SUPPLEMENTAL MATERIAL
Supplemental Methods

ODYSSEY OUTCOMES Trial

Design, demographic information, and clinical endpoint data for ODYSSEY OUTCOMES have been reported previously\textsuperscript{22,44} (Table 1 contains additional demographic information). This study was approved by all required regulatory agencies and ethics committees. All trial participants provided written informed consent. Briefly, qualifying patients had an acute coronary syndrome event and levels of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, or apolipoprotein B exceeding 70, 100, or 80 mg/dL, respectively, on high-intensity or maximum tolerated statin treatment. The study comprised a run-in period (2–16 weeks) and a randomized treatment period. During the run-in period, subjects were maintained on high-dose atorvastatin (40 or 80 mg) or rosuvastatin (20 or 40 mg), or the maximum tolerated dose of 1 of these agents, with or without non-statin lipid-lowering agents. After at least 2 weeks on stable lipid-lowering therapy, lipid levels were measured. Qualifying patients were randomly assigned to treatment with alirocumab (active study drug) or placebo, added to ongoing treatment with the established background statin and/or non-statin lipid-lowering therapies. The primary trial outcome was a composite of major adverse cardiovascular events comprising death from coronary heart disease, non-fatal myocardial infarction, ischemic stroke, and hospitalization for unstable angina pectoris.
Definition of Statin Intolerance and Clinical and Biochemical Phenotypes

Trial participants were monitored for adverse drug events. Investigators could attribute adverse events during the trial to the study drug and/or background therapies (eg, atorvastatin or rosvastatin). Laboratory testing, including for creatine kinase (CK) levels, was performed centrally at baseline and at protocol-specified intervals after randomization.

Patients were classified as statin-intolerant at baseline if the investigator documented that they had discontinued at least 2 different statins prior to enrollment or during run-in due to muscle symptoms and/or elevated CK. For the present pharmacogenomic analysis, we defined 2 separate phenotypes. The first was a clinical phenotype based upon documented statin intolerance prior to randomization or an investigator-documented adverse event of statin-associated muscle symptoms (SAMS; i.e., cramping, myalgia, or myopathy attributed to statin use by the investigator) developing after randomization. We also defined a biochemical phenotype as the maximum value of CK determined on regular, protocol-specified laboratory testing during the study treatment period (after randomization) for subjects taking high-dose atorvastatin or rosvastatin. Only randomized subjects who received at least 1 dose of placebo or alirocumab were included in the genetic analysis, except for 2 randomized subjects with documented statin intolerance prior to randomization who did not receive alirocumab or placebo. While patients deemed “statin intolerant” during run-in were unable to take high-dose atorvastatin or rosvastatin, they could down-titrate dosage or switch to another statin or lipid-modifying therapy to meet criteria for trial randomization.
Hence, all known “statin intolerant” cases documented during the run-in period were included in the genetic sub-study. Only adverse events and laboratory measures prior to study drop-out or completion were considered for analysis. See Table I for additional exclusion/inclusion criteria for each phenotype. Both phenotypes were assessed for accuracy/quality using R Studio (Vienna, Austria).

These phenotypes were tested for association against 8,921,030 (minor allele frequency [MAF]>0.01) genetic variants genome-wide, including several candidate genes and variants based on previously reported studies.

**Baseline Statin Intolerance or Investigator-Documented SAMS During the Treatment Period**

Patients with available genetic data and documented statin intolerance due to muscle symptoms (e.g., cramping, myalgia, or myopathy) and/or elevated CK prior to randomization (n=657) were included as cases for the baseline statin intolerance phenotype. Of these, 555 were intolerant to both atorvastatin and rosuvastatin during the run-in period, while 102 subjects had documentation of prior intolerance to at least 2 statins (not necessarily atorvastatin and rosuvastatin) prior to study enrollment.

Additionally, of the 9,931 subjects taking high-dose atorvastatin or rosuvastatin at randomization, 237 developed muscle symptoms (e.g., cramping, myalgia, or myopathy), with or without elevated CK, that were attributed to statin use by the investigator (investigator-document SAMS) while actively on statin therapy during the treatment period. These 237 subjects (194 atorvastatin, 43 rosuvastatin), in addition to
the 657 subjects with statin intolerance at randomization, comprised the overall case population (n=894) for this phenotype. All subjects taking high-dose atorvastatin or rosvastatin at randomization, who were followed for at least 4 months and had no indication of investigator-documented SAMS or statin intolerance prior to randomization, comprised the control group (n=9,723). Additionally, all high-dose atorvastatin- and rosvastatin-treated subjects with documented myalgia or myopathy after randomization due to unknown etiology or not directly attributed to statin use by study investigator were excluded from the analysis (n=472; Table I).

