This is REPRIEVE Primary SAP Version 2.1 with names of authors, trial principal investigators and vice chairs redacted.

A5332 and EU5332

Randomized Trial to Prevent Vascular Events in HIV

A5332 Protocol Version 6.0, EU5332 Protocol Version 6.0

ClinicalTrials.gov Identifier: NCT02344290

PRIMARY STATISTICAL ANALYSIS PLAN

Version 2.1

June 6, 2022

Created by: REPRIEVE Study Statisticians

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Version History

Version	Changes Made	Date Finalized
1.0	Original Version	12/21/2015
2.0	Sections 1, 2.1, 4.2.1, 4.3: Incorporated REPRIEVE (EU5332). Section 2.1: Updated Study Overview based on REPRIEVE (A5332) protocol version 5.0. Sections 2.4, 4.1, 4.2.6: - Updated Formal Efficacy and Futility Review based on the study design change implemented in REPRIEVE (A5332) protocol version 4.0 (expected total number of endpoints of 288). - Changed to two interim reviews, at 50% and 75% information (refer to the DSMB recommendations from the December 2019 review). - Clarified that the same critical values will be used for both the primary and secondary outcome measures at the interim analyses, as discussed with the DSMB at the December 2020 meeting. Sections 3.1, 3.3, 5.3, 5.3.1: - Clarified primary outcome measure to include undetermined deaths, as specified in the CEC Charter, version 1.0. Consequently, “primary MACE” was used to refer to the primary endpoint throughout the document. - Analysis of confirmed MACE (i.e. not including undetermined deaths) will be conducted if indicated by the primary endpoint results or requested by the DSMB. Sections 3.2, 5.3, 5.3.1, 6: - Added a supporting analysis of time to MACE or all-cause death including data from vital status and endpoint follow-up implemented in REPRIEVE (A5332) protocol version 5.0. - Added vital status followup and currency to report contents. Sections 5.1.1, 5.3: “Per-protocol” is used to refer to the sensitivity analysis population rather than “as-treated” to reflect the analysis according to randomized treatment with censoring at the time of its discontinuation. Sections 5.1.4, 5.3, 5.3.1: Specified sensitivity analyses for evaluating the potential impact of missing data.	02/16/2021

	Sections 5.1.4, 5.3.4: Analysis of lipid profiles over time will use mixed effects models to better handle missing data. The Student's t-tests were removed. Section 5.1.5: It was clarified that the final primary efficacy analysis will use significance level adjusted for interim looks to ensure study-wide alpha no greater than 5%. Section 5.2: Following the SARS-Cov-2 pandemic, COVID-19 and serious COVID-19 diagnoses were added to the list of targeted events (REPRIEVE (A5332) protocol version 5.0, CM #1). Sections 5.3, 5.3.1: The Gray's test and model for cumulative incidence function specified as supporting analyses were removed. Cumulative incidence function will still be estimated and displayed. Breslow estimators of the cause-specific hazard from the Cox model will be used for estimation, instead of product-limit estimator with delta method standard errors. Section 5.3.2: The list of factors to include in the analyses of prognostic factors of MACE was updated based on the enrolled population, and to provide further details on definitions and thresholds. - Ethnicity, collected according to the NIH definition applies to North America and Puerto Rico only. As such, ethnicity was removed from this analysis of the global REPRIEVE cohort. - Hypertension will be used as a composite of systolic and diastolic blood pressures, use of anti-hypertensive agents and hypertension diagnosis, instead of using each component separately. - ASCVD risk score was added. - Metabolic syndrome definition was clarified. - HIV-1 RNA, nadir CD4, duration of ART exposure, BMI thresholds were added or edited. Coding details, data sources, validation requirements and table/figure specifications were moved into a separate Analysis Implementation Plan. The document was re-formatted and re-arranged based on the current CBAR standard operating procedures. Minor edits and clarifications were made throughout the document.	
2.1	Protocol amendment review (V6.0)	06/06/2022

	– No changes to the analytical approaches described in this Primary SAP. – Analytic approaches to address COVID-19-related objectives are described in a separate REPRIEVE COVID Supplement SAP. – Title page was updated to reflect changes in the study team.	

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Glossary

AIP	Analysis Implementation Plan
ART	Antiretroviral treatment
ASCVD	Atherosclerotic cardiovascular disease
CEC	Clinical Events Committee
CBAR	Center for Biostatistics in AIDS Research, the REPRIEVE statistical analysis center at Harvard T. H. Chan School of Public Health
CVD	Cardiovascular disease
DSMB	Data and Safety Monitoring Board
ESRD	End-stage renal disease
IPCW	Inverse probability censoring weights
ITT	Intention-to-treat
MACE	Major adverse cardiovascular events
NHLBI	National Heart, Lung, and Blood Institute
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the content proposed for the primary statistical analysis of REPRIEVE. The REPRIEVE trial is branched into two parallel, identical sister protocols:

REPRIEVE (A5332) **funded by NHLBI with infrastructure support by the NIH Division of AIDS (DAIDS) and conducted in US and select international sites (approximately 120 sites in 11 countries).**

REPRIEVE (EU5332) **co-sponsored by NEAT-ID and Massachusetts General Hospital and conducted at approximately 15 sites in Spain.**

Due to the different regulatory landscape in US (e.g. HIPAA) vs. EU (e.g. GDPR) and different funding sources, the study conduct, site monitoring, data collection and storage will be separate for the two identical sister protocols. In the final analyses of the overall REPRIEVE trial, the data from REPRIEVE (A5332) and REPRIEVE (EU5332) will be pooled. Likewise, the data will be pooled for all presentations to the Data and Safety Monitoring Board DSMB.

The focus of this SAP is on analyses that address the primary and secondary objectives. Plans for interim review by the DSMB while the study is ongoing are also provided. As such, this analysis plan includes the key analyses which may lead to modification or termination of the study, and hence also form the core of any presentation or publication used to disseminate the primary conclusions of the study. Also included is a summary of analysis plans for secondary outcome measures analyzed either at the time of the core final analyses or later, determined by the priority of the REPRIEVE study team. Outlines of analyses for other objectives and outcome measures will be provided in separate SAPs. Analysis plans for REPRIEVE Ancillary studies, including the REPRIEVE COVID Supplement are not included in this document.

This document outlines the general statistical approaches that will be used in the analysis. It has been developed to facilitate discussion of the statistical analysis components among the study team, and to provide agreement between the study team and statisticians regarding the statistical analyses to be performed and presented in the primary analysis report. Detailed outlines of tables and figures that will be included in the Primary Analysis Report, and analysis coding descriptions are included in the separate Analysis Implementation Plan (AIP).

This analysis plan may be modified by the study team as new information becomes available outside of the study, or to reflect recommendations made by the DSMB. In addition, some analyses may be omitted at interim analyses if there are insufficient data to warrant analysis or at the request of the DSMB. Unless otherwise noted (for example, analyses to be presented in open DSMB reports), the analyses outlined in this document will be performed by treatment group.

All analyses will be performed by REPRIEVE Statisticians at CBAR[1].

