Supplementary Appendix

Supplement to: Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to prevent cardiovascular disease in HIV infection. N Engl J Med 2022;389:687-99. DOI: 10.1056/NEJMoa2304146

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

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Contributions to Design, Conduct and Reporting of REPRIEVE

REPRIEVE (A5332) was funded the National Heart Lung and Blood Institute (NHLBI) of the NIH through a cooperative UO1 grants for the Clinical (CCC) and Data (DCC) Coordinating Centers with additional support from the National Institutes of Allergy and Infectious Diseases (NIAID) and supplemental funding from the Office of AIDS Research. Kowa Pharmaceuticals America, Inc. Gilead Sciences and ViiV Healthcare also supported the study. NIAID was the regulatory sponsor and IND holder.

REPRIEVE (A5332) was designed by the Co-PIs (Drs. Grinspoon and Douglas, Co-Chairs of the CCC and Drs. Hoffmann and Ribaudo, Co-Chairs of the DCC) with guidance and approval from the NHLBI and NIAID. Dr. Lu replaced Dr. Hoffmann as Co-PI and Co-Chair of the DCC in 2021. The overall leadership of the trial was provided by the Executive Committee, Chaired by Dr. Grinspoon, with members including the other Co-PIs and representatives of the NIH. Guidance regarding protocol development and implementation was provided from the Protocol Committee and site performance evaluation overseen by the Site Selection, Performance and Close Out Committee (SSPCC).

REPRIEVE (EU5332) was a scientifically identical protocol launched in 2019 to expand enrollment to sites in the European Union. EU5332 was co-sponsored by European Treatment Network for HIV, Hepatitis, and Global Infectious Diseases (NEATid) and Massachusetts General Hospital with industry support. Study conduct, site monitoring, and data collection was overseen by Research Organisation (KC) Ltd (ROKC) and was separate for the two study protocols, pooling of their data was planned for interim monitoring and final analysis.

A DSMB appointed by NHLBI met regularly, every 6 months to review safety and efficacy data and advised the NIH on the status of the study. DSMB meetings and calls were organized into Open, Closed, and Executive Sessions. The open session dealt with issues relating to the general conduct and progress of the study, such as accrual, retention, and safety and all data were presented pooled over treatment group. Following the Open Session and before the Closed Session, a restricted group including only the DSMB, the REPRIEVE NIH team, the REPRIEVE CCC PIs and statisticians reviewed aggregate primary events pooled across treatment groups to discuss trial feasibility and possible sample size adjustments. During the closed session, the DSMB, NHLBI Executive Secretary (ES) and NHLBI statistician, and unblinded REPRIEVE statisticians reviewed data presented by unmasked treatment group. Efficacy data by treatment group were not reviewed until adequacy of the study sample size assumptions was determined. The DSMB closed the meeting in executive session in which only the DSMB members and NHLBI ES were present. A DSMB Charter is available on request.

Study operations were conducted by the Operational Leadership Committee and various governance committees as described below. Data management was conducted by Frontier Science Foundation, Inc. and site monitoring by the NIH Division of AIDS (DAIDS). The REPRIEVE trial leadership remained blinded until March 31, 2023 following acceptance of the DSMB recommendation by the NIH. The manuscript was written by Dr. Steven Grinspoon with a writing group named as authors on the manuscript. The decision to publish these results was based on recommendations from the REPRIEVE DSMB and the NIH at their meeting on March 30, 2023 as detailed in the methods section of the manuscript.

Blinding Status of the REPRIEVE Biostatistics Team

Blinded: Heather Ribaudo (Lead Statistician, DCC Co-PI), Sara McCallum (Statistical Programmer), Janeway Granche (Statistician)

Unblinded: Triin Umbleja (Coordinating Statistician), Jorge Leon-Cruz (Protocol Statistician), Amy Kantor (Statistician), Sean Brummel (Internal Review), Carlee Moser (Internal Review), Laura Smeaton (Internal Review)

Blinded members of the Biostatistics team had no access to study data linked or aggregated by treatment group assignment. All team members were unblinded on March 31, 2023 following the DSMB recommendation to stop the trial.

Author Affiliations

Author Name	**Author Affiliation**	**Declarations of Interest**
Steven K. Grinspoon	Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA	Reports grant support through his institution from NIH, Kowa Pharmaceuticals America, Inc., Gilead Sciences, Inc., and ViiV Healthcare for the conduct of the study; personal fees from Theratechnologies and ViiV; and service on the Scientific Advisory Board of Marathon Asset Management, all outside the submitted work.
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		the conduct of the study, as well as grants from NIH/NIAID and NIH/NHLBI; support for attending CROI and International Workshop for HIV and Women from conference organizing committee when abstract reviewer and/or speaker; and participation in DSMB for NIH funded studies, outside the submitted work.
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		AstraZeneca; research grant support paid to Hadassah Hebrew University Hospital from Novo Nordisk, AstraZeneca; and Speaker's Bureau from AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, and Boehringer Ingelheim.
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Jorge Leon-Cruz	Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA	No disclosures to report
Sara McCallum	Metabolism Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA	No disclosures to report
Udo Hoffmann	Cleerly, Denver, CO, USA	Reports being an employee of Cleerly, Inc. and reports an NIH grant to his institution in support of the present work, as well as consulting fees from Stanford University, Clinical Cardiovascular Sciences, MedTrace Inc., and Rapid AI and holding a leadership role as Chief Scientific Officer and stock/stock options for Cleerly Inc., outside of the submitted work.
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NIH Grants Policy Statement

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute or the National Institute of Allergy and Infectious Diseases; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Section 2: Supplemental Methods

Eligibility Criteria

Inclusion Criteria

- Documentation of HIV-1 infection by means of any one of the following:
  - Documentation of HIV diagnosis in the medical record by a licensed health care provider;
  - OR HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL;
  - OR any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay such as a HIV-1 Western blot confirmation or HIV rapid Multispot antibody differentiation assay.

  NOTE: A "licensed" assay refers to a US FDA-approved assay, which is required for all IND studies. Non-US sites are encouraged to use FDA-approved methods; if not available, then each non-US site must use an assay that has been certified or licensed by an oversight body within that country and validated internally.

  WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment.

- Combination antiretroviral therapy (ART) for at least 180 days prior to study entry.
  NOTE: Treatment interruptions for up to 30 days total in the last 180 days are permitted as long as the participant has been continuously on therapy for the 30 days prior to study entry.

- CD4+ cell count >100 cells/mm^3 obtained within 180 days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices and participates in appropriate external quality assurance programs.

- Laboratory values drawn at screen and/or obtained from clinical care (as indicated in section 6.1 Schedule of Evaluations of the Protocol) within 90 days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices and participates in appropriate external quality assurance programs.

  - Fasting LDL cholesterol as follows:
    - If ASCVD risk score <7.5%, LDL cholesterol must be <190 mg/dL
    - If ASCVD risk score ≥7.5% and ≤10%, LDL must be <160 mg/dL
    - If ASCVD risk score >10% and ≤15%, LDL must be <130 mg/dL

    NOTE: If LDL <70 mg/dL, participant is eligible regardless of 10-year ASCVD risk score in line with the ACC/AHA 2013 Prevention Guidelines.

- Fasting triglycerides <500 mg/dL

- Hemoglobin >8 g/dL for female participants and >9 g/dL for male participants.

- Glomerular filtration rate (GFR) ≥60 mL/min/1.73m^2 or creatinine clearance (CrCl) ≥60 mL/min
  NOTE: See the A5332 Manual of Procedures (MOPS) for links to GFR and CrCl calculators.

- ALT ≤2.5 x ULN
  NOTE: Participants co-infected with chronic active hepatitis B or C must have ALT ≤2 x ULN.

- For persons with known chronic active hepatitis B or C, calculated FIB-4 score must be ≤3.25.
  NOTE: Active is defined as hepatitis B surface antigen positive, hepatitis B DNA positive, or hepatitis C RNA positive.

  NOTE: Refer to the calculator for the FIB-4 equation in the MOPS.

- Female participants of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, i.e, who have had menses within 24 months prior to study entry, and women who have not undergone surgical sterilization, specifically hysterectomy or bilateral oophorectomy) must have a negative serum or urine pregnancy test within 48 hours prior to entry by any US laboratory or clinic that has a CLIA certification or its equivalent, or is using a point-of-care (POC)/CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with Good Clinical Laboratory Practices and participates in appropriate external quality assurance programs.
  NOTE: Participant-reported history is considered acceptable documentation of hysterectomy, bilateral oophorectomy, and menopause. Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH (follicle stimulating hormone) of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months.

- For women of reproductive potential, willingness to use contraceptives as described in the product information for pitavastatin. Contraceptives must be used at least two weeks before initiation of study drug and must be continued 6 weeks after cessation of study drug.
  If participating in sexual activity that could lead to pregnancy, women must use a form of contraceptive. At least one of the following methods must be used appropriately:

  - Condoms (male or female) with or without spermicidal agent
  - Diaphragm or cervical cap with spermicidal agent
  - Intrauterine device (IUD)
  - Hormone-based contraceptive
  - Tubal ligation
  - Tubal micro-inserts

  Women who are not of reproductive potential as defined above are eligible without the use of contraception.

- Men and women age ≥40 and ≤75 years of age.

- Ability and willingness of participant or legal representative to provide written informed consent.

Exclusion Criteria

- Clinical ASCVD, as defined by 2013 ACC/AHA guidelines, including a previous diagnosis of any of the following:
  - AMI
  - Acute coronary syndromes
  - Stable or unstable angina

- Coronary or other arterial revascularization
- Stroke
- TIA
- Peripheral arterial disease presumed to be of atherosclerotic origin

- Current diabetes mellitus if LDL ≥70 mg/dL
  NOTE: Current diabetes is defined by patient report of physician diagnosis. Participants with a history of diabetes that has resolved and no longer requires therapy are not considered to have current diabetes, eg, women with a history of gestational diabetes, steroid-induced or medication-induced.

- 10-year ASCVD risk score estimated by Pooled Cohort Equations >15%
  NOTES:

  - If LDL <70 mg/dL, participant is eligible regardless of risk score in line with the ACC/AHA 2013 Prevention Guidelines.
  - See Fasting LDL Inclusion Criteria for LDL requirements by risk score.
  - Cardiovascular Risk Assessment Tool, for detailed instructions concerning access and use of the 10-year ASCVD risk score calculator (see Section 6.3.4 of Protocol).

