Supplementary Appendix

Supplement to: Grinspoon SK, Ribaudo HJ, Douglas PS. Trial update of pitavastatin to prevent cardiovascular events in HIV infection. N Engl J Med 2024;390:1626-28. DOI: 10.1056/NEJMc2400870

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

This appendix has been provided by the authors to give readers additional information about the work, and provide updates to the tables and figures originally presented in *Grinspoon et al.*[1] based on the trial final database.

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Section 1: Supplemental Methods

Statistical Methods

The results reported by Grinspoon et al.[1] provide the primary inference for REPRIEVE. We here present updates to the estimated treatment effects based on the full trial follow-up including closeout visits.

Statistical analyses were performed in accordance with the REPRIEVE Statistical Analysis Plan (Version 2.0). The details were summarized in the Supplementary Appendix to the Grinspoon et al.[1] Key analytic methods are repeated below, as well as additional data and analysis considerations for the results presented in this final update.

Data Considerations

The primary publication of the REPRIEVE results was based on the database used for reporting for the March 2023 DSMB review on which the decision to stop the trial was made.[1] Data for the DSMB efficacy analyses were administratively censored at December 30, 2022 to allow time for event adjudication packet submission and adjudication.

Following the DSMB action, participants were asked to return for the final study visit. All final visits were completed by August 21, 2023. The clinical database was locked on November 16, 2023, following adjudication of all potential MACE endpoints, completion of QA/QC, and collection of investigator signatures. Participant unblinding notification memo was distributed on November 20, 2023.

Outcome Measures

Efficacy

The primary estimand was the cause-specific relative hazard of prescribed pitavastatin versus placebo with statin initiation if clinically indicated. The primary outcome measure for efficacy was time to first event of a composite of primary major adverse cardiovascular events (MACE) including:

- Atherosclerotic or other cardiovascular disease death
- Nonfatal myocardial infarction
- Unstable angina hospitalization
- Coronary, carotid, or peripheral arterial revascularization
- Nonfatal stroke or transient ischemic attack
- Peripheral arterial ischemia (acute or chronic limb ischemia, amputation, etc.)

All primary events were prospectively determined and adjudicated by an expert Clinical Events Committee (CEC) based on standardized criteria used in prior cardiovascular trials and developed by consensus groups and the FDA.[2]

All deaths classified as undetermined by CEC were considered primary MACE endpoints for this outcome measure, as specified in the Clinical Event Committee Charter.

Secondary outcome and supportive outcome measures include:

- Time to confirmed MACE (Primary MACE, excluding deaths of undetermined cause)
- Time to first Primary MACE on treatment (as-treated)
- Time to first MACE or death (all-cause)
  - An additional supportive analysis includes data from vital status and endpoint follow-up
- Time to death (all-cause)
- Time to the first of each individual component of the primary outcome measure
  - Events that resulted in death are included (e.g. first cardiac ischemia or MI includes MIs that resulted in death)

In addition to the previously reported outcome measures, a supportive outcome measure limited to the hard clinical endpoints of myocardial infarction, stroke and CV death is presented. This outcome measure was added to provide event incidence of the CVD events included in the development of the American Heart Association and American College of Cardiology 2013 Pooled Cohort Equation risk equations.[3]

Adverse Events

Adverse events presented are those with onset date after randomization that met the protocol reporting requirements. Events with a start date on the date of randomization were assumed to have occurred after randomization and were included. Targeted clinical events for pitavastatin efficacy evaluation (i.e., Primary MACE, deaths, COVID-19, and heart failure) were not included in AE summaries, regardless of severity or seriousness. Similarly, potential MACE and heart failure endpoints (i.e., adjudicated events or "triggers") adjudicated as duplicate are excluded — these occurred subsequent to a positively adjudicated event. Non-fatal MACE triggers reviewed and determined as not MACE or heart failure (i.e., downgraded events) were included if they met REPRIEVE AE reporting criteria (see protocol). Of note, since deaths were not included as AEs, all SAEs are non-fatal. All deaths were summarized separately as part of efficacy analyses.

Targeted adverse events included incident diabetes mellitus, myalgia, muscle weakness, or myopathy that was treatment-limiting or Grade 3 or higher, rhabdomyolysis, ALT elevation of grade 3 or higher.

Diabetes events were identified based on MedDRA terminology search strings. Diabetes includes a preferred term search for *diabetes* across all reported events, as well as *blood glucose increased*, *hyperglycemia* and *hyperglycemic* in the subset of Grade 3 or higher events. *Gestational diabetes* and *pre-diabetes* were excluded. Diabetes is classified as confirmed based on initiation of *anti-diabetic therapy*. If a participant was taking anti-diabetic therapy at the time of the diabetes diagnosis, the event was confirmed at diagnosis. Incidence rate estimation was limited to the participants without pre-existing diabetes at enrollment.

Myalgia, muscle weakness, and myopathy events were identified based on MedDRA terminology by a preferred term search on: *myalgia*, *myopathy*, and *muscular weakness*. Targeted events were those that were grade 3 or higher or resulted in a change to study treatment. Grade 3 or higher myopathy is also described.

Rhabdomyolysis events are identified via MedDRA preferred term search for *rhabdomyolysis,* excluding *Haff syndrome* based on the literal entered by the site. Note that participants with rhabdomyolysis are separate from those with myalgia/myopathy due REPRIEVE reporting requirements to enter the primary diagnosis only.

<u>Analysis Population</u>

Unless otherwise specified, summaries by treatment group follow intention-to-treat approach, where participants are included according to their randomized treatment group, whether or not they started study treatment or subsequent changes to that treatment.

<u>Confidence Level</u>

The primary treatment effect estimate is presented with a 95% repeated confidence interval (RCI) that adjusts for interim looks according to the realized Lan and DeMets implementation of the O'Brien-Fleming sequential stopping boundary. To summarize, the first interim analysis occurred at 55% information (n=159 endpoints) and the second at 78% (n=225 endpoints) information, at which point the trial stopped for efficacy. An additional 32 endpoints accumulated subsequently, yielding a total of 257 endpoints in the final database (89% of the planned 288 endpoints). The 95% RCI was constructed based on the boundary at 89% information (assuming the study had not been stopped). The corresponding efficacy boundary Z-value is 2.19. All other estimated treatment effects are provided with two-sided 95% confidence intervals.

Except the adjustment for interim monitoring in the primary treatment effect estimation described above, no adjustment is made for multiple comparisons. However, with the primary clinical and substudy hypotheses, and various secondary outcome measures, it is recognized that there is a multiplicity of analyses to be performed and inference is tempered accordingly.

Analysis Approaches

Event incidence for first Primary MACE and associated secondary and supportive outcomes were estimated as number of events divided by total person years of follow-up. Stratified incidence rate ratios estimated from Poisson regression models adjusted for stratification factors (sex and screening CD4 cell count) are provided with nominal 95% confidence intervals.

The primary analysis of treatment efficacy used a stratified Cox proportional hazards regression model with cause-specific hazards, with separate cause-specific baseline hazards by sex and screening CD4 cell count. Time from randomization to the first event of interest was evaluated. In line with the primary estimand, treatment discontinuation was ignored, including the initiation of statin therapy as part of clinical care (intention to treat policy). Deaths from non-CV causes (competing events precluding occurrence of Primary MACE) are censored at the time of death in accordance with the ICH E9(R1) “while alive” strategy. Nonproportional hazards were evaluated with treatment-by-time interaction. Missing data (due to loss to follow-up) were assumed to be non-informative, and administratively censored. The relative cause-specific hazard of pitavastatin versus placebo for First Primary MACE was estimated with a repeated 95% confidence interval.

Cumulative incidence functions were estimated using Aalen estimator for probability of subdistribution of failure of interest.

Similar analyses are presented for the secondary and supporting outcome measures. In the analysis of First Confirmed MACE, both non-CV deaths and deaths of undetermined cause are competing events. For First MACE or Death cumulative incidence over time is presented as one minus Kaplan-Meier survival estimate. Estimation for the first peripheral arterial revascularization component used a Bayes analysis with a non-informative prior using adaptive rejection Metropolis sampling. In this case, the interval shown is a 95% highest posterior density (HPD) interval. This unplanned analysis approach was used when conventional partial likelihood methods failed to provide a confidence interval as a result of zero events in the pitavastatin group. Given the highly skewed distribution of the posterior density, instability in the upper bound of the HPD interval was apparent with the values oscillating between one of 6 values between 0.13 and 0.66 despite otherwise good convergence diagnostics. The most conservative (widest) interval is displayed.

To supplement the primary estimand, an as-treated estimand was defined that censored treatment discontinuation as a competing risk event to estimate the pitavastatin effect when taken as prescribed as compared to no statin therapy. Although the original analysis plan called for censoring of follow-up at the time of discontinuation, on review of the results this approach appeared to be over censoring events (nearly 50% of first Primary MACE events were censored). Without further review of the data, the as-treated censoring plan was changed to censor follow-up 30 days after treatment discontinuation. Upon further review of the data, it was clear that treatment discontinuation due to death was being incorrectly censored at the date of that known dose often many weeks prior to the death. In these cases, the last known dose reported likely reflects the last contact with the participant at previous scheduled study visit (quarterly visits +/- 30-day window). For the as-treated analysis presented, participants discontinuing due to death with a last known dose within 180 days of death were assumed to have continued treatment until death; if last known dose was more than 180 days prior to death, the participant was considered to have been lost to follow-up and censored at 30 days after last known dose.

Further, to better reflect the REPRIEVE treatment conditions of pitavastatin versus statin initiation when clinically indicated, a per-protocol estimand was added in which treatment discontinuation due to clinical

need for statin therapy was not considered a treatment discontinuation event, thus estimating the effect of immediate pitavastatin when taken as prescribed as compared to delayed statin therapy initiated when clinically indicated.

Incidence rates for adverse events were estimated using Poisson distribution based on date of the first event of interest or latest participant contact on study (in absence of a preceding event), with time calculated from date of randomization. Incidence rate ratios are provided for comparisons between the two treatment groups. Poisson models adjusted for stratification factors (sex and screening CD4 cell count) were used for estimation.

