5 (20.8)	0
Injection site swelling	0	0	2 (8.3)	0	0	0	0	1 (4.2)	0
Infections and infestations	5 (20.0)	1 (4.2)	2 (8.3)	5 (19.2)	1 (4.5)	3 (12.0)	4 (16.0)	7 (29.2)	4 (17.4)
Nasopharyngitis	5 (20.0)	1 (4.2)	1 (4.2)	5 (19.2)	1 (4.5)	3 (12.0)	4 (16.0)	2 (8.3)	4 (17.4)
Pharyngitis	1 (4.0)	0	1 (4.2)	0	0	0	0	5 (20.8)	0
Injury, poisoning and procedural complications	1 (4.0)	1 (4.2)	0	1 (3.8)	0	0	3 (12.0)	0	2 (8.7)
Contusion	0	1 (4.2)	0	0	0	0	1 (4.0)	0	2 (8.7)
Fall	1 (4.0)	1 (4.2)	0	1 (3.8)	0	0	3 (12.0)	0	1 (4.3)
Investigations	1 (4.0)	0	0	0	0	0	0	2 (8.3)	0
Blood alkaline phosphatase increased	1 (4.0)	0	0	0	0	0	0	2 (8.3)	0
Musculoskeletal and connective tissue disorders	1 (4.0)	1 (4.2)	0	3 (11.5)	0	3 (12.0)	1 (4.0)	0	1 (4.3)
Back pain	0	0	0	2 (7.7)	0	0	1 (4.0)	0	0
Myalgia	1 (4.0)	1 (4.2)	0	1 (3.8)	0	3 (12.0)	0	0	1 (4.3)
Nervous system disorders	1 (4.0)	2 (8.3)	2 (8.3)	0	0	1 (4.0)	0	1 (4.2)	2 (8.7)
Dizziness	0	0	2 (8.3)	0	0	0	0	0	0
Headache	1 (4.0)	2 (8.3)	0	0	0	1 (4.0)	0	1 (4.2)	2 (8.7)
Reproductive system and breast disorders	0	0	1 (8.3)	0	0	0	0	0	0
Ejaculation disorder	0	0	1 (8.3)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (8.0)	3 (12.5)	0	2 (7.7)	0	0	0	0	0

Table 21. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 17.1) Preferred Term	Population A					Population B			
	Atorvastatin +					Bococizumab			Placebo
	Bococizumab 50 mg n (%)	Bococizumab 100 mg n (%)	Bococizumab 150 mg n (%)	Placebo n (%)	Ezetimibe 10 mg n (%)	50 mg n (%)	100 mg n (%)	150 mg n (%)	n (%)
Upper respiratory tract inflammation	2 (8.0)	3 (12.5)	0	2 (7.7)	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (4.0)	2 (8.3)	0	0	1 (4.5)	3 (12.0)	0	0	1 (4.3)
Eczema	1 (4.0)	0	0	0	1 (4.5)	3 (12.0)	0	0	1 (4.3)
Pruritus	0	2 (8.3)	0	0	0	1 (4.0)	0	0	0

Subjects were only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
MedDRA (Version 17.1) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects.

Adverse Events by Treatment Relationship:

Population A:

Treatment-emergent treatment-related AEs (number [%] of subjects) observed in ≥5% subjects in any bococizumab dose arm by PT are presented in Table 22. These events were not reported in the placebo and ezetimibe arms.

- Injection site erythema: bococizumab 50 mg, 2 (8.0%); 100 mg, 6 (25.0%); 150 mg, 8 (33.3%);
- Injection site pruritus: bococizumab 50 mg, 2 (8.0%); 100 mg, 4 (16.7%); 150 mg, 7 (29.2%);
- Injection site swelling: bococizumab 50 mg, 0; 100 mg, 0; 150 mg, 2 (8.3%);
- Pruritus: bococizumab 50 mg, 0; 100 mg, 2 (8.3%); 150 mg, 0.

The dose-response relationship was observed in the incidence of injection site erythema and injection site pruritus increased with increasing the dose of bococizumab. Injection site swelling occurred only in the highest dose (150 mg) arm.