- Active cancer within 12 months prior to study entry.
  NOTE: Exceptions:

  - Successfully treated non-melanomatous skin cancer
  - Kaposi sarcoma without visceral organ involvement

- Known decompensated cirrhosis.

- History of myositis or myopathy with active disease in the 180 days prior to study entry.

- Known untreated symptomatic thyroid disease.

- History of allergy or severe adverse reaction to statins.

- Use of specific immunosuppressants or immunomodulatory agents, including but not limited to tacrolimus, sirolimus, rapamycin, mycophenolate, cyclosporine, TNF-alpha blockers or antagonists, azathioprine, interferon, growth factors, or intravenous immunoglobulin (IVIG), in the 30 days prior to study entry.
  NOTE: Use of oral prednisone ≤10 mg/day or equivalent dosage is allowed.

  NOTE: Refer to the MOPS for clarification regarding medications in these categories.

- Current use of erythromycin, colchicine, or rifampin.

- Use of any statin drugs, gemfibrozil, or PCSK9 inhibitors in the 90 days prior to study entry.

- Current use of an investigational new drug that would be contraindicated.
  NOTE: Please contact the protocol core team via e-mail as described in the Study Management section of Protocol for guidance on coenrollment of participants on investigational new drugs.

- Serious illness or trauma requiring systemic treatment or hospitalization in the 30 days prior to study entry.

- Known active or recent (not fully resolved within 30 days prior to study entry) systemic bacterial, fungal, parasitic, or viral infections (except HIV, HBV, human papillomavirus [HPV], or HCV).

- Current breastfeeding.

  Alcohol or drug use that, in the opinion of the site investigator, would interfere with completion of study procedures,

- Other medical, psychiatric, or psychological condition that, in the opinion of the site investigator, would interfere with completion of study procedures and or adherence to study drug.

Diet, Activity, and Smoking Cessation Guidance

Information on diet, activity, smoking cessation, adhering to antiretroviral therapy, and adhering to the study medications was given to participants at each annual visit. The guidance on lifestyle was based on the NHLBI's Management of Blood Cholesterol in Adults[1] and was based on the and Included Information on the topics listed below.

- Goals of Therapeutic Lifestyle Changes (TLC)
- Physical Activity
- TLC Diet: Daily Food Guide Food Groups
  - Fruits and Vegetables
  - Meat, Poultry, Fish, Dry Beans, Eggs, and Nuts
  - Fats and Oils
  - Breads, Cereals, Rice, Pasta, and Other Grains
  - Sweets and Snacks
- Recommendations on Quitting Smoking
- Recommendations on adhering to the HIV medications prescribed by your doctor
- Recommendations on adhering to the study medication (pitavastatin or placebo) for pitavastatin

Primary and Secondary Outcome Measures

Primary and Secondary outcome measures according to Version 6.0 of the protocol are listed below. Outcome measures reported in the present manuscript include those related to major adverse cardiovascular events (MACE) and safety outcomes relevant to the DSMB recommendations to close the study. Analyses of other serious clinical diagnoses, including cancer, AIDS-defining events and COVID-19 (secondary outcome measures 4, 7-9) will be performed once REPRIEVE follow-up is complete and the database is final. Likewise, descriptive summaries of lipid outcomes are presented; full analysis will be based on the full study database upon completion of the study and assays.

Primary Outcome Measure
1. Time to the first event of a composite of major 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 will be 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 will be considered primary MACE events for this outcome measure, as specified in the Clinical Event Committee Charter.
Secondary Outcome Measures
1. Time to the first of each individual component of the primary outcome measure (described above)
2. Time to death (all-cause mortality)
3. Time to death (all-cause mortality) and/or MACE
4. Time to any (composite) or each (individual) of the following incident clinical diagnoses (including recurrent diagnoses as appropriate) • Non AIDS-defining cancers (excluding basal cell and squamous cell carcinomas of the skin) • AIDS-defining events (based on CDC 2014 classification) • End-stage renal disease, defined as initiation of dialysis or renal transplantation. • End-stage liver disease, defined as cirrhosis, or hepatic decompensation requiring hospitalization
5. Calculated fasting LDL cholesterol (LDL-C) and non-HDL cholesterol at study entry and annually thereafter, as well as change from baseline expressed as absolute change and as a percentage of baseline.
6. Time to any of the following adverse events (including recurrent events as appropriate) • Serious adverse event as defined by ICH criteria • Incident Diabetes mellitus • Grade 3 or 4 alanine transaminase • Grade 3 or 4 myopathy All events will be included regardless of relationship to treatment as determined by sites. Grading is defined per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017.
7. Time to COVID-19 diagnosis

8. Time to serious COVID-19 (i.e., a COVID-19 diagnosis that is life threatening or results in hospitalization or death)
9. Antibody-positive COVID-19 infection assessed cross-sectionally at specific calendar time points from samples collected annually

Interim Monitoring Plan and Monitoring Benchmarks

Interim review of REPRIEVE by an NHLBI-appointed DSMB was governed by the REPRIEVE DSMB Charter. The DSMB meetings were held every 6 to 12 months, as necessary, to review the conduct, safety, and ongoing feasibility of the study.

For reference, the following table summarizes the benchmarks for REPRIEVE monitoring agreed upon by the study team and NHLBI.

Type	Threshold for concern
Enrollment	Accrual rate <75% of the target.
Premature study discontinuation	Annualized pooled rate of premature study discontinuation >5%.
Treatment Crossover	Rate of crossover in any treatment group >15%.
MACE Rate	Average pooled event rate ≤10/1000 PY based on predicted intervals under a range of realistic scenarios.
Efficacy & Futility	Lan & DeMets implementation of the O'Brien-Fleming group sequential boundary with information measured on the cumulative number of Primary MACE endpoints.

REPRIEVE is an event-driven trial designed to detect a hazard ratio of 0.70, a 30% reduction in First Primary MACE endpoints (defined above) with pitavastatin compared to placebo, in a two-sided test with significance level of 5% and 85% power. The final planned number of participants with a First Primary MACE endpoint (i.e., total information) is 288.

As described in the Statistical Analysis Plan and DSMB Charter, the first evaluation of the pooled MACE endpoint rate was scheduled to occur approximately 2 years after the enrollment of the first participant (in June 2017). Since then, event rate summaries were provided for each DSMB review.

The REPRIEVE Statistical Analysis Plan called for DSMB monitoring for efficacy and futility based on the Lan & DeMets implementation of the O'Brien-Fleming group sequential boundary scheduled based on information measured on the cumulative number of First Primary MACE endpoints. Four interim looks were planned originally: at 20% (if requested by DSMB), 40%, 60%, and 80% information. Per recommendation of NHLBI, endorsed by the DSMB at the December 2019 meeting, the timing of interim looks was changed to at 50% and 75% information to allow for the optimal decision making about extending study follow-up duration.

The first interim efficacy analysis occurred on September 21, 2021 at 55% information (n=159 endpoints). The second review occurred on March 30, 2023 at 78% information (n=225 endpoints) and resulted in a DSMB recommendation that the trial be stopped for efficacy. The efficacy boundary p-value for this analysis was 0.02084, and a Z-value of 2.31.

Statistical Methods

All statistical analyses were performed in accordance with the REPRIEVE Statistical Analysis Plan (Version 2.0). Details are summarized below with additional data and considerations for the results presented.

Data and Statistical Considerations

We report on the database used for reporting for the DSMB review on March 30, 2023 on which the decision to stop the trial was made. These data were retrieved from the A5332 and EU5332 databases on February 27, 2023 and reflect data in the electronic data capture system as of February 25, 2023. To prepare for that DSMB review, sites were asked to provide complete data and submit any event adjudication packets for all visits up to and including December 30, 2022. Thorough QA/QC for these visits was completed, as much as possible.

Data from REPRIEVE (A5332) and REPRIEVE (EU5332) are pooled for all summaries. Percentages are calculated out of participants with data. Continuous outcomes are summarized using descriptive statistics including median and first and third quartiles.

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 primary major adverse cardiovascular event (MACE) (See Primary and Secondary Outcome Measures). Per NEJM request, a supportive analysis of first primary MACE including endpoints and follow-up time captured from vital status and endpoint follow-up was added.

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).

Unless otherwise noted, only MACE outcomes that had completed the adjudication process at the time of data retrieval were included and efficacy analyses were administratively censored at December 30, 2022. Specifically, all MACE outcomes after December 30, 2022 were excluded and all participant follow-up beyond December 30, 2022 was censored. This was done to avoid underestimation of the event incidence rate by inclusion of accumulated person-years beyond the time in which a potential MACE outcome could have completed the adjudication process. Since determination of CV vs. non-CV death was unnecessary to identify endpoints, analyses including all-cause death include all on-study deaths and follow-up time out to last contact without censoring.

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). MACE triggers pending adjudication were excluded throughout. Of note, since deaths were not included as AEs, all SAEs are non-fatal. All deaths were summarized separately as part of efficacy analyses.

All adverse events reported at the time of data retrieval were included.

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.

Analysis Population

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.

Statistical Significance

Except for the primary efficacy analysis, statistical comparisons are presented with two-sided 95% confidence intervals are provided. The primary efficacy analysis uses significance level according to the realized Lan and DeMets implementation of the O'Brien-Fleming sequential stopping boundary with associated repeated confidence interval. The first interim analysis occurred at 55% (n=159 endpoints) and the second at 78% (n=225 endpoints) information, at which point the trial stopped for efficacy. As such, the primary efficacy analysis uses the boundary information from the interim analysis at 78% information. The corresponding efficacy boundary p-value is 0.02084, and the Z-value 2.31; the 95% repeated confidence interval (RCI) is a 97.9% nominal confidence interval.

Except the adjustment for interim monitoring in the primary analysis 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 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. The relative cause-specific hazard of pitavastatin versus placebo for First Primary MACE was estimated with a repeated 95% confidence interval and a nominal p-value from a Wald test is presented.