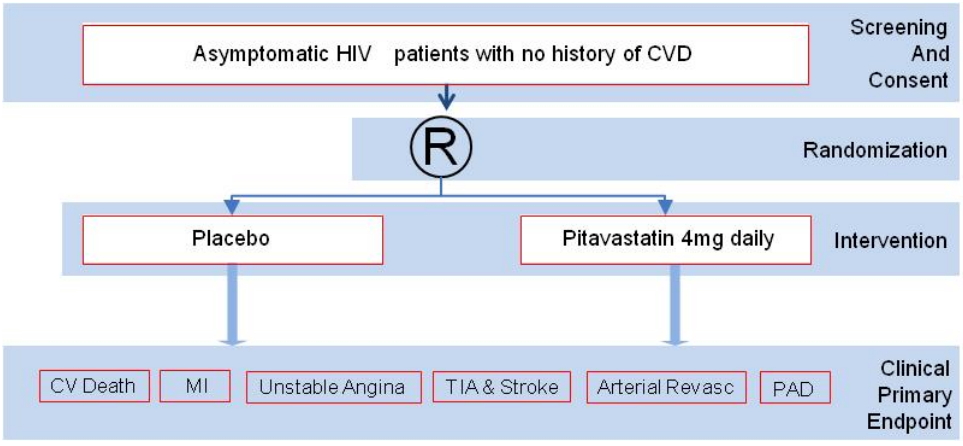
1.2 Summary of Major Changes

Analysis plan was updated to version 2.0 to reflect changes in the study design (increase in sample size and followup duration, change to event-driven design with expected total number of endpoints of 288, and implementation of vital status and endpoint follow-up), to incorporate REPRIEVE (EU5332), and to update formal efficacy and futility review details for a total of two interim looks, at 50% and 75% information, per recommendation of NHLBI endorsed by the DSMB at the December 2019 meeting. It was clarified that the final primary efficacy analysis will use significance level adjusted for interim looks to ensure study-wide alpha no greater than 5%. Sensitivity analyses for evaluating the potential impact of missing data were also added. The related key edits are listed in the version history table above and are shown in bold face throughout the document. Note that there were no changes to existing outcome measures or primary analytic approaches.

[1] *While the study is ongoing, the head statistician and REPRIEVE DCC co-PI [Dr. Ribaudo] will remain blinded to treatment assignment and will review only pooled data summaries. The other REPRIEVE statisticians at CBAR will be unblinded and have access to treatment assignment.*

2 Study Overview

2.1 Study Design

Title	Randomized Trial to Prevent Vascular Events in HIV – REPRIEVE
Indication	To study the efficacy of statins to reduce the risk of cardiovascular disease in HIV-infected patients
Location	US, **EU** and select international sites[2]
Brief Rationale	HIV-infected persons face an increased risk of CVD morbidity and mortality, yet no preventive strategies for CVD risk reduction have been proven for this population. Among HIV-infected individuals, immune activation may contribute in unique ways to atherosclerosis and ensuing cardiovascular events. Statins affect both traditional CVD risk factors (LDL cholesterol) and have pleiotropic effects to reduce inflammation and immune activation. Thus, statins may target the unique mechanisms of cardiovascular disease in HIV.
Experimental Design	Phase III, prospective, double-blind, randomized (1:1), placebo-controlled, parallel-group, multicenter efficacy study
Sample size	Approximately **7500** participants[3,4]
Duration	**96** months from enrollment of the first participant[5,6]
Treatment	Pitavastatin 4 mg PO daily or matching placebo
Stratification	Sex (male/female) Screening CD4+ T-cell count (≤500 vs. >500 cells/mm^3)[7]
Abbreviated Study Flow	

[2] *REPRIEVE (A5332): US and select international sites;* ***REPRIEVE (EU5332): Spain.***
[3] ***Originally, 6500 participants. The sample size was increased to approximately 7500 participants per the DSMB recommendations following the December 2017 review.***
[4] ***REPRIEVE (A5332): 7500 participants; REPRIEVE (EU5332): 250 participants.***
[5] ***Originally, 72 months. The follow-up was extended per DSMB recommendations following the December 2017 review.***
[6] ***REPRIEVE (A5332): median participant follow-up 6 years (72 months); REPRIEVE (EU5332): median follow-up approximately 4 years (50 months).***
[7] *During REPRIEVE (A5332) mechanistic substudy A5333S enrollment, randomization was also stratified by whether or not a participant had elected to participate in A5333S (yes/no).*

2.2 Hypotheses

Study hypotheses as specified in the study protocol are as follows.

2.2.1 Primary Hypothesis

Statin therapy will prevent atherosclerotic cardiovascular disease (ASCVD)-related MACE (major adverse cardiovascular events) in HIV-infected persons on antiretroviral therapy (ART) in whom traditional CVD risk is not significantly increased.

2.2.2 Secondary Hypotheses

1. Statin therapy will be associated with reductions in specific CVD-related events and all-cause mortality.
2. Decreases in LDL and non-HDL cholesterol levels associated with statin therapy will be predictive of reduction in CVD events.
3. Statin therapy will reduce serious non-cardiovascular events, including malignancies, end stage kidney or liver disease.
4. Statin therapy will be safe and well tolerated in the HIV-infected population.

2.3 Study Objectives

This Primary SAP addresses the below primary and secondary objectives, as listed in the study protocol *[the corresponding objective number in the study protocol is provided in brackets]*. The primary analysis including these objectives will be conducted upon study completion. Other study objectives in the protocol will be addressed in subsequent analysis plans.

All objectives will be analyzed under a superiority framework.

2.3.1 Primary Objective

To determine the effects of pitavastatin as a primary prevention strategy for MACE in HIV. *[Objective 1.2.1 in the protocol.]*

2.3.2 Secondary Objectives

1. To evaluate the effects of pitavastatin on each of the components of the primary composite MACE endpoint and all-cause mortality. *[Objective 1.2.2.1]*
2. To determine the effects of pitavastatin on LDL and non-HDL cholesterol in the HIV population and assess the relationship of changes in LDL and non-HDL to the incidence of MACE. *[Objective 1.2.2.2]*
3. To evaluate whether baseline traditional risk factors (including smoking, hypertension, dyslipidemia, glucose) and time updated HIV-specific (immunological and virological) risk factors are predictive of MACE and pitavastatin effects on MACE in the HIV population. *[Objective 1.2.2.3]*
4. To evaluate whether baseline and time updated inflammatory and immune activation biomarkers are predictive of MACE and pitavastatin effects on MACE in the HIV population. *[Objective 1.2.2.4]*

5. To determine the effects of pitavastatin on the incidence of serious non-cardiovascular events and AIDS-defining events. *[Objective 1.2.2.5]*
6. To determine the safety of pitavastatin in the HIV population, including the development of diabetes mellitus (DM), liver dysfunction, and myopathy. *[Objective 1.2.2.6]*

2.4 Overview of Sample Size Considerations

The REPRIEVE (A5332) protocol version 4.0 implemented an event-driven study design. To summarize, under the assumption that MACE events (pooled across treatment groups) will occur at rates consistent with those predicted by the ASCVD risk score, a total of 288 events (i.e. participants experiencing a primary MACE event) will provide 85% power to detect the target 30% reduction in event rates (HR = 0.70). To accumulate this target total number of events, the sample size was increased to approximately 7500 participants and followup has been extended to 8 years from first enrollment. Further details on the original sample size considerations and updated design considerations are provided in protocol sections 9.4.1 and 9.4.2, respectively.