**CK Maximum Value During the Treatment Period**

All trial participants included in the pharmacogenomic analysis (n=11,880) had CK levels drawn at least once during the randomized treatment period; 11,865 also had a baseline CK measurement at randomization. Of this population, 10,653 (89.7%) patients were taking high-dose atorvastatin or rosvastatin at randomization. Of these 10,653 subjects, 810 had a myocardial infarction during the treatment period and were excluded to avoid false/confounding CK elevations due to myocardial damage/injury (Table I). Additional subjects were excluded from analysis due to less than 4 months of follow-up. Overall, 9,630 subjects were included in the analysis for the maximum CK phenotype. Each patient’s maximum CK level during the treatment period was utilized for the analysis and treated as a continuous variable. Maximum CK, rather than baseline CK, was used for the following reasons: 1) Using baseline CK would have limited our analysis to a single point in time, making the phenotype more susceptible to inherent biases. 2) Baseline CK was drawn at randomization, which occurred only two
weeks following statin initiation for some patients and may have been too early to detect statin-associated maximum CK given the median time to SAMS with CK elevation following statin initiation is reported to be 6.3 months\textsuperscript{45}. 3) Using maximum CK allows for longitudinal investigation of this phenotype without limiting the analysis to shorter durations of statin therapy. The upper limit of normal (ULN) for CK used by the central study laboratory was 198 IU/L. Due to several outliers (>\~1,000 IU/L), CK values underwent rank-based inverse normalized transformation.

**DNA Samples**

DNA samples were available from 12,118 study participants who provided written informed consent to participate in the genetic sub-study. Of these, 11,953 (98%) met quality control (QC) procedures for genetic data provided below. Of the samples that passed QC, 11,880 subjects had both genotyping and whole-exome sequencing data available for analysis.

**Genotyping Methodology**

The Illumina Global Screening Array v1.0 (Illumina, San Diego, CA) was used to generate microarray genotypes for the genome-wide association study (GWAS). Individual samples or variants were excluded if more than 10% of calls were missing. Familial relationships were identified using identity by descent (IBD) analysis. If a paired sample with IBD ≥0.1875 was detected, the sample with the higher missingness rate was removed. Samples were also removed if gender discordance was detected between gender reported in the clinical database and X-chromosome-inferred gender.
Sequencing Methodology

Generation of whole exome data was conducted using the IDT xGen Exome Research Panel v1.0 (Integrated DNA Technologies, Coralville, IA), and sequencing was performed using the Illumina HiSeq 2500 Sequencing System (Illumina, San Diego, CA). Whole-exome sequencing was conducted by the Regeneron Genetics Center (Tarrytown, NY) as described previously. The average 20X coverage for target regions was 95.8%, and 98.9% of samples had coverage >90%. Quality control (QC) metrics for sample and site missingness followed the thresholds outlined for genotyping. For inclusion in the analyses, samples had to pass both genotyping array and whole exome sequencing QC metrics.

Population Structure

The population structure was assessed using principal component analysis within PLINK version 1.9. The top 12 principal components (depending on ancestry) were used as covariates in analyses when analyzing all ancestry groups combined, while the top 6 principal components were used as covariates when analyzing the European-only cohort.

Imputation

Genotype imputation was conducted with Minimac4. Reference populations for imputation were obtained from 1000 Genomes phase 3 version 5. Post-QC variants were restricted to those with INFO score >0.3. Similar thresholds with respect to
missingness were applied. Hard-call genotype data were used for all imputed variants included in the GWAS.

**ExWAS/GWAS**

Several covariates were tested for inclusion in regression models for each phenotype using multivariate analysis in R Studio. Covariates of clinical relevance with $P<0.3$ were included and adjusted for in linear/logistic regression models. Table I includes a full list of covariate adjustments tested for or included in regression models. Variants with a Hardy Weinberg Equilibrium $P$ value $<1 \times 10^{-6}$ were removed from the analysis.

ExWAS/GWAS analysis (additive models) with 8,921,030 variants that passed all QC measures were performed separately for each phenotype using PLINK versions 1.9 and 2.0. Manhattan and quantile-quantile plots were generated, and a genome-wide significance threshold of $P<5 \times 10^{-8}$ was used for each ExWAS/GWAS analysis.

**Candidate Gene/Variant Studies**

Candidate genes ($n=18$) and variants ($n=11$) related to atorvastatin and rosvastatin pharmacokinetics or SAMS pharmacodynamics were selected based on published literature$^{3,9}$ and clinical/variant annotations in PharmGKB$^{50}$ for atorvastatin and rosvastatin. Each candidate variant/gene locus was extracted from ExWAS/GWAS analysis results for each phenotype (Table II).

