Supplementary Appendix

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

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SUPPLEMENTARY APPENDIX: GENETIC AND PHARMACOLOGIC INACTIVATION OF ANGPTL3 AND CARDIOVASCULAR DISEASE

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Supplementary Methods

Population Studies of *ANGPTL3* Loss-of-Function Variants and Coronary Artery Disease

DiscovEHR Study: The DiscovEHR human genetics study is an ongoing study. The human genetics studies were conducted as part of the DiscovEHR study of the Regeneron Genetics Center and the Geisinger Health System. The Regeneron Genetics Center funded study sample collection, sequence data generation, and clinical and sequence data analysis. Participants were recruited from outpatient primary care and specialty clinics, the cardiac catheterization laboratory, and from patient populations referred for bariatric and abdominal vascular surgery between 2007 and 2016. Clinical laboratory measurements, International Classification of Diseases, Ninth Revision (ICD-9) disease diagnosis codes, medications, and procedural codes were extracted from the patient's electronic health records (EHR). Median values for serially measured total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides were calculated for all individuals following removal of likely spurious values that were > 3 standard deviations from the intra-individual median value for individuals with two or more measurements in the EHR. Total cholesterol and LDL-C were adjusted for lipid-altering medication use by dividing by 0.8 and 0.7, respectively, to estimate pre-treatment lipid values based on the average reduction in LDL-C and total cholesterol for the average statin dose.[1] HDL–C and triglyceride values were not adjusted for lipid-altering medication use. We calculated trait residuals for medication-adjusted LDL-C and total cholesterol, and $\log_{10}$(triglycerides) and $\log_{10}$(HDL-C) after adjustment for age, age^2, sex, and the first five principal components of ancestry.

Phenotype definitions of coronary artery disease and myocardial infarction were developed to capture cases and controls with greater specificity compared to ICD-9 codes alone.[2] See **Table S1** for codes corresponding to diagnoses, procedures, and laboratory tests below.

- Coronary artery disease cases were defined as those patients meeting any of the criteria below:

    - Discharge diagnosis code of Myocardial Infarction AND Myocardial Biomarkers above threshold for positivity (excluding results associated with encounter diagnoses for sepsis, GI bleed, hypertensive crisis, trauma or rhabdomyolysis)
    - Angiographic evidence of CAD, as defined by angiographic stenosis of any severity with fractional flow reserve ≤ 0.8, angiographic stenosis ≥ 50%, or functional evidence of inducible ischemia, as defined by stress induced or resting wall motion abnormality in a coronary distribution on stress echocardiography, or a fixed or reversible hypoperfusion in a coronary distribution on stress SPECT/PET
    - History of Percutaneous Coronary Intervention or Coronary Artery Bypass Graft by procedure or diagnosis codes
- Coronary artery disease controls were defined as those patients who are not coronary artery diseases cases AND those meeting all the criteria below:
    - No diagnosis codes (inpatient or outpatient) of Myocardial Infarction, Unstable Angina, Angina, Acute Coronary Syndrome or Coronary Artery Disease
    - No history of Percutaneous Coronary Intervention or Coronary Artery Bypass Graft by procedure or diagnosis codes
    - No Myocardial Biomarkers[2] above threshold for positivity
- Myocardial infarction (MI) cases were defined as those patients meeting the criteria below:
    - >=1 Problem List OR >=2 encounter diagnosis codes of Myocardial Infarction
- MI controls were defined as those patients who are not CAD Cases AND who are not MI Cases AND those meeting ALL the criteria below (same as Coronary Artery Disease Control definition):
    - No diagnosis codes (inpatient or outpatient) of Myocardial Infarction, Unstable Angina, Angina, Acute Coronary Syndrome or Coronary Artery Disease
    - No history of Percutaneous Coronary Intervention or Coronary Artery Bypass Graft by procedure or diagnosis codes
    - No Myocardial Biomarkers above threshold for positivity

Copenhagen General Population Studies: A total of 107,888 individuals from the Copenhagen City Heart Study, Copenhagen General Population Study and Copenhagen Ischemic Heart Disease Study were included in the analysis.[3,4] Participants were directly genotyped for the p.Ser17Ter, p.Asn121fs, p.Asn147fs, and c.495+6T>C variants with the use of the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) and TaqMan-based assays or with the use of an allele-specific PCR system (KASPer, LGC Genomics).

Penn Medicine Biobank:

Participants in the Penn Medicine Biobank were recruited from phlebotomy labs, preadmission testing, and cardiac catheterization labs at the University of Pennsylvania Health System and consented for biospecimen storage, access to electronic health record (EHR) data, and permission to recontact. A total of 7,549 participants of European ancestry were included in this analysis. Coronary artery disease case status was defined as in **Table S2**. *ANGPTL3* LoFs were extracted from exome sequence data generated at the Regeneron Genetics Center according to protocols as described below.

Duke CATHGEN: A total of 5,988 individuals from the Duke CATHeritization GENetics (CATHGEN) bio-repository were included in this analysis. CATHGEN includes clinical data and biological samples from individuals undergoing cardiac catheterization between 2001 and 2010.[5] Coronary artery disease case status was defined as in **Table S2**. *ANGPTL3* LoFs were extracted from exome sequence data generated at the Regeneron Genetics Center according to protocols as described below, with the following modification: samples were processed using the Kapa HyperPlus kit modified for the Regeneron Genetics Center's custom automation and captured with the xGen Exome Research Panel v1.0 from Integrated DNA Technologies (IDT).

TAICHI: A total of 9,058 samples from the TAIwan metaboCHIp (TAICHI) consortium,[6-8] which aims to identify genetic determinants of atherosclerosis- and metabolic-related traits in Taiwanese Chinese, were included in this analysis. Academic centers participating include Taichung Veteran's General Hospital, Tri-Service General Hospital and the National Taiwan University Hospital, and the National Health Research Institute in Taiwan for subject ascertainment and phenotyping. Coronary artery disease case status was defined as in **Table**

S2. *ANGPTL3* LoFs were extracted from exome sequence data generated at the Regeneron Genetics Center according to protocols as described below.

A summary of all studies used for meta-analysis, including definitions for coronary artery disease, for the association between *ANGPTL3* loss-of-function variants and coronary artery disease is provided in **Table S2**.

Sequencing of *ANGPTL3* and Identification of Loss-of-Function Variants

Sequence data for *ANGPTL3* were extracted from exome sequences generated at the Regeneron Genetics Center with the use of protocols as described.[2,9] In brief, sample quantity was determined by fluorescence (Life Technologies) and quality assessed by running 100ng of sample on a 2% pre-cast agarose gel (Life Technologies). The DNA samples were normalized and one aliquot was sent for genotyping (Illumina, Human OmniExpress Exome Beadchip) and another sheared to an average fragment length of 150 base pairs using focused acoustic energy (Covaris LE220). The sheared genomic DNA was prepared for exome capture with a custom reagent kit from Kapa Biosystems using a fully-automated approach developed at the Regeneron Genetics Center. A unique 6 base pair barcode was added to each DNA fragment during library preparation to facilitate multiplexed exome capture and sequencing. Equal amounts of sample were pooled prior to exome capture with NimbleGen probes (SeqCap VCRome). Captured fragments were bound to streptavidin-conjugated beads and non-specific DNA fragments removed by a series of stringent washes according to the manufacturer's recommended protocol (Roche NimbleGen). The captured DNA was PCR amplified and quantified by qRT-PCR (Kapa Biosystems). The multiplexed samples were sequenced using 75 bp paired-end sequencing on an Illumina v4 HiSeq 2500 to a coverage depth sufficient to provide greater than 20x haploid read depth of over 85% of targeted bases in 96% of samples (approximately 80x mean haploid read depth of targeted bases). Sequence reads were aligned to the human reference build GRCh37.p13, and single nucleotide variants (SNV) and insertion/deletion (indel) sequence variants were identified using the Genome Analysis Toolkit,[10] and annotated using SnpEff.[11] Variants in *ANGPTL3* were identified via positional intersection with Ensembl transcript ENST00000371129 (RefSeq mRNA sequence NM_014495.3). Loss-of-function variants were defined as any of the following: SNVs leading to

a premature stop codon, loss of a start codon, or loss of a stop codon; SNVs or indels disrupting canonical splice acceptor or donor dinucleotides; open reading frame shifting indels leading to the formation of a premature stop codon. Visual inspection of read stacks and Sanger sequencing of LoF variant regions was used to confirm these genetic variants.

Analysis of Associations of *ANGPTL3* Loss-of-Function Variants with Lipid Levels and Coronary Artery Disease

We used mixed linear models of association implemented in GCTA v1.2.4[12] to test for associations between lipid trait residuals defined as above and genotype (for aggregated *ANGPTL3* LoFs and the individual variants p.Ser17Ter, p.Asn121fs, p.Asn147fs, and c.495+6T>C) under an additive model (alleles coded 0,1 for non-carriers and heterozygotes, respectively; no homozygotes or compound heterozygotes were observed) in DiscovEHR. We included a genetic relatedness matrix (GRM), which captures population structure from ancestry and relatedness, as a random-effects covariate. The GRM was constructed from 39,858 non-MHC markers in approximate linkage equilibrium, with no greater than 1% genotype missingness, and with minor allele frequency > 0.1%. Odds ratios for coronary artery disease were estimated separately in each study using logistic regression adjusted for age, age^2, and sex (CGPS) or Firth's penalized likelihood logistic regression,[13] implemented in the *logistf* package (v1.22) in R, adjusting for age, age^2, sex, and the first five (DiscovEHR, Duke, Penn) or ten (TAICHI) principal components of ancestry. Study-level association results for *ANGPTL3* LoF variants and CAD were meta-analyzed using inverse variance weighted fixed effect meta-analysis using the *metagen* package (v.4.7.0) in R (v.3.3.1) and Mantel-Haenszel fixed-effects methods without continuity correction.