The full distributions of fasting LDL and non-LDL cholesterols over time are presented with both distribution summaries (median and first and 3rd quartiles) and population averages (mean and 95% confidence interval) by treatment group. The pre-specified analyses of lipids are planned based upon completion of laboratory testing. LDL cholesterol is limited to participants with triglycerides <500 mg/dL; derived as calculated LDL at triglycerides <400 mg/dL and direct LDL at triglycerides 400-<500 mg/dL.

Sensitivity Analyses for Unknown Primary Endpoint Status (see Figure S5)

In the primary analysis of pitavastatin effect on First Primary MACE, endpoints and follow-up time were censored at the last contact or at the time of primary or competing event, whichever occurred earliest. A total of 40,394 PYs were observed for 7769 participants, 20,183 for 3888 pitavastatin group participants and 20,211 for 3881 placebo group participants.

At the end of the study (August 21, 2023), 639 (16%) participants in the pitavastatin group and 610 (16%) in the placebo group had unknown primary endpoint status and no contact for more than 10 months. For these participants, a total of 5,171 PYs would have accrued between their last contact and August 21, 2023 ("unobserved follow-up time"): 2,703 PYs in the pitavastatin and 2,468 PYs in the placebo group.

In order to assess the impact of missing data from these participants, we performed a simulation study to evaluate the overall statin effect based on the accumulated data out to August 21, 2023 (aka observed data) and under a range of scenarios for the unobserved data.

Event accumulation for unobserved data in each treatment group was assumed to follow the current trends (Figure S3) times a constant (1 for current trend; 2x, 3x and 5x higher; and 2x, 3x and 10x lower than the current trend). For example, in one scenario, events for unobserved follow-up time in the pitavastatin group were assumed to occur at a rate twice (2x) that observed (i.e., 9.91 / 1000 PY) whereas those in the placebo group were assumed to occur at the observed rate (7.77 /1000PY). In each case, simulations for future data also assume: follow-up from last contact to August 21, 2023; a rate of non-CVD death of 5/ 1000 PY (consistent with the original sample size considerations, and the observed data); and no further loss to follow-up. Endpoints (n=8) and non-CV deaths (n=9) from vital status follow-up were included as observed data in the simulations. 1,000 simulations for unobserved data were performed for each scenario. The stratified Cox proportional hazards model was used to estimate the treatment effect (HR with 95% RCI) based on observed and simulated data combined.

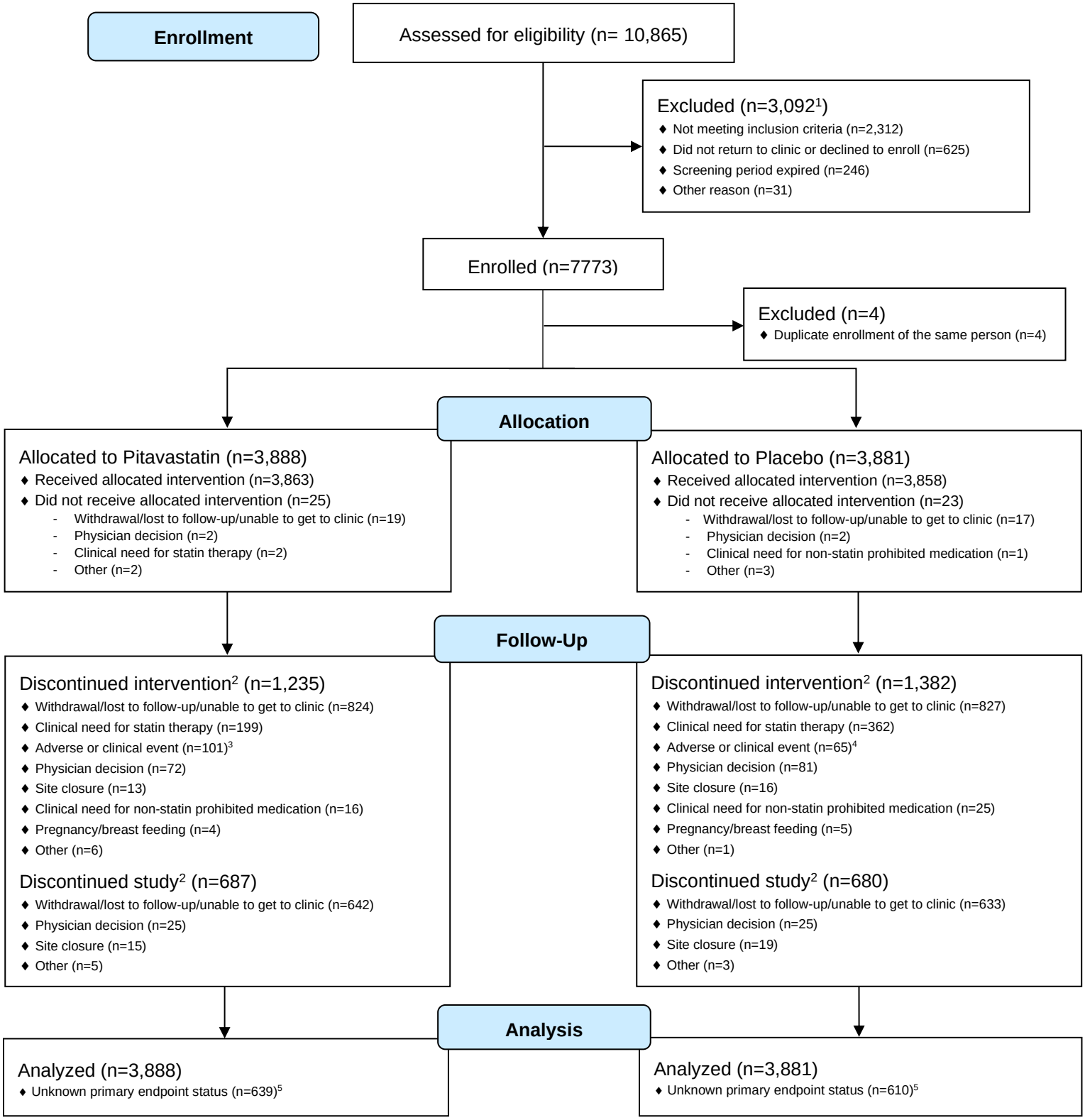
Averages across 1,000 simulations are shown, including for lower and upper bounds of the 95% RCI. As such, the actual coverage probability of the confidence intervals may differ slightly from 95%.

The Number Needed to Treat (NNT) to Prevent One Primary MACE (see Figure S10)

The NNT was determined in a supportive post-hoc analysis of the primary endpoint of first MACE. The NNT to prevent one primary endpoint of first MACE was 100 and decreased with increasing AHA/ACC pooled cohort equation risk score. The NNT observed in REPRIEVE compares favorably with other strategies, particularly considering the low overall risk of the trial population.[4]

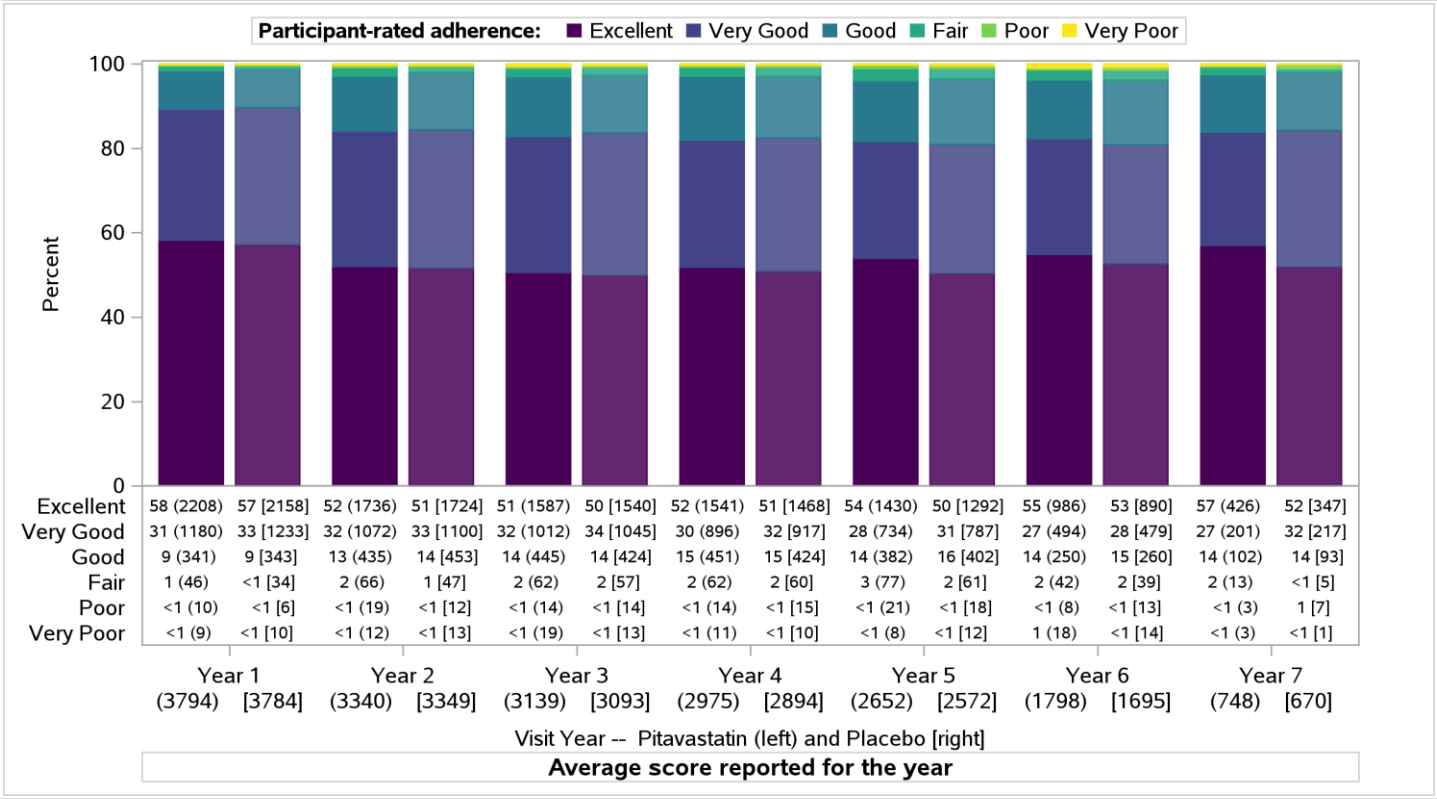
Section 2: Supplementary Figures and Tables