**Gene Burden Tests**

In each Ensembl-defined gene,$^{51}$ nonsynonymous variants were filtered according to 20 masks, 5 different masks/criteria based on 5 allele frequency thresholds (MAFs: <5%,
<1%, <0.1%, and <0.01%, and singletons only) and 4 based on the predicted protein coding impact of the variant. For the coding impact, the masks ranging from most restrictive to least restrictive are: 1) predicted loss of function (pLoF); 2) pLoF or missense predicted to be damaging by 5/5 deleterious algorithms; 3) pLoF or missense predicted to be damaging by at least 1/5 deleterious algorithms; and 4) pLoF or missense. The 5 algorithms used to assess deleteriousness were SIFT, Polyphen2 HDIV, Polyphen2 HVAR, LRT, and MutationTaster. For the variants that met filtering criteria for a given mask, the variants were collapsed into a single summary measure per individual (e.g., 0, 1, or 2) and analyzed in a similar manner to single-point analysis. A gene burden analysis of rare-variants in 18,878 Ensembl-defined genes was then performed for both phenotypes using the same covariates and regression methodology described above (Table I). An exome-wide significance threshold of $P<1\times10^{-6}$ was used for gene burden analysis.

**Investigation of Genomic Signals**

Single-tissue expression quantitative trait loci (eQTLs) were queried for top genetic associations using the NIH Genotype-Tissue Expression (GTEx) Portal.
Supplemental Table I. Full Inclusion/Exclusion Criteria for the ODYSSEY OUTCOMES Pharmacogenomic Analysis Subgroup \( (n = 11,880) \) and Regression Model Covariate Adjustments by Phenotype.

| Phenotype                                                                 | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Covariate adjustments                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------|
| Baseline statin intolerance or investigator-document SAMS during treatment period ExWAS/GWAS | 1. Taking high-dose atorvastatin or rosuvastatin at randomization OR documented statin intolerance during run-in or from prior medical history due to muscle symptoms and/or elevated CK | 1. Documented statin intolerance during run-in due to reason other than muscle symptoms and/or elevated CK 2. Did not complete \( \geq 4 \) months of treatment period AND no documentation of statin intolerance during run-in period or investigator-document SAMS during treatment period. 3. Experienced muscle symptoms (e.g., cramping, myalgia, myopathy) during treatment period due to unknown etiology or reason not directly attributed to statin use. 4. Did not complete run-in period (study drop-out prior to randomization) | Age, sex, body mass index, diabetes mellitus, hypothyroidism, fibromyalgia, first 12 principal components of ancestry |
| CK maximum value during treatment period ExWAS/GWAS                       | 1. Taking high-dose atorvastatin or rosuvastatin at randomization* 2. Baseline CK level available | 1. Myocardial infarction during treatment period 2. Did not complete \( \geq 4 \) months of treatment period AND did not have CK elevation \( \geq 4 \times \) ULN before drop-out | Age, sex, body mass index, diabetes mellitus, hypothyroidism, baseline† CK level, first 12 principal components of ancestry |
At least 1 CK level available after baseline measurement at randomization

3. Did not complete run-in period (study drop-out prior to randomization)

CK indicates creatine kinase; ExWAS, exome-wide association study; GWAS, genome-wide association study; SAMS, statin-associated muscle symptoms; and ULN, upper limit of normal.

Other relevant covariates that were investigated but ultimately not included in final regression model due to P value > 0.3 and/or insufficient clinical validity in SAMS were: hypertension, self-reported race, concomitant medications that may impact atorvastatin and/or rosuvastatin pharmacokinetics (e.g., colchicine, cyclosporin, erythromycin, fenofibrate, gemfibrozil, ketoconazole) (these medications were evaluated individually and by victim drug interaction [see Table 1]), atorvastatin dose (40 mg vs 80 mg), rosuvastatin dose (20 mg vs 40 mg), hepatic/hepatobiliary disorder, renal impairment, smoking status (current vs former), and randomization strata (study drug vs placebo).

*Subjects with baseline statin intolerance (n=657) were not included in CK phenotype analysis.

†CK level drawn at randomization (Day 1) used as baseline CK level.
Supplemental Table II. Skeletal Muscle QTLs for Top Genetic Associations in the ODYSSEY OUTCOMES Population.

| Variant of interest | Associated eQTL |
|---------------------|-----------------|
| Chr:Pos:Ref:Alt     | rsID            | Gene*          | Effect gene | NES  | P value | Tissue |
| 13:73612794:C:T†    | rs7993814       | LINC00393/KLF12| KLF5        | −0.30| 2.4×10^{-20} | Skeletal muscle |
| 13:73531052:G:T†    | rs9600129       | LINC00393/KLF12| KLF5        | −0.36| 1.5×10^{-28} | Skeletal muscle |

| Variant of interest | Associated sQTL |
|---------------------|-----------------|
| Chr:Pos:Ref:Alt     | rsID            | Gene*          | Effect gene | NES | P value | Tissue |
| 1:201148730:C:G§    | rs6667912       | TMEM9          | TMEM9       | 0.28| 1.1×10^{-8}  | Skeletal muscle |

Alt indicates alternative allele; Chr, chromosome; CK, creatine kinase; eQTL, expression quantitative trait loci; NES, normalized effect size; Pos, position; QTL, quantitative trait loci; Ref, reference allele; SAMS, statin-associated muscle symptoms; and sQTL, splicing quantitative trait loci.