3 Outcome Measures

3.1 Primary Outcome Measure

The outcome measure to address the primary objective of the study *[objective 1.2.1]* and secondary objectives 1.2.2.3 – 1.2.2.5 in the study protocol is as follows.

Time to the first event of a composite of major cardiovascular events (MACE) including:

- Atherosclerotic or other CVD death
- Nonfatal myocardial infarction
- Unstable angina hospitalization
- Coronary or peripheral arterial revascularization
- Nonfatal stroke or TIA
- Urgent PAD ischemic event (acute or chronic limb ischemia, amputation, etc.)

Supportive analyses incorporating repeated events will also be performed.

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 [Hicks 2015].

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, Version 1.0 (dated March 19, 2015), page 15. The MACE and undetermined deaths are subsequently collectively referred to as the primary MACE.

Participants discontinuing follow-up without experiencing the event will be censored at the time of the last evaluation for which an assessment for MACE was made; deaths from non-CV causes will be considered as competing risk events in the primary analysis. **For the primary analysis, only events identified while the participant is in study follow-up will be included. See**

below for supportive outcome measures that incorporate vital status follow-up after premature study discontinuation.

3.2 Secondary Outcome Measures

The corresponding secondary objectives (see Section 2.3.2) are provided in the brackets at the end.

1) Time to the first of each individual component of the primary outcome measure *[Objective 1.2.2.1]*

   For each event, participants discontinuing follow-up without experiencing the event will be censored; deaths from other causes will be considered competing risk events.

2) Time to death (all-cause mortality) *[Objective 1.2.2.1]*

   Based on independent review, death will be classified as cardiovascular event or non-cardiovascular event. Non-cardiovascular events will be further characterized as HIV-associated clinical diagnosis, non-AIDS malignancy, accidental, suicide, homicide, other sudden death of unknown etiology, or other.

3) Time to death (all-cause mortality) and/or MACE *[Objective 1.2.2.1]*

   Participants discontinuing follow-up without experiencing the event (death from any cause or MACE) will be censored. Supportive analyses incorporating repeated events will also be performed. **An additional supportive analysis including data from vital status and endpoint follow-up will also be conducted.**

4) Time to any (composite) or each (individual) of the following incident clinical diagnoses (including recurrent diagnoses as appropriate) *[Objective 1.2.2.5]*

   - 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 (ESRD), defined as initiation of dialysis or renal transplantation.
   - End-stage liver disease, defined as cirrhosis, or hepatic decompensation requiring hospitalization

   For specific case definitions, see MOPS.

   For each event, participants discontinuing follow-up without experiencing each event will be censored; deaths from other causes will be considered as competing events.

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. For participants with triglycerides >400 mg/dL and <500 mg/dL, direct LDL will be used; and for participants with triglycerides ≥500 mg/dL, LDL will be missing. Non-HDL cholesterol will be calculated as the difference between total cholesterol and HDL cholesterol. *[Objective 1.2.2.2]*

6) Time to any of the following adverse events (including recurrent events as appropriate) *[Objective 1.2.2.6]*

- Serious adverse event as defined by ICH criteria
- Incident Diabetes mellitus (DM)
- Grade 3 or 4 ALT
- 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.

3.3 Other Outcome Measures

Other outcome measures used in supporting and exploratory analyses include the below.

1. **Time to confirmed MACE defined as the Primary Outcome Measure (Section 3.1), without undetermined deaths considered events; both undetermined deaths and non-CV deaths as competing risks. *[Objective 1.2.1]***

   This supporting outcome measure will be analyzed conditional on primary endpoint results, should the treatment effect appear driven by the undetermined deaths or if requested by the DSMB.
2. Time to heart failure. *[Objective 1.2.1]*
3. Strategic Timing of Retroviral Treatment (START), a composite outcome measure defined as time to any of the below. *[Objective 1.2.2.5]*
   - AIDS or death from AIDS
     - Opportunistic events consistent with the 2014 CDC expanded surveillance definition plus additional events associated with immunosuppression in the patient population targeted for enrollment. Esophageal candidiasis and chronic Herpes simplex infection will be counted as primary endpoints only if they result in death.
   - Non-AIDS event
     - CVD: myocardial infarction, stroke, coronary revascularization
     - ESRD: initiation of dialysis, renal transplantation
     - Decompensated liver disease
     - Non-AIDS-defining cancers, excluding basal and squamous cell skin cancers. Basal and squamous cell skin cancer will be counted as a primary endpoint only if they result in death.
   - Death not attributable to AIDS, including death of unknown cause.
4. Fasting Total cholesterol level (TC) at study entry and annually thereafter. *[Objective 1.2.2.2]*
5. Fasting HDL cholesterol level (HDLC) at study entry and annually thereafter. *[Objective 1.2.2.2]*
6. LDL-C/HDL-C ratio at study entry and annually thereafter. *[Objective 1.2.2.2]*
7. Triglycerides (TG) at study entry and annually thereafter. *[Objective 1.2.2.2]*

4 Interim Review Considerations

4.1 Overview

REPRIEVE will undergo interim review at least every 6 - 12 months by an NHLBI-appointed Data Safety Monitoring Board (DSMB) for study conduct, continued feasibility, safety, and efficacy with the first review before start of enrollment and the second approximately 6 months after enrollment of the first participant. Data from REPRIEVE (A5332) and REPRIEVE (EU5332) will be pooled for all presentations to the DSMB. This section outlines general considerations for REPRIEVE Interim Reviews.

An outline of the focus of each review, as well as their frequency (as specified in the DSMB Charter V1.0), is provided in **Table A** below.

Benchmarks for monitoring of study accrual, retention, and treatment cross-over are also provided, as well as a general overview of the framework for efficacy and futility monitoring. Finally, an overview of the anticipated reporting documents to be prepared for each review is given. Analytical details will appear in the relevant sections in the body of the SAP.

Throughout the duration of study follow-up, the REPRIEVE DCC co-PI and lead statistician (herein referred to as blinded statistician) will remain blinded to data by treatment group. She will not have access to data broken out by treatment group (even if masked). Instead, during any internal CBAR review, if needed, the blinded statistician will review tables broken out by a randomly permuted treatment assignment.