Figure S1: CONSORT Diagram



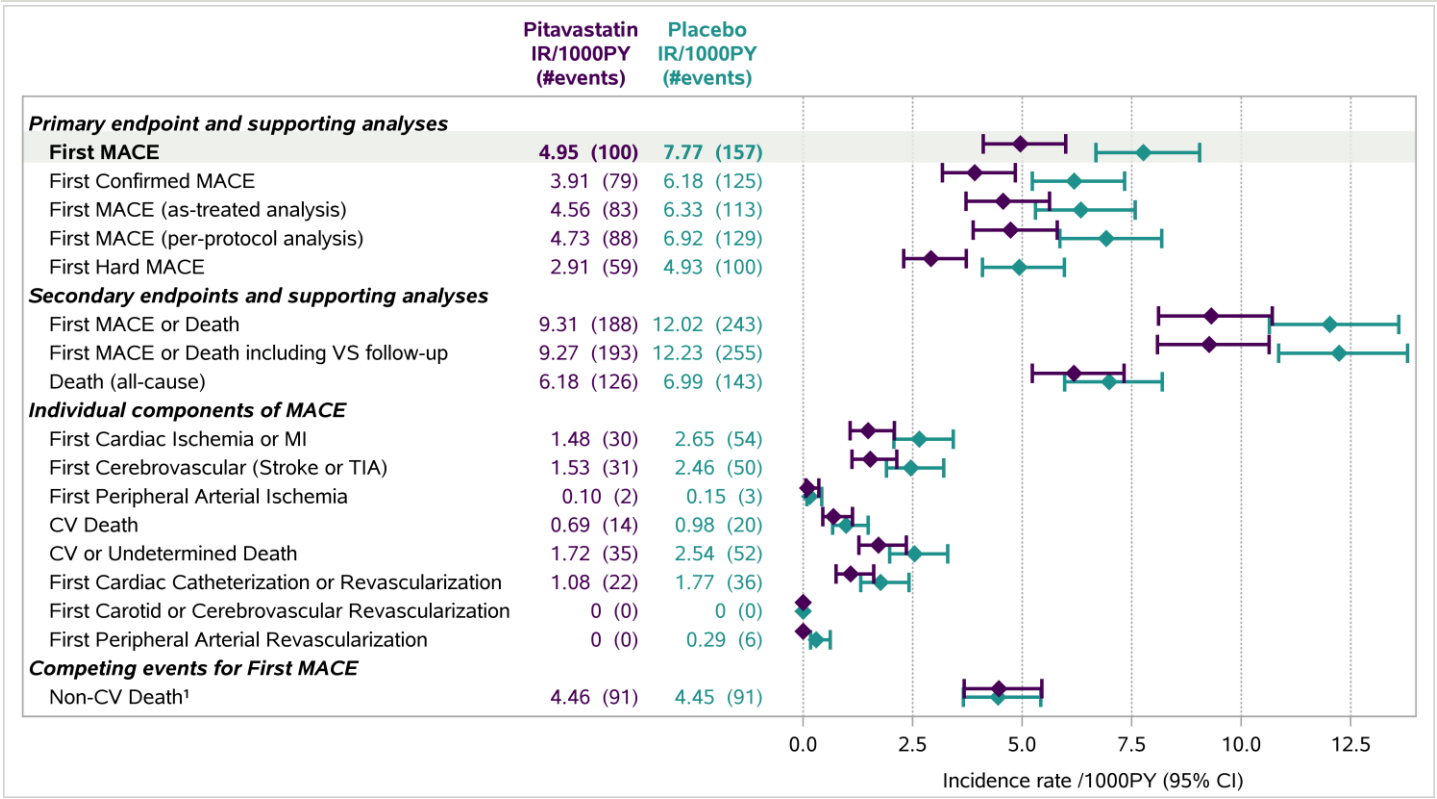
[1] Multiple screening failure reasons could be reported.
[2] Treatment and/or study discontinuation concurrent with death is not considered premature discontinuation and is excluded.
[3] Of the treatment discontinuations due to adverse or clinical events in the pitavastatin group, 6 were due to MACE and 0 due to diabetes.
[4] Of the treatment discontinuations due to adverse or clinical events in the placebo group, 9 were due to MACE and 3 due to diabetes.
[5] Unknown primary endpoint status as of study closure on August 21, 2023 defined as no contact for more than 10 months.

Figure S2: Adherence by Participant Report



Participants were asked to rate their adherence to study medication since the last visit. An average of the assessments in each year is shown. Percentage (no.) of participants for the pitavastatin and percentage [no.] for the placebo group are shown below bars. Percentages are out of participants with at least one questionnaire completed in a given time period shown below each time point.

Figure S3: Incidence of First MACE and Other Efficacy Endpoints

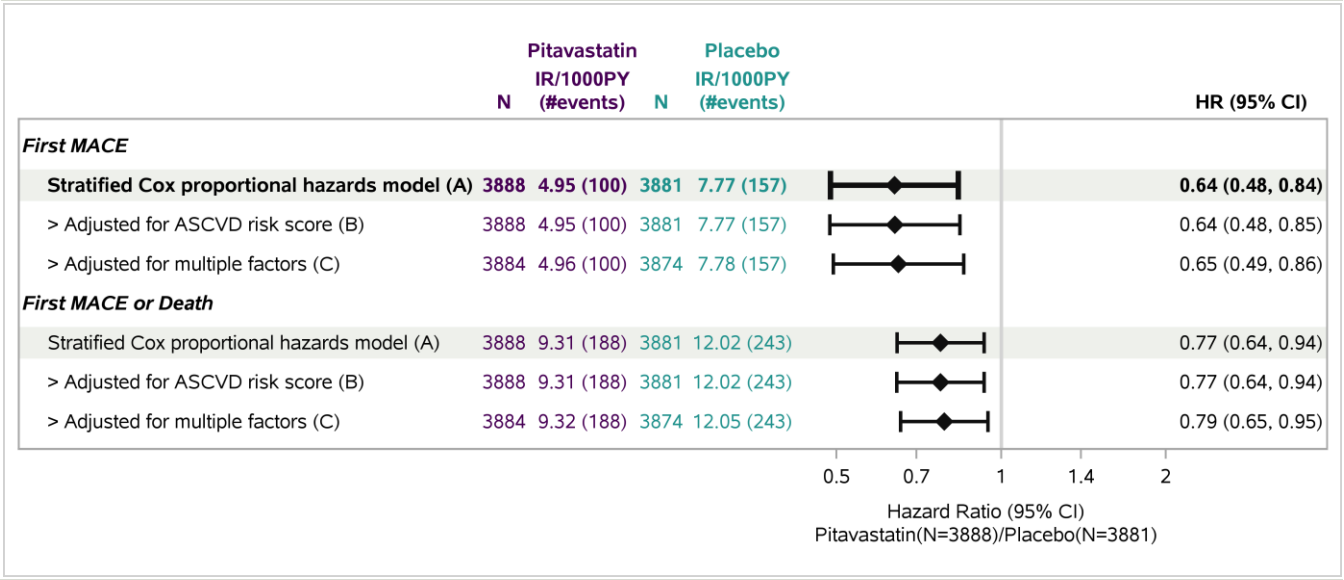


Incidence rates were estimated using Poisson distribution based on the earliest event or last contact, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.

¹ All non-CV deaths are included; 3 in the pitavastatin group and 5 in the placebo group occurred subsequent to MACE endpoints.

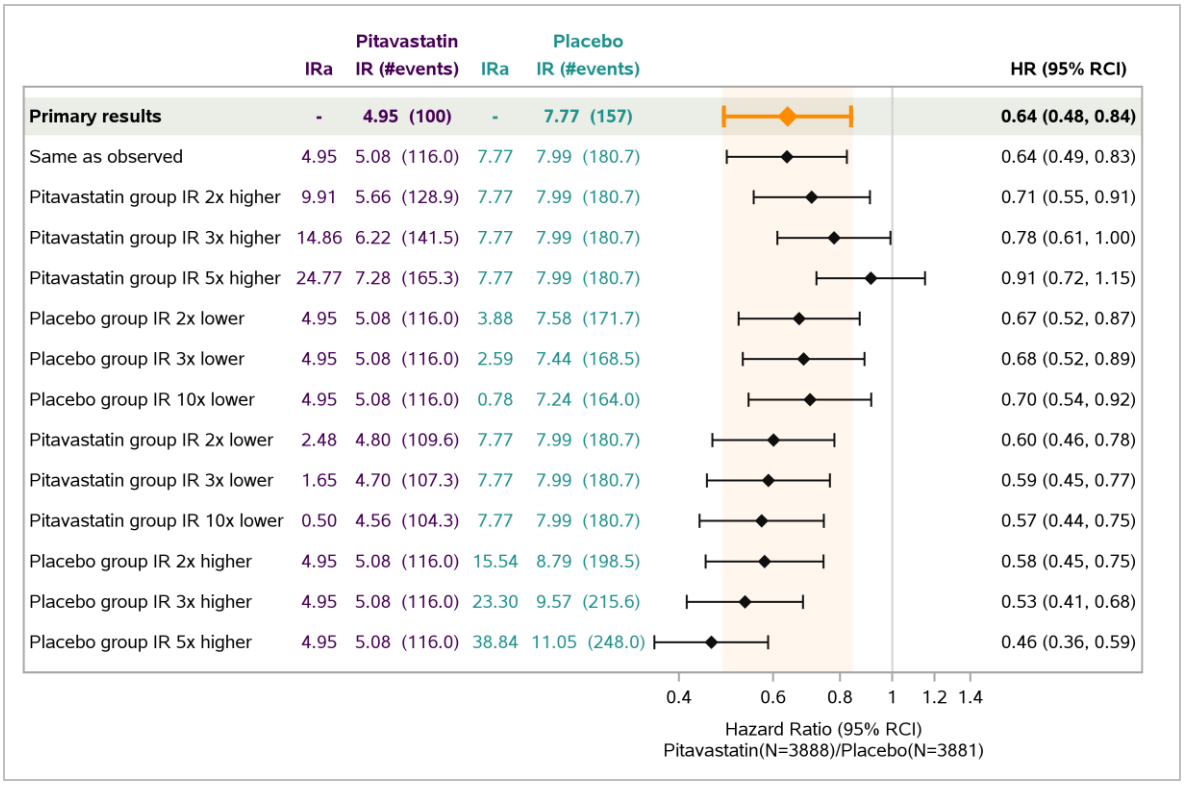
CI denotes confidence interval, CV cardiovascular, IR incidence rate, MACE major adverse cardiovascular event, MI myocardial infarction; PY person-years, TIA transient ischemic attack, VS vital status.