Quantification of ANGPTL3 Protein Abundance

Serum ANGPTL3 levels were measured using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA). The assay employed anti-human ANGPTL3 monoclonal antibody as the capture reagent, recombinant human ANGPTL3 as standard and anti-human ANGPTL3 polyclonal antibody conjugated with biotin as the detection reagent. The lower limit of quantitation (LLOQ) of the assay for measuring ANGPTL3 was 19.5 ng/mL in neat serum. The

assay accuracy ranged from 79.0% to 108.5% with intra- and inter-assay coefficients of variation (CV) less than 15%. To understand whether the LoFs were associated with reduced circulating levels of ANGPTL3 protein, we measured ANGPTL3 protein levels in available serum samples from 125 mutation carriers, which included carriers of each of the identified LoF variants, and 52 non-carriers matched for age, sex, and body mass index.

Antibodies

Evinacumab (REGN1500),[14] was derived using Regeneron's Velocimmune® technology platform[15] and is a fully human monoclonal antibody with high affinity to ANGPTL3 from mouse, rat, monkey, and humans. Evinacumab has a human IgG4 constant region with a stabilizing mutation in the hinge region (serine to proline in position 108 in Genbank #P01864) to minimize half-antibody formation, which is known to occur for the natural IgG4 isotype.[16] An isotype-matched antibody with irrelevant specificity was used as control antibody.

Animal Studies

APOE*3Leiden.CETP mice, a well-established model for hyperlipidemia with all features of mixed or familial dysbetalipoproteinemia and atherosclerosis,[17] were used for the evaluation of the effects of evinacumab[14,15,18] on atherosclerosis. Fifty female transgenic mice,[19] 7-10 weeks of age at the start, received a semi-synthetic cholesterol-rich Western-type diet for run-in period of 4 weeks. The mice were housed 5/cage, in clean-conventional animal rooms (relative humidity 50-60%, temperature ~21˚C, light cycle 7 am to 7 pm). At the end of run-in period mice were matched to one control group (n=20) and one evinacumab treated group (n=30) based on body weight, plasma total cholesterol, and triglycerides and treated with evinacumab or isotype-matched antibody with irrelevant specificity (control antibody) by weekly subcutaneous injections at a dose of 25 mg/kg for 13 weeks. Mice that developed a mouse anti-human antibody response were excluded, as described below. Blood samples were collected after a 4-hr fast every 2-4 weeks to measure plasma cholesterol and triglycerides. In addition, lipoprotein profiles were measured at weeks 0 and 13 in plasma samples, pooled per group. At 13 weeks mice were sacrificed and atherosclerosis development in the aortic root was measured (n=15/group) as described below. The study was conducted at TNO Metabolic Health

Research (Netherlands). All animal experiments were approved by the Institutional Animal Care and Use Committee of the Netherlands Organization for Applied Scientific Research.

Multiple administrations of human antibodies to mice often lead to development of mouse-anti-human antibodies and results in fast clearance of the human antibody from the circulation. Based on our previous knowledge, around 25-40% of mice develop such a response after evinacumab or the control antibody administration. Thus, additional animals were added to groups at the beginning of the atherosclerosis study (n=30 for evinacumab and n=20 for control antibody). This allowed us to exclude the animals that developed an anti-drug response and have n=15 per group available for the lesions analysis at the end of the study. Levels of circulating human antibodies (evinacumab and control antibody) were evaluated by human Fc ELISA at 8, 11, and 13 weeks of the study and the animals with the hFc concentrations below detection level were excluded from the study. Briefly, plates were coated with a goat anti-human Fc antibody (Sigma-Aldrich, MO) for capture. Mouse serum was then added to the plates and captured antibodies were detected by chemiluminescence using a horseradish peroxidase (HRP) conjugated goat anti-human IgG antibody (Sigma-Aldrich, MO). After that, the human-anti-mouse response was measured in samples collected at weeks 6 and 13 by a sandwich ELISA specific for the detection of anti-evinacumab or anti-control mouse IgG. Briefly, the plates were coated with 1 µg/mL of evinacumab or control Ab. Serial dilutions of serum samples were then added to the plates and the captured evinacumab or control antibody-specific mouse-anti-human antibodies were detected using horseradish peroxidase (HRP)-conjugated anti-mouse Fcγ (Sigma-Aldrich, MO). The chromogenic HRP-substrate 3,3',5,5'-tetramethylbenzidine (TMB) was used to detect HRP activity; and the resultant optical density of 450 nm (OD_{450}) was read on a Victor X4 Multimode Plate Reader (Perkin Elmer, CT). Data of binding signal versus dilution factor were analyzed by non-linear regression using GraphPad Prism software and titers were calculated. Animals with very high titers (above 100,000) were excluded from the groups. An additional single mouse was excluded from the control group as an outlier after atherosclerotic lesion analysis. In total, 6 mice were excluded from the control group and 8 mice from evinacumab group based on the criteria described above. Although lipid levels were measured in 14 control and 22 evinacumab-treated mice (**Figure 3, A-D**), we

randomly excluded 7 additional mice from the evinacumab treatment group for atherosclerotic lesion analysis. This was done to reduce group size to n=15, as was planned at the initiation of the study (**Figure 3, E-H**).

Histological Assessment of Atherosclerosis in APOE*3Leiden.CETP Mice Treated with Evinacumab or Control Antibody

Hearts were isolated, fixed in formalin, and embedded in paraffin. They were then sectioned perpendicular to the axis of the aorta, starting within the heart and working in the direction of the aortic arch. Once the aortic root was identified by the appearance of aortic valve leaflets and smooth muscle cells instead of collagen-rich tissue, serial cross sections (5 µm thick with intervals of 50 µm) were taken and mounted on AAS-coated slides. These sections were stained with hematoxylinphloxine- saffron (HPS) for histological analysis. For each mouse, atherosclerosis was measured in 4 subsequent cross sections. Each section consisted of 3 segments. The average total lesion area per cross section was then calculated.[20,21] For determination of lesion severity the lesions were classified into five categories according to the American Heart Association classification[22]: 0) no lesion, I) early fatty streak, II) regular fatty streak, III) mild plaque, IV) moderate plaque, and V) severe plaque. The percentage of each lesion type was calculated, where type I-III lesions were classified as mild lesions and type IV-V lesions were classified as severe lesions.[20,21] In the aortic root, lesion composition was determined for the severe lesions (type IV-V) as a percentage of lesion area after immunostaining with anti-alpha smooth muscle actin (1:400; PROGEN Biotechnik GmbH, Heidelberg, Germany) which cross-reacts with mouse alpha actin for smooth muscle cells (SMC), and anti-mouse Mac-3 (1:50; BD Pharmingen, the Netherlands) for macrophages followed by sirius red staining for collagen. Necrotic area was measured after HPS staining.[20,21,23] In addition to results presented in the main text, no significant differences were found in the number of lesions, undiseased segments, or lesion severity, nor did evinacumab affect monocyte recruitment to the activated endothelium (data not shown).

Evinacumab Clinical Trial Oversight and Participants

R1500-HV-1214 was a phase 1, first-in-human, randomized, ascending single-dose, placebo-controlled, double-blind study to assess the safety, tolerability, and pharmacodynamics of REGN1500 (evinacumab) administered subcutaneously (SC) or intravenously (IV) to the following 3 groups: Group A: subjects with elevations of fasting triglycerides (in mg/dL: 150 ≥ triglycerides ≤450) and/or direct measured LDL-C (LDL-C ≥100 mg/dL); Group B: subjects with elevations of fasting triglycerides ≥450 mg/dL; Group C: subjects with elevations of fasting triglycerides >1000 mg/dL on lipid lowering therapy. Only results from a pre-specified separate analysis of Group A are provided in this report; Groups B and C focused on subjects with severe hypertriglyceridema. Demographics of Group A, which consisted of healthy males and females, ages 18 to 65 years, inclusive, with elevations of triglycerides (in mg/dL: 150≤ triglycerides ≤450) and LDL-C (LDL ≥100 mg/dL) are presented in **Tables S8-S9** and patient disposition is summarized in **Figure S1**. The study was designed to assess safety as the primary endpoint. The study enrolled participants from the following three sites: Comprehensive Clinical Development Inc (3400 Enterprise Way, Miramar, FL 33025); University of Pennsylvania Perelman School of Medicine (3400 Spruce Street, Philadelphia, PA 19104); Vince and Associates Clinical Research Inc. (10103 Metcalf Ave, Overland Park, KS 66212). Safety was assessed by means of evaluation of the incidence of adverse events, assessment of vital signs, physical examination, clinical laboratory testing, and electrocardiography. Pre-specified secondary endpoints included pharmacokinetic parameters, serum concentration of ANGPTL3, and anti-drug antibody titers. Exploratory endpoints included change from baseline in serum levels of several pharmacodynamics parameters including triglyceride, LDL-C (direct measure and calculated), HDL-C, and subfractions; VLDL-C; total cholesterol; Lp(a); and apolipoproteins A-1, B and C-III. An analysis of covariance (ANCOVA) model was used to compare the treatment effect of evinacumab and the pooled placebo group; in the case of TG rank-based ANCOVA was used. The model included dose levels as a factor and baseline levels as a covariate. Missing data were imputed with the last observation carried forward (LOCF) method. The least square (LS) mean differences between each evinacumab dose versus placebo, along with the 95% CI and p-values were calculated for HDL-C and LDL-C. The Hodges-Lehmann estimator of the median difference,

the 95% CI, and p-value were reported for TG. All tests were 2-sided tests with an alpha of 0.05 being considered statistically significant. All analyses were performed using SAS version 9.2.