Table A: Overview of DSMB Monitoring Focus and Frequency of Review

Review Type	Primary Focus	Frequency of Review[1]
Feasibility and Conduct	Site activation, enrollment, data and visit completeness, rates of loss to follow-up and cross-over.	Approximately every 6 months
Safety	Rates of adverse events by treatment group	Approximately every 6 months
Event Rate Evaluation	Pooled rates of events observed to date; predicted confidence interval of the pooled event rate under a range of realistic scenarios[2]	Approximately every 6 months, starting 1 year after enrollment of first participant
Formal Efficacy and Futility Review	Treatment group comparison of the Primary MACE events utilizing group sequential methods	At least annually starting once the adequacy of the sample size has been established. A total of **2** interim looks for efficacy are planned, at **50%** and **75%** of information (defined as the expected total number of primary endpoints).[3]

[1] Unless otherwise requested by the DSMB.
[2] To be conducted if the pooled rate falls below a specified target (see Benchmarks below). This review occurred in December 2017.
[3] Interim looks were originally scheduled at 20% (tentative, if requested by the DSMB), 40%, 60% and 80% information. Per recommendation of NHLBI, endorsed by the DSMB at the December 2019 meeting, there will be 2 interim looks, at 50% and 75% information.

4.2 Benchmarks for Study Monitoring

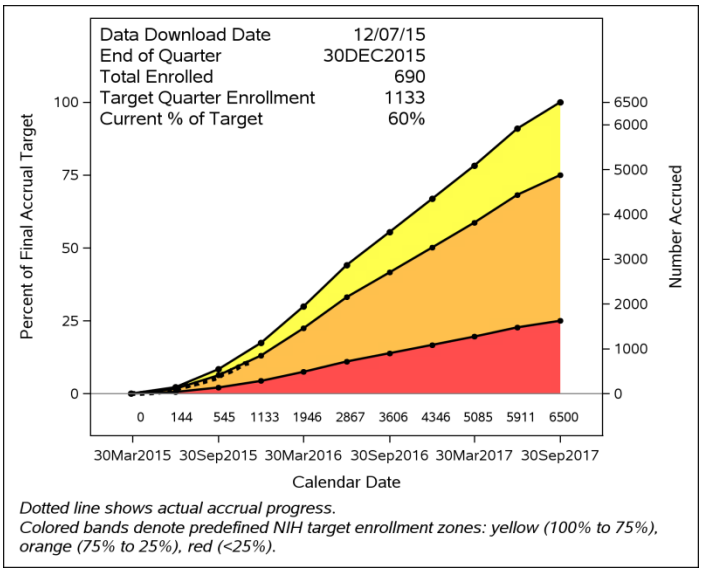
A summary of the benchmarks for interim monitoring of the various aspects of REPRIEVE are provided in **Table B** below; broader details and rationale are provided in the subsequent sections. These benchmarks are intended to guide the DSMB as to when corrective action or modification of the REPRIEVE study may be warranted; they are not intended to be used as strict rules.

Table B: Benchmarks for Study Monitoring

Type of Benchmark	Threshold for concern
1. Enrollment	Accrual rate lower than 75% of the target
2. Loss to follow-up	Annualized rate of loss to follow-up more than 5%
3. Treatment Crossover	Rate of crossover in any treatment group more than 15%
4. MACE Endpoint Rate	Average pooled rate of event 10/1000PY or lower under a range of realistic scenarios
5. Efficacy & Futility	Lan & DeMets implementation of the O'Brien-Fleming group sequential boundary with information measured on the cumulative number of primary MACE events

4.2.1 Enrollment

Figure A



Dotted line shows actual accrual progress.
Colored bands denote predefined NIH target enrollment zones: yellow (100% to 75%), orange (75% to 25%), red (<25%).

REPRIEVE (A5332) Enrollment

The original REPRIEVE (A5332) enrollment benchmarks, as provided in the Statistical Analysis Plan, Version 1.0, are included below. These were retained with the following addition, for completeness: A row was added to Table C below to reflect the increase in the study sample size by 1000 participants (to a total of 7500 participants), as implemented in REPRIEVE (A5332) Protocol Version 4.0 (dated March 28, 2018), and the target date to complete this enrollment (April 1, 2019).

Benchmarks for site activation and enrollment are in line with commitments that have been mutually agreed upon between the REPRIEVE (A5332) PIs and NHLBI. These benchmarks will allow the study to be fully enrolled in 2.5 years from the date of first enrollment and no more than 3.5 years. To achieve these goals, REPRIEVE (A5332) will need to enroll at a rate at least 75% of the projected accrual rate. Accrual targets for the entire enrollment course of REPRIEVE (A5332) have been set by the team and are shown in **Figure A**.

Table C provides a summary of the REPRIEVE quarterly benchmarks where each quarter is defined based on the expected 2.5 year enrollment period.

Table C: Accrual Benchmarks by Enrollment Quarter

	End Date of Enrollment Quarter	Percentage of Enrollment Target		
		100%	**75%**	**25%**
Q1	11/15/2015	844	633	211
Q2	6/30/2016	2873	2154	718
Q3	2/13/2017	4722	3542	1181
Q4	9/30/2017	6500	4875	1625
*	**4/1/2019**	**7500**	**5625**	**1875**

** Enrollment of additional 1000 participants according to the increased sample size in protocol version 4.0.*

REPRIEVE (EU5332) Enrollment

The target enrollment for REPRIEVE (EU5332) is 250 participants. The enrollment benchmarks are:

- **Enroll 200 participants by May 1, 2019**
- **Enroll 250 participants by July 1, 2019**

4.2.2 Loss to Follow-up

Power calculations for REPRIEVE have assumed a worst case scenario of 5% dropout per year. While the power of REPRIEVE will be maintained if the rate of dropout is as high as this level, it is desired that study dropout is substantially lower than this rate at the end of the study to avoid bias that may be introduced by participant dropout. While it is anticipated that risk of dropout may be higher during the first year of follow-up than at later times, if the annual rate of dropout at any time exceeds the 5% threshold, it is felt that corrective action to maintain retention be advised.

4.2.3 Treatment Crossover

Note that the rationale for treatment crossover monitoring benchmark is based on the original REPRIEVE study design, as specified in the SAP, Version 1.0.

The original REPRIEVE study design provided 90% power to detect a 30% reduction in the composite CVD endpoint with statins (assumed effectiveness, or hazard ratio of 0.70 and MACE endpoint rate of 15/1000 PY). This assumed a true efficacy of statins for CVD prevention of 0.66 (HR) in this population and up to an overall 10% treatment cross-over rate similarly distributed across both treatment groups. Simulations under equivalent conditions suggested that with overall crossover rates of 16% (again similarly distributed across treatment groups), the statin effectiveness may be further attenuated to 0.74 and reduce the power of REPRIEVE to detect a positive statin effect to 84%; overall crossover rate as high as 21.5% would further reduce power below 80% (estimated 77%). Based on these estimates, conservatively it is felt that a corrective action plan to reduce treatment crossover may be warranted if the rate of treatment crossover in any one treatment group exceeds a 15% threshold.

4.2.4 Safety

Consideration of the emergence of safety-related issues is left to the discretion of the DSMB. Given the known safety profile of pitavastatin, broad adverse event/safety issues of concern are not anticipated.