Figure S4: Treatment Effect from Adjusted Stratified Cox Proportional Hazards Models



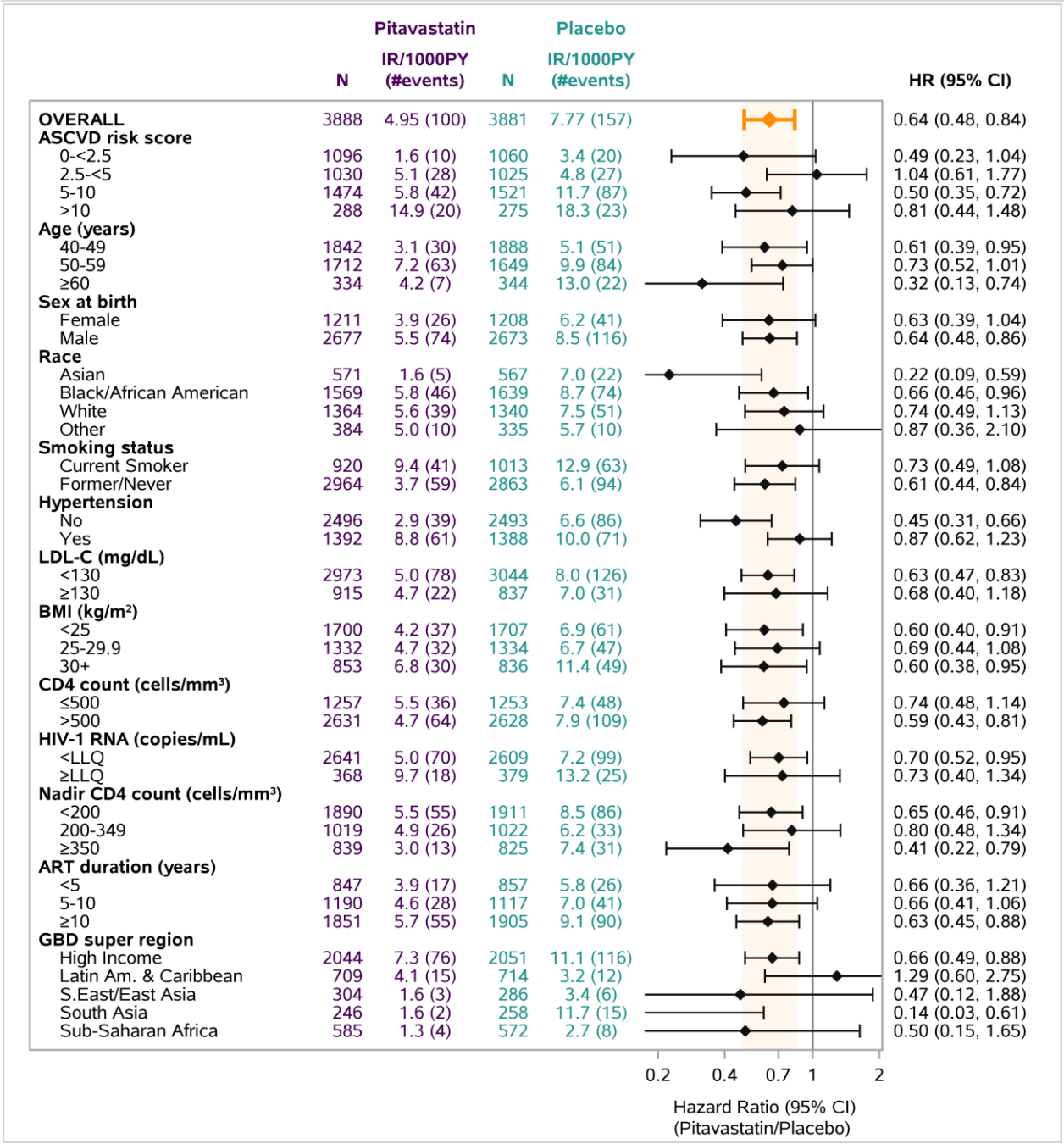
Stratified (by natal sex and screening CD4 cell count) Cox proportional hazards model with treatment group as the only covariate is the primary analysis (A). Further models were evaluated adjusting for (B) ASCVD risk score, and for (B) age, race, smoking status, race, presence of hypertension, LDL-C, nadir CD4, total ART duration and GBD region as covariates. For the First MACE endpoint, non-CV deaths without MACE were treated as competing events and censored.
Cause-specific HR estimates with CIs for treatment effect are shown; two-sided 95% repeated CIs for the First MACE and two-sided nominal 95% CIs the First MACE or Death. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.
For visual purposes, the data on the x-axis are shown in the log scale.
ASCVD denotes atherosclerotic cardiovascular disease, ART antiretroviral therapy, CI confidence interval, HR hazard ratio, IR incidence rate, GBD global burden of disease, LDL-C LDL cholesterol, PY person-years.

Figure S5: Sensitivity Analyses for Primary Endpoint to Assess Impact of Missing Data



The data presented are: assumed incidence rate /1000 PY for time with unknown endpoint status (IRa), number of participants with events, estimated incidence rate /1000 PY (IR), HR with 95% CI. Incidence rates are estimated using Poisson distribution.
For simulated data, the mean IR and the mean number of events across 1000 simulations are shown. Cause-specific HR estimates with 95% repeated CI are from stratified (by sex and screening CD4 cell count) Cox proportional hazards models. For simulations, the means of HR estimate, lower and upper bounds of the repeated 95% CI across 1000 simulations are shown.
CI denotes confidence interval, HR hazard ratio, IR incidence rate, IRa assumed incidence rate, PY person-years.

Figure S6: Treatment Effect on First MACE in Predefined Subgroups

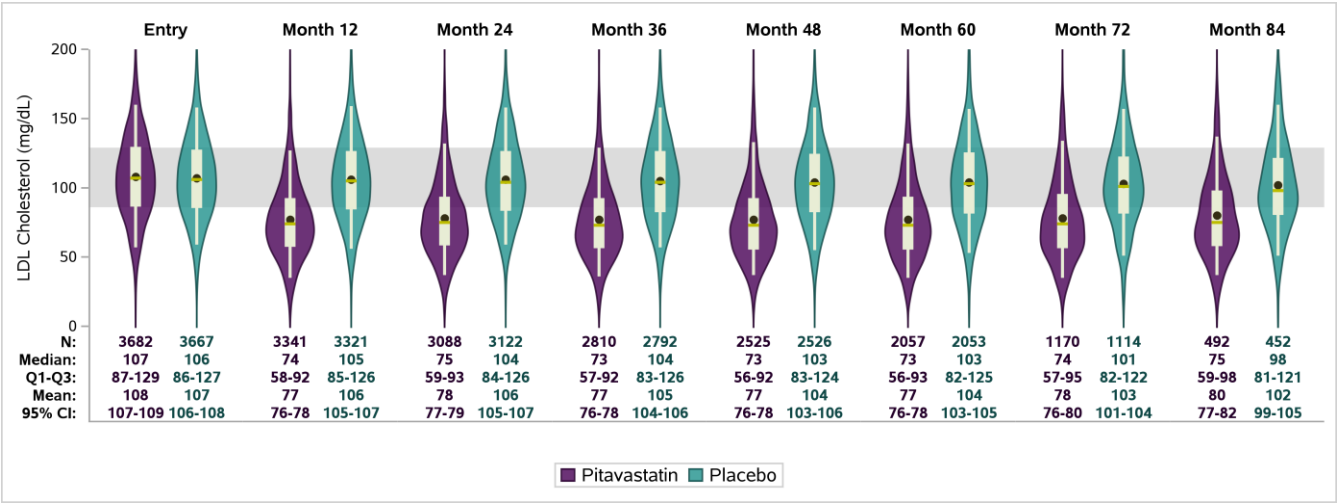


Each factor was included individually in a cause-specific Cox proportional hazards model that was stratified by sex at birth and CD4 cell count at screening. Modification of the statin effect was assessed via factor interaction with treatment. For reference, the overall treatment effect in the primary analysis is shown at the top of the graph. The widths of the confidence intervals have not been adjusted for multiplicity and therefore may not be used in place of hypothesis testing. The 95% confidence intervals in subgroups with small numbers of events have been truncated. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

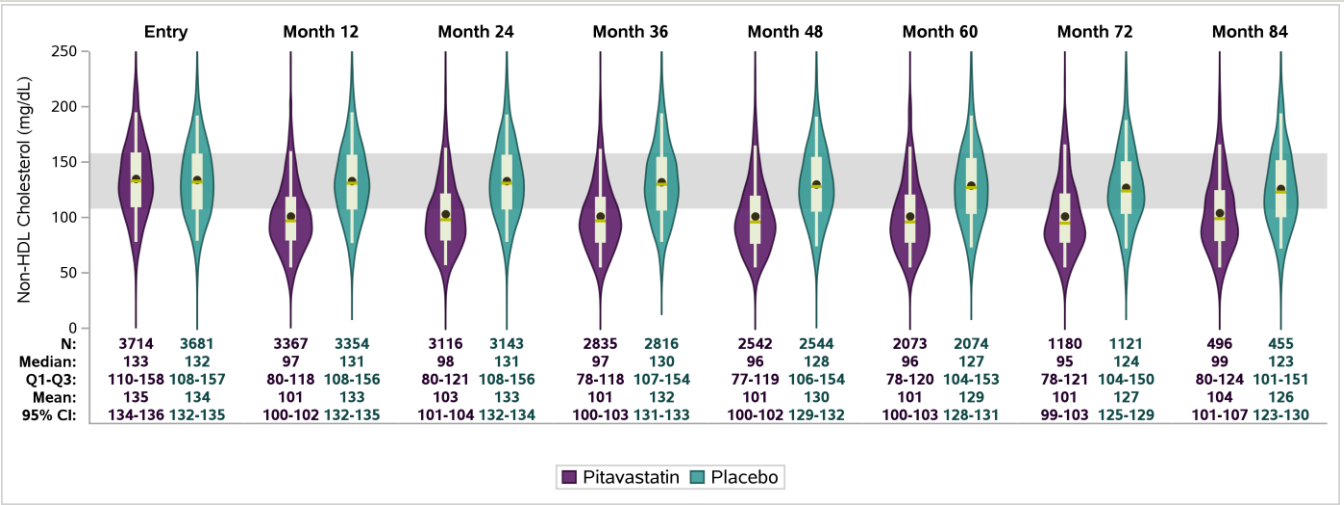
ART denotes antiretroviral therapy, ASCVD denotes atherosclerotic cardiovascular disease, CI confidence interval, GBD global burden of disease, HR hazard ratio, IR incidence rate, LDL-C low-density lipoprotein cholesterol, PY person-years.