Supplementary Figures

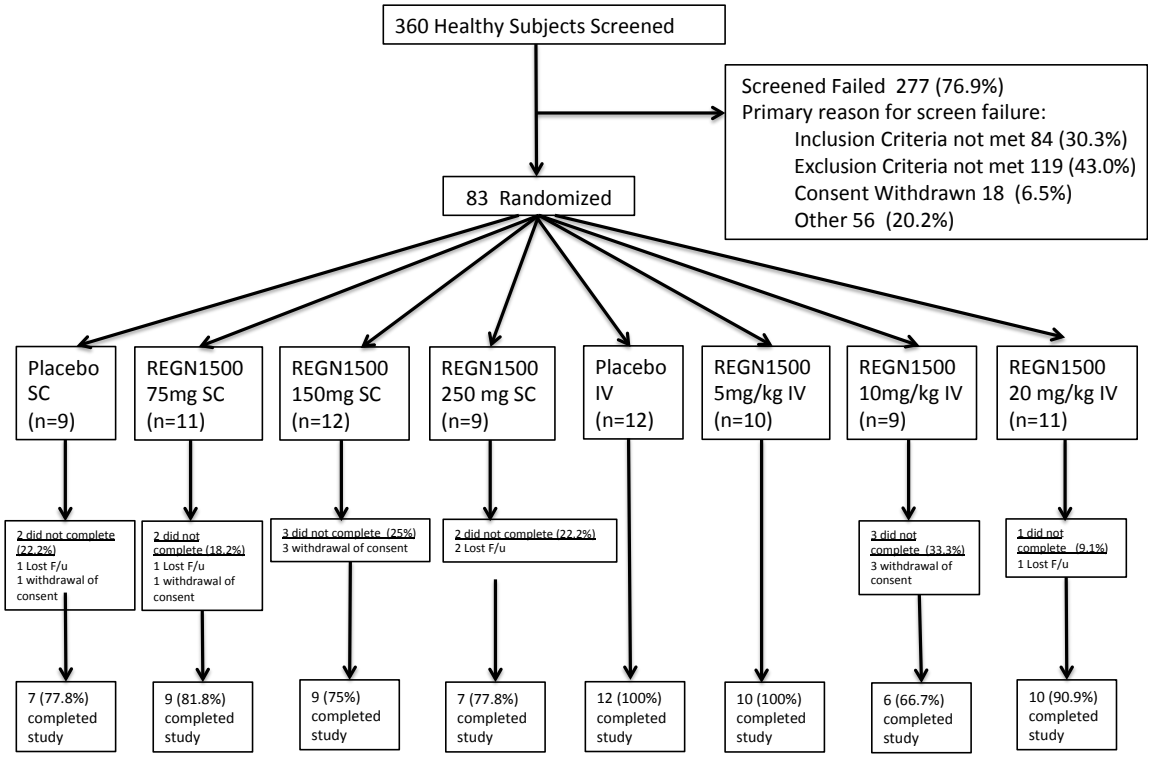
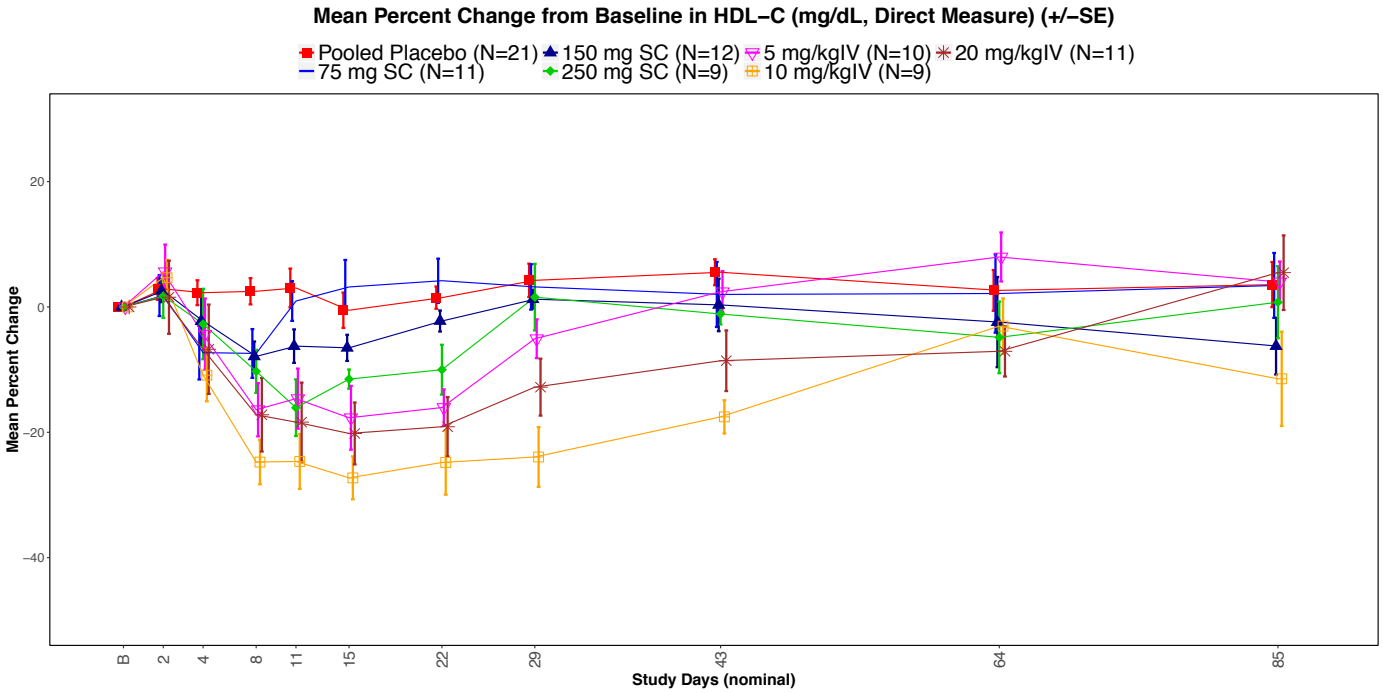


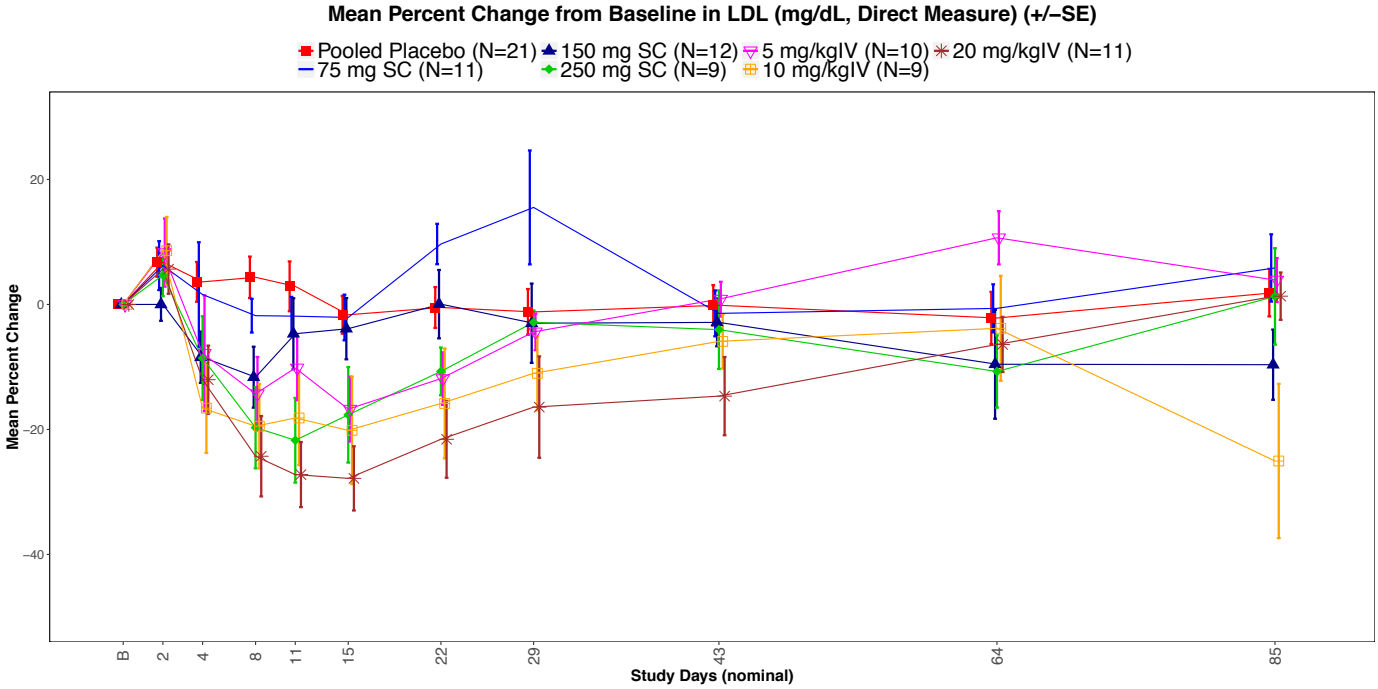
Figure S1. Patient disposition in R1500-HV-1214: Part A



Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg SC	11	11	11	9	10	10	9	8	8	9	9
150 mg SC	12	12	12	12	12	12	11	11	10	8	8
250 mg SC	9	9	9	7	7	7	7	7	7	7	6
5 mg/kgIV	9	10	10	10	10	9	10	10	10	9	9
10 mg/kgIV	9	9	9	9	8	9	8	8	8	7	6
20 mg/kgIV	11	11	11	11	11	11	11	10	10	10	10

Figure S2. Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody in Human Volunteers on HDL-C.