4.2.5 Event Rate Evaluation

The considerations for event rate evaluation in SAP, Version 1.0, were based on the original REPRIEVE study design and are retained below for completeness. The formal evaluation of pooled event rate including a predicted confidence interval analysis occurred at the DSMB review in December 2017. Following that DSMB review, pooled rates of all accumulated primary MACE endpoints will continue to be reviewed by the DSMB at each review (see Pooled Event Summary Report in Section 4.3), until otherwise requested by the DSMB.

Pooled rates of all accumulated primary MACE endpoints will be reviewed by the DSMB at all reviews to evaluate the adequacy of the sample size assumptions. Given the expected rate of accumulation of events it is anticipated that sufficient events will have been accrued to the study by the time of reviews occurring 2-2.5 years after enrollment of the first subject to allow reasonable determination of whether the underlying rate of event accumulation is inconsistent with observing the required total number of events to achieve 90% power to detect a HR of 0.70

at the study conclusion. This is illustrated by the anticipated rate of event accumulation dependent on the interim review timing shown in **Table D** below.

Table D: Anticipated data and event accumulation dependent of interim review timing

Timing of review (y)	Number of subjects enrolled*	Accumulated person years of follow-up*	Expected total accumulation of events under given event rate in control group (assuming the target HR of 0.7)		Expected number of events at the threshold of 10/1000 PY
			15/1000	12/1000	
1.0	1399	616	8	6	6
1.5	3099	2138	27	22	21
2.0	3609	3393	43	34	34
2.5	6167	7339	93	74	73
3.0	6500	10595	134	107	105
3.5	6500	13845	174	140	137

**Assumes data freeze 4 months prior to DSMB review and enrollment benchmarks agreed with NHLBI.*

In the event that the observed pooled number of events falls short of the number expected number assuming a rate of 10/1000PY (see **Table D**), a predicted confidence interval analysis will be performed to assess the total expected number of MACE endpoints at trial conclusion based on accumulated data to date and a range of scenarios for accumulation of future data. This formal event rate evaluation will be performed by the REPRIEVE statisticians (blinded and unblinded). It will include, but not be limited to, continued accumulation as observed and a control MACE endpoint rate of a) 12/1000PY and b) 15/1000PY (under the target effect size of HR=0.70). Unless otherwise requested by the DSMB, these assessments along with recommendations for any study design changes will be presented only in the closed study report, and thus available only to members of the DSMB. Release of the information to the REPRIEVE Executive Committee will be at the discretion of the DSMB. Potential design changes recommended as a result of this assessment may include (but will not be limited to) extending the study duration, increasing the target sample size, and/or broadening the study entry criteria to include individuals with low/moderate traditional CVD risk who are willing to be randomized to statin therapy or placebo, for example subjects who have an ASCVD risk score of ≥ 7.5%.

Note: Unless otherwise requested by the DSMB and agreed by the REPRIEVE PIs and NHLBI and NIAID representatives, to ensure that all decisions that may impact future study design consideration for REPRIEVE are made without knowledge of any relative treatment efficacy, all primary event data will be presented pooled across treatment groups until such a time as the DSMB is satisfied that adequacy of the sample size assumptions has been shown.

4.2.6 Formal Efficacy and Futility Review

Unless there are emerging feasibility or safety concerns, guidelines for stopping or modifying the trial will be guided by formal efficacy and futility review. As previously noted, these guidelines are not intended to be kept as strict rules. Given the scope of secondary outcomes of REPRIEVE and the REPRIEVE (A5332) substudy, in the event of interim findings indicative of futility for the primary objective, deliberations should also consider the other components of the study's scientific goals that could still be realized. Any consideration for early termination of the study

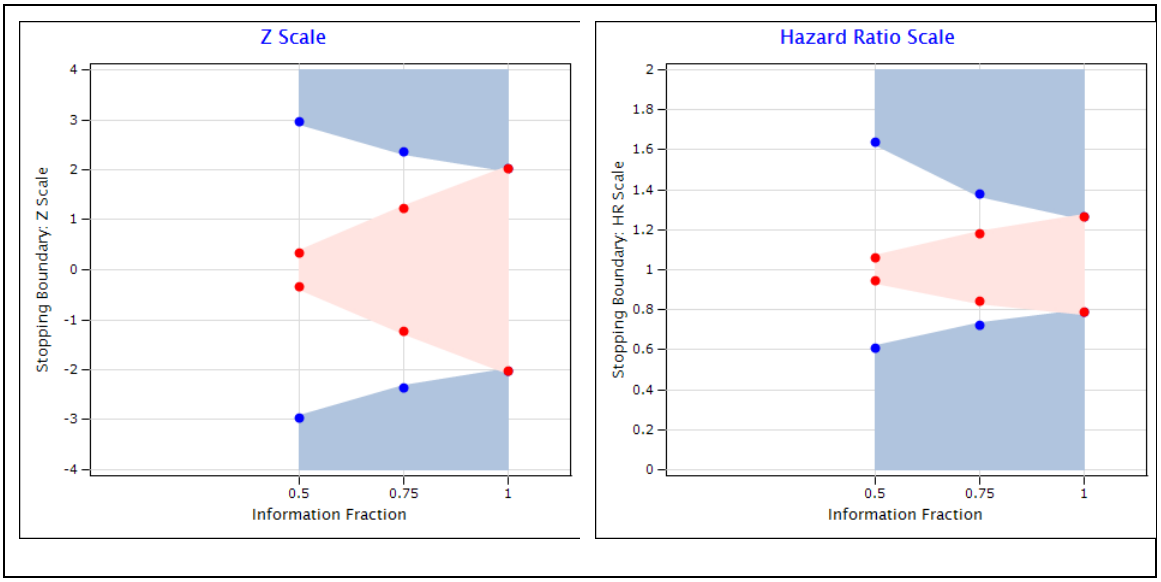
other than for participant safety should carefully weigh the value and scientific importance of all components of the entire trial, in addition to realization of the primary outcome.

Formal efficacy and futility reviews will occur once the adequacy of the sample size has been established. **A total of 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 best possible decision about extending study follow-up duration. The information on the efficacy and futility boundaries below has been updated accordingly.** A Lan and DeMets implementation of the O'Brien-Fleming sequential stopping boundary with information measured on the cumulative number of first primary composite MACE endpoints will be used to guide the DSMB in interpretation of accumulated data for both efficacy and futility; predicted interval plots assuming a range of event rates for each treatment group for unobserved data may also be provided.