Figure S7: Fasting Cholesterol Levels Over Time

(a) LDL Cholesterol

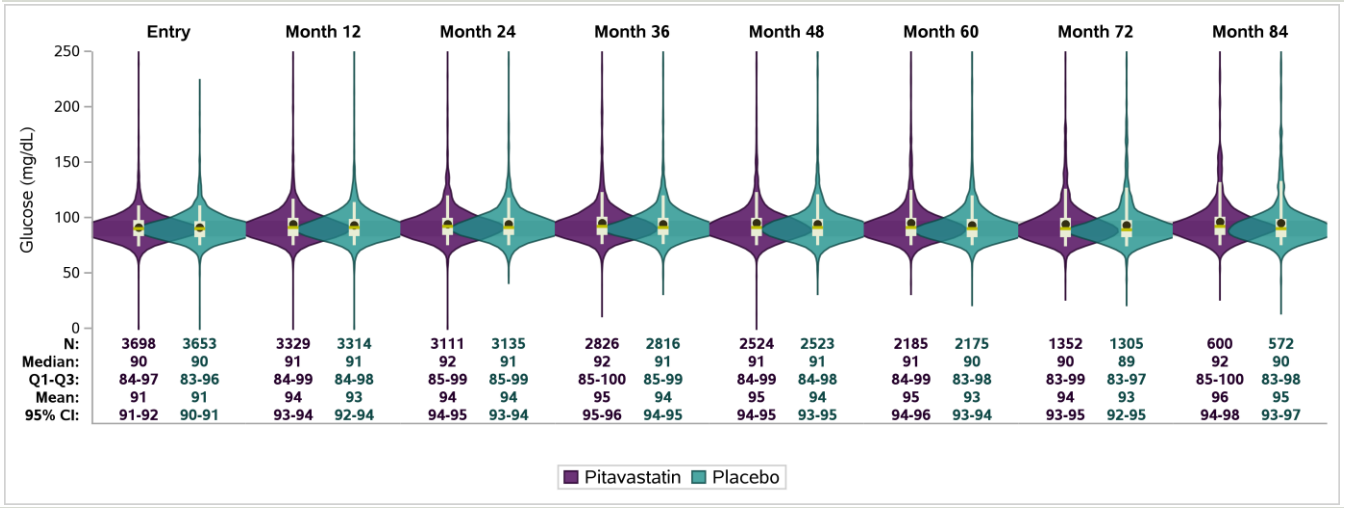


(b) Non-HDL Cholesterol



Shown are violin plots of data regarding LDL cholesterol (Panel A) and non-high-density lipoprotein (HDL) cholesterol (Panel B) in the pitavastatin group and the placebo group. In each plot, the mean value is indicated by a circle, the median by a horizontal line, and the interquartile range (Q1 - Q3) by the top and bottom of a box; whiskers indicate the 5th and 95th percentiles, and the tapering points reflect the shape of the distribution. For reference, the shaded area indicates the matching interquartile ranges in the pitavastatin and placebo groups at trial entry. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect. Fasting samples are tested centrally in batch, and testing is in progress; results available as of December 22, 2023 are presented. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

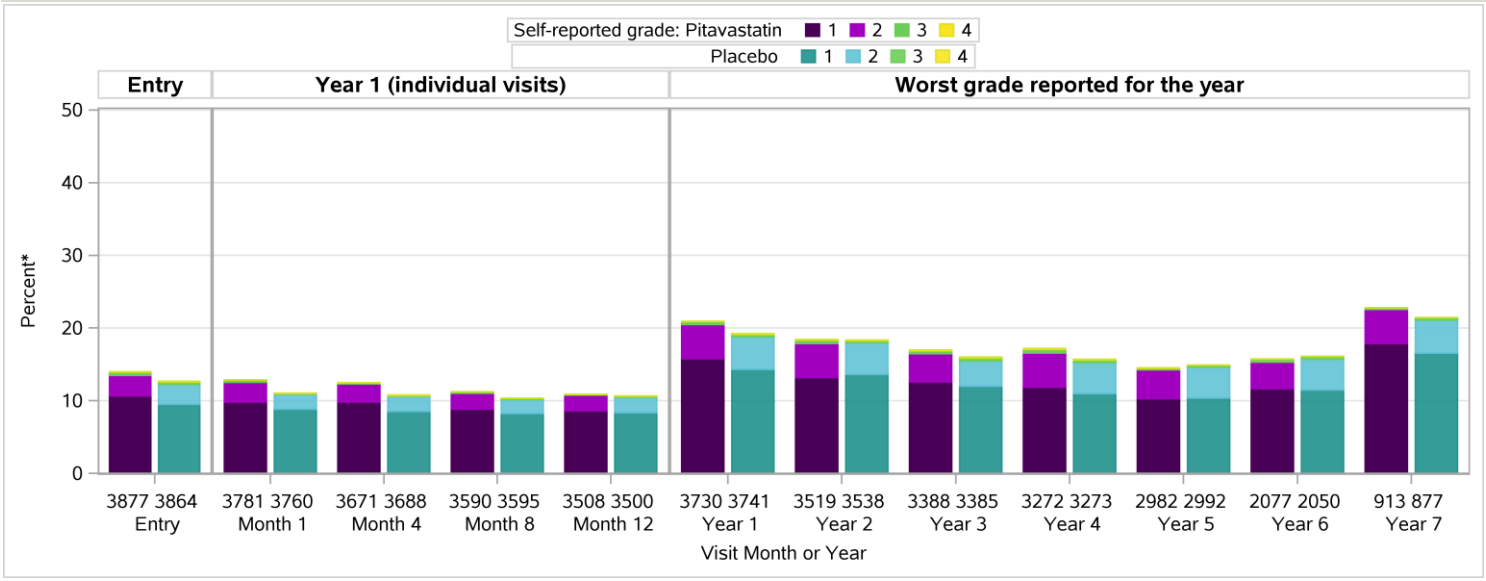
Figure S8: Fasting Glucose Over Time



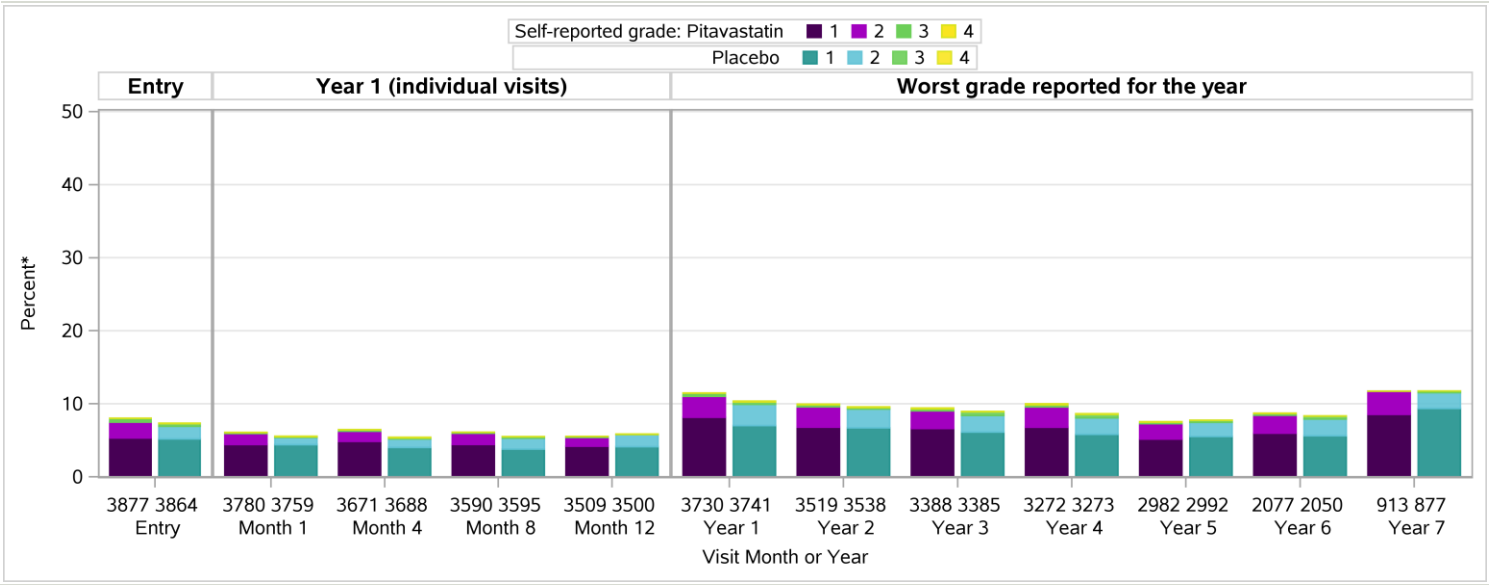
Violin plots presenting Kernel estimate of probability density function, and mean (circle), median (yellow dash), Q1-Q3 (box) and P5-P95 (whiskers); means with 95% CIs are shown in the axis table. For reference, the shaded area indicates the matching interquartile ranges in the pitavastatin and placebo groups at trial entry. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect. Fasting samples are tested centrally in batch, and testing is in progress; results available as of December 22, 2023 are presented.
CI denotes confidence interval, P5 5th percentile, P95 95th percentile, Q1 lower quartile, Q3 upper quartile.