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 is planned based on the full study database. 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 on December 30, 2022, the last contact, or at the time of primary or competing event, whichever occurred earliest. A total of 37,091 PYs were observed for 7769 participants, 18,521 for 3888 pitavastatin group participants and 18,570 for 3881 placebo group participants.

As of December 30, 2022, 623 (16%) participants in the pitavastatin group, and 592 (15%) in the placebo group, had unknown primary endpoint status and no contact >10 months. For these participants, 4,532 PYs would have accrued between their last contact and December 30, 2022 ("unobserved follow-up time"): 2,379 PYs in the pitavastatin and 2,153 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 December 30, 2022 (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 currently observed (i.e., 9.61 / 1000 PY) whereas those in the placebo group were assumed to occur at the current observed rate (7.32 /1000PY). In each case, simulations for future data also assume: follow-up from last contact to December 30, 2022; 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=2) and non-CV deaths (n=7) from vital status follow-up were included as observed data in 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.

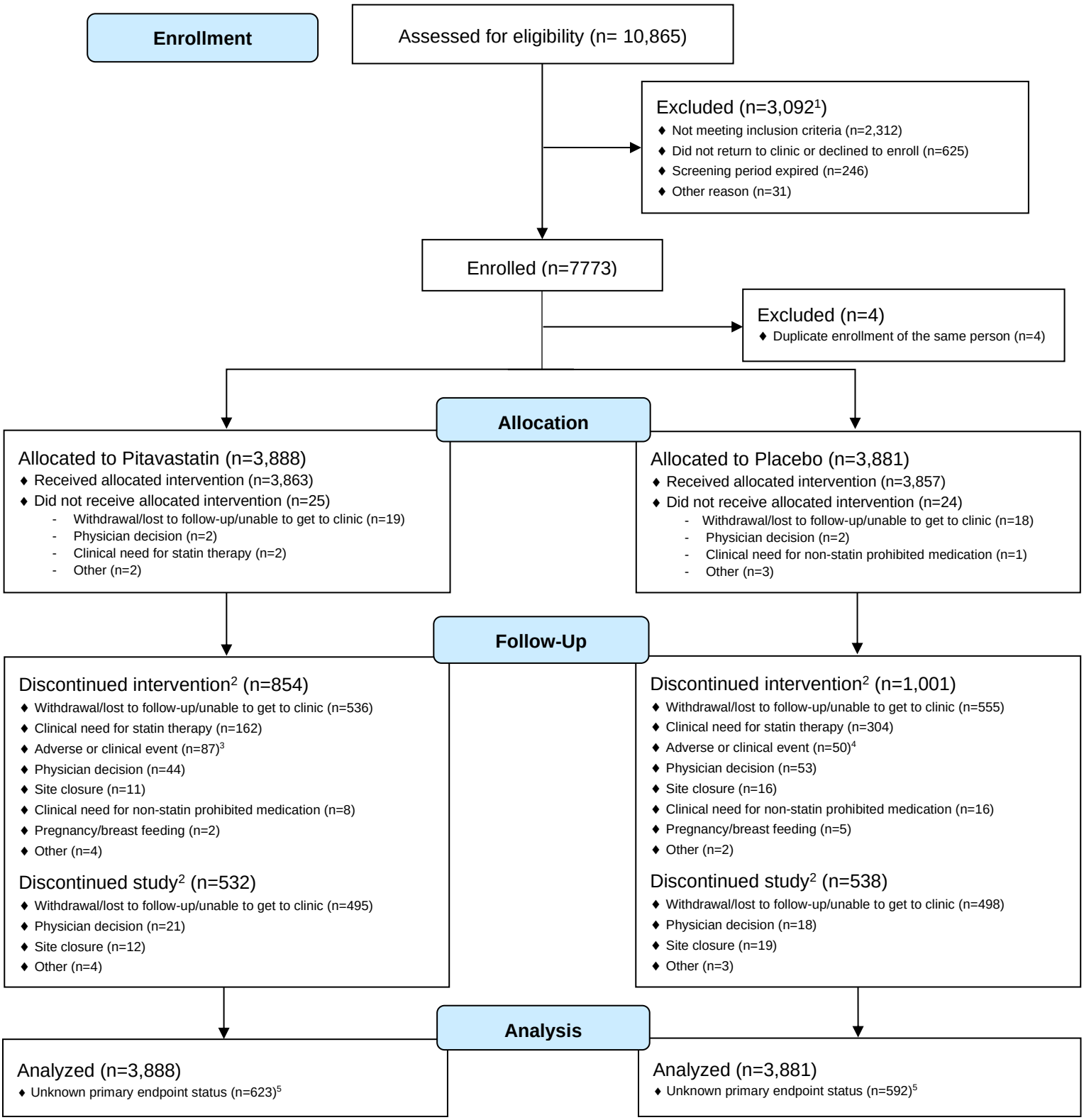
Averages across 1,000 simulations are shown, including for lower and upper bounds of the 95% RCI. As such, the actual coverage probability of the confidence intervals may differ slightly from 95%.

Methods for Lipids and Glucose

Fasting lipids using serum obtained from separator tubes and plasma glucose from sodium fluoride/potassium oxalate tubes were collected and stored at ultrafreezer temperatures in a central repository for batch testing at approximately 6-month intervals by Quest Diagnostics (Baltimore, MD and Teterboro/Clifton, NJ) using commercially available US Food and Drug Administration cleared methods. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured by enzymatic techniques and low-density lipoprotein cholesterol was calculated for those specimens with triglyceride levels <400 mg/dL. Specimens with triglyceride quantities above that level were reflex tested using a direct low-density lipoprotein cholesterol technique. Glucose was measured using a hexokinase technique.

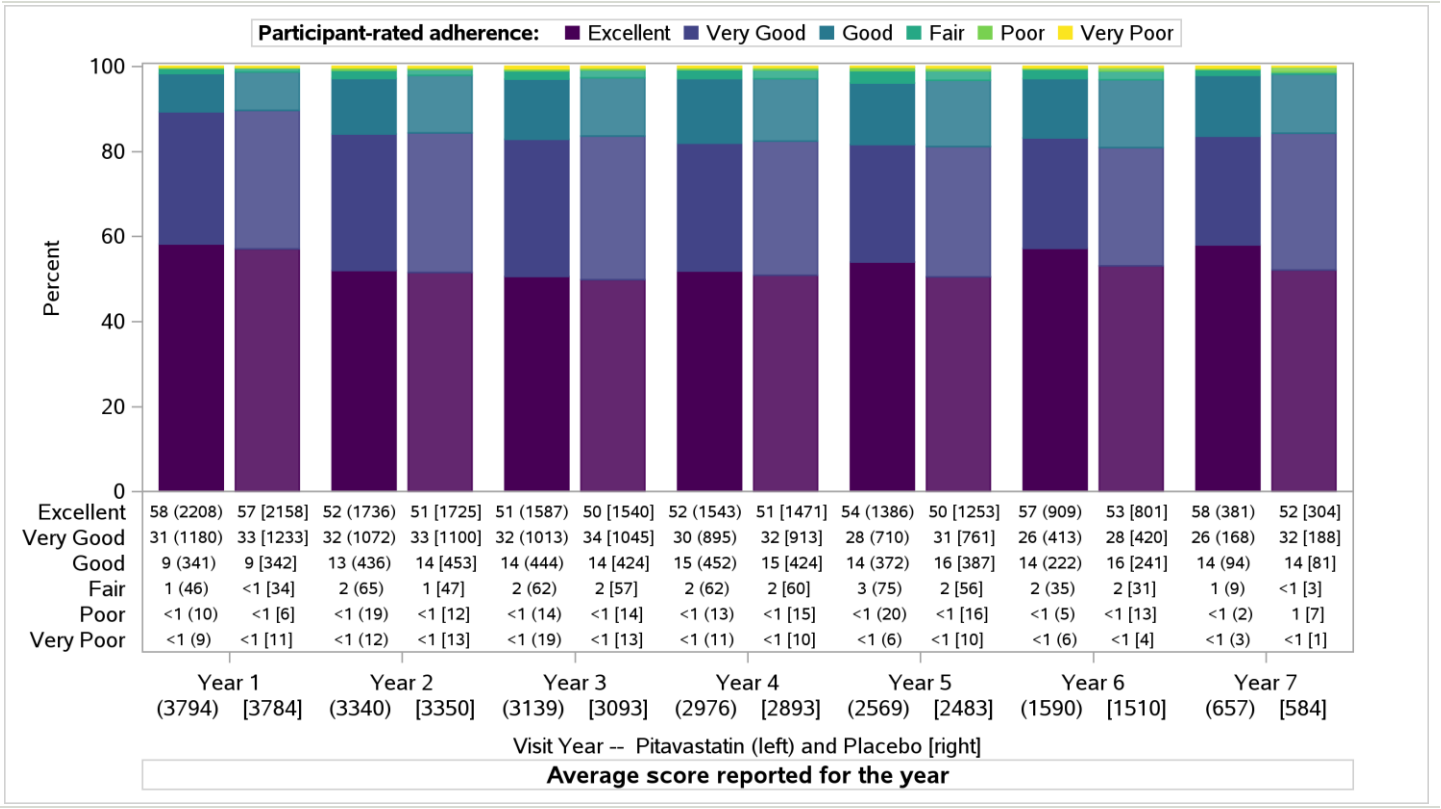
Section 3: Supplementary Figures and Tables