Expected Information: Under the original study design, with the assumed baseline event rate of 15/1000 PY and accrual duration of 2.5 years, a sample size of 6500 participants followed for 6 years after the enrollment of the first participant (median follow-up 4.75 years) was projected to yield approximately 350 total events and provide 90% power to detect the target 30% reduction in event rates (hazard ratio, HR=0.70). **Following the formal review of the pooled event rate (see Section 4.2.5), changes were made to the REPRIEVE design (REPRIEVE (A5332) protocol version 4.0, dated March 28, 2018) to assure that the study will have 85% power to detect a hazard ratio of 0.7. Specifically, study sample size was increased by 1000 participants (to 7500 participants) and study duration was extended by 1 year (to 7 years), potentially further extending follow-up at a later time. As a result, the expected total information (i.e. final number of participants with a primary MACE event) is 288. Note that the follow-up was further extended to 8 years in REPRIEVE (A5332) protocol version 5.0 (dated April 1, 2019) to ensure that the expected total number of events will be observed.**

Efficacy and Futility Boundaries: **Figure B** presents the O'Brien-Fleming boundaries for the nominal Z-statistics and hazard ratio estimates that would lead to rejection of H0 or H1 at analyses performed at a given number of accumulated primary events. Point estimates are shown at **50%**, **75%** and 100% (final) of the study's expected total information of **N=288** primary MACE endpoints; the breakdown of the ratio of observed endpoints by treatment group at these specific time points are further broken down in **Table E.**

Figure B: Efficacy and Futility Boundaries (On Z Scale and on Hazard Ratio Scale)



Observe that to reach the O'Brien-Fleming *efficacy* boundary at the interim review with **50%** information, the placebo group would need to have at least **34** excess MACE endpoints (**55** on statin treatment, and **89** on placebo). This corresponds to a hazard ratio of **0.61**, and a Z-score of **2.96**. At the same time, the O'Brien-Fleming *futility* boundary would be reached when there are **70** observed MACE endpoints in the statin group and **74** in the placebo group, corresponding to a hazard ratio of **0.95** (rounded), or Z-score of **0.34**. After another interim review, at the final analysis, the O'Brien-Fleming efficacy boundary would be reached when there are **127** events observed in the statin group, and **161** in the placebo group, corresponding to a hazard ratio of **0.79** and Z-score of **2.01**.

Note that while the total expected information is based on the primary endpoint of first primary MACE, the same critical values will be used for secondary outcome measures at interim looks.

Table E: Efficacy and Futility Boundaries at 50%, 75% and 100% information

		Efficacy Boundaries				Futility Boundaries			
% Expected Information Observed	**Expected Events**	**Z**	**HR**	**Statin events**	**Placebo events**	**Z**	**HR**	**Statin events**	**Placebo events**
50%	**144**	**2.96**	**0.61**	**55**	**89**	**0.34**	**0.95**	**70**	**74**
75%	**216**	**2.36**	**0.73**	**91**	**125**	**1.24**	**0.85**	**99**	**117**
100%	288	2.01	0.79	127	161	2.01	0.79	127	161

4.3 Interim Analysis Reports

Unless otherwise noted, the unblinded REPRIEVE statisticians at CBAR will be responsible for all data analysis and report preparation to the DSMB. For each review, three summary reports will be prepared: an Open Report with administrative and safety information and Pooled Event Rate

Summary Report pooled over treatment groups, and a Closed Report containing all information broken down by treatment group (unmasked) distributed only to participants attending the closed session of the DSMB review (see DSMB Charter for details). Report distribution for the DSMB will occur at least one and preferably two weeks or two weekends prior to the DSMB meeting via secure electronic transfer utilizing secure file transfer system.

Specific contents of reports are outlined here; more detail is provided in the relevant sections below and data summaries are described in the AIP.

A. Open Administrative Report:

Distribution: DSMB members, REPRIEVE NIH team, REPRIEVE PIs, DAIDS Clinical Representative, REPRIEVE Executive Committee members**, NEAT-ID Representative**.

Administrative Summary:

- Study Design Overview
- Minutes from previous meetings
- Study History including major protocol changes

Data Summaries:

All information will be presented pooled over treatment groups and, as appropriate, by Country of Enrollment and/or Continent).

1. Screening and Enrollment (during accrual period only)
2. Baseline Characteristics (including baseline demographics and clinical characteristics)
3. Study and Treatment Status (including study disposition monitoring benchmarks, except treatment cross-over)
4. Protocol Deviations
5. Safety

B. Pooled Event Rate Summary Report

Distribution: DSMB members, REPRIEVE NIH team, REPRIEVE CCC PIs

All information will be presented pooled over treatment groups.

1. Accumulation of Triggers and Adjudication Status
2. Accumulation of MACE Endpoints
3. Pooled Event Rate Estimation for Primary, key Secondary and Supportive Outcome Measures overall and within key subgroups (including by ASCVD risk score at enrollment, age, natal sex, continent)

C. Closed Report:

Distribution: DSMB members, NHLBI statistician

All information will be presented by unmasked treatment group unless otherwise noted.

1. Study and Treatment Status (including study disposition monitoring benchmarks)
2. Safety

3. Mortality
4. Primary and Supportive Outcome Measure Analysis (efficacy/futility analyses)

Appendices: Baseline characteristics by treatment group; adverse event details.

4.4 REPRIEVE Mechanistic Substudy (A5333S) Interim Review

Note: A separate Substudy analysis plan will be finalized at least 6 months before A5333S final analysis.

At every REPRIEVE Interim Review Meeting, A5333S Substudy data will also be reviewed, until A5333S completion. *[Note: A5333S completed follow-up in June 2020. A5333S data are no longer included in the REPRIEVE Interim Reviews. The following sections are retained for completeness.]*

For items that are the same between the Main Study and the Substudy (such as baseline data), the presentation and/or analysis will be the same.

The following Substudy data will be presented REPRIEVE Interim Review:

- * Enrollment statistics, accrual benchmarks, pre-enrollment site metrics (during accrual period only). Differences from main study:
  - Enrollment status table will be subset to REPRIEVE (A5332)-enrolled participants from a substudy site.
- * Baseline characteristics (during accrual period only)
- Study and Treatment Status, substudy-specific (study treatment is main study treatment)
- Data Completeness (data from MITC):
  - CCTA's (Number, %): expected, received, not received.
- Safety (data from MITC):
  - Listing of Adverse CT events.
  - Incidental Findings (Number, %): Yes/No.
  - CCTA Radiation Exposure: overall and by-site (mean, median, standard deviation, min, max).

** Denotes sections for which presentation and/or analysis will be the same as for the Main Study.*

5 Statistical Principles

5.1 General Considerations

5.1.1 Analysis Populations and Treatment Crossover

Intention-To-Treat Population

All treatment comparisons between randomized groups will be performed according to the principle of "intention-to-treat" (ITT), where participants will be analyzed (and events attributed) according to the randomized treatment assignment, regardless of subsequent changes to that treatment. Note that according to the ITT principle, participants retrospectively identified not to have met the study eligibility criteria and participants who did not initiate study treatment will be included. Duplicate enrollments of the same participant will be excluded from all analyses.

Per-Protocol Population

For the primary outcome measure, a sensitivity analysis following the "per-protocol" (PP) approach will be performed, with censoring at the time of final randomized treatment discontinuation. In this approach, participants who did not initiate study treatment or received the wrong treatment will be censored at day 1. Duplicate enrollments of the same participant will be excluded from all analyses.

Safety Population

There will be no separate "Safety Population." All safety analyses will use ITT population as defined above. Select supporting analyses following the PP approach described above may also be conducted.