Figure S9: Muscle Ache and Weakness by Participant Report

(a) Muscle ache

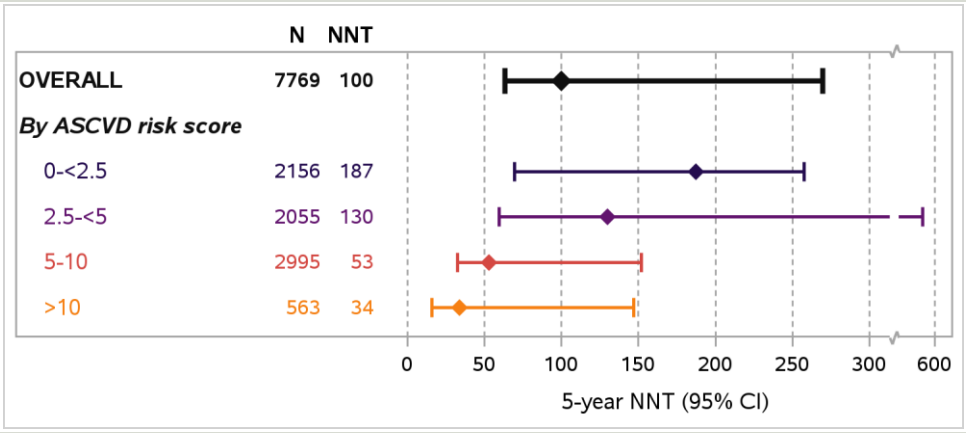


(b) Muscle weakness



Evaluations were conducted as participant interviews by the site staff. Assessments at individual visits are shown to Month 12, the worst grade across quarterly visits is shown annually.
Percentages are out of participants with at least one questionnaire completed in a given period, shown below bars.
**Y-axis is truncated at 50%. Bars show percentage of participant reports by grade (grade 0 not shown).*

Figure S10: 5-year Number Needed To Treat



NNT was estimated in a post-hoc supportive analysis of the primary endpoint of First MACE as previously described[1] based on the final data. 5-year NNT overall and by baseline ASCVD risk score is shown. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.

ASCVD denotes atherosclerotic cardiovascular disease, CI confidence interval, NNT number needed to treat.

Table S1: Incidence of Adverse Events

Event	Treatment Group	No. at risk	Total PY at risk	No. with event	Incidence Rate /100PY (95% CI)		Incidence Rate Ratio[4] (95% CI)	
Non-fatal SAE	Pitavastatin	3888	17,986	750	4.17	(3.88, 4.48)	1.00	(0.90, 1.10)
	Placebo	3881	18,053	755	4.18	(3.89, 4.49)	-	
Diabetes[1]	Pitavastatin	3864	19,655	232	1.18	(1.04, 1.34)	1.29	(1.07, 1.57)
	Placebo	3867	19,901	182	0.91	(0.79, 1.06)	-	
Grade ≥3 or treatment-limiting myalgia, muscle weakness or myopathy[2]	Pitavastatin	3888	19,982	92	0.46	(0.38, 0.56)	1.58	(1.14, 2.19)
	Placebo	3881	20,241	59	0.29	(0.23, 0.38)	-	
Grade ≥3 or treatment-limiting rhabdomyolysis	Pitavastatin	3888	20,375	3	0.015	(0.005, 0.046)	0.75	(0.17, 3.37)[5]
	Placebo	3881	20,462	4	0.020	(0.007, 0.052)	-	
Grade ≥3 ALT	Pitavastatin	3888	20,350	12	0.059	(0.033, 0.10)	1.34	(0.56, 3.18)[5]
	Placebo	3881	20,439	9	0.044	(0.023, 0.085)	-	
Any AE[3]	Pitavastatin	3888	15,678	1385	8.83	(8.38, 9.31)	1.04	(0.97, 1.12)
	Placebo	3881	15,961	1355	8.49	(8.05, 8.95)	-	

[1] Evaluation of diabetes incidence is limited to participants without pre-existing diabetes at baseline. Diabetes events are defined as diabetes diagnoses with an initiation of anti-diabetic therapy. Incident diagnosis of diabetes without initiation of antidiabetic therapy occurred in 10 participants in the pitavastatin group and 14 participants in the placebo group.
[2] Myopathy of grade 3 occurred in 3 participants in the pitavastatin group and 1 participant in the placebo group; none had grade 4 myopathy.
[3] Any adverse event was defined according to the protocol collection criteria (grade 3 or higher, leading to a change in trial treatment regardless of grade, serious adverse event, or targeted adverse event).
[4] Incidence rate ratios (reference=placebo) were adjusted for sex at birth and CD4 cell count at screening, except as indicated.
[5] An unadjusted incidence rate ratio is shown because no events were reported in a stratum according to sex at birth and CD4 count at screening.
The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.
AE denotes adverse event, ALT alanine transaminase, CI confidence interval, PY person-years, SAE serious adverse event.

Table S2: Details of First MACE Endpoints

Event type		Total (N=257)	Pitavastatin (N=100)	Placebo (N=157)
All Cardiac Ischemia or MI Events — no. (%)		**80 (31%)**	**28 (28%)**	**52 (33%)**
Myocardial Infarction	Type 1	55 (21%)	17 (17%)	38 (24%)
	Type 2	15 (6%)	8 (8%)	7 (4%)
	Type 3	1 (0%)	0 (0%)	1 (1%)
Unstable Angina		9 (4%)	3 (3%)	6 (4%)
All Cerebrovascular Events (Stroke or TIA) — no. (%)		**80 (31%)**	**31 (31%)**	**49 (31%)**
Stroke	Ischemic	48 (19%)	16 (16%)	32 (20%)
	Hemorrhagic	11 (4%)	2 (2%)	9 (6%)
	Undetermined	2 (1%)	1 (1%)	1 (1%)
Transient Ischemic Attack (TIA)		19 (7%)	12 (12%)	7 (4%)
All Deaths — no. (%)		**76 (30%)**	**33 (33%)**	**43 (27%)**
CV Death	Sudden Cardiac Death	20 (8%)	10 (10%)	10 (6%)
	Cardiovascular Causes	1 (0%)	1 (1%)	0 (0%)
	Cardiovascular Hemorrhage	1 (0%)	0 (0%)	1 (1%)
	Heart Failure	1 (0%)	1 (1%)	0 (0%)
Undetermined		53 (21%)	21 (21%)	32 (20%)
All Cardiac Catheterization or Revascularization Events — no. (%)		**14 (5%)**	**6 (6%)**	**8 (5%)**
Percutaneous (PCI)	Elective	11 (4%)	4 (4%)	7 (4%)
	Urgent	1 (0%)	1 (1%)	0 (0%)
Surgical (CABG)	Elective	2 (1%)	1 (1%)	1 (1%)
All Peripheral Arterial Ischemia Events — no. (%)		**4 (2%)**	**2 (2%)**	**2 (1%)**
Acute Limb Ischemia (ALI)		2 (1%)	1 (1%)	1 (1%)
Critical Limb Ischemia (CLI)		2 (1%)	1 (1%)	1 (1%)
All Peripheral Arterial Revascularization Events — no. (%)		**3 (1%)**	**0 (0%)**	**3 (2%)**
Percutaneous	Elective	2 (1%)	0 (0%)	2 (1%)
Surgical	Elective	1 (0%)	0 (0%)	1 (1%)

Percentages are out of all first MACE endpoints in total, and within each treatment group.
Some event names have been abbreviated: unstable angina requiring hospitalization as unstable angina, hospitalization for acute limb ischemia (ALI) as acute limb ischemia (ALI), hospitalization for critical limb ischemia (CLI) as critical limb ischemia (CLI).
ALI denotes acute limb ischemia, CABG coronary artery bypass grafting, CLI critical limb ischemia, MI myocardial infarction, PCI percutaneous coronary intervention, TIA transient ischemic attack.

Table S3: Details of First MACE or Death Endpoints Captured from Vital Status Follow-up

Event type		Total (N=17)	Pitavastatin (N=5)	Placebo (N=12)
All Deaths *— no. (%)*		**14 (82%)**	**4 (80%)**	**10 (83%)**
CV Death	Sudden Cardiac Death	1 (6%)	0 (0%)	1 (8%)
Non-CV Death	Non-AIDS-Defining Malignancies	4 (24%)	1 (20%)	3 (25%)
	Accident or Homicide	1 (6%)	0 (0%)	1 (8%)
	Central Nervous System	1 (6%)	0 (0%)	1 (8%)
	Lung Disease	1 (6%)	0 (0%)	1 (8%)
	Renal Failure	1 (6%)	1 (20%)	0 (0%)
	Suicide or Psychiatric Disease	1 (6%)	0 (0%)	1 (8%)
Undetermined		4 (24%)	2 (40%)	2 (17%)
All Cardiac Ischemia or MI Events *— no. (%)*		**2 (12%)**	**1 (20%)**	**1 (8%)**
Myocardial Infarction	Type 1	2 (12%)	1 (20%)	1 (8%)
All Cerebrovascular Events (Stroke or TIA) *— no. (%)*		**1 (6%)**	**0 (0%)**	**1 (8%)**
Stroke	Ischemic	1 (6%)	0 0%)	1 (8%)

Percentages are out of all first MACE or death endpoints captured from vital status and endpoint follow-up in total, and within each treatment group.
AIDS denotes acquired immunodeficiency syndrome, CV cardiovascular, MI myocardial infarction, TIA transient ischemic attack.