Table 22. Treatment-Emergent Adverse Events (Treatment-Related per Investigator Causality Assessment) (Population A) – Safety Analysis Set

System Organ Class Preferred Term (MedDRA Version 17.1)	Number (%) of Subjects				
		Atorvastatin +			
	Placebo	Bococizumab			Ezetimibe 10 mg
		50 mg	100 mg	150 mg	
	(N=26)	(N=25)	(N=24)	(N=24)	(N=22)
Total	3 (11.5)	4 (16.0)	7 (29.2)	9 (37.5)	0
Cardiac disorders	0	0	0	1 (4.2)	0
Ventricular extrasystoles	0	0	0	1 (4.2)	0
Gastrointestinal disorders	0	0	1 (4.2)	1 (4.2)	0
Gastrointestinal disorder	0	0	1 (4.2)	0	0
Nausea	0	0	0	1 (4.2)	0
General disorders and administration site conditions	3 (11.5)	3 (12.0)	6 (25.0)	9 (37.5)	0
Asthenia	0	1 (4.0)	0	0	0
Injection site discolouration	1 (3.8)	0	0	0	0
Injection site erythema	0	2 (8.0)	6 (25.0)	8 (33.3)	0
Injection site haemorrhage	1 (3.8)	0	0	1 (4.2)	0
Injection site hypersensitivity	1 (3.8)	0	0	0	0
Injection site pain	0	0	1 (4.2)	0	0
Injection site pruritus	0	2 (8.0)	4 (16.7)	7 (29.2)	0
Injection site swelling	0	0	0	2 (8.3)	0
Investigations	0	1 (4.0)	0	0	0
White blood cell count decreased	0	1 (4.0)	0	0	0
Nervous system disorders	0	0	0	1 (4.2)	0
Dizziness	0	0	0	1 (4.2)	0
Skin and subcutaneous tissue disorders	0	0	3 (12.5)	0	0
Pruritus	0	0	2 (8.3)	0	0
Rash	0	0	1 (4.2)	0	0
Urticaria	0	0	1 (4.2)	0	0

Serious adverse events and nonserious adverse event results were not separated out.
Subjects were only counted once per treatment for each row.
MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects evaluable for adverse events.

Population B:

Treatment-emergent treatment-related AEs (number [%] of subjects) observed in ≥5% subjects in any bococizumab dose arm by PT are presented in Table 23 and are as follows:

- Injection site erythema: bococizumab 50 mg, 4 (16.0%); 100 mg, 7 (28.0%); 150 mg, 6 (25.0%); placebo, 1 (4.3%);
- Injection site pruritus: bococizumab 50 mg, 4 (16.0%); 100 mg, 6 (24.0%); 150 mg, 5 (20.8%); placebo, 0;
- Injection site pain: bococizumab 50 mg, 0; 100 mg, 0; 150 mg, 3 (12.5%); placebo, 0.

The incidence of injection site erythema was higher in the bococizumab dose arms compared with the placebo arm. All events of injection site pruritus were reported in the 3 bococizumab dose arms. Injection site pain occurred only in the highest dose (150 mg) arm.

Table 23. Treatment-Emergent Adverse Events (Treatment-Related per Investigator Causality Assessment) (Population B) – Safety Analysis Set

System Organ Class Preferred term (MedDRA Version. 17.1)	Number (%) of Subjects			
	Placebo	Bococizumab		
		50 mg	100 mg	150 mg
	(N=23)	(N=25)	(N=25)	(N=24)
Total	3 (13.0)	7 (28.0)	10 (40.0)	7 (29.2)
Gastrointestinal disorders	1 (4.3)	0	0	0
Abdominal pain	1 (4.3)	0	0	0
General disorders and administration site conditions	2 (8.7)	5 (20.0)	9 (36.0)	7 (29.2)
Feeling hot	0	1 (4.0)	0	0
Injection site bruising	1 (4.3)	0	1 (4.0)	0
Injection site eczema	0	1 (4.0)	0	0
Injection site erythema	1 (4.3)	4 (16.0)	7 (28.0)	6 (25.0)
Injection site haemorrhage	0	1 (4.0)	1 (4.0)	0
Injection site induration	0	0	1 (4.0)	0
Injection site nodule	0	0	1 (4.0)	0
Injection site pain	0	0	0	3 (12.5)
Injection site pruritus	0	4 (16.0)	6 (24.0)	5 (20.8)
Injection site swelling	0	0	0	1 (4.2)
Injection site warmth	0	0	0	1 (4.2)
Hepatobiliary disorders	0	0	1 (4.0)	0
Hepatic function abnormal	0	0	1 (4.0)	0
Metabolism and nutrition disorders	0	1 (4.0)	0	0
Hyperuricaemia	0	1 (4.0)	0	0
Musculoskeletal and connective tissue disorders	0	1 (4.0)	0	0
Myalgia	0	1 (4.0)	0	0
Nervous system disorders	1 (4.3)	0	0	0
Headache	1 (4.3)	0	0	0
Skin and subcutaneous tissue disorders	1 (4.3)	1 (4.0)	0	0
Eczema	1 (4.3)	1 (4.0)	0	0
Pruritus	0	1 (4.0)	0	0

Serious adverse events and nonserious adverse event results were not separated out.
Subjects were only counted once per treatment for each row.
MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects evaluable for adverse events.