5.1.2 Stratification

All treatment group comparisons will adjust for stratification factors: sex at birth and screening CD4 cell count (see Section 2).

5.1.3 Time to Event Analysis (Including Censoring and Competing Risks)

Unless otherwise noted, time to event is defined as time from randomization to time of event (a) as adjudicated by CEC (for MACE, death and heart failure) or (b) as recorded on eCRF by the site (non-adjudicated events).

Unless otherwise noted, in a time-to-event analysis, participants will be censored at the time of their last contact on study at which an assessment for events was made. Unless otherwise specified, the data (events and follow-up time) from vital status and endpoint follow-up will be excluded. In the final analysis, death from any cause (not part of outcome measure) will be considered a competing risk event.

5.1.4 Missing Data

Given the strong plans for participant follow-up as part of the study, it is anticipated that missing data will be minimized. Unless examination of the data suggest otherwise, missing data will be assumed to be ignorable. For time-to-event analysis, participants lost to follow-up or participants who otherwise discontinue study prematurely without experiencing an event will be censored. **The rate and reasons for premature study discontinuation will be evaluated by treatment group. For the primary outcome measure, sensitivity analyses to account for missing data will be performed, as needed (see Section 5.3).**

Proportion of missing data for the lipid outcome measures will be summarized. **Analyses of lipid outcomes will use mixed effect models that assume missing data are missing at random (that is, given the data observed, missing data can be assumed ignorable).**

5.1.5 Statistical Significance

In the final analyses, **with the exception of the primary efficacy analysis,** statistical comparisons will be performed using two-sided significance tests with a 5% Type I error, and two-sided 95% confidence intervals will be provided. The primary efficacy analysis will use

significance level according to **the realized** Lan and DeMets implementation of the O'Brien-Fleming sequential stopping **boundary with associated repeated confidence interval** (see Section 4.2.6).

There will be no adjustment for multiple comparisons. However, with the primary clinical and substudy hypotheses and the various secondary outcome measures that have been outlined, it is recognized that there is a multiplicity of analyses to be performed, which leads to an increased probability that at least one comparison could be "significant" by chance. Although the overall level of significance for all treatment comparisons will be 0.05, we will be conservative in the interpretation of our supporting analyses, taking into account the degree of significance, and looking for consistency across outcome measures.

5.1.6 General Model Considerations, including Assumption Checks

Modeling analyses including competing events will use cause-specific Cox proportional hazards models. Cox Proportional Hazards model assumptions will be checked by examining the standardized score process. In the event of failure of the proportional hazards assumption, modification of the treatment effect over time (non-proportional hazards) using piecewise constant hazard will be evaluated with Wald test for treatment by time interaction. Cut points for the piecewise hazard will be determined post-hoc via visual examination of the observed residual score process. In addition, the model assumptions will be checked using log(-log(survival)) vs. log(survival) plots, as well as via a graphical examination of the standardized score process.

Chi-squared goodness of fit test will be used to assess Poisson regression model assumptions.

5.2 SAFETY ANALYSIS APPROACHES

Unless otherwise noted, the data summaries will be presented at interim and final analyses.

Post-entry, the protocol requires reporting of Grade 3 and higher signs/symptoms and laboratory events, all events that led to a change in study treatment and select diagnoses. Targeted adverse events of specific interest in REPRIEVE include grade 3 or higher ALT elevations, treatment-limiting or grade 3 or higher myalgia/myopathy, rhabdomyolysis, and incident diabetes. **Following the SARS-Cov-2 pandemic, COVID-19 and serious COVID-19 diagnoses have been added to the list of targeted events.**

Only adverse events that have onset date after randomization date and meet protocol reporting requirements will be reported. Positively adjudicated adverse events (including MACE and heart failure), AIDS-defining illnesses and other non-adjudicated clinical endpoints (see Section 3.2) will be excluded. While REPRIEVE follow-up is ongoing, all adverse events that have been submitted as potential MACE or heart failure triggers and are undergoing event adjudication or are adjudicated as not meeting endpoint criteria will also be excluded. All events will be included, regardless of relationship to treatment.

Incidence estimation of each targeted event, all reportable events, serious adverse events (SAE) and all-cause mortality (secondary objective 1.2.2.6; Section 2.3.2) will be performed based on time to first qualifying event for each participant. Follow-up will be censored at last participant

contact on study. Incidence rates will be estimated via a Poisson model. In estimation of incident diabetes, participants with pre-existing diabetes at baseline will be excluded. Incidence rates will be compared by treatment group via incidence rate ratios with 95% confidence intervals. P-values will also be provided, along with event counts and total person-years at risk. In the final analysis, secondary analyses that incorporate repeated events with robust variance estimation and Kaplan-Meier (K-M) Plot (time to first occurrence of each event) will be shown by treatment group; follow-up for participants without events will be censored at last participant evaluation.

In descriptive adverse events summaries, participants will be counted once (at the highest reported grade) for the MedDRA Higher Level Group Term (HLGT) (or higher level term, HLT), System Organ Class (SOC) and overall totals.

5.3 EFFICACY ANALYSIS APPROACHES

A summary of the planned efficacy analyses is provided in **Table F** below. Analyses that will be included in the interim reviews of efficacy and futility are marked with an asterisk (*). The focus of the analyses below is treatment comparison of pitavastatin versus placebo for pitavastatin, except for analyses evaluating prognostic factors of MACE. Further details on the Primary Analyses and Secondary/Exploratory Analyses are in the sections that follow.

Table F: Summary of Efficacy Analysis Approaches

Analysis	Analytic method	Notes (details in respective section)
Primary analyses		
Time to first primary MACE (primary outcome measure)*	Stratified Cox Regression (primary analysis)*	Analysis population: ITT Competing risks handled via cause-specific hazards
	Stratified Cox Regression (supportive analysis)	Analysis population: PP Competing risks handled via cause-specific hazards
	Adjusted Stratified Cox Regression (supportive analysis)*[1]	Assessment of modification of treatment effect by sex, race and other select risk factors.
	Cumulative Incidence (supportive analysis)	Cumulative incidence functions for first primary MACE, and for non-CV death as a competing event.
	Stratified Cox Regression with IPCW (sensitivity analysis)	**For accounting for missing data, if needed, IPCW to adjust for a potential informative censoring.**
	Event Incidence (supportive analysis)*	Estimated via a Poisson model.
	Event incidence (sensitivity analysis)	**For accounting for missing data, if needed, imputation of events for unobserved follow-up under various event rates in each treatment group**