QTL associations were queried using Genotype-Tissue Expression (GTEx) Portal. It should be noted that single QTL data can sometimes be misleading and should be interpreted cautiously in absence of validated colocalization data.

*Nearest gene reported.

†Genome-wide significant association with CK maximum value during treatment period phenotype in the ODYSSEY OUTCOMES cohort.

‡Previously associated with CK levels in a separate cohort.
$\text{Genome-wide significant association with baseline statin intolerance or investigator-documented SAMS phenotype in ODYSSEY OUTCOMES cohort.}$
Supplemental Table III. Candidate Variant/Gene Analysis Across Both Phenotypes.

| Candidate variants | Chr:Pos:Ref:Alt | rsID    | Region or impact | Gene     | OR (95% CI)   | P value | Per-allele β (95% CI) | P value |
|---------------------|-----------------|---------|------------------|----------|---------------|---------|------------------------|---------|
| 7:87509329:A:G†     | rs1045642       | Missense | ABCB1            |          | 1.01 (0.92, 1.12) | 0.81    | 0.01 (−0.01, 0.04)    | 0.32    |
| 19:45317925:T:C‡    | rs11559024      | Missense | CKM              |          | 0.99 (0.64, 1.54) | 0.97    | −0.18 (−0.04, −0.31)  | 9.0x10⁻³ |
| 4:83269878:A:G†     | rs6535454       | Synonymous | COQ2            |          | 1.12 (1.00, 1.25) | 0.05    | 0.01 (−0.03, 0.04)    | 0.74    |
| 4:83271015:G:C‡     | rs4693075       | Intronic  | COQ2            |          | 1.04 (0.94, 1.16) | 0.43    | 0.00 (−0.02, 0.03)    | 0.78    |
| 11:113933165:A:G‡   | rs2276307       | Intronic  | HTR3B            |          | 0.87 (0.77, 0.99) | 0.03    | −0.03 (−0.06, 0.00)   | 0.07    |
| 10:90834586:C:T‡    | rs1935349       | Intronic  | HTR7             |          | 0.99 (0.86, 1.14) | 0.85    | 0.00 (−0.04, 0.04)    | 0.94    |
| 19:54255498:T:C‡    | rs12975366      | Missense  | LILRB5           |          | 0.97 (0.87, 1.07) | 0.53    | −0.08 (−0.05, −0.11)  | 8.68x10⁻⁸ |
| 13:73531052:G:T‡    | rs9600129       | Intergenic | LINC00393       |          | 1.04 (0.93, 1.16) | 0.51    | 0.07 (0.03, 0.10)     | 3.30x10⁻⁵ |
| 13:73531994:G:A‡    | rs7318906       | Intergenic | LINC00393       |          | 0.94 (0.85, 1.05) | 0.30    | −0.06 (−0.03, −0.09)  | 2.30x10⁻⁴ |
| 1:237826822:A:G‡    | rs2819742       | Intronic  | RYR2             |          | 1.02 (0.92, 1.13) | 0.71    | −0.029 (−0.06, 0.00)  | 0.06    |
Candidate Genes (variants with $P<1\times10^{-3}$ for either phenotype)

| Chr:Pos:Ref:Alt | rsID       | Region or Impact | Gene       | OR (95% CI) | $P$ value | Per allele β (95% CI) | $P$ value |
|-----------------|------------|------------------|------------|-------------|-----------|----------------------|-----------|
| 1:201106103:A:G | rs12239772 | Intronic         | CACNA1S    | 1.46 (1.21, 1.76) | 8.08x10^{-5} | −0.05 (−0.11, 0.00) | 0.07      |
| 1:201083182:A:T | rs12742169 | Missense         | CACNA1S    | 0.82 (0.73, 0.91) | 3.62x10^{-4} | −0.005 (−0.04, 0.03) | 0.77      |
| 2:11732909:C:G  | rs112281768| Intronic         | LPIN1      | 1.78 (1.29, 2.46) | 4.13x10^{-4} | −0.08 (−0.18, 0.02) | 0.11      |
| 19:38488916:A:T | rs34370689 | Intronic         | RYR1       | 0.98 (0.85, 1.15) | 0.84       | −0.07 (−0.12, −0.04) | 4.92x10^{-4} |

Alt indicates alternative allele; β, effect size beta; Chr, chromosome; CI, confidence interval; CK, creatine kinase; ExWAS, exome-wide association study; GWAS, genome-wide association study; OR, odds ratio; Pos, position; Ref, reference allele; RINT, rank-based inverse normalized transformation; and SAMS, statin-associated muscle symptoms.

Other candidate genes, informed by PharmGKB, investigated that had variants with associations of $P>1\times10^{-3}$ in both phenotypes include: ABCB1, ABCC1, ABCC2, ABCG2, CPT2, CYP2C9, CYP3A4, CYP3A5, LILRB5, PYGM, SLC10A1, SLCO1B1, SLCO1B3, SLCO2B1, and UGT1A3. Only the top index variant (lowest $P$ value) is shown per linkage disequilibrium (LD) cluster ($r^2>0.2$). Per-allele β effect size was reported based on RINTed values for continuous phenotype.