Table S4: Details of Non-CV Deaths

Cause of death	Total (N=182)	Pitavastatin (N=91)	Placebo (N=91)
Non-AIDS-Defining Malignancies — no. (%)	65 (36%)	33 (36%)	32 (35%)
Non-AIDS-Related Infections — no. (%)	47 (26%)	21 (23%)	26 (29%)
Substance Use — no. (%)	27 (15%)	16 (18%)	11 (12%)
Accident or Homicide — no. (%)	17 (9%)	7 (8%)	10 (11%)
AIDS Opportunistic Infections — no. (%)	11 (6%)	5 (5%)	6 (7%)
Suicide or Psychiatric Disease — no. (%)	6 (3%)	5 (5%)	1 (1%)
Liver Failure — no. (%)	2 (1%)	1 (1%)	1 (1%)
Renal Failure — no. (%)	2 (1%)	1 (1%)	1 (1%)
AIDS-Defining Malignancies — no. (%)	1 (1%)	1 (1%)	0 (0%)
Gastrointestinal — no. (%)	1 (1%)	0 (0%)	1 (1%)
Lung Disease — no. (%)	1 (1%)	1 (1%)	0 (0%)
AIDS Other — no. (%)	1 (1%)	0 (0%)	1 (1%)
Other — no. (%)	1 (1%)	0 (0%)	1 (1%)

Deaths adjudicated as non-CV deaths with cause of death determined by the adjudication committee are shown.
The total number of non-CV deaths is shown in column headers. Percentages are out of all non-CV deaths in total, and within each treatment group.

Table S5: Incidence of Heart Failure

Event	Treatment Group	# Participants at risk	Total at-risk person-years	# Participants with event	Incidence Rate /1000PY (95% CI)
First Heart Failure	Pitavastatin	3888	20,361	13	0.64 (0.37, 1.10)
	Placebo	3881	20,436	15	0.73 (0.44, 1.22)

Hospitalization for heart failure events as determined by the adjudication committee are summarized, including events positively adjudicated as MACE endpoints. These are presented in Table S2, and include 1 fatal heart failure.
Incidence rates were estimated using Poisson distribution based on the earliest event or last contact, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time.
The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.

Table S6: Non-Fatal Serious Adverse Events by MedDRA System Organ Class

	Total (N=7769)	Pitavastatin (N=3888)					Placebo (N=3881)				
	All	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
All participants with non-fatal SAEs — no. (%)	**1505 (19%)**	**4 (<1%)**	**29 (<1%)**	**601 (15%)**	**116 (3%)**	**750 (19%)**	**2 (<1%)**	**32 (<1%)**	**582 (15%)**	**139 (4%)**	**755 (19%)**
Infections and infestations	546 (7%)	0 (0%)	8 (<1%)	241 (6%)	24 (<1%)	273 (7%)	0 (0%)	10 (<1%)	234 (6%)	29 (<1%)	273 (7%)
Injury, poisoning and procedural complications	218 (3%)	2 (<1%)	4 (<1%)	89 (2%)	11 (<1%)	106 (3%)	1 (<1%)	3 (<1%)	92 (2%)	16 (<1%)	112 (3%)
Gastrointestinal disorders	149 (2%)	1 (<1%)	3 (<1%)	70 (2%)	2 (<1%)	76 (2%)	0 (0%)	2 (<1%)	67 (2%)	4 (<1%)	73 (2%)
Respiratory, thoracic and mediastinal disorders	140 (2%)	0 (0%)	4 (<1%)	51 (1%)	12 (<1%)	67 (2%)	0 (0%)	2 (<1%)	49 (1%)	22 (<1%)	73 (2%)
Nervous system disorders	139 (2%)	0 (0%)	2 (<1%)	68 (2%)	3 (<1%)	73 (2%)	0 (0%)	4 (<1%)	56 (1%)	6 (<1%)	66 (2%)
Neoplasms benign, malignant and unspecified	138 (2%)	2 (<1%)	2 (<1%)	43 (1%)	15 (<1%)	62 (2%)	1 (<1%)	8 (<1%)	49 (1%)	18 (<1%)	76 (2%)
Psychiatric disorders	123 (2%)	0 (0%)	0 (0%)	44 (1%)	20 (<1%)	64 (2%)	0 (0%)	2 (<1%)	46 (1%)	11 (<1%)	59 (2%)
Musculoskeletal and connective tissue disorders	110 (1%)	0 (0%)	6 (<1%)	53 (1%)	2 (<1%)	61 (2%)	0 (0%)	2 (<1%)	47 (1%)	0 (0%)	49 (1%)
Renal and urinary disorders	71 (<1%)	0 (0%)	0 (0%)	28 (<1%)	9 (<1%)	37 (<1%)	0 (0%)	0 (0%)	24 (<1%)	10 (<1%)	34 (<1%)
Metabolism and nutrition disorders	65 (<1%)	0 (0%)	1 (<1%)	15 (<1%)	14 (<1%)	30 (<1%)	0 (0%)	0 (0%)	21 (<1%)	14 (<1%)	35 (<1%)
Cardiac disorders[1]	59 (<1%)	0 (0%)	3 (<1%)	21 (<1%)	4 (<1%)	28 (<1%)	0 (0%)	3 (<1%)	21 (<1%)	7 (<1%)	31 (<1%)
General disorders and administration site conditions	59 (<1%)	0 (0%)	3 (<1%)	23 (<1%)	2 (<1%)	28 (<1%)	2 (<1%)	1 (<1%)	27 (<1%)	1 (<1%)	31 (<1%)
Vascular disorders	56 (<1%)	1 (<1%)	4 (<1%)	17 (<1%)	3 (<1%)	25 (<1%)	0 (0%)	4 (<1%)	22 (<1%)	5 (<1%)	31 (<1%)
Hepatobiliary disorders	51 (<1%)	0 (0%)	0 (0%)	21 (<1%)	2 (<1%)	23 (<1%)	0 (0%)	1 (<1%)	25 (<1%)	2 (<1%)	28 (<1%)
Investigations	47 (<1%)	0 (0%)	0 (0%)	11 (<1%)	13 (<1%)	24 (<1%)	1 (<1%)	1 (<1%)	11 (<1%)	10 (<1%)	23 (<1%)
Blood and lymphatic system disorders	45 (<1%)	0 (0%)	0 (0%)	15 (<1%)	10 (<1%)	25 (<1%)	0 (0%)	0 (0%)	6 (<1%)	14 (<1%)	20 (<1%)
Surgical and medical procedures	34 (<1%)	0 (0%)	3 (<1%)	11 (<1%)	0 (0%)	14 (<1%)	0 (0%)	4 (<1%)	16 (<1%)	0 (0%)	20 (<1%)
Reproductive system and breast disorders	30 (<1%)	0 (0%)	0 (0%)	16 (<1%)	1 (<1%)	17 (<1%)	0 (0%)	0 (0%)	13 (<1%)	0 (0%)	13 (<1%)
Eye disorders	29 (<1%)	1 (<1%)	2 (<1%)	19 (<1%)	0 (0%)	22 (<1%)	0 (0%)	0 (0%)	7 (<1%)	0 (0%)	7 (<1%)
Skin and subcutaneous tissue disorders	18 (<1%)	0 (0%)	0 (0%)	8 (<1%)	0 (0%)	8 (<1%)	0 (0%)	1 (<1%)	9 (<1%)	0 (0%)	10 (<1%)
Ear and labyrinth disorders	8 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	6 (<1%)	0 (0%)	7 (<1%)
Endocrine disorders	7 (<1%)	0 (0%)	0 (0%)	3 (<1%)	2 (<1%)	5 (<1%)	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	2 (<1%)
Immune system disorders	6 (<1%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	3 (<1%)	1 (<1%)	4 (<1%)
Pregnancy, puerperium and perinatal conditions	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Social circumstances	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Product issues	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Events are described by MedDRA System Organ Class (SOC) ordered by overall frequency, and are presented by Grade within each treatment group. Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially life-threatening) according to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.

[1]Cardiac disorders include events classified under MedDRA SOC of Cardiac Disorders that are not part of the composite MACE outcome as well as events reviewed and determined as not MACE by the independent adjudication committee.

For the overall and SOC totals, each participant is counted only once and at the highest reported grade. A total of 2688 non-fatal SAEs were reported for 1505 participants. The most frequently reported MedDRA HLT was "lower respiratory tract and lung infections" (experienced by 2% of participants overall, and within each treatment group), no other HLT occurred in ≥1% participants. HLT denotes higher level term, MedDRA Medical Dictionary for Regulatory Activities, NEC not elsewhere classified, SAE serious adverse event, SOC system organ class.