Figure S1: CONSORT Diagram



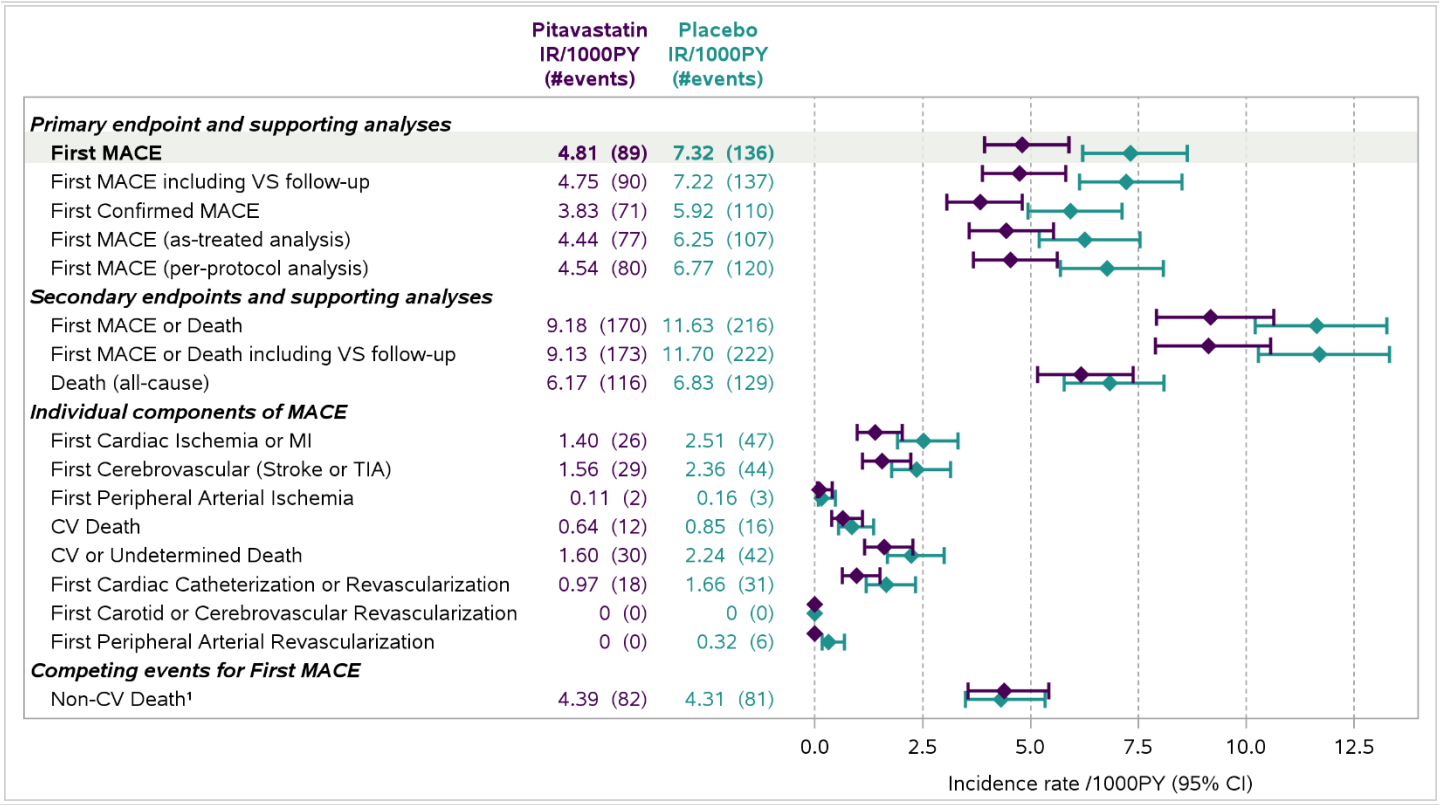
[1] Multiple screening failure reasons could be reported.
[2] Treatment and/or study discontinuation concurrent with death is not considered premature discontinuation and is excluded.
[3] Of the treatment discontinuations due to adverse or clinical events in the pitavastatin group, 5 were due to MACE and 1 due to diabetes.
[4] Of the treatment discontinuations due to adverse or clinical events in the placebo group, 4 were due to MACE and 2 due to diabetes.
[5] Unknown primary endpoint status as of December 30, 2022 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

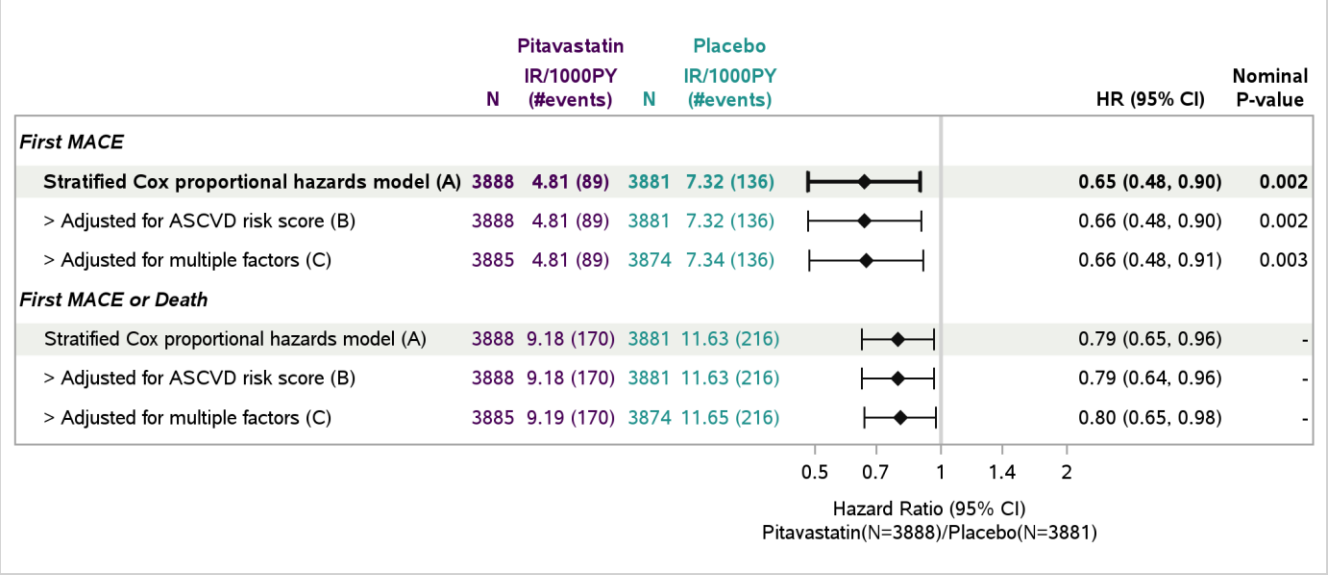


Incidence rates were estimated using Poisson distribution based on the earliest event, last contact or 12/30/2022, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time. The widths of the CIs have not been adjusted for multiplicity. Thus, the confidence intervals should not be used to reject or not reject pitavastatin effect.

[1] All non-CV deaths are included; 2 in the pitavastatin group and 4 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 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, screening 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.

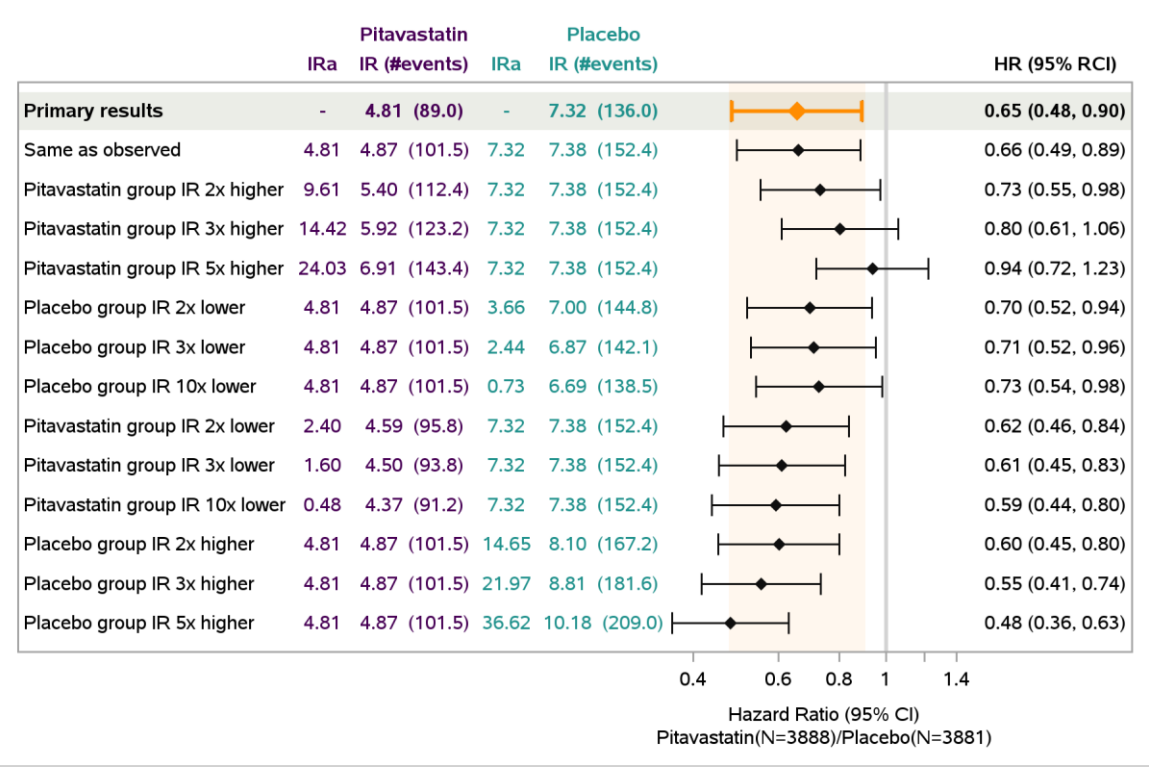
For the First MACE, two-sided 95% repeated CIs round the cause-specific HR estimates and nominal Wald test p-values are shown. For reference, the efficacy boundary p-value for First MACE comparison accounting for interim looks is 0.02084.

For the First MACE or Death, two-sided nominal 95% CIs are 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.

For visual purposes, the data on the x-axis are shown in the log scale.