Mean percent change from baseline for HDL-C (mg/dL) for patients in the R1500-HV-1214 study.



Placebo	21	21	21	21	20	18	19	19	19	18	19
75 mg SC	11	11	11	9	10	10	9	8	8	9	9
150 mg SC	12	12	12	12	12	12	11	11	10	8	8
250 mg SC	9	9	9	7	7	7	7	7	7	7	6
5 mg/kgIV	9	10	10	10	10	9	10	10	10	9	9
10 mg/kgIV	9	9	9	9	8	9	8	8	8	7	6
20 mg/kgIV	11	11	11	11	11	11	11	10	10	10	10

Figure S3. Effects of Inhibition of ANGPTL3 with a Monoclonal Antibody in Human Volunteers on LDL-C.

Mean percent change from baseline for LDL-C (mg/dL) for patients in the R1500-HV-1214 study.

Supplementary Tables

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

Diagnosis, procedure, or laboratory test	Code	Description	Code system
MYOCARDIAL INFARCTION	410.0	Acute myocardial infarction, of anterolateral wall	ICD9CM
MYOCARDIAL INFARCTION	410.00	Acute myocardial infarction of anterolateral wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.01	Acute myocardial infarction of anterolateral wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.02	Acute myocardial infarction of anterolateral wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.1	Acute myocardial infarction, of other anterior wall	ICD9CM
MYOCARDIAL INFARCTION	410.10	Acute myocardial infarction of other anterior wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.11	Acute myocardial infarction of other anterior wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.12	Acute myocardial infarction of other anterior wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.2	Acute myocardial infarction, of inferolateral wall	ICD9CM
MYOCARDIAL INFARCTION	410.20	Acute myocardial infarction of inferolateral wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.21	Acute myocardial infarction of inferolateral wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.22	Acute myocardial infarction of inferolateral wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.3	Acute myocardial infarction, of inferoposterior wall	ICD9CM
MYOCARDIAL INFARCTION	410.30	Acute myocardial infarction of inferoposterior wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.31	Acute myocardial infarction of inferoposterior wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.32	Acute myocardial infarction of inferoposterior wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.4	Acute myocardial infarction, of other inferior wall	ICD9CM
MYOCARDIAL INFARCTION	410.40	Acute myocardial infarction of other inferior wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.41	Acute myocardial infarction of other inferior wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.42	Acute myocardial infarction of other inferior wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.5	Acute myocardial infarction, of other lateral wall	ICD9CM
MYOCARDIAL INFARCTION	410.50	Acute myocardial infarction of other lateral wall, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.51	Acute myocardial infarction of other lateral wall, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.52	Acute myocardial infarction of other lateral wall, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.6	Acute myocardial infarction, true posterior wall infarction	ICD9CM
MYOCARDIAL INFARCTION	410.60	True posterior wall infarction, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.61	True posterior wall infarction, initial episode of care	ICD9CM

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

MYOCARDIAL INFARCTION	410.62	True posterior wall infarction, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.7	Acute myocardial infarction, subendocardial infarction	ICD9CM
MYOCARDIAL INFARCTION	410.70	Subendocardial infarction, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.71	Subendocardial infarction, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.72	Subendocardial infarction, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.8	Acute myocardial infarction, of other specified sites	ICD9CM
MYOCARDIAL INFARCTION	410.80	Acute myocardial infarction of other specified sites, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.81	Acute myocardial infarction of other specified sites, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.82	Acute myocardial infarction of other specified sites, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.9	Acute myocardial infarction, unspecified site	ICD9CM
MYOCARDIAL INFARCTION	410.90	Acute myocardial infarction of unspecified site, episode of care unspecified	ICD9CM
MYOCARDIAL INFARCTION	410.91	Acute myocardial infarction of unspecified site, initial episode of care	ICD9CM
MYOCARDIAL INFARCTION	410.92	Acute myocardial infarction of unspecified site, subsequent episode of care	ICD9CM
MYOCARDIAL INFARCTION	411.0	Postmyocardial infarction syndrome	ICD9CM
MYOCARDIAL INFARCTION	411.89	Other acute and subacute forms of ischemic heart disease, other	ICD9CM
MYOCARDIAL INFARCTION	412	Old myocardial infarction	ICD9CM
MYOCARDIAL BIOMARKERS	10839-9	Troponin I.cardiac [Mass/volume] in Serum or Plasma	LOINC
MYOCARDIAL BIOMARKERS	42757-5	Troponin I.cardiac [Mass/volume] in Blood	LOINC
MYOCARDIAL BIOMARKERS	6598-7	Troponin T.cardiac [Mass/volume] in Serum or Plasma	LOINC
MYOCARDIAL BIOMARKERS	12187-1	Creatine kinase.MB/Creatine kinase.total in Serum or Plasma by Electrophoresis	LOINC
MYOCARDIAL BIOMARKERS	13969-1	Creatine kinase.MB [Mass/volume] in Serum or Plasma	LOINC
UNSTABLE ANGINA	411.1	Intermediate coronary syndrome	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	00.66	PTCA OR CORONARY ATHERECTOMY	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.01	RMVL COR ART OBSTR/STENT	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.02	REMOV COR ART OBSTR NOS	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.03	1 PTCA/ATHERECT W/O TL	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.04	1 PTCA/ATHERECT W TL	ICD9CM
PERCUTANEOUS CORONARY	36.05	OPN CORONARY ANGIOPLASTY	ICD9CM

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

INTERVENTION			
PERCUTANEOUS CORONARY INTERVENTION	36.06	INTRACORONARY ARTERY TL	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.07	PTCA/ATHERECT-MULT VESS	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	36.09	NON-DRUG-ELUT COR STENT	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	V45.82	PCI	ICD9CM
PERCUTANEOUS CORONARY INTERVENTION	33572	Coronary endarterectomy, open, any method, of left anterior descending, circumflex, or right coronary artery performed in conjunction with coronary artery bypass graft procedure, each vessel (List separately in addition to primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92920	Percutaneous transluminal coronary angioplasty; single major coronary artery or branch	CPT
PERCUTANEOUS CORONARY INTERVENTION	92921	Percutaneous transluminal coronary angioplasty; each additional branch of a major coronary artery (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92924	Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; single major coronary artery or branch	CPT
PERCUTANEOUS CORONARY INTERVENTION	92925	Percutaneous transluminal coronary atherectomy, with coronary angioplasty when performed; each additional branch of a major coronary artery (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92928	Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	CPT
PERCUTANEOUS CORONARY INTERVENTION	92929	Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92933	Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	CPT
PERCUTANEOUS CORONARY INTERVENTION	92934	Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92937	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel	CPT
PERCUTANEOUS CORONARY INTERVENTION	92938	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92941	Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel	CPT
PERCUTANEOUS CORONARY INTERVENTION	92943	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel	CPT
PERCUTANEOUS CORONARY INTERVENTION	92944	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft (List	CPT

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

		separately in addition to code for primary procedure)	
PERCUTANEOUS CORONARY INTERVENTION	92973	Percutaneous transluminal coronary thrombectomy mechanical (List separately in addition to code for primary procedure)	CPT
PERCUTANEOUS CORONARY INTERVENTION	92974	Transcatheter placement of radiation delivery device for subsequent coronary intravascular brachytherapy (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	36.10	AORTOCORONARY BYPASS NOS	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.11	AO-COR BYPASS-1 COR ART	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.12	AO-COR BYPASS-2 COR ART	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.13	AO-COR BYPASS-3 COR ART	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.14	AO-COR BYPASS-4+ COR ART	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.15	1 INT MAM-COR ART BYPASS	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.16	2 INT MAM-COR ART BYPASS	ICD9CM
CORONARY ARTERY BYPASS GRAFT	36.19	HRT REVASC BYP ANAST NEC	ICD9CM
CORONARY ARTERY BYPASS GRAFT	V45.81	CABG	ICD9CM
CORONARY ARTERY BYPASS GRAFT	0205T	Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33503	Repair of anomalous coronary artery from pulmonary artery origin; by graft, without cardiopulmonary bypass	CPT
CORONARY ARTERY BYPASS GRAFT	33504	Repair of anomalous coronary artery from pulmonary artery origin; by graft, with cardiopulmonary bypass	CPT
CORONARY ARTERY BYPASS GRAFT	33510	Coronary artery bypass, vein only; single coronary venous graft	CPT
CORONARY ARTERY BYPASS GRAFT	33511	Coronary artery bypass, vein only; 2 coronary venous grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33512	Coronary artery bypass, vein only; 3 coronary venous grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33513	Coronary artery bypass, vein only; 4 coronary venous grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33514	Coronary artery bypass, vein only; 5 coronary venous grafts	CPT
CORONARY ARTERY BYPASS	33516	Coronary artery bypass, vein only; 6 or more coronary venous grafts	CPT

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

GRAFT			
CORONARY ARTERY BYPASS GRAFT	33517	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33518	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33519	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33521	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33522	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33523	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33530	Reoperation, coronary artery bypass procedure or valve procedure, more than 1 month after original operation (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	33533	Coronary artery bypass, using arterial graft(s); single arterial graft	CPT
CORONARY ARTERY BYPASS GRAFT	33534	Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33535	Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33536	Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	CPT
CORONARY ARTERY BYPASS GRAFT	33548	Surgical ventricular restoration procedure, includes prosthetic patch, when performed (eg, ventricular remodeling, SVR, SAVER, Dor procedures)	CPT
CORONARY ARTERY BYPASS GRAFT	35500	Harvest of upper extremity vein, 1 segment, for lower extremity or coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	35600	Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	4110F	Internal mammary artery graft performed for primary, isolated coronary artery bypass graft procedure (CABG)	CPT
CORONARY ARTERY BYPASS GRAFT	4115F	Beta blocker administered within 24 hours prior to surgical incision (CABG)	CPT
CORONARY ARTERY BYPASS GRAFT	92937	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel	CPT
CORONARY ARTERY BYPASS GRAFT	92938	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft (List separately in addition to code for primary procedure)	CPT
CORONARY ARTERY BYPASS GRAFT	92943	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; single vessel	CPT