Table S7: All Adverse Events by MedDRA System Organ Class and Higher Level Term

	Total (N=7769)	Pitavastatin (N=3888)					Placebo (N=3881)				
	All	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
All participants with Adverse Events — no. (%)	**2740 (35%)**	**51 (1%)**	**200 (5%)**	**993 (26%)**	**141 (4%)**	**1385 (36%)**	**64 (2%)**	**172 (4%)**	**962 (25%)**	**157 (4%)**	**1355 (35%)**
Metabolism and nutrition disorders	**661 (9%)**	**46 (1%)**	**183 (5%)**	**98 (3%)**	**22 (<1%)**	**349 (9%)**	**50 (1%)**	**142 (4%)**	**99 (3%)**	**21 (<1%)**	**312 (8%)**
Diabetes mellitus (incl subtypes)	**435**	44	189	5	2	240	39	136	17	3	195
General nutritional disorders NEC	**123**	0	0	64	9	73	0	0	40	10	50
Infections and infestations	**626 (8%)**	**3 (<1%)**	**22 (<1%)**	**264 (7%)**	**24 (<1%)**	**313 (8%)**	**0 (0%)**	**29 (<1%)**	**255 (7%)**	**29 (<1%)**	**313 (8%)**
Lower respiratory tract and lung infections	**142**	0	3	68	2	73	0	6	61	2	69
Abdominal and gastrointestinal infections	**85**	0	1	39	2	42	0	3	38	2	43
Investigations	**566 (7%)**	**5 (<1%)**	**5 (<1%)**	**239 (6%)**	**35 (<1%)**	**284 (7%)**	**6 (<1%)**	**8 (<1%)**	**242 (6%)**	**26 (<1%)**	**282 (7%)**
Renal function analyses	**254**	0	0	119	9	128	1	0	120	5	126
Physical examination procedures and organ system status	**130**	3	4	51	4	62	1	0	61	6	68
Musculoskeletal and connective tissue disorders	**382 (5%)**	**13 (<1%)**	**58 (1%)**	**141 (4%)**	**2 (<1%)**	**214 (6%)**	**17 (<1%)**	**26 (<1%)**	**125 (3%)**	**0 (0%)**	**168 (4%)**
Muscle pains	**126**	8	37	34	0	79	12	8	27	0	47
Musculoskeletal and connective tissue pain and discomfort	**97**	5	5	40	0	50	6	6	35	0	47
Injury, poisoning and procedural complications	**257 (3%)**	**2 (<1%)**	**5 (<1%)**	**110 (3%)**	**11 (<1%)**	**128 (3%)**	**1 (<1%)**	**3 (<1%)**	**109 (3%)**	**16 (<1%)**	**129 (3%)**
Limb fractures and dislocations	**113**	0	1	51	2	54	0	2	56	1	59
Gastrointestinal disorders	**253 (3%)**	**9 (<1%)**	**14 (<1%)**	**107 (3%)**	**2 (<1%)**	**132 (3%)**	**9 (<1%)**	**12 (<1%)**	**96 (2%)**	**4 (<1%)**	**121 (3%)**
Nervous system disorders	**237 (3%)**	**6 (<1%)**	**16 (<1%)**	**101 (3%)**	**3 (<1%)**	**126 (3%)**	**7 (<1%)**	**9 (<1%)**	**89 (2%)**	**6 (<1%)**	**111 (3%)**
Respiratory, thoracic and mediastinal disorders	**171 (2%)**	**2 (<1%)**	**4 (<1%)**	**65 (2%)**	**12 (<1%)**	**83 (2%)**	**0 (0%)**	**4 (<1%)**	**62 (2%)**	**22 (<1%)**	**88 (2%)**
Vascular disorders	**170 (2%)**	**2 (<1%)**	**10 (<1%)**	**60 (2%)**	**3 (<1%)**	**75 (2%)**	**12 (<1%)**	**7 (<1%)**	**70 (2%)**	**6 (<1%)**	**95 (2%)**
Vascular hypertensive disorders NEC	**99**	2	5	35	1	43	10	3	40	3	56
Psychiatric disorders	**164 (2%)**	**1 (<1%)**	**10 (<1%)**	**60 (2%)**	**20 (<1%)**	**91 (2%)**	**5 (<1%)**	**3 (<1%)**	**54 (1%)**	**11 (<1%)**	**73 (2%)**
Neoplasms benign, malignant and unspecified	**161 (2%)**	**2 (<1%)**	**2 (<1%)**	**56 (1%)**	**15 (<1%)**	**75 (2%)**	**1 (<1%)**	**10 (<1%)**	**57 (1%)**	**18 (<1%)**	**86 (2%)**
General disorders and administration site conditions	**160 (2%)**	**7 (<1%)**	**18 (<1%)**	**56 (1%)**	**2 (<1%)**	**83 (2%)**	**10 (<1%)**	**6 (<1%)**	**60 (2%)**	**1 (<1%)**	**77 (2%)**
Pain and discomfort NEC	**101**	4	8	33	0	45	6	4	46	0	56
Renal and urinary disorders	**118 (2%)**	**3 (<1%)**	**2 (<1%)**	**49 (1%)**	**9 (<1%)**	**63 (2%)**	**3 (<1%)**	**2 (<1%)**	**40 (1%)**	**10 (<1%)**	**55 (1%)**
Cardiac disorders[1]	**104 (1%)**	**2 (<1%)**	**7 (<1%)**	**36 (<1%)**	**4 (<1%)**	**49 (1%)**	**1 (<1%)**	**10 (<1%)**	**37 (<1%)**	**7 (<1%)**	**55 (1%)**
Blood and lymphatic system disorders	**85 (1%)**	**0 (0%)**	**0 (0%)**	**37 (<1%)**	**10 (<1%)**	**47 (1%)**	**1 (<1%)**	**0 (0%)**	**23 (<1%)**	**14 (<1%)**	**38 (<1%)**
Hepatobiliary disorders	**80 (1%)**	**4 (<1%)**	**2 (<1%)**	**33 (<1%)**	**3 (<1%)**	**42 (1%)**	**2 (<1%)**	**1 (<1%)**	**33 (<1%)**	**2 (<1%)**	**38 (<1%)**

Events are described by MedDRA HLT grouped within system organ class (SOC) ordered by overall frequency. Only SOCs and HLTs reported by 1% or more participants are shown, the summary rows include all events. The summary is presented by Grade within each treatment group. Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially life-threatening) according to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.
For the overall, SOC and HLT totals, each participant is counted only once and at the highest reported grade. A total of 5665 AEs were reported for 2740 participants.
[1]Cardiac disorders include events classified under MedDRA SOC of Cardiac Disorders that are not part of the composite MACE outcome as well as events reviewed and determined as not MACE by the independent adjudication committee. AE denotes adverse event, HLT higher level term, MedDRA Medical Dictionary for Regulatory Activities, NEC not elsewhere classified, SOC system organ class.

Table S8: Details of Myalgia and Myopathy Events

	Total (N=7769)	Pitavastatin (N=3888)					Placebo (N=3881)				
	All	Grade 1	Grade 2	Grade 3	Grade 4	All	Grade 1	Grade 2	Grade 3	Grade 4	All
Participants with Myalgia or Myopathy — no. (%)	**151 (2%)**	**8 (<1%)**	**39 (1%)**	**45 (1%)**	**0 (0%)**	**92 (2%)**	**12 (<1%)**	**13 (<1%)**	**34 (<1%)**	**0 (0%)**	**59 (2%)**
Myalgia	**126**	8	37	34	0	**79**	12	8	27	0	**47**
Muscular weakness	**42**	3	4	18	0	**25**	2	3	12	0	**17**
Myopathy	**9**	0	1	3	0	**4**	1	3	1	0	**5**

Events are described by MedDRA PT, ordered by overall frequency. For the overall and event totals, each participant is counted only once and at the highest reported grade. Of the 7769 participants enrolled, 151 participants experienced at least one myalgia/myopathy event. Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially life-threatening) according to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.
MedDRA denotes Medical Dictionary for Regulatory Activities, PT preferred term.

Table S9: Representativeness of Study Participants

Category	Example
Disease, problem, or condition under investigation	Atherosclerotic cardiovascular disease (ASCVD) among people with HIV. The risk of incident ASCVD is estimated to be increased 2-fold among people with HIV vs. individuals without HIV.[5]
Special considerations related to:	
Geography, Race, and Ethnicity	Based on 2021 estimates, among the 38.4 million people with HIV:[6] 20.6 million reside in Eastern and Southern Africa 5 million reside in Western and Central Africa 180,000 reside in North Africa and the Middle East 6 million reside in Asia and the Pacific 2.3 million reside in Latin America and the Caribbean 1.8 million reside in Eastern Europe and Central Asia 2.3 million reside in Western/Central Europe and North America Globally, the majority of people with HIV are Black. In the US, HIV disproportionately affects individuals who are Black and Hispanic. In 2019, Black people comprised 13.4% of the US population but 40.3% of the US population living with HIV. Hispanic people comprised 18.5% of the US population, but 24.7% of the US population living with HIV.[7] There are no previous data as to whether risks of atherosclerotic cardiovascular disease among the global population of people with HIV differ by region of residence, race, or ethnicity.
Sex and Gender	Across the globe, 54% of people with HIV are women or girls.[6] There are no globally representative data describing the percentage of people with HIV whose gender identity differs from their sex assigned at birth. There are no previous data as to whether risk of ASCVD among the global population of people with HIV differs by sex or gender.
Age	More than 95% of people with HIV globally are adults.[6] Among people with HIV, life-expectancy varies by geographic region. The lifespan of people with HIV has increased markedly over the last decade in the context of expanded access to antiretroviral therapy (ART) (7.8 million people with HIV accessing ART in 2010 vs. 28.7 million people living with HIV accessing ART in 2021).[6,8,9] Atherosclerotic cardiovascular disease risk increases with age.[10] The population-attributable fraction of atherosclerotic cardiovascular disease attributable to HIV has been steadily increasing in concert with the lifespan of the people with HIV globally.[5]
Overall representativeness of this trial	REPRIEVE enrolled 7,769 participants from 12 countries: USA (N=3787), Canada (N=131), Spain (N=213), Brazil (N=1099), Peru (N=148), Haiti (N=140), Thailand (N=590), India (N=504), South Africa (N=570), Botswana (N=281), Uganda (N=181), and Zimbabwe (N=125).

REPRIEVE permitted enrollment of participants age 40 to 75 years. The median age of enrolled participants was 50 years (Q1 45 years, Q3 56 years).

Among all enrolled participants, 41% were Black or African American, 35% were White, 15% were Asian, and 9% were Other. Among the subset of participants enrolled in the US and Canada, and 18% were Hispanic or Latinx.

With respect to natal sex, 31% of REPRIEVE participants were female (see below for ascertainment). As per the table below, the enrollment of female participants in the US, Brazil, Thailand, South Africa, and Botswana approximated, paralleled, or exceeded the percent of female persons with HIV in each of these countries, while the enrollment of female participants in Canada, Spain, Peru, Haiti, India, Uganda, and Zimbabwe did not.

Country	Percentage of Females enrolled in REPRIEVE	Percentage of Females among population living with HIV in country
US	23	23[11]
Canada	10	29[12]
Spain	9	18[13]
Brazil	29	34[14]
Peru	8	24[13]
Haiti	42	57[13]
Thailand	56	42[13]
India	26	39[15]
South Africa	66	64[13]
Botswana	63	61[13]
Uganda	51	60[13]
Zimbabwe	24	58[13]

Data on gender identity or identities were collected through participant interviews. Research team members recorded all gender identifies endorsed by each participant. Options included: “male”, “female”, “transgender male”, “transgender female”, “gender queer”, “gender variant”, “gender nonconforming”, and “self-identify”, or an open-text field for identity not otherwise captured. Two additional reporting categories included “prefer not to answer” (to record participant opt-outs) and “information not collected” (to record lack of performance of participant

	interview on gender identities by research team). Overall, acceptance of gathering gender identity was 96%. Among REPRIEVE participants, 1.6% identified across the transgender spectrum (2.2% of natal males, 0.3% of natal females).

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