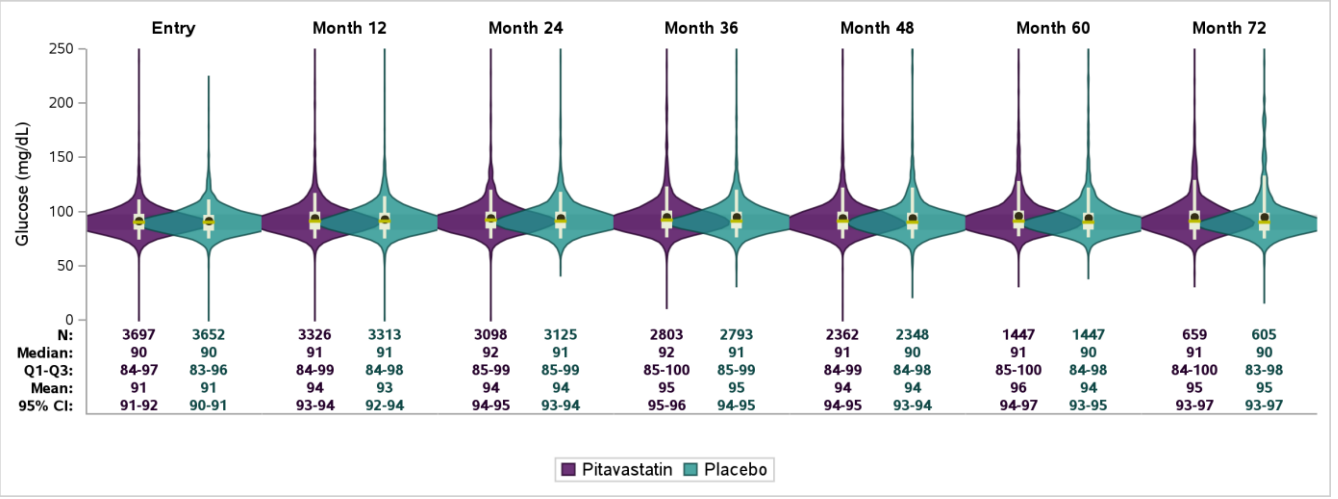
ASCVD denotes atherosclerotic cardiovascular disease, ART antiretroviral therapy, CI confidence interval, HR hazard ratio, IR incidence rate, GBD global burden of disease, LDL-C LDL cholesterol, PY person-years.

Figure S5: Sensitivity Analyses for the 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 hazard ratio 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.

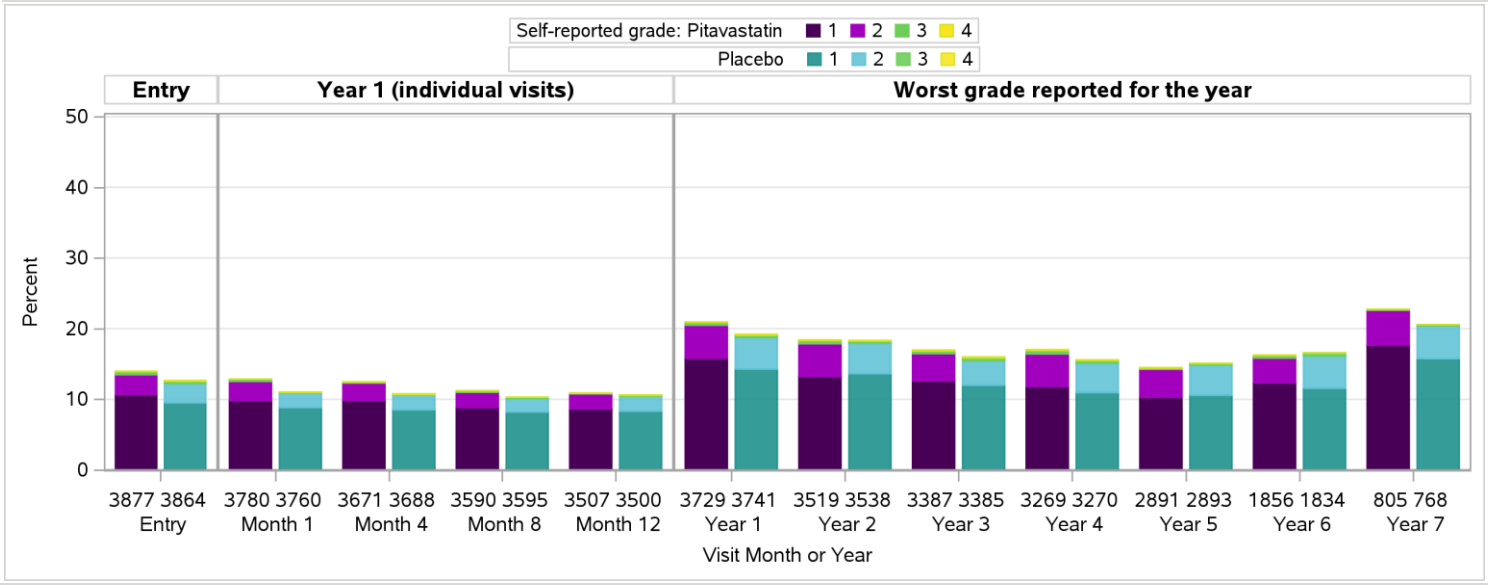
Figure S6: Fasting Glucose Over Time



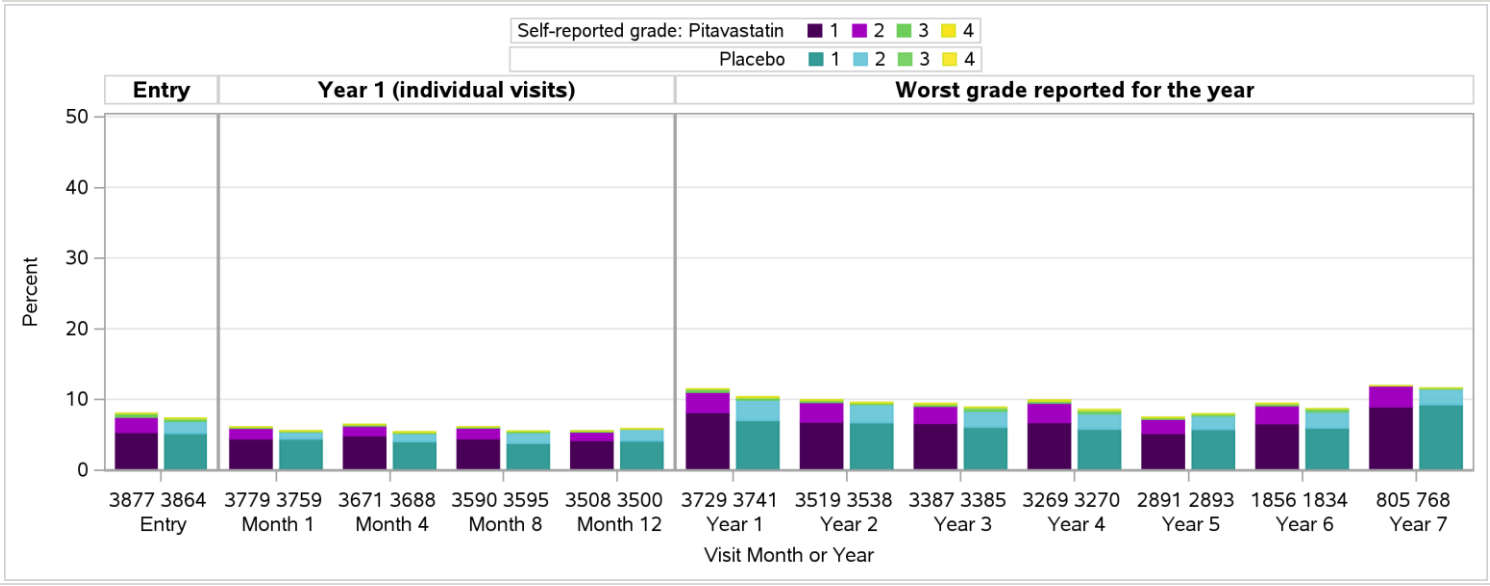
Violin plots presenting Kernel estimate of probability density function, and mean (circle), median (yellow dash), Q1-Q3 (box) and P5-P95 (whiskers); means with 95% CIs are shown in the axis table. Fasting samples are tested centrally in batch; results available as of 12/30/2022 are presented.
CI denotes confidence interval, P5 5th percentile, P95 95th percentile, Q1 lower quartile, Q3 upper quartile.

Figure S7: Muscle Ache and Weakness by Participant Report*

(a) Muscle ache



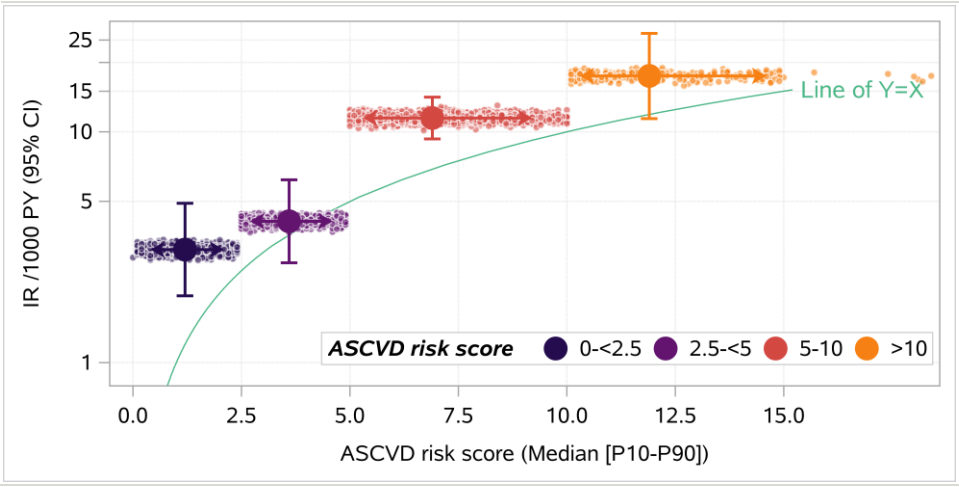
(b) Muscle weakness



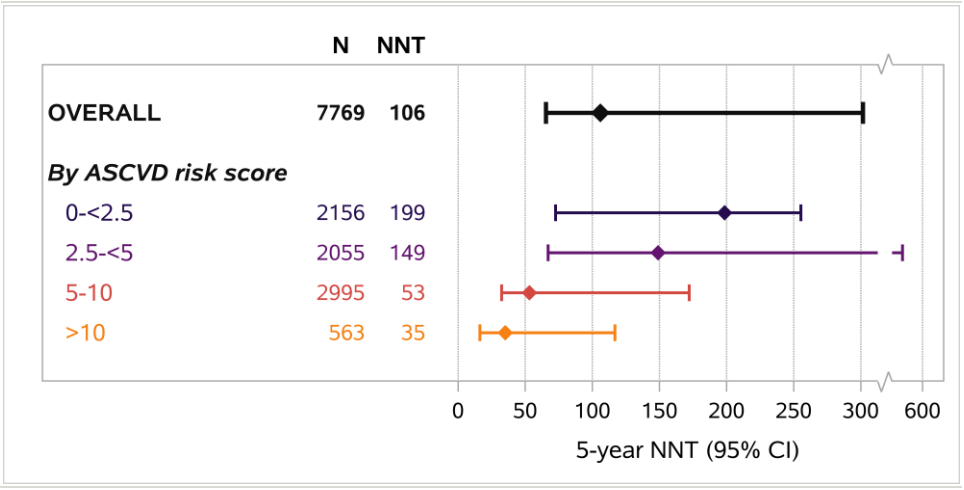
Evaluations are conducted as participant interviews by the site staff. Assessments at individual visits are shown to Month 12, the worst grade across quarterly visits is shown annually. Percentages are out of participants with at least one questionnaire completed in a given period, shown below bars.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