*Previously associated with rosuvastatin and atorvastatin pharmacokinetics, low evidence for association with rosuvastatin- and/or atorvastatin-mediated SAMS; phenotype association test of main interest in ODYSSEY population = baseline statin intolerance or investigator-documented SAMS during the treatment period.
†Previously associated with SAMS in an atorvastatin and/or rosuvastatin cohort,\textsuperscript{39,57-59} phenotype association test of main interest in ODYSSEY population = baseline statin intolerance or investigator-documented SAMS during the treatment period.

‡Previously associated with CK levels in statin users,\textsuperscript{24-26,34} phenotype association test of main interest in ODYSSEY population = CK maximum value during the treatment period.
Supplemental Table IV. Genetic Burden Analysis (MAF<0.05) of Both Phenotypes.

| Gene   | Burden test | OR (95% CI)   | P value  | Cases (Carrier|Non-Carrier) | Controls (Carrier|Non-Carrier) | AAF  |
|--------|-------------|---------------|----------|----------------|----------------|----------------|------|
| SOAT1  | M3-singleton| 10.07 (4.05, 25.00) | 5.86x10^-7 | 886|8            | 9,710|13              | 0.00099 |
| MSLN   | M4-singleton| 4.75 (2.51, 8.99) | 2.17x10^-6 | 880|14          | 9,682|41             | 0.0026  |
| CLDN17 | M3          | 4.69 (2.47, 8.92) | 2.37x10^-6 | 880|14          | 9,677|46             | 0.0028  |
| OSGEP  | M4          | 3.80 (2.17, 6.65) | 3.10x10^-6 | 876|18          | 9,668|55             | 0.0034  |
| EDDM3A | M2          | 2.22 (1.58, 3.11) | 4.31x10^-6 | 850|44          | 9,474|249            | 0.013   |
| MYO5C  | M3          | 1.94 (1.46, 2.58) | 5.49x10^-6 | 833|61          | 9,360|363            | 0.020   |
| PRL    | M4-singleton| 10.33 (3.74, 28.51) | 6.53x10^-6 | 887|7          | 9,712|11             | 0.00085 |
| KIAA0040| M2        | 31.73 (7.06, 142.73) | 6.58x10^-6 | 889|5          | 9,720|3              | 0.00037 |
| ISG20L2| M2         | 5.18 (2.53, 10.59) | 6.77x10^-6 | 882|12          | 9,691|32             | 0.0021  |
| PHYKPL | M2         | 3.53 (2.02, 6.15) | 8.74x10^-6 | 876|18          | 9,661|62             | 0.0038  |
| CTLA4  | M4         | 8.17 (3.23, 20.66) | 9.09x10^-6 | 885|9          | 9,712|11             | 0.00094 |
| PLEKHJ1| M4-singleton| 9.45 (3.48, 25.67) | 1.04x10^-5 | 887|7          | 9,712|11             | 0.00085 |

*Baseline statin intolerance or investigator-documented SAMS during treatment period*
|     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|
| HGD | M4-singleton | 5.30 (2.52, 11.11) | 1.05x10^{-5} | 883|11 | 9,696|27 | 0.0018 |
| ARPC4- | M1 | 5.67 (2.55, 12.59) | 2.06x10^{-5} | 885|9 | 9,696|27 | 0.0017 |
| TTL3 |     |     |     |     |     |     |
| SRP14 | M4 | 6.21 (2.67, 14.43) | 2.16x10^{-5} | 884|10 | 9,707|16 | 1.43x10^{-5} |
| PKP1 | M3 | 1.81 (1.38, 2.39) | 2.26x10^{-5} | 831|63 | 9,245|478 | 0.026 |
| LAT2 | M3 | 24.70 (5.51, 110.77) | 2.82x10^{-5} | 889|5 | 9,720|3 | 0.00038 |
| ABCB1* | M2 | 1.79 (1.36, 2.35) | 3.23x10^{-5} | 827|67 | 9,213|510 | 0.027 |
| KMT2C | M3 | 3.93 (2.06, 7.50) | 3.45x10^{-5} | 881|13 | 9,678|45 | 0.0027 |
| KRT75 | M3-singleton | 6.10 (2.59, 14.38) | 3.60x10^{-5} | 886|8 | 9,703|20 | 0.0013 |
| CRSL1 | M3 | 13.74 (3.89, 48.49) | 4.67x10^{-5} | 889|5 | 9,717|6 | 0.00052 |
| SLC25A26 | M2 | 4.51 (2.18, 9.32) | 4.78x10^{-5} | 883|11 | 9,694|29 | 0.0019 |
| BZW1 | M3 | 7.79 (2.89, 20.98) | 4.95x10^{-5} | 887|7 | 9,712|11 | 0.00085 |
| ZNF224 | M2 | 1.72 (1.32, 2.24) | 4.97x10^{-5} | 822|72 | 9,243|480 | 0.026 |
| DHRS9 | M3 | 5.42 (2.39, 12.29) | 5.08x10^{-5} | 885|9 | 9,701|22 | 0.0015 |
| SNAI3 | M3 | 5.87 (2.47, 13.95) | 6.24x10^{-5} | 885|9 | 9,699|24 | 0.0016 |
| BTD | M1 | 8.81 (3.03, 25.59) | 6.41x10^{-5} | 888|6 | 9,713|10 | 0.00075 |
| CHRNB2 | M1 | 23.91 (5.02, 113.87) | 6.71x10^{-5} | 891|3 | 9,719|4 | 0.00033 |
| ZP2 | M2 | 1.84 (1.36, 2.48) | 6.99x10^{-5} | 838|56 | 9,354|369 | 0.020 |
| Gene  | Burden test | β (95% CI)       | P value  | Cases (RR|RA|AA) | Controls (RR|RA|AA) | AAF     |
|-------|-------------|------------------|----------|----------------|------------------|---------|
| SCP2  | M1          | 18.12 (4.32, 75.93) | 7.42x10^-5 | 890|4               | 9,719|4               | 0.00038 |
| DHX35 | M3          | 2.71 (1.65, 4.44)  | 7.86x10^-5 | 873|21              | 9,620|103             | 0.0058  |
| GPX4  | M4          | 2.65 (1.63, 4.33)  | 9.09x10^-5 | 873|21              | 9,614|109             | 0.0062  |
| NRG3  | M3          | 5.29 (2.29, 12.22) | 9.60x10^-5 | 885|9               | 9,705|18              | 0.0013  |