Anti-drug Antibody

Incidence:

Incidence of positive ADA and positive neutralizing antibody (nAb) are summarized in Table 24. Of 147 subjects who received bococizumab treatment, 74 (50.3%) subjects were ADA positive. A dose dependent relationship was not observed for ADA incidence and there was no difference in ADA incidence between Populations A and B. Due to interference by

bococizumab concentration and/or PCSK9, nAb was assayed for only 55 of 74 ADA positive subjects. Thirty-five (35) of the 55 ADA positive subjects (63.6%) tested in the nAb assay showed positive nAb titers, resulting in an overall nAb incidence of 23.8% (out of 147 bococizumab treated subjects). The nAb incidence across the 3 dose groups ranged from 8.3% to 34.0% when Populations A and B data were combined. However since samples from 19 ADA positive subjects were not tested in the nAb assay, the true incidence of positive nAb may be underestimated.

Table 24. Immunogenicity Incidence Following Q14D SC PF-04950615 Administration

Population	Bococizumab Dose	N	ADA Positive n (%)	N[a]	nAb Positive n (%[b])	nAb Positive n/N (%[c])
Population A Uncontrolled by a stable dose of atorvastatin	50 mg	25	14 (56.0)	14	8 (32.0)	8/14 (57.1)
	100 mg	24	6 (25.0)	4	3 (12.5)	3/4 (75.0)
	150 mg	24	14 (58.3)	8	3 (12.5)	3/8 (37.5)
	All Doses	73	34 (46.6)	26	14 (19.2)	14/26 (53.8)
Population B Treatment naïve	50 mg	25	13 (52.0)	12	9 (36.0)	9/12 (75.0)
	100 mg	25	16 (64.0)	13	11 (44.0)	11/13 (84.6)
	150 mg	24	11 (45.8)	4	1 (4.2)	1/4 (25.0)
	All Doses	74	40 (54.1)	29	21 (28.4)	21/29 (72.4)
Population A + B	50 mg	50	27 (54.0)	26	17 (34.0)	17/26 (65.4)
	100 mg	49	22 (44.9)	17	14 (28.6)	14/17 (82.3)
	150 mg	48	25 (52.1)	12	4 (8.3)	4/12 (33.3)
Overall	All Doses	147	74 (50.3)	55	35 (23.8)	35/55 (63.6)

ADA Negative: Titer < 6.23; ADA Positive: Titer ≥6.23.
ADA=anti-drug antibody; nAb=neutralizing antibody; Q14D=once every 14 days; SC=subcutaneous.
a. Number of ADA positive subject data tested in the nAb assay.
b. Percent nAb positive subjects calculated using total N in each treatment arm.
c. Percent nAb positive subjects calculated as % of ADA positive subjects tested in the nAb assay.

CONCLUSIONS:

Primary Objective:

- Bococizumab administered SC Q14D to hypercholesterolemic subjects on background treatment with a stable dose of atorvastatin resulted in a statistically significant reduction in LDL-C (Weeks 12 and 16) at all 3 doses tested compared to placebo. A clear dose response was observed at Weeks 12 and 16.

- Bococizumab administered SC Q14D to hypercholesterolemic subjects who were naïve for a treatment by lipid lowering drug resulted in a statistically significant reduction in LDL-C (Weeks 12 and 16) at all 3 doses tested compared to placebo.

Secondary Objectives:

- The decreases in serum levels of other lipids (including total cholesterol, ApoB, Lp(a), and non-HDL-C) in subjects who received bococizumab were generally consistent with the effect of LDL-C lowering.

- There were no apparent differences in the PK profiles between Population A and Population B following single and multiple SC doses of bococizumab. Exposure based

on geometric mean AUC_τ and C_{max} values appeared to increase in a slightly less than dose proportional manner across the 50 mg -150 mg doses following a single SC dose on Day 1 and they appeared to increase in a greater than dose proportional manner following multiple SC doses on Day 99. However, the dose related exposure should be interpreted with caution since large variability in bococizumab was observed across all dose groups and populations. Mean terminal $t_{½}$ values ranged between 8-11 days. Apparent steady state was achieved by Day 43 for the 50 and 100 mg dose groups, however, apparent steady state was not observed for the 150 mg dose group in both populations even by Day 113.

- Similar total plasma PCSK9 concentrations were seen at baseline across placebo and bococizumab treatment groups in Population A and B, respectively. Percent change in PCSK9 from baseline quickly reached steady state at Day 15 or Day 22 for all dose groups, and the increase in mean total plasma PCSK9 concentrations from baseline ranged from 10- to 15-fold in Population A and 11- to 13-fold in Population B.

- SC Q14D administration of bococizumab at a dose of up to 150 mg in hypercholesterolemic subjects was generally well-tolerated at each dose in both populations.

- Of 147 subjects who received bococizumab treatment, 74 subjects were ADA positive. There was no apparent dose dependent relationship for ADA incidence and no difference in ADA incidence between the 2 populations.