Figure S8: 5-year Number Needed To Treat by ASCVD Risk Score at Enrollment

(a) Incidence of First MACE in the Placebo Group



(b) 5-year NNT



Panel (a): The distribution of ASCVD risk at enrollment is shown on the x-axis; estimated incidence of first MACE is shown on the Y-axis in the placebo group. The point estimate shows the estimated incidence rate plotted at the median ASCVD risk score by subgroups of ASCVD risk score. The vertical error bars on the point estimate show the 95% CI on the estimated incidence rate; the horizontal error bars give the P10 and P90 of the ASCVD risk distribution. The individual observed ASCVD risk scores are jittered on the X and Y-axes for clarity.
Panel (b): 5-year NNT overall and by ASCVD risk score at enrollment. For the 5-year NNT by ASCVD risk score, cumulative incidence of first MACE by 5 years in the placebo group was estimated using Cox proportional hazards model; cumulative incidence in the pitavastatin group was calculated based on the placebo group estimates and the overall treatment effect of 35% reduction in events with pitavastatin.
ASCVD denotes atherosclerotic cardiovascular disease, CI confidence interval, IR incidence rate, NNT number needed to treat, P10 10th percentile, P90 90th percentile, PY person-years.

Table S1: Baseline Characteristics by Treatment Group and Global Burden of Disease Super Region

		Pitavastatin (N=3888)	Placebo (N=3881)	Total (N=7769)	High Income (N=4095)	Latin America and Caribbean (N=1423)	S.East/East Asia (N=590)	South Asia (N=504)	Sub-Saharan Africa (N=1157)
Age (yr)	Median (Q1, Q3)	50 (45, 55)	50 (45, 55)	50 (45, 55)	51 (46, 55)	50 (45, 55)	47 (44, 52)	47 (44, 52)	49 (44, 54)
	Min, Max	40, 72	40, 74	40, 74	40, 74	40, 74	40, 66	40, 70	40, 72
— no. (%)	40-49	1842 (47)	1888 (49)	3730 (48)	1724 (42)	694 (49)	371 (63)	335 (66)	606 (52)
	50-59	1712 (44)	1649 (42)	3361 (43)	1996 (49)	583 (41)	194 (33)	140 (28)	448 (39)
	60+	334 (9)	344 (9)	678 (9)	375 (9)	146 (10)	25 (4)	29 (6)	103 (9)
Sex — no. (%)	Male	2677 (69)	2673 (69)	5350 (69)	3217 (79)	1019 (72)	257 (44)	375 (74)	482 (42)
	Female	1211 (31)	1208 (31)	2419 (31)	878 (21)	404 (28)	333 (56)	129 (26)	675 (58)
Gender identity — no. (%)	Cisgender	3687 (95)	3680 (95)	7367 (95)	3742 (91)	1398 (98)	568 (96)	503 (100)	1156 (100)
	Transgender Spectrum	63 (2)	64 (2)	127 (2)	87 (2)	21 (1)	18 (3)	1 (<1)	0 (0)
	Not reported	138 (4)	137 (4)	275 (4)	266 (6)	4 (<1)	4 (1)	0 (0)	1 (<1)
Race[1] — no. (%)	Black or African American	1569 (40)	1639 (42)	3208 (41)	1675 (41)	379 (27)	0 (0)	0 (0)	1154 (100)
	White	1364 (35)	1340 (35)	2704 (35)	2154 (53)	546 (38)	2 (<1)	0 (0)	2 (<1)
	Asian	571 (15)	567 (15)	1138 (15)	44 (1)	2 (<1)	588 (100)	504 (100)	0 (0)
	Other	384 (10)	335 (9)	719 (9)	222 (5)	496 (35)	0 (0)	0 (0)	1 (<1)
Ethnicity for North America[2] — no. (%)	Hispanic or Latino	366 (19)	332 (17)	698 (18)	662 (1)	36 (100)	-	-	-
	Not Hispanic or Latino	1575 (80)	1611 (82)	3186 (81)	3186 (82)	0 (0)	-	-	-
	Unknown	16 (1)	18 (1)	34 (1)	34 (1)	0 (0)	-	-	-
Smoking status — no. (%)	Current	920 (24)	1014 (26)	1934 (25)	1289 (32)	292 (21)	69 (12)	69 (14)	215 (19)
	Former	986 (25)	918 (24)	1904 (25)	1217 (30)	368 (26)	122 (21)	21 (4)	176 (15)
	Never	1979 (51)	1944 (50)	3923 (51)	1581 (39)	763 (54)	399 (68)	414 (82)	766 (66)
Substance use — no. (%)	Current	75 (2)	77 (2)	152 (2)	124 (3)	24 (2)	4 (1)	0 (0)	0 (0)
	Former	1142 (29)	1134 (29)	2276 (29)	2057 (50)	176 (12)	39 (7)	0 (0)	4 (<1)
	Never	2669 (69)	2664 (69)	5333 (69)	1906 (47)	1223 (86)	547 (93)	504 (100)	1153 (100)

Table S1: Baseline Characteristics by Treatment Group and Global Burden of Disease Super Region, Continued

		Pitavastatin (N=3888)	Placebo (N=3881)	Total (N=7769)	High Income (N=4095)	Latin America and Caribbean (N=1423)	S.East/East Asia (N=590)	South Asia (N=504)	Sub-Saharan Africa (N=1157)
ASCVD risk score (%)	Median (Q1, Q3)	4.5 (2.1, 7.0)	4.5 (2.2, 7.0)	4.5 (2.1, 7.0)	5.2 (2.9, 7.6)	4.4 (2.5, 6.9)	1.8 (0.9, 4.2)	2.7 (1.1, 5.2)	3.8 (1.3, 6.6)
— no. (%)	0-<2.5	1096 (28)	1060 (27)	2156 (28)	820 (20)	348 (24)	344 (58)	225 (45)	419 (36)
	2.5-<5	1030 (26)	1025 (26)	2055 (26)	1090 (27)	435 (31)	117 (20)	135 (27)	278 (24)
	5-<7.5	934 (24)	960 (25)	1894 (24)	1137 (28)	338 (24)	83 (14)	87 (17)	249 (22)
	7.5-10	540 (14)	561 (14)	1101 (14)	696 (17)	209 (15)	32 (5)	41 (8)	123 (11)
	>10	288 (7)	275 (7)	563 (7)	352 (9)	93 (7)	14 (2)	16 (3)	88 (8)
BMI (kg/m²)	Median (Q1, Q3)	25.7 (22.8, 29.4)	25.8 (22.7, 29.3)	25.8 (22.8, 29.4)	26.8 (23.9, 30.6)	25.8 (23.3, 28.7)	22.7 (20.5, 25.0)	22.9 (20.2, 25.9)	24.7 (21.2, 29.6)
— no. (%)	<18.5	151 (4)	136 (4)	287 (4)	56 (1)	22 (2)	49 (8)	63 (13)	97 (8)
	18.5-24.9	1548 (40)	1570 (40)	3118 (40)	1354 (33)	581 (41)	393 (67)	285 (57)	505 (44)
	25-29.9	1331 (34)	1332 (34)	2663 (34)	1535 (38)	572 (40)	138 (23)	123 (24)	295 (25)
	30+	856 (22)	839 (22)	1695 (22)	1144 (28)	248 (17)	10 (2)	33 (7)	260 (22)
Diabetes mellitus — no. (%)		23 (1)	14 (<1)	37 (<1)	25 (1)	5 (<1)	1 (<1)	5 (1)	1 (<1)
Chronic active HCV — no. (%)		72 (2)	82 (2)	154 (2)	131 (3)	7 (<1)	15 (3)	0 (0)	1 (<1)
Hypertension — no. (%)		1392 (36)	1382 (36)	2774 (36)	1538 (38)	522 (37)	141 (24)	165 (33)	408 (35)
Family history of premature CVD — no. (%)		724 (19)	692 (18)	1416 (19)	968 (25)	296 (22)	55 (9)	22 (4)	75 (7)
Ever been on a statin — no. (%)		250 (6)	244 (6)	494 (6)	324 (8)	81 (6)	47 (8)	17 (3)	25 (2)
Total cholesterol (mg/dL)[3]	Median (Q1, Q3)	186 (163, 209)	184 (161, 208)	185 (162, 209)	184 (162, 208)	191 (167, 215)	201 (177, 223)	181 (159, 206)	174 (154, 198)
HDL-C (mg/dL)[3]	Median (Q1, Q3)	48 (39, 59)	48 (39, 59)	48 (39, 59)	49 (40, 59)	44 (36, 55)	48 (40, 57)	41 (35, 51)	55 (44, 66)
LDL-C (mg/dL)[3]	Median (Q1, Q3)	109 (87, 128)	108 (87, 127)	108 (87, 128)	107 (87, 126)	114 (93, 134)	122 (103, 141)	107 (87, 126)	97 (78, 118)
— no. (%)	<70	393 (10)	407 (10)	800 (10)	412 (10)	110 (8)	16 (3)	63 (13)	199 (17)
	70-<130	2580 (66)	2637 (68)	5217 (67)	2841 (69)	890 (63)	347 (59)	332 (66)	807 (70)
	130-<160	717 (18)	681 (18)	1398 (18)	693 (17)	330 (23)	165 (28)	88 (17)	122 (11)
	160+	198 (5)	156 (4)	354 (5)	149 (4)	93 (7)	62 (11)	21 (4)	29 (3)
Triglycerides (mg/dL)[3]	Median (Q1, Q3)	115 (82, 169)	114 (80, 169)	114 (81, 169)	112 (80, 165)	138 (94, 200)	122 (87, 179)	137 (96, 205)	89 (67, 128)