**Phenotype**

*CK maximum value during treatment period*

| Gene  | Burden test | β (95% CI)       | P value  | Cases (RR|RA|AA) | Controls (RR|RA|AA) | AAF     |
|-------|-------------|------------------|----------|----------------|------------------|---------|
| KIAA0513 | M3-singleton | -1.10 (-1.55, -0.65) | 1.97x10^-6 | N/A             | N/A             | 0.00094 |
| MAP1S  | M4          | -0.19 (-0.26, -0.11) | 2.01x10^-6 | N/A             | N/A             | 0.033   |
| ATG4C  | M1          | -0.71 (-1.01, -0.42) | 2.64x10^-6 | N/A             | N/A             | 0.0022  |
| IL24   | M3          | -3.13 (-4.49, -1.76) | 6.85x10^-6 | N/A             | N/A             | 0.00010 |
| CPA2   | M3          | -0.49 (-0.72, -0.28) | 1.16x10^-5 | N/A             | N/A             | 0.0038  |
| SLC36A1 | M1          | -1.74 (-2.53, -0.96) | 1.41x10^-5 | N/A             | N/A             | 0.00031 |
| KANSL1 | M3-singleton | -0.91 (-1.32, -0.50) | 1.44x10^-5 | N/A             | N/A             | 0.0011  |
| GLTP   | M3          | -0.79 (-1.15, -0.43) | 1.54x10^-5 | N/A             | N/A             | 0.0015  |
| RPN2   | M3          | 0.66 (0.35, 0.98)   | 3.40x10^-5 | N/A             | N/A             | 0.0020  |
| TTC22  | M1-singleton | -4.07 (-5.99, -2.14) | 3.42x10^-5 | N/A             | N/A             | 5.19x10^-5 |
| ARAP3  | M4          | 0.23 (0.12, 0.34)   | 3.50x10^-5 | N/A             | N/A             | 0.016   |
| Gene   | Mask  | pLoF or missense status | Heterozygous (95% CI) | pLoF OR | pLoF | pLoF or missense OR | pLoF or missense | SAMS |
|--------|-------|-------------------------|-----------------------|---------|------|--------------------|-----------------|------|
| KBTBD6 | M1    | singleton               | 2.34 (1.23, 3.45)     | 3.59x10^-5 | N/A  | N/A                | 0.00016         |      |
| NEUROD1| M2    |                        | 0.66 (0.35, 0.97)     | 3.65x10^-5 | N/A  | N/A                | 0.0020          |      |
| SSUH2  | M2    |                        | 0.19 (0.10, 0.29)     | 5.98x10^-5 | N/A  | N/A                | 0.023           |      |
| UBC    | M2    |                        | -0.65 (-0.97, -0.33)  | 6.10x10^-5 | N/A  | N/A                | 0.0019          |      |
| KANSL1 | M4    | singleton               | -0.46 (-0.69, -0.23)  | 6.64x10^-5 | N/A  | N/A                | 0.0038          |      |
| LPP    | M4    |                        | -0.46 (-0.68, -0.23)  | 7.17x10^-5 | N/A  | N/A                | 0.0038          |      |
| SLC25A42| M2 | singleton                | 0.97 (0.49, 1.45)     | 8.14x10^-5 | N/A  | N/A                | 0.00083         |      |
| KSR2   | M3    | singleton               | 1.16 (0.58, 1.75)     | 8.94x10^-5 | N/A  | N/A                | 0.00057         |      |
| LRPAP1 | M4    |                        | 0.13 (0.06, 0.19)     | 9.05x10^-5 | N/A  | N/A                | 0.050           |      |
| PTPN4  | M2    |                        | -0.12 (-0.18, -0.06)  | 9.33x10^-5 | N/A  | N/A                | 0.050           |      |
| OR4E2  | M2    |                        | -0.36 (-0.55, -0.18)  | 9.67x10^-5 | N/A  | N/A                | 0.0059          |      |
| SPATS1 | M3    |                        | -0.69 (-1.03, -0.34)  | 9.92x10^-5 | N/A  | N/A                | 0.0016          |      |