Table S1. Diagnosis, procedure, and laboratory code components of coronary artery disease case definition in DiscovEHR

CORONARY ARTERY BYPASS GRAFT	92944	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft (List separately in addition to code for primary procedure)	CPT
ANGINA	413	Angina pectoris	ICD9CM
ANGINA	413.0	Angina decubitus	ICD9CM
ANGINA	413.1	Prinzmetal angina	ICD9CM
ANGINA	413.9	Other and unspecified angina pectoris	ICD9CM
ACUTE CORONARY SYNDROME	411.1	Intermediate coronary syndrome	ICD9CM
ACUTE CORONARY SYNDROME	411.81	Acute coronary occlusion without myocardial infarction	ICD9CM
ACUTE CORONARY SYNDROME	411.89	Other acute and subacute forms of ischemic heart disease, other	ICD9CM
CORONARY ARTERY DISEASE	414.0	Coronary atherosclerosis	ICD9CM
CORONARY ARTERY DISEASE	414.00	Coronary atherosclerosis of unspecified type of vessel, native or graft	ICD9CM
CORONARY ARTERY DISEASE	414.01	Coronary atherosclerosis of native coronary artery	ICD9CM
CORONARY ARTERY DISEASE	414.02	Coronary atherosclerosis of autologous vein bypass graft	ICD9CM
CORONARY ARTERY DISEASE	414.03	Coronary atherosclerosis of nonautologous biological bypass graft	ICD9CM
CORONARY ARTERY DISEASE	414.04	Coronary atherosclerosis of artery bypass graft	ICD9CM
CORONARY ARTERY DISEASE	414.05	Coronary atherosclerosis of unspecified bypass graft	ICD9CM
CORONARY ARTERY DISEASE	414.06	Coronary atherosclerosis of native coronary artery of transplanted heart	ICD9CM
CORONARY ARTERY DISEASE	414.07	Coronary atherosclerosis of bypass graft (artery) (vein) of transplanted heart	ICD9CM
CORONARY ARTERY DISEASE	414.1	Aneurysm and dissection of heart	ICD9CM
CORONARY ARTERY DISEASE	414.10	Aneurysm of heart (wall)	ICD9CM
CORONARY ARTERY DISEASE	414.11	Aneurysm of coronary vessels	ICD9CM
CORONARY ARTERY DISEASE	414.12	Dissection of coronary artery	ICD9CM
CORONARY ARTERY DISEASE	414.19	Other aneurysm of heart	ICD9CM
CORONARY ARTERY DISEASE	414.2	Chronic total occlusion of coronary artery	ICD9CM
CORONARY ARTERY DISEASE	414.3	Coronary atherosclerosis due to lipid rich plaque	ICD9CM
CORONARY ARTERY DISEASE	414.8	Other specified forms of chronic ischemic heart disease	ICD9CM
CORONARY ARTERY DISEASE	414.9	Chronic ischemic heart disease, unspecified	ICD9CM

Table S2. Study Populations For Association Between Loss of Function Variants in *ANGPTL3* And Coronary Artery Disease

Study	CAD case definition	Ancestry	CAD Cases	CAD-free Controls	*ANGPTL3 L*oF ascertainment
DiscovEHR	History of coronary revascularization in the electronic health record or angiographic evidence of obstructive coronary atherosclerosis (>50% stenosis in at least one major epicardial vessel from catheterization report) or history of acute coronary syndrome (ICD-9 codes 410,* 412*) with accompanying biochemical or electrocardiographic evidence.	European	13,102	40,430	Whole exome sequencing
CGPS/CCHS/CIHDS	Patients from the Copenhagen Ischemic Heart Disease Study with verified coronary artery disease and participants from the CCHS and CGPS with myocardial infarction.	European	11,172	96,716	Targeted genotyping
Penn	Angiographically-confirmed coronary artery disease (stenosis > 50% in any epicardial vessel), history of revascularization, or one or more diagnosis codes corresponding to acute or old myocardial infarction (ICD-9 410* or, 412*), or two or more diagnosis codes on separate calendar days corresponding to chronic ischemic heart disease (ICD-9 414*).	European	3,991	3,558	Whole exome sequencing
Duke	Angiographically-confirmed coronary artery disease (stenosis > 50% in any epicardial vessel), or history of revascularization or myocardial infarction.	European	4,519	1,469	Whole exome sequencing
TAICHI	Angiographically-confirmed coronary artery disease (stenosis > 50% in any epicardial vessel), or history of revascularization or myocardial infarction.	Taiwanese Chinese	3,635	5,423	Whole exome sequencing

Abbreviations: CAF, cumulative allele frequency; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CIHDS, Copenhagen Ischemic Heart Disease Study; CI, confidence interval; LoF, loss-of-function variant.

Table S3. Loss of Function Variants in *ANGPTL3*

Chromosome	Position	Reference allele	Alternate allele	Mutation	Variant Type	Carriers
1	63063287	CC	GA	p.Ser17Ter	Nonsense	21
1	63063526	A	T	p.Lys97Ter	Nonsense	2
1	63063556	C	T	p.Gln107Ter	Nonsense	1
1	63063592	GAACTC	G	p.Asn121fs	Frameshift indel	91
1	63063667	CAACT	C	p.Asn147fs	Frameshift indel	52
1	63063738	T	C	c.495+6T>C	Splice region	57
1	63064442	CA	C	p.Gln191fs	Frameshift indel	1
1	63066839	GA	G	p.Asn232fs	Frameshift indel	7
1	63066869	T	C	c.721+2T>C	Splice donor	1
1	63068052	G	GT	c.931+2dupT	Splice donor	3
1	63069895	AG	A	p.Gly397fs	Frameshift indel	3
1	63070316	G	A	p.Trp404Ter	Nonsense	6
1	63070433	C	CT	p.Ile444fs	Frameshift indel	1
Total						**246**

Table S4. Clinical Characteristics of DiscovEHR Participants According to *ANGPTL3* Loss-of-Function Variant Status

	***ANGPTL3* loss of function variant carriers (n=246)**	**Sequenced non-carriers (n = 58,089)**
Age, yr, median (IQR)*	63 (49-73)	61 (48-72)
Female sex, n (%)	141 (57%)	34,548 (59%)
BMI, kg/m2, median (IQR)	30 (26-34)	30 (26-36)
Current smoker, n (%)	28 (11%)	10,092 (17%)
Medications		
Lipid lowering medication, n (%)	72 (29%)	22,111 (38%)
Anti-hypertensive medication, n (%)	140 (57%)	34,976 (60%)
Hypoglycemic medication, n (%)	39 (16%)	9,651 (17%)
Medical history		
Hypertension, n (%)	133 (54%)	34,318 (59%)
Diabetes mellitus type 2, n (%)	56 (23%)	12,829 (22%)

*At last encounter

Abbreviations: BMI, body mass index; IQR, interquartile range; kg, kilograms; yr, year.

Table S5. Associations Between Loss of Function Variants in *ANGPTL3* And Fasting Lipid Levels in DiscovEHR

Trait	N	β	SE	P value
Total cholesterol, mg/dl	45,068	-24.42	2.87	1.74E-17
HDL-C, $\log_{10}$(mg/dl)	45,226	-0.02	0.01	1.74E-02
LDL-C, mg/dl	44,819	-11.16	2.66	2.82E-05
Triglycerides, $\log_{10}$(mg/dl)	45,206	-0.14	0.01	2.52E-21

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SE, standard error.

Actual values are displayed in **Figure 1.**

LDL-C and total cholesterol were adjusted for lipid-lowering medication use by dividing by 0.7 and 0.8, respectively.

*According to mixed linear model association analysis of lipid residuals after adjustment for age, age^2, sex, and the first five principal components of ancestry. A genetic relatedness matrix was included as a random effects covariate. Triglycerides and HDL-C were $\log_{10}$ transformed prior to analysis.

Table S6. Associations Between Individual Loss of Function Variants in *ANGPTL3* And Fasting Lipid Levels in DiscovEHR

	Total cholesterol, mg/dl			HDL-C, log_{10} (mg/dl)			LDL-C, mg/dl			TGs, log_{10} (mg/dl)		
Variant	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**	**β**	**SE**	**P value**
p.S17X (n=21 heterozygotes)	-31.74	9.57	9.09E-04	-0.05	0.03	4.01E-02	-14.19	8.87	1.10E-01	-0.13	0.05	6.01E-03
p.N121fs (n=91 heterozygotes)	-25.05	4.77	1.48E-07	0.00	0.01	9.87E-01	-12.46	4.42	4.79E-03	-0.17	0.02	6.70E-12
p.N147fs (n=52 heterozygotes)	-33.06	6.06	4.99E-08	-0.02	0.02	3.37E-01	-18.65	5.62	9.00E-04	-0.16	0.03	2.17E-07
c.495+6T>C (n=57 heterozygotes)	-12.32	5.97	3.92E-02	-0.02	0.02	1.46E-01	-0.82	5.53	8.82E-01	-0.11	0.03	1.61E-04

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SE, standard error; SE, standard error; TGs, triglycerides. LDL-C and total cholesterol were adjusted for lipid-lowering medication use by dividing by 0.7 and 0.8, respectively.