Table S1: Baseline Characteristics by Treatment Group and Global Burden of Disease Super Region, Continued

		Pitavastatin (N=3888)	Placebo (N=3881)	Total (N=7769)	High Income (N=4095)	Latin America and Caribbean (N=1423)	S.East/East Asia (N=590)	South Asia (N=504)	Sub-Saharan Africa (N=1157)
Time since HIV diagnosis (years)	Median (Q1, Q3)	12 (7, 19)	13 (8, 19)	13 (8, 19)	15 (9, 22)	9 (5, 15)	17 (12, 20)	10 (7, 13)	10 (7, 13)
Nadir CD4 (cells/mm³) — no. (%)	<200	1890 (49)	1911 (49)	3801 (49)	1945 (47)	610 (43)	359 (61)	313 (62)	574 (50)
	200-349	1019 (26)	1022 (26)	2041 (26)	1014 (25)	412 (29)	190 (32)	141 (28)	284 (25)
	350+	840 (22)	825 (21)	1665 (21)	938 (23)	377 (26)	41 (7)	50 (10)	259 (22)
	Unknown	139 (4)	123 (3)	262 (3)	198 (5)	24 (2)	0 (0)	0 (0)	40 (3)
Total ART use (years) — no. (%)	<5	847 (22)	857 (22)	1704 (22)	675 (16)	490 (34)	55 (9)	143 (28)	341 (29)
	5-10	1190 (31)	1118 (29)	2308 (30)	1115 (27)	462 (32)	123 (21)	205 (41)	403 (35)
	10+	1851 (48)	1904 (49)	3755 (48)	2303 (56)	471 (33)	412 (70)	156 (31)	413 (36)
Entry ART regimen class — no. (%)	NRTI + NNRTI	1843 (47)	1826 (47)	3669 (47)	996 (24)	815 (57)	466 (79)	410 (81)	982 (85)
	NRTI + INSTI	998 (26)	993 (26)	1991 (26)	1875 (46)	85 (6)	3 (1)	3 (1)	25 (2)
	NRTI + PI	728 (19)	708 (18)	1436 (18)	674 (16)	442 (31)	105 (18)	82 (16)	133 (11)
	NRTI-sparing	95 (2)	108 (3)	203 (3)	164 (4)	18 (1)	9 (2)	9 (2)	3 (<1)
	Other NRTI-containing	224 (6)	246 (6)	470 (6)	386 (9)	63 (4)	7 (1)	0 (0)	14 (1)
CD4 count (cells/mm³)	Median (Q1, Q3)	620 (449, 832)	622 (445, 824)	621 (448, 827)	615 (447, 835)	658 (482, 865)	626 (476, 784)	591 (378, 758)	598 (433, 802)
HIV-1 RNA (copies/mL)[4] — no. (%)	<LLQ	2641 (88)	2609 (87)	5250 (88)	3391 (86)	1011 (93)	476 (97)	62 (82)	310 (81)
	LLQ -< 400	305 (10)	312 (10)	617 (10)	483 (12)	55 (5)	16 (3)	5 (7)	58 (15)
	400+	63 (2)	67 (2)	130 (2)	84 (2)	24 (2)	0 (0)	9 (12)	13 (3)
Quantifiable HIV-1 RNA (copies/mL)	N	368	379	747	567	79	16	14	71
	Median (Q1, Q3)	63 (34, 198)	62 (34, 202)	62 (34, 199)	54 (31, 152)	109 (52, 733)	54 (33, 68)	6265 (119, 68112)	122 (40, 299)

Frequency and percentage are presented for categorical measures and medians with lower and upper quartiles (Q1, Q3) for continuous measures. For age, minimum (min) and maximum (max) are also shown. All statistics are calculated out of participants with data collected. Missing data include: BMI (n=6), Family history of premature CVD (n=252), Smoking status (n=8), Substance use (n=8), Time since HIV diagnosis (n=4), Total ART use (n=2), HIV-1 RNA (n=1772).

[1] 'Other' race includes participants self-identifying as: native or indigenous to the enrollment region, more than one race (with no single race noted as predominant), or of unknown race.

[2] Ethnicity presented per NIH definition for participants in the US (including Puerto Rico) and Canada only; not applicable in other geographic regions.

[3] Screening lipid panel from clinical care used for eligibility is presented. Fasting was not required, if random laboratory values to determine eligibility were within the range specified by the protocol.

[4] HIV-1 RNA was captured if available through standard of care. The assays used for testing varied, including assays with LLQ between 20 and 400 copies/mL. Summary of quantifiable levels is limited to those with HIV-1 RNA ≥LLQ.

ART denotes antiretroviral therapy, ASCVD atherosclerotic cardiovascular disease, BMI body mass index, HCV, hepatitis C virus, HDL-C HDL cholesterol, LDL-C LDL cholesterol, LLQ lower limit of quantitation, NRTI nucleoside reverse transcriptase inhibitor, INSTI integrase strand transfer inhibitor, NNRTI non-nucleoside reverse transcriptase inhibitor, PI protease inhibitor.

Table S2: Details of First MACE Endpoints

Event type		Total (N=225)	Pitavastatin (N=89)	Placebo (N=136)
All Cerebrovascular Events (Stroke or TIA) — no. (%)		**72 (32)**	**29 (33)**	**43 (32)**
Stroke	Ischemic	43 (19)	15 (17)	28 (21)
	Hemorrhagic	10 (4)	2 (2)	8 (6)
	Undetermined	2 (1)	1 (1)	1 (1)
Transient Ischemic Attack (TIA)		17 (8)	11 (12)	6 (4)
All Cardiac Ischemia or MI Events — no. (%)		**71 (32)**	**25 (28)**	**46 (34)**
Myocardial Infarction	Type 1	50 (22)	16 (18)	34 (25)
	Type 2	13 (6)	7 (8)	6 (4)
Unstable Angina		8 (4)	2 (2)	6 (4)
All Deaths — no. (%)		**63 (28)**	**28 (31)**	**35 (26)**
CV Death	Sudden Cardiac Death	16 (7)	8 (9)	8 (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		44 (20)	18 (20)	26 (19)
All Cardiac Catheterization or Revascularization Events — no. (%)		**12 (5)**	**5 (6)**	**7 (5)**
Percutaneous (PCI)	Elective	9 (4)	3 (3)	6 (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 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 MACE and Death Endpoints Captured from Vital Status Follow-up

Event type		Total (N=9)	Pitavastatin (N=3)	Placebo (N=6)
All Deaths — no. (%)		**8 (89)**	**3 (100)**	**5 (83)**
Non-CV Death	Non-AIDS-Defining Malignancies	3 (33)	1 (33)	2 (33)
	Accident or Homicide	1 (11)	0 (0)	1 (17)
	Central Nervous System	1 (11)	0 (0)	1 (17)
	Renal Failure	1 (11)	1 (33)	0 (0)
	Suicide or Psychiatric Disease	1 (11)	0 (0)	1 (17)
Undetermined		1 (11)	1 (33)	0 (0)
All Cardiac Ischemia or MI Events — no. (%)		**1 (11)**	**0 (0)**	**1 (17)**
Myocardial Infarction	Type 1	1 (11)	0 (0)	1 (17)

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

Table S4: Details of Non-CV Deaths

Cause of death	Total (N=163)	Pitavastatin (N=82)	Placebo (N=81)
Non-AIDS-Defining Malignancies — no. (%)	57 (35)	30 (37)	27 (33)
Non-AIDS-Related Infections — no. (%)	44 (27)	19 (23)	25 (31)
Substance Use — no. (%)	24 (15)	15 (18)	9 (11)
Accident or Homicide — no. (%)	16 (10)	7 (9)	9 (11)
AIDS Opportunistic Infections — no. (%)	11 (7)	5 (6)	6 (7)
Suicide or Psychiatric Disease — no. (%)	4 (2)	3 (4)	1 (1)
AIDS-Defining Malignancies — no. (%)	1 (1)	1 (1)	0 (0)
Gastrointestinal — no. (%)	1 (1)	0 (0)	1 (1)
Liver Failure — no. (%)	1 (1)	0 (0)	1 (1)
Lung Disease — no. (%)	1 (1)	1 (1)	0 (0)
Renal Failure — 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.

Table S5: Incidence of Non-Fatal Heart Failure

Event	Treatment Group	# Participants at risk	Total at-risk person-years	# Participants with event	Incidence Rate /1000PY (95% CI)
First non-fatal heart failure	Pitavastatin	3888	18,672	13	0.70 (0.40, 1.20)
	Placebo	3881	18,751	12	0.64 (0.36, 1.13)