AA indicates homozygous alternative allele genotype; AAF, alternative allele frequency; β, effect size beta; CI, confidence interval; CK, creatine kinase; MAF, minor allele frequency; OR, odds ratio; pLoF, predicted loss of function; RA, heterozygous genotype; RR, homozygous reference allele genotype; and SAMS, statin-associated muscle symptoms.

Top associations ($P<1x10^{-4}$) in genetic burden analysis (only top mask association per gene shown). An exome-wide threshold of $P<1x10^{-6}$ was used for genetic burden analysis. Variant composition for each mask was as follows: M1, pLoF; M2, pLoF or missense predicted to be damaging by 5/5 deleterious algorithms; M3, pLoF or missense predicted to be damaging by at least 1/5 deleterious algorithms; M4, pLoF or missense.
*Candidate gene identified prior to analysis (Supplemental Table II).
Supplemental Table V. CK Distribution Across Top ExWAS/GWAS Variant Associations with CK Phenotype.

| Chr:Pos:Ref:Alt | rsID-Risk Allele | Gene | Region     | Mean CK (IU/L) (Ref/Ref | Ref/Alt | Alt/Alt) | Maximum CK >10x ULN (Ref/Ref | Ref/Alt | Alt/Alt) |
|-----------------|------------------|------|------------|-------------------------|---------|----------|-------------------------|---------|----------|
| 13:73612794:C:T | rs7993814-T      | LINC00393/KL F12 | Intergenic     | 265.9 | 272.9 | 277.6 | Cases: 26 | 24 | 5 |
|                 |                  |      |            | Controls: 3,451 | 4,097 | 1,270    |
| 19:54251270:T:C | rs12986064-C     | LILRB5 | Intrinsic  | 329.7 | 259.4 | 243.6 | Cases: 13 | 16 | 11 |
|                 |                  |      |            | Controls: 1,507 | 3,459 | 1,245    |
| 1:62285404:G:A  | rs149062268-A    | KANK4 | Intrinsic  | 274.2 | 223.4 | 112.5 | Cases: 56 | 1  | 0  |
|                 |                  |      |            | Controls: 8,869 | 458  | 4        |
| 19:54255498:T:C | rs7993814-T      | LILRB5 | Exonic     | 294  | 259.3 | 254.2 | Cases: 22 | 22 | 14 |
|                 |                  |      |            | Controls: 3,602 | 4,460 | 1,510    |
| 10:84196512:C:A | rs12986064-C     | CDHR1 | Exonic     | 274  | 242.4 | 158.4 | Cases: 55 | 3  | 0  |
|                 |                  |      |            | Controls: 8,880 | 671  | 19        |
| 15:40266281:A:G | rs149062268-A    | PAK6  | Exonic     | 268.7 | 275.7 | 435.3 | Cases: 48 | 7  | 3  |
|                 |                  |      |            | Controls: 7,893 | 1,585 | 94        |
| 17:66220697:C:T | rs8178847-T      | APOH  | Exonic     | 267.9 | 298.2 | 291.6 | Cases: 11 | 16 | 13 |
|                 |                  |      |            | Controls: 1,245 | 3,459 | 1,507    |
| 19:55391573:G:A | rs45448592-A     | RPL28 | Exonic     | 269.2 | 292.7 | 237.2 | Cases: 48 | 10 | 0  |
|                 |                  |      |            | Controls: 8,529 | 1,006 | 37        |
Alt indicates alternative allele; Chr, chromosome; CK, creatine kinase; ExWAS, exome-wide association study; GWAS, genome-wide association study; Pos, position; Ref, reference allele; and ULN, upper limit of normal.