*According to mixed linear model association analysis of lipid residuals after adjustment for age, age^2, sex, and the first five principal components of ancestry. A genetic relatedness matrix was included as a random effects covariate. Triglycerides and HDL-C were log_{10} transformed prior to analysis.

Table S7. Associations Between Individual Loss of Function Variants in *ANGPTL3* And Coronary Artery Disease in DiscovEHR

Variant	Case heterozygotes	Control heterozygotes	Carrier frequency-cases (%)	Carrier frequency-controls (%)	Odds ratio (95% CI)*	P value*
p.S17X	3/13,102	15/40,430	0.02	0.04	0.44 (0.11-1.36)	1.59E-01
p.N121fs	16/13,102	71/40,430	0.12	0.18	0.56 (0.30-0.99)	4.76E-02
p.N147fs	9/13,102	39/40,430	0.07	0.10	0.57 (0.25-1.22)	1.54E-01
c.495+6T>C	10/13,102	40/40,430	0.08	0.10	0.69 (0.31-1.44)	3.34E-01

Abbreviations: CAF, cumulative allele frequency; CI, confidence interval; pLOF, predicted loss-of-function variant.
Odds ratios are from Firth's penalized likelihood logistic regression adjusted for age, age^2, sex, and the first five principal components of ancestry.

Table S8. Baseline Demographics and Clinical Characteristics of Healthy Volunteers Treated with SQ Evinacumab

	Placebo (n=9)	Evinacumab 75 mg (n=11)	Evinacumab 150 mg (n=12)	Evinacumab 250 mg (n=9)
Age, mean (SD), yr	46.9 (8.87)	45.7 (12.63)	43.8 (10.22)	48.6 (8.97)
Ethnicity				
Hispanic or Latino, n (%)	9 (100%)	9 (81.8%)	12 (100%)	8 (88.9%)
Not Hispanic or Latino, n (%)	0	2 (18.2%)	0	1 (11.1%)
Race				
Black or African American, n (%)	0	0	0	1 (11.1%)
White, n (%)	9 (100%)	11 (100%)	12 (100%)	8 (88.9%)
Female, n (%)	2 (22.2%)	6 (54.5%)	3 (25.0%)	5 (55.6%)
Height, mean (SD), cm	171.22 (5.041)	163.78 (10.251)	171.59 (7.036)	166.28 (10.007)
Body mass, mean (SD), kg	81.08 (11.486)	76.35 (9.187)	85.08 (15.625)	78.51 (16.467)
Body mass index, mean (SD), kg/m2	27.71 (4.141)	28.49 (2.756)	28.74 (4.047)	28.12 (3.049)
Fasting lipids				
LDL-C, direct measured, mean (SD), mg/dl	143.67 (24.255)	139.33 (37.169)	136.38 (31.933)	149.78 (28.348)
LDL-C, calculated, mean (SD), mg/dl	131.61 (24.301)	129.66 (31.596)	123.22 (30.833)	137.03 (30.699)
Triglycerides, median (Q1-Q3) mg/dl	183.5 (126-217)	161.5 (126-227)	171.75 (119.25-202.75)	208.5 (149.5-268)
HDL-C, mean (SD), mg/dl	48.00 (8.452)	49.30 (12.805)	47.36 (15.692)	54.50 (23.448)
Non-HDL cholesterol, mean (SD), mg/dl	168.83 (21.588)	164.12 (28.377)	159.13 (35.595)	175.94 (45.120)
Total cholesterol, mean (SD), mg/dl	216.83 (25.137)	213.42 (32.270)	206.49 (39.298)	230.44 (31.196)
VLDL-cholesterol, median (Q1-Q3) mg/dl	37 (26-50)	30 (25.5-39)	38.5 (23.25-44.5)	37.5 (29.5-39)
ApoA1, mean (SD), mg/dl	143.11 (18.889)	145.85 (22.462)	136.82 (24.018)	150.00 (26.424)
ApoB, mean (SD), mg/dl	121.39 (16.744)	119.00 (21.404)	115.50 (28.960)	125.39 (28.776)
ApoB/ApoA1 Ratio	0.86 (0.151)	0.83 (0.189)	0.86 (0.220)	0.87 (0.271)
Hs-CRP, median (Q1-Q3) mg/L	1.59 (1.34-3.24)	1.81 (0.7-3.59)	1.35 (0.83-2.385)	1.09 (0.83-3.2)

Cohort includes subjects with elevations of TG (in mg/dL: 150<= TG<=450) and/or LDL-C (LDL-C >=100 mg/dL). [1] Age is calculated as an integer value indicating the number of full years passed since birth at screening visit. Baseline for triglycerides is defined as the median of the available measurements taken prior to the administration of evinacumab (including screening). For all other variables, the baseline is defined as the average of Day -1 and Day 1 pre-dose measurements values.

Table S9. Baseline Demographics and Clinical Characteristics of Healthy Volunteers Treated with IV Evinacumab

	Placebo (n=12)	Evinacumab 5 mg/kg (n=10)	Evinacumab 10 mg/kg (n=9)	Evinacumab 20 mg/kg (n=11)
Age, mean (SD), yr	41.5 (11.16)	49.2 (9.99)	43.1 (8.49)	51.5 (8.31)
Ethnicity				
Hispanic or Latino, n (%)	7 (58.3%)	7 (70.0%)	8 (88.9%)	1 (9.1%)
Not Hispanic or Latino, n (%)	5 (41.7%)	3 (30.0%)	1 (11.1%)	10 (90.9%)
Race				
Black or African American, n (%)	5 (41.7%)	1 (10.0%)	1 (11.1%)	2 (18.2%)
White, n (%)	7 (58.3%)	9 (90.0%)	8 (88.9%)	9 (81.8%)
Female, n (%)	2 (16.7%)	5 (50.0%)	0	1 (9.1%)
Height, mean (SD), cm	175.19 (9.758)	164.98 (9.678)	174.10 (8.619)	172.30 (8.232)
Body mass, mean (SD), kg	92.98 (16.246)	79.60 (13.131)	85.87 (14.924)	86.75 (10.564)
Body mass index, mean (SD), kg/m2	30.16 (3.640)	29.21 (3.915)	28.27 (4.031)	29.16 (1.834)
Fasting lipids				
LDL-C, direct measured, mean (SD), mg/dl	130.44 (23.547)	138.77 (28.462)	142.56 (20.430)	132.64 (29.318)
LDL-C, calculated, mean (SD), mg/dl	120.87 (23.896)	137.52 (30.876)	134.00 (23.688)	124.86 (24.540)
Triglycerides, median (Q1-Q3) mg/dl	174 (80.5-246)	193 (134-212)	188 (143-250.5)	161.5 (93-244)
HDL-C, mean (SD), mg/dl	42.17 (11.873)	42.78 (14.552)	44.83 (19.923)	43.00 (4.899)
Non-HDL cholesterol, mean (SD), mg/dl	158.40 (23.959)	175.68 (42.805)	179.50 (29.667)	160.55 (23.897)
Total cholesterol, mean (SD), mg/dl	200.57 (24.071)	218.47 (38.910)	224.33 (28.632)	203.55 (26.142)
VLDL-cholesterol, median (Q1-Q3) mg/dl	37 (18-52.92)	38.5 (20.5-56)	37.5 (27.5-57)	35 (21-49)
ApoA1, mean (SD), mg/dl	129.79 (21.041)	131.48 (21.490)	135.72 (34.085)	135.55 (11.890)
ApoB, mean (SD), mg/dl	117.49 (16.983)	129.33 (31.654)	135.00 (16.136)	114.59 (16.569)
ApoB/ApoA1 Ratio	0.93 (0.227)	1.02 (0.311)	1.05 (0.267)	0.85 (0.129)
Hs-CRP, median (Q1-Q3) mg/L	2.34 (1.02-3.73)	2.22 (0.91-4.33)	2.35 (1.54-4.47)	1.32 (1-2.7)

Cohort includes subjects with elevations of TG (in mg/dL: 150<= TG <=450) and/or LDL-C (LDL-C >=100 mg/dL). [1] Age is calculated as an integer value indicating the number of full years passed since birth at screening visit. Baseline for triglycerides is defined as the median of the available measurements taken prior to the administration of evinacumab (including screening). For all other variables, the baseline is defined as the average of Day -1 and Day 1 pre-dose measurements values.

Table S10. Summary of Treatment Emergent Adverse Events in Healthy Volunteers Treated with Evinacumab

	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Number of TEAEs	9	8	8	11	9	17	9	15	18	68	86
Number of TEAEs related to study drug	0	4	3	2	1	9	7	3	1	28	29
Number of serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Number of TEAEs resulting in discontinuation [1]	0	0	0	0	0	0	0	0	0	0	0
Subjects with no TEAEs	5 (55.6%)	8 (72.7%)	7 (58.3%)	3 (33.3%)	7 (58.3%)	5 (50.0%)	2 (22.2%)	5 (45.5%)	12 (57.1%)	30 (48.4%)	42 (50.6%)
Subjects with at least one TEAE	4 (44.4%)	3 (27.3%)	5 (41.7%)	6 (66.7%)	5 (41.7%)	5 (50.0%)	7 (77.8%)	6 (54.5%)	9 (42.9%)	32 (51.6%)	41 (49.4%)
Subjects with study drug related TEAEs	0	2 (18.2%)	2 (16.7%)	1 (11.1%)	1 (8.3%)	3 (30.0%)	5 (55.6%)	2 (18.2%)	1 (4.8%)	15 (24.2%)	16 (19.3%)
Subjects with serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
Subjects with TEAEs resulting in discontinuation [1]	0	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: IV, intravenous, SC, subcutaneous; TEAE; Treatment Emergent Adverse Events.
[1] Refers to subjects who permanently discontinued study drug (from AE panel).