Hospitalization for heart failure events as determined by the adjudication committee are summarized; events positively adjudicated as MACE endpoints are excluded. These are presented in Table S2,and include 1 fatal heart failure.
Incidence rates were estimated using Poisson distribution based on the earliest event, last contact or 12/30/2022, 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. (%)	**1389 (18)**	**4 (<1)**	**28 (<1)**	**562 (14)**	**101 (3)**	**695 (18)**	**2 (<1)**	**29 (<1)**	**541 (14)**	**122 (3)**	**694 (18)**
Infections and infestations	**509 (7)**	0 (0)	7 (<1)	228 (6)	19 (<1)	**254 (7)**	0 (0)	10 (<1)	219 (6)	26 (<1)	**255 (7)**
Injury, poisoning and procedural complications	**197 (3)**	2 (<1)	4 (<1)	78 (2)	11 (<1)	**95 (2)**	1 (<1)	3 (<1)	83 (2)	15 (<1)	**102 (3)**
Gastrointestinal disorders	**135 (2)**	1 (<1)	4 (<1)	67 (2)	1 (<1)	**73 (2)**	0 (0)	0 (0)	59 (2)	3 (<1)	**62 (2)**
Respiratory, thoracic and mediastinal disorders	**128 (2)**	0 (0)	4 (<1)	48 (1)	11 (<1)	**63 (2)**	0 (0)	2 (<1)	45 (1)	18 (<1)	**65 (2)**
Neoplasms benign, malignant and unspecified	**125 (2)**	2 (<1)	3 (<1)	37 (<1)	15 (<1)	**57 (1)**	1 (<1)	5 (<1)	47 (1)	15 (<1)	**68 (2)**
Nervous system disorders	**125 (2)**	0 (0)	3 (<1)	59 (2)	3 (<1)	**65 (2)**	0 (0)	3 (<1)	53 (1)	4 (<1)	**60 (2)**
Psychiatric disorders	**117 (2)**	0 (0)	0 (0)	44 (1)	19 (<1)	**63 (2)**	0 (0)	2 (<1)	41 (1)	11 (<1)	**54 (1)**
Musculoskeletal and connective tissue disorders	**98 (1)**	0 (0)	5 (<1)	48 (1)	2 (<1)	**55 (1)**	0 (0)	2 (<1)	41 (1)	0 (0)	**43 (1)**
Renal and urinary disorders	**61 (<1)**	0 (0)	0 (0)	26 (<1)	7 (<1)	**33 (<1)**	0 (0)	0 (0)	20 (<1)	8 (<1)	**28 (<1)**
General disorders and administration site conditions	**56 (<1)**	0 (0)	4 (<1)	19 (<1)	2 (<1)	**25 (<1)**	2 (<1)	1 (<1)	27 (<1)	1 (<1)	**31 (<1)**
Metabolism and nutrition disorders	**54 (<1)**	0 (0)	1 (<1)	12 (<1)	9 (<1)	**22 (<1)**	0 (0)	1 (<1)	19 (<1)	12 (<1)	**32 (<1)**
Vascular disorders	**52 (<1)**	1 (<1)	4 (<1)	16 (<1)	3 (<1)	**24 (<1)**	0 (0)	3 (<1)	21 (<1)	4 (<1)	**28 (<1)**
Cardiac disorders[1]	**51 (<1)**	0 (0)	3 (<1)	18 (<1)	4 (<1)	**25 (<1)**	0 (0)	2 (<1)	18 (<1)	6 (<1)	**26 (<1)**
Hepatobiliary disorders	**47 (<1)**	0 (0)	0 (0)	19 (<1)	2 (<1)	**21 (<1)**	0 (0)	1 (<1)	23 (<1)	2 (<1)	**26 (<1)**
Investigations	**43 (<1)**	1 (<1)	0 (0)	11 (<1)	10 (<1)	**22 (<1)**	1 (<1)	0 (0)	10 (<1)	10 (<1)	**21 (<1)**
Blood and lymphatic system disorders	**39 (<1)**	0 (0)	0 (0)	12 (<1)	9 (<1)	**21 (<1)**	0 (0)	0 (0)	5 (<1)	13 (<1)	**18 (<1)**
Surgical and medical procedures	**27 (<1)**	0 (0)	1 (<1)	7 (<1)	0 (0)	**8 (<1)**	0 (0)	4 (<1)	15 (<1)	0 (0)	**19 (<1)**
Eye disorders	**27 (<1)**	1 (<1)	2 (<1)	17 (<1)	0 (0)	**20 (<1)**	0 (0)	0 (0)	7 (<1)	0 (0)	**7 (<1)**
Reproductive system and breast disorders	**26 (<1)**	0 (0)	0 (0)	15 (<1)	0 (0)	**15 (<1)**	0 (0)	0 (0)	11 (<1)	0 (0)	**11 (<1)**
Skin and subcutaneous tissue disorders	**17 (<1)**	0 (0)	0 (0)	8 (<1)	0 (0)	**8 (<1)**	0 (0)	1 (<1)	8 (<1)	0 (0)	**9 (<1)**
Ear and labyrinth disorders	**8 (<1)**	0 (0)	0 (0)	1 (<1)	0 (0)	**1 (<1)**	0 (0)	2 (<1)	5 (<1)	0 (0)	**7 (<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)**
Endocrine disorders	**6 (<1)**	0 (0)	0 (0)	2 (<1)	2 (<1)	**4 (<1)**	0 (0)	1 (<1)	1 (<1)	0 (0)	**2 (<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 2431 non-fatal SAEs were reported for 1389 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. (%)	**2560 (33)**	**53 (1)**	**188 (5)**	**940 (24)**	**123 (3)**	**1304 (34)**	**60 (2)**	**162 (4)**	**894 (23)**	**140 (4)**	**1256 (32)**
Infections and infestations — no. (%)	**588 (8)**	3 (<1)	21 (<1)	250 (6)	19 (<1)	**293 (8)**	1 (<1)	28 (<1)	240 (6)	26 (<1)	**295 (8)**
Lower respiratory tract and lung infections — no.	**137**	0	3	68	2	73	0	5	58	1	64
Abdominal and gastrointestinal infections — no.	**80**	0	1	37	1	39	0	3	36	2	41
Metabolism and nutrition disorders — no. (%)	**585 (8)**	46 (1)	163 (4)	86 (2)	17 (<1)	**312 (8)**	46 (1)	123 (3)	89 (2)	15 (<1)	**273 (7)**
Diabetes mellitus (including subtypes) — no.	**383**	42	166	6	1	215	36	114	15	3	168
General nutritional disorders NEC — no.	**105**	0	0	57	7	64	0	0	35	6	41
Investigations — no. (%)	**508 (7)**	6 (<1)	5 (<1)	216 (6)	28 (<1)	**255 (7)**	7 (<1)	7 (<1)	214 (6)	25 (<1)	**253 (7)**
Renal function analyses — no.	**206**	0	0	95	9	104	1	0	97	4	102
Physical examination procedures and organ system status — no.	**122**	3	4	50	3	60	1	0	55	6	62
Musculoskeletal and connective tissue disorders — no. (%)	**356 (5)**	14 (<1)	56 (1)	131 (3)	3 (<1)	**204 (5)**	15 (<1)	27 (<1)	108 (3)	2 (<1)	**152 (4)**
Muscle pains — no.	**120**	8	37	34	0	79	9	8	22	2	41
Musculoskeletal and connective tissue pain and discomfort — no.	**92**	5	4	39	0	48	6	6	32	0	44
Injury, poisoning and procedural complications — no. (%)	**232 (3)**	2 (<1)	5 (<1)	97 (2)	11 (<1)	**115 (3)**	1 (<1)	3 (<1)	98 (3)	15 (<1)	**117 (3)**
Limb fractures and dislocations — no.	**99**	0	1	43	2	46	0	2	50	1	53
Gastrointestinal disorders — no. (%)	**231 (3)**	9 (<1)	12 (<1)	101 (3)	1 (<1)	**123 (3)**	8 (<1)	10 (<1)	87 (2)	3 (<1)	**108 (3)**
Nervous system disorders — no. (%)	**221 (3)**	6 (<1)	17 (<1)	91 (2)	3 (<1)	**117 (3)**	7 (<1)	8 (<1)	85 (2)	4 (<1)	**104 (3)**
Vascular disorders — no. (%)	**158 (2)**	4 (<1)	8 (<1)	57 (1)	3 (<1)	**72 (2)**	9 (<1)	10 (<1)	61 (2)	6 (<1)	**86 (2)**
Vascular hypertensive disorders NEC — no.	**93**	4	4	34	1	43	7	5	35	3	50
Psychiatric disorders — no. (%)	**157 (2)**	1 (<1)	11 (<1)	60 (2)	19 (<1)	**91 (2)**	5 (<1)	3 (<1)	47 (1)	11 (<1)	**66 (2)**
Respiratory, thoracic and mediastinal disorders — no. (%)	**154 (2)**	2 (<1)	4 (<1)	62 (2)	11 (<1)	**79 (2)**	0 (0)	4 (<1)	53 (1)	18 (<1)	**75 (2)**
General disorders and administration site conditions — no. (%)	**154 (2)**	7 (<1)	20 (<1)	52 (1)	2 (<1)	**81 (2)**	10 (<1)	7 (<1)	55 (1)	1 (<1)	**73 (2)**
Pain and discomfort NEC — no.	**96**	4	9	29	0	42	6	5	43	0	54
Neoplasms benign, malignant and unspecified — no. (%)	**148 (2)**	2 (<1)	4 (<1)	47 (1)	15 (<1)	**68 (2)**	1 (<1)	8 (<1)	56 (1)	15 (<1)	**80 (2)**
Renal and urinary disorders — no. (%)	**104 (1)**	3 (<1)	2 (<1)	46 (1)	8 (<1)	**59 (2)**	3 (<1)	1 (<1)	33 (<1)	8 (<1)	**45 (1)**
Cardiac disorders[1] — no. (%)	**93 (1)**	2 (<1)	7 (<1)	31 (<1)	4 (<1)	**44 (1)**	1 (<1)	8 (<1)	34 (<1)	6 (<1)	**49 (1)**
Blood and lymphatic system disorders — no. (%)	**78 (1)**	0 (0)	0 (0)	34 (<1)	9 (<1)	**43 (1)**	1 (<1)	0 (0)	21 (<1)	13 (<1)	**35 (<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 5114 AEs were reported for 2560 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. (%)	**144 (2)**	**8 (<1)**	**39 (1)**	**43 (1)**	**1 (<1)**	**91 (2)**	**10 (<1)**	**13 (<1)**	**28 (<1)**	**2 (<1)**	**53 (1)**
Myalgia — **no.**	**120**	8	37	34	0	**79**	9	8	22	2	**41**
Muscular weakness — **no.**	**41**	3	4	16	1	**24**	3	3	11	0	**17**
Myopathy — **no.**	**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, 144 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.[3]
Special considerations related to:	
Geography, Race, and Ethnicity	Based on 2021 estimates, among the 38.4 million people with HIV:[4] 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.[5] 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.[4] 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.[4] 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).[4,6,7] Atherosclerotic cardiovascular disease risk increases with age.[8] 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.[3]
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[9]
Canada	10	29[10]
Spain	9	18[11]
Brazil	29	34[12]
Peru	8	24[11]
Haiti	42	57[11]
Thailand	56	42[11]
India	26	39[13]
South Africa	66	64[11]
Botswana	63	61[11]
Uganda	51	60[11]
Zimbabwe	24	58[11]

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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