Top associations from Tables 4 and 5 included above.
Supplemental Figure I. Identification of two SAMS-related phenotypes for genetic analysis \((n = 11,880)\) in relation to the ODYSSEY OUTCOMES trial timeline \((n = 18,924)\). Non-standardized definitions of SAMS were used for the binary phenotype due to dataset limitations. SAMS cases were identified irrespective of concomitant CK elevation. Maximum CK was evaluated as a separate, continuous phenotype in subjects taking high-dose atorvastatin or rosuvastatin therapy during the treatment period, irrespective of SAMS diagnosis. All subjects included in the pharmacogenomic analysis underwent randomization for inclusion in the ODYSSEY OUTCOMES trial.
ACS indicates acute coronary syndrome; CK, creatine kinase; ExWAS, exome-wide association study; GWAS, genome-wide association study; and SAMS, statin-associated muscle symptoms.
Supplemental Figure II. Manhattan plot for both phenotypes in the European-only population. a) Manhattan plot of baseline statin intolerance or investigator-documented SAMS during treatment period ExWAS/GWAS in OUTCOMES subjects with genetic European ancestry only (cases=774, controls=7,594). The top association from the all-ancestry population (rs6667912, TMEM9, $P=3.71\times10^{-8}$) showed a slightly stronger association ($P=6.01\times10^{-9}$) in the European-only population. Overall, no notable differences were observed for ExWAS/GWAS results between all-ancestry and European-only genetic strata with this phenotype. b) Manhattan plot of maximum CK during treatment period ExWAS/GWAS with European ancestry-only subjects (n=7,568). The top association from the all-ancestry population (rs7993814, LINC00393, $P=9.77\times10^{-9}$) was slightly below the genome-wide threshold ($P=8.68\times10^{-7}$) when stratifying the OUTCOMES population based on European ancestry. This change in association may be due to differences in sample sizes between the all-ancestry and European genetic cohorts rather than a reflection of underlying differences between ancestral groups.
CK indicates creatine kinase; ExWAS, exome-wide association study; GWAS, genome-wide association study; and SAMS, statin-associated muscle symptoms.
Supplemental Figure III. Manhattan plot for CK >4x ULN and CK >10x ULN phenotypes. a) Manhattan plot of CK >4x ULN in ODYSSEY OUTCOMES subjects of all ancestries taking high-dose atorvastatin or rosuvastatin during the treatment period (cases=317, controls=9,313). No genome-wide associations were identified. A subthreshold association was observed with an intronic variant (rs1370277) in the FAH gene (OR [95% CI]: 1.89 [1.50, 2.37], \(P=5.25\times10^{-8}\)).

b) Manhattan plot of CK >10x ULN in ODYSSEY OUTCOMES subjects of all ancestries taking high-dose atorvastatin or rosuvastatin during the treatment period (cases=58, controls=9,572). One genome-wide association was observed for a variant (rs7911825) located in a pseudogene (RN7SKP143) on chromosome 10 (OR [95% CI]: 3.98 [2.47, 6.44], \(P=1.63\times10^{-8}\)). No other noteworthy associations were observed. Both phenotypes were tested against 6,441,523 variants (MAF>0.05). A MAF cutoff of 0.05 was used for these analyses to avoid \(P\) value inflation, as indicated by abnormal quantitle-quantile plots with an MAF cutoff of 0.01 with both phenotypes. This observation is likely due to relatively smaller case numbers for these phenotypes.
CI indicates confidence interval; CK, creatine kinase; OR, odds ratio; MAF, minor allele frequency; and ULN, upper limit of normal.
Supplemental Figure IV. Proposed physiological role of TMEM9 in SAMS. Rs6667912, an intronic variant in *TMEM9* was associated with an increased risk of SAMS in the ODYSSEY OUTCOMES pharmacogenomic sub-group (cases=894, controls=9,723), the largest atorvastatin/rosuvastatin SAMS cohort to date. The exact physiological mechanisms by which TMEM9 may modulate SAMS is unknown, and the impact of rs6667912 on TMEM9 expression/function has yet to be elucidated. Yet, there are limited preclinical and in vitro data suggesting its role in skeletal muscle regeneration/proliferation. Increased *Tmem9* expression was observed in skeletal muscle of a muscular atrophy mouse model, suggesting a role in myocyte energy conservation\(^{29}\). TMEM9 was also shown to amplify the Wnt-beta catenin pathway in vitro, a finding that was validated ex vivo and in a mouse model\(^{28}\). A role of the Wnt-beta catenin pathway in skeletal muscle regeneration/repair and myocyte proliferation following injury has been proposed\(^{60,61}\), but remains controversial\(^{62}\). Figure created with BioRender.com.
Physiological Role of TMEM9 in SAMS

LRP indicates lipoprotein receptor-related protein; mRNA messenger RNA; SAMS, statin-associated muscle symptoms; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; and Wnt, Wingless/Integrated
Supplemental Figure V. Quantile-quantile plots of phenotype ExWAS/GWAS. Quantile-quantile plots of observed (y axis) versus expected (x axis) -$\log_{10}(p)$ for both phenotypes: a) Baseline statin intolerance or investigator-documented SAMS during treatment period ExWAS/GWAS; and b) Creatine kinase maximum value during treatment period ExWAS/GWAS.
ExWAS indicates exome-wide association study; GWAS, genome-wide association study; and SAMS, statin-associated muscle symptoms.