Table S11. Summary of TEAEs by System Organ Class and Preferred Term – Subjects in Group A (All Subjects)

System Organ Class MedDRA Preferred Term	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Subjects with at least one TEAE	4 (44.4%)	3 (27.3%)	5 (41.7%)	6 (66.7%)	5 (41.7%)	5 (50.0%)	7 (77.8%)	6 (54.5%)	9 (42.9%)	32 (51.6%)	41 (49.4%)
Infections and infestations	3 (33.3%)	2 (18.2%)	1 (8.3%)	1 (11.1%)	3 (25.0%)	1 (10.0%)	0	1 (9.1%)	6 (28.6%)	6 (9.7%)	12 (14.5%)
Upper respiratory tract infection	1 (11.1%)	1 (9.1%)	1 (8.3%)	1 (11.1%)	0	0	0	1 (9.1%)	1 (4.8%)	4 (6.5%)	5 (6.0%)
Viral upper respiratory tract infection	1 (11.1%)	1 (9.1%)	0	0	1 (8.3%)	0	0	0	2 (9.5%)	1 (1.6%)	3 (3.6%)
Molluscum contagiosum	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
Pharyngitis	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Rhinitis	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Viral rhinitis	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Investigations	0	1 (9.1%)	0	3 (33.3%)	0	1 (10.0%)	4 (44.4%)	1 (9.1%)	0	10 (16.1%)	10 (12.0%)
Alanine aminotransferase increased	0	0	0	1 (11.1%)	0	1 (10.0%)	4 (44.4%)	1 (9.1%)	0	7 (11.3%)	7 (8.4%)
Aspartate aminotransferase increased	0	0	0	1 (11.1%)	0	1 (10.0%)	2 (22.2%)	0	0	4 (6.5%)	4 (4.8%)

Table S11. Summary of TEAEs by System Organ Class and Preferred Term – Subjects in Group A (All Subjects)

System Organ Class MedDRA Preferred Term	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Blood creatine phosphokinase increased	0	0	0	2 (22.2%)	0	0	0	0	0	2 (3.2%)	2 (2.4%)
Electrocardiogram T wave abnormal	0	1 (9.1%)	0	0	0	0	0	0	0	1 (1.6%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	0	0	2 (16.7%)	2 (22.2%)	1 (8.3%)	1 (10.0%)	1 (11.1%)	2 (18.2%)	1 (4.8%)	8 (12.9%)	9 (10.8%)
Myalgia	0	0	0	1 (11.1%)	1 (8.3%)	1 (10.0%)	0	0	1 (4.8%)	2 (3.2%)	3 (3.6%)
Arthralgia	0	0	0	0	0	0	1 (11.1%)	1 (9.1%)	0	2 (3.2%)	2 (2.4%)
Back pain	0	0	1 (8.3%)	1 (11.1%)	0	0	0	0	0	2 (3.2%)	2 (2.4%)
Pain in extremity	0	0	1 (8.3%)	0	0	0	0	1 (9.1%)	0	2 (3.2%)	2 (2.4%)
Nervous system disorders	0	2 (18.2%)	1 (8.3%)	0	1 (8.3%)	2 (20.0%)	1 (11.1%)	1 (9.1%)	1 (4.8%)	7 (11.3%)	8 (9.6%)
Headache	0	2 (18.2%)	1 (8.3%)	0	0	2 (20.0%)	1 (11.1%)	1 (9.1%)	0	7 (11.3%)	7 (8.4%)
Dizziness	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Paraesthesia	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Gastrointestinal disorders	0	0	2 (16.7%)	1 (11.1%)	0	1 (10.0%)	1 (11.1%)	1 (9.1%)	0	6 (9.7%)	6 (7.2%)
Abdominal pain	0	0	1 (8.3%)	0	0	0	0	1 (9.1%)	0	2 (3.2%)	2 (2.4%)
Constipation	0	0	1 (8.3%)	1 (11.1%)	0	0	0	0	0	2 (3.2%)	2 (2.4%)
Dyspepsia	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)

Table S11. Summary of TEAEs by System Organ Class and Preferred Term – Subjects in Group A (All Subjects)

System Organ Class MedDRA Preferred Term	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Toothache	0	0	0	0	0	0	1 (11.1%)	0	0	1 (1.6%)	1 (1.2%)
Skin and subcutaneous tissue disorders	0	1 (9.1%)	0	0	1 (8.3%)	1 (10.0%)	0	2 (18.2%)	1 (4.8%)	4 (6.5%)	5 (6.0%)
Dermatitis contact	0	0	0	0	0	0	0	2 (18.2%)	0	2 (3.2%)	2 (2.4%)
Alopecia	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Dermatitis	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Hyperhidrosis	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Pruritus	0	1 (9.1%)	0	0	0	0	0	0	0	1 (1.6%)	1 (1.2%)
Rash	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Skin irritation	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Injury, poisoning and procedural complications	0	0	1 (8.3%)	0	2 (16.7%)	0	0	1 (9.1%)	2 (9.5%)	2 (3.2%)	4 (4.8%)
Excoriation	0	0	1 (8.3%)	0	1 (8.3%)	0	0	0	1 (4.8%)	1 (1.6%)	2 (2.4%)
Ligament sprain	0	0	0	0	1 (8.3%)	0	0	0	1 (4.8%)	0	1 (1.2%)
Muscle strain	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	0	0	0	2 (22.2%)	0	1 (10.0%)	0	1 (9.1%)	0	4 (6.5%)	4 (4.8%)

Table S11. Summary of TEAEs by System Organ Class and Preferred Term – Subjects in Group A (All Subjects)

System Organ Class MedDRA Preferred Term	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Rhinorrhoea	0	0	0	2 (22.2%)	0	0	0	0	0	2 (3.2%)	2 (2.4%)
Cough	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Oropharyngeal pain	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Respiratory tract congestion	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Sinus congestion	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Blood and lymphatic system disorders	1 (11.1%)	0	0	1 (11.1%)	0	0	0	1 (9.1%)	1 (4.8%)	2 (3.2%)	3 (3.6%)
Anaemia	0	0	0	1 (11.1%)	0	0	0	0	0	1 (1.6%)	1 (1.2%)
Leukopenia	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Neutropenia	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Neutrophilia	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
General disorders and administration site conditions	1 (11.1%)	1 (9.1%)	0	0	0	0	0	1 (9.1%)	1 (4.8%)	2 (3.2%)	3 (3.6%)
Asthenia	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
Chest pain	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Chills	0	0	0	0	0	0	0	1 (9.1%)	0	1 (1.6%)	1 (1.2%)
Fatigue	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
Pyrexia	0	1 (9.1%)	0	0	0	0	0	0	0	1 (1.6%)	1 (1.2%)

Table S11. Summary of TEAEs by System Organ Class and Preferred Term – Subjects in Group A (All Subjects)

System Organ Class MedDRA Preferred Term	SC Regimen				IV Regimen				All		
	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)	Placebo Combined (N=21)	Evinacumab Combined (N=62)	Total (N=83)
Cardiac disorders	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
Palpitations	1 (11.1%)	0	0	0	0	0	0	0	1 (4.8%)	0	1 (1.2%)
Reproductive system and breast disorders	0	0	1 (8.3%)	0	0	0	0	0	0	1 (1.6%)	1 (1.2%)
Dysmenorrhoea	0	0	1 (8.3%)	0	0	0	0	0	0	1 (1.6%)	1 (1.2%)
Vascular disorders	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)
Flushing	0	0	0	0	0	1 (10.0%)	0	0	0	1 (1.6%)	1 (1.2%)

Table S12. Summary of Triglyceride (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with SC Evinacumab

	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)
Triglycerides (Day 4)				
N	9	11	12	9
Median (Q1:Q3) at Day 1 (baseline)	153.0 (126.0:248.0)	156.0 (132.0:220.0)	188.5 (120.0:258.5)	182.0 (148.0:288.0)
Median (Q1:Q3) at Day 4	169 (160.0 : 208.0)	189 (134.0 : 197.0)	105.5 (95.0 : 212.0)	96 (54.0 : 154.0)
Percent change from baseline Median (Q1 : Q3)	25.3 (13.4 : 31.4)	-1 (-13.4 : 8.9)	-29.1 (-47.3 : 12.3)	-51.1 (-60.1 : -30.2)
Percent change from baseline Difference v.s. placebo				
Median Difference		-20.84 (14.986)	-40.79 (20.057)	-64.42 (19.454)
95% C.I.		(-48.11,10.63)	(-71.60, 7.02)	(-91.46,-15.20)
P-value		0.2121	0.0168	0.0017
Triglycerides (Day 15)				
N	7	10	12	7
Median (Q1:Q3) at Day 15	144 (93.0 : 250.0)	141 (122.0 : 236.0)	169.5 (95.5 : 219.0)	118 (104.0 : 198.0)
Percent change from baseline Median (Q1 : Q3)	-3.8 (-53.7 : 5.1)	-10.9 (-23.1 : 29.3)	-10.9 (-20.4 : 5.3)	-32.2 (-43.4 : 12.8)
Percent change from baseline Difference v.s. placebo				
Median Difference		5.98 (23.147)	4.14 (20.419)	-9.57 (24.082)
95% C.I.		(-29.68, 61.05)	(-26.79,53.25)	(-59.33, 35.07)
P-value		0.8038	0.8642	0.6173

Abbreviations: C.I., confidence interval; Q1, quartile 1; Q3, quartile 3, SC, subcutaneous.

Table S13. Summary of Triglyceride (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with IV Evinacumab

	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)
Triglycerides (Day 4)				
N	12	10	9	11
Median (Q1:Q3) at Day 1 (Baseline)	173.5 (82.5 : 243.5)	190.0 (118.0 : 230.0)	197.0 (130.0 : 327.0)	158.0 (101.0 :271.0)
Median (Q1:Q3) at Day 4	183.5 (91.0 : 209.5)	65.5 (49.0 : 100.0)	49 (31.0 : 65.0)	47 (32.0 : 58.0)
Percent change from baseline Median (Q1:Q3)	9 (-5.1 : 23.4)	-64.1 (-68.9 : -63.5)	-74.4 (-76.8 : -71.1)	-75 (-80.2 : -67.1)
Percent change from baseline Difference v.s. placebo				
Median Difference		-71.04 (7.965)	-79.62 (8.504)	-76.01 (8.999)
95% C.I.		(-88.99, -57.77)	(-98.66, -65.33)	(-97.29, -62.02)
P-value		<0.0001	<0.0001	<0.0001
Triglycerides (Day 15)				
N	11	9	9	11
Median (Q1 : Q3) at Day 15	149 (88.0 : 225.0)	88 (59.0 : 102.0)	71 (46.0 : 121.0)	58 (38.0 : 64.0)
Percent change from baseline Median (Q1 : Q3)	-18.4 (-19.3 : -5.1)	-49.4 (-51.9 : -34.3)	-60.1 (-71.3 : -55.0)	-63.1 (-69.6 : -55.7)
Percent change from baseline Difference v.s. placebo				
Median Difference		-31.01 (8.956)	-48.72 (7.148)	-50.43 (6.157)
95% C.I.		(-46.35, -11.24)	(-60.17, -32.15)	(-62.79, -38.65)
P-value		0.0026	<0.0001	<0.0001

Abbreviations: C.I., confidence interval; IV, intravenous; Q1, quartile 1; Q3, quartile 3.

Table S14. Summary of LDL-C (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with SC Evinacumab

	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)
LDL Cholesterol (Day 4)-Direct				
N	9	11	12	9
Mean (SD) at Day 1 (Baseline)	148.8 (24.93)	141.8 (41.21)	138.5 (33.48)	150.9 (28.00)
Mean (SD) at Day 4	140.3 (19.76)	136.3 (28.59)	122.3 (23.84)	135.3 (33.86)
Percent change from baseline				
Mean (SD)	-0.8 (17.08)	1.6 (27.76)	-8.4 (14.21)	-8.6 (20.11)
LS Mean (SE)	-0.09 (5.918)	0.78 (5.355)	-10.26 (5.147)	-5.85 (5.963)
LS Mean Difference vs. Placebo (SE)		0.86 (7.986)	-10.17 (7.855)	-5.77 (8.385)
95% C.I.		(17.06, -15.33)	(5.76, -26.10)	(11.24, -22.77)
P-value		0.9144	0.2037	0.496
LDL Cholesterol (Day 15)-Direct				
N	7	10	12	7
Mean (SD) at Day 15	144.0 (18.80)	136.8 (39.72)	127.2 (19.28)	129.7 (31.76)
Percent change from baseline				
Mean (SD)	2.8 (12.80)	-2.1 (11.55)	-3.9 (16.98)	-17.7 (20.22)
LS Mean (SE)	2.61 (5.336)	-2.64 (4.468)	-5.34 (4.107)	-14.13 (5.476)
LS Mean Difference vs. Placebo (SE)		-5.25 (6.957)	-7.95 (6.728)	-16.74 (7.657)
95% C.I.		(8.94, -19.44)	(5.77, -21.67)	(-1.12, -32.36)
P-value		0.4558	0.2462	0.0365

Abbreviations: C.I., confidence interval; LS, least squares; SC, subcutaneous; SD, standard deviation; SE, standard error.

Table S15. Summary of LDL-C (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with IV Evinacumab

	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)
LDL Cholesterol (Day 4)-Direct				
N	11	10	9	11
Mean (SD) at Day 1 (Baseline)	134.6 (23.79)	140.6 (30.32)	142.7 (20.54)	134.7 (26.88)
Mean (SD) at Day 4	138.8 (25.95)	131.3 (55.25)	118.9 (34.12)	115.6 (29.28)
Percent change from baseline				
Mean (SD)	6.9 (12.11)	-7.8 (29.29)	-16.6 (21.45)	-12.0 (18.09)
LS Mean (SE)	7.20 (6.078)	-8.00 (6.630)	-17.01 (7.034)	-11.86 (6.321)
LS Mean Difference vs. Placebo (SE)		-15.19 (9.026)	-24.20 (9.363)	-19.06 (8.739)
95% C.I.		(3.09, -33.48)	(-5.23, -43.17)	(-1.35, -36.76)
P-value		0.1007	0.0138	0.0356
LDL Cholesterol (Day 15)-Direct				
N	11	9	9	11
Mean (SD) at Day 15	125.3 (25.82)	116.1 (39.52)	111.2 (30.67)	94.2 (24.66)
Percent change from baseline				
Mean (SD)	-4.5 (12.55)	-16.8 (15.56)	-20.1 (25.80)	-27.8 (17.03)
LS Mean (SE)	-5.00 (5.456)	-16.52 (6.013)	-19.31 (6.060)	-28.19 (5.446)
LS Mean Difference vs. Placebo (SE)		-11.52 (8.133)	-14.31 (8.200)	-23.19 (7.688)
95% C.I.		(4.99, -28.03)	(2.34, -30.96)	(-7.59, -38.80)
P-value		0.1656	0.0898	0.0047

Abbreviations: C.I., confidence interval; IV, intravenous; LS, least squares; SD, standard deviation; SE, standard error.

Table S16. Summary of HDL-C (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with SC Evinacumab

	Placebo (N=9)	Evinacumab 75 mg (N=11)	Evinacumab 150 mg (N=12)	Evinacumab 250 mg (N=9)
HDL Cholesterol (Day 4)				
N	9	11	12	9
Mean (SD) at Day 1 (Baseline)	47.7 (7.81)	48.4 (12.55)	46.1 (15.56)	53.0 (22.46)
Mean (SD) at Day 4	47.6 (9.17)	44.8 (9.87)	47.3 (20.38)	51.0 (13.66)
Percent change from baseline				
Mean (SD)	-0.7 (10.20)	-7.3 (14.22)	-2.3 (13.37)	-2.7 (16.84)
LS Mean (SE)	-0.96 (4.586)	-7.34 (4.143)	-2.66 (3.979)	-1.85 (4.633)
LS Mean Difference vs. Placebo (SE)		-6.38 (6.179)	-1.70 (6.060)	-0.89 (6.543)
95% C.I.		(6.15, -18.91)	(10.59, -13.99)	(12.38, -14.16)
P-value		0.3087	0.781	0.8922
HDL Cholesterol (Day 15)				
N	7	10	12	7
Mean (SD) at Day 15	49.4 (8.42)	51.6 (13.13)	44.3 (15.29)	42.1 (5.87)
Percent change from baseline				
Mean (SD)	1.4 (9.67)	3.2 (13.63)	-6.5 (7.21)	-11.5 (4.06)
LS Mean (SE)	1.49 (3.619)	3.39 (3.037)	-6.67 (2.768)	-11.62 (3.620)
LS Mean Difference vs. Placebo (SE)		1.91 (4.721)	-8.16 (4.558)	-13.11 (5.120)
95% C.I.		(11.53, -7.72)	(1.14, -17.45)	(-2.67, -23.55)
P-value		0.6893	0.0834	0.0155

Abbreviations: C.I., confidence interval; LS, least squares; SC, subcutaneous; SD, standard deviation; SE, standard error.

Table S17. Summary of HDL-C (mg/dL) Percent Change from Baseline by Dose Level by Visit Subjects in Group A (Safety Analysis Set) Treated with IV Evinacumab

	Placebo (N=12)	Evinacumab 5 mg/kg (N=10)	Evinacumab 10 mg/kg (N=9)	Evinacumab 20 mg/kg (N=11)
HDL Cholesterol (Day 4)				
N	12	10	9	11
Mean (SD) at Day 1 (Baseline)	41.5 911.57)	43.6 (14.82)	44.0 (19.47)	43.3 (6.59)
Mean (SD) at Day 4	43.9 (12.14)	41.8 (17.76)	40.0 (17.58)	40.0 (11.10)
Percent change from baseline				
Mean (SD)	4.5 (7.86)	-4.3 (17.99)	-10.9 (12.50)	-6.7 (23.62)
LS Mean (SE)	4.58 (4.834)	-4.32 (5.292)	-11.04 (5.589)	-6.74 (5.045)
LS Mean Difference vs. Placebo (SE)		-8.89 (7.166)	-15.62 (7.398)	-11.31 (6.987)
95% C.I.		(5.63, -23.41)	(-0.63, -30.61)	(2.84, -25.47)
P-value		0.2224	0.0415	0.1138
HDL Cholesterol (Day 15)				
N	11	9	9	11
Mean (SD) at Day 15	41.5 (13.38)	37.1 (15.07)	31.9 (11.58)	34.0 (6.34)
Percent change from baseline				
Mean (SD)	-1.8 (13.50)	-17.7 (15.26)	-27.3 (10.28)	-20.2 (16.38)
LS Mean (SE)	-1.85 (4.326)	-17.63 (4.779)	-27.19 (4.783)	-20.21 (4.322)
LS Mean Difference vs. Placebo (SE)		-15.79 (6.451)	-25.34 (6.457)	-18.36 (6.112)
95% C.I.		(-2.69, -28.88)	(-12.24, -38.45)	(-5.96, -30.77)
P-value		0.0196	0.0004	0.0049

Abbreviations: C.I., confidence interval; IV, intravenous; LS, least squares; SD, standard deviation; SE, standard error.

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