		[such as performed by the INSIGHT START Study Group, *NEJM,* 2015].
Time to primary MACE (including repeated events)	Event Incidence (supporting analysis)	Estimated via a Poisson model with robust variance to account for repeated events.
Time to first confirmed MACE[2]	**Stratified Cox Regression (supporting analysis)[2]***	**Analysis of time to first confirmed MACE, not including deaths classified as undetermined by CEC.**
Time to each MACE component (secondary outcome measure)	Stratified Cox Regression, Event Incidence	Stratified Cox Regression for time to the first event. Event Incidence estimated via a Poisson model with robust variance to account for repeated events.
Time to all-cause death (secondary outcome measure)	Stratified Cox Regression	
Time to MACE and/or all-cause death (secondary outcome measure)*	Stratified Cox Regression*, Event Incidence	Stratified Cox Regression for time to the first event. Event Incidence estimated via a Poisson model with robust variance to account for repeated events.
	Stratified Cox Regression, Event Incidence	**Follow-up and events from vital status and endpoint follow-up will be included. Stratified Cox Regression for time to the first event. Event Incidence estimated via a Poisson model with robust variance to account for repeated events.**
Secondary analyses		
Prognostic factors of MACE	Stratified Cox Regression Landmarked Cox Regression	Primary MACE outcome measure will be used. Covariates: Risk Factors (baseline and time-updated), biomarkers. Landmarked approach for HIV suppression.
Serious non-CV events and AIDS-defining illnesses	Stratified Cox Regression	
Lipid profiles over time	Stratified Mixed Effect Model	Time will be modeled as a class statement to allow for estimation of annual treatment group difference.
Exploratory analyses		
Lipid Profiles over time (additional)	Stratified Mixed effect model	Time will be modeled as a class statement to allow for estimation of annual treatment group difference. Restricted to participants at risk for first primary MACE event after 12 months

Time to heart failure (secondary outcome measure)	Stratified Cox Regression, Event Incidence	Stratified Cox Regression for time to the first event. Event Incidence estimated via a Poisson model with robust variance to account for repeated events.

** The analyses indicated with an asterisk will be provided for the formal interim reviews.*
[1]If trends seen during interim analysis suggest a significant treatment effect close to the interim boundary, assessment of modification of treatment effect by risk factors will also be presented at interim review.
[2] If requested by the DSMB or otherwise indicated by the results of the first primary MACE endpoint.

Note: It is anticipated that the Primary Manuscript will report results of the primary analysis, as well as the analyses of safety, lipids (both secondary and exploratory) and heart failure. Analyses of the prognostic factors of MACE and of the targeted non-CVD events are anticipated to be reported as part of secondary manuscripts.

5.3.1 Primary Efficacy Analyses

The primary outcome measure to evaluate the primary objective of the study is time to first primary MACE (time to first event of the composite MACE outcome measure, as defined in Section 3.1). The primary analysis of the treatment effect on the first primary MACE in the ITT population (see Section 5.1.1.) will use a Cox proportional hazards regression model with cause-specific hazards, stratified by sex at birth and screening CD4 cell count (referred to as Stratified Cox Regression from here on). Time from randomization to the first event of interest will be evaluated. Death from any cause will be incorporated as a competing risk. The relative cause-specific hazard of pitavastatin versus placebo for Primary MACE will be estimated with a 95% confidence interval and compared via a Wald test; modification of the statin effect over time (non-proportional hazards) will be evaluated with treatment by time interaction; and piecewise hazards will be implemented in case of failure of the proportional hazards assumption.

Cumulative incidence function, defined as the probability that an event of interest occurs before a fixed time in the presence of competing events, will be estimated using the Breslow estimators of the cause-specific hazard from the Cox model and plotted over time for both the primary outcome and the competing event. Cumulative incidence rate and confidence intervals will be shown for both the event of interest and the competing event, by treatment group, and separately by treatment group and each stratification factor.

Poisson regression with robust variance estimates will also be used to incorporate multiple and repeated events in evaluation of event incidence rates by treatment group and rate ratios. We note that Cox analysis is preferred for inference for the primary analysis of the treatment group comparisons over a comparison of incidence rates as it is more flexible than the Poisson model, allowing for a changing hazard of events over time, whereas the incidence rate (from the Poisson model) represents a single average rate across follow-up duration.

Stratified Cox Regression will also be used to assess modification of the treatment effect. The model will be adjusted for race and other risk factors including age, hypertension, LDL and non-HDL cholesterol at entry, BMI, metabolic syndrome and smoking status. Each of these factors will be included individually as a covariate in the model, with time to first primary MACE as the

outcome. Modification of the statin effect will be assessed via covariate interaction with treatment for each factor. Further details and cut points for the continuous variables are specified in Section 5.3.2 and AIP. Note that these analyses include treatment comparisons summarized by sex and by race, and evaluation of treatment interactions with sex and race, in line with NIH requirements.

Several other supporting and sensitivity analyses are planned for the primary outcome measure including the following.

- Stratified Cox Regression in per-protocol (PP) population, with censoring at the time of final randomized treatment discontinuation (see Section 5.1.1).
- **In the Primary MACE outcome measure, undetermined deaths are considered events. While it is anticipated that most deaths will be classifiable as CV or non-CV and undetermined deaths are rare, an analysis of confirmed MACE events (i.e. not including undetermined deaths as events) may also be conducted if indicated by the primary endpoint analysis or requested by the DSMB.**
- Another sensitivity analysis will censor individuals for whom critically significant Coronary Artery Disease (CAD) was identified during the CCTA evaluation performed as part of the Mechanistic Substudy of REPRIEVE (A5333S), with censoring at the date of the apparent CCTA study findings.
- **While missing data are assumed ignorable in the primary analysis, sensitivity analyses will be considered, as needed, to evaluate robustness of treatment effect and potential bias due to missing data, given the observed results and the extent of missing data. These may include the following.**
  - **Inverse probability censored weighting (IPCW) may be used to adjust for a potentially informative censoring, if appropriate.**
  - **For participants with primary outcome status unknown at the time of study completion, event rates may be imputed for the unobserved follow-up time based on a range of event rates for each treatment group [such as the analysis performed by the INSIGHT START Study Group, *NEJM,* 2015].**

The analyses of secondary time to event outcome measures will use Stratified Cox Regression and, if appropriate, Poisson models to account for the repeating events as described for the Primary MACE outcome measure above and specified in Table F. To complement the primary analyses, the same analytic approach will be used for evaluation of each individual component of the Primary MACE outcome measure (Objective 1.2.2.1; Section 2.3.2). In the absence of a competing risk event, treatment comparisons of time to all-cause death and time to Primary MACE or all-cause death will use a stratified log-rank test. Analyses of secondary outcome measures will be conducted in the ITT population.

A supporting analysis of time to death (all-cause mortality) and/or MACE will be conducted including the data (follow-up time and events) from the vital status and endpoint follow-up, after premature study discontinuation. Time will be censored at the time of participant's last contact on study or at the last vital status contact after premature study discontinuation. **Adequacy of the documentation for adjudication of events observed on**

study compared to events identified as part of vital status and endpoint follow-up will be summarized.

5.3.2 Secondary Efficacy Analyses: Prognostic Factors of MACE

An important secondary aim of the REPRIEVE trial is to evaluate whether baseline traditional risk factors, time updated HIV-specific risk factors, lipid levels, and/or biomarker values are predictive of MACE and pitavastatin effects on MACE in the HIV population (Objectives 1.2.2.2 – 1.2.2.4; see Section 2.2.2.).

Targeted risk factors of interest at (or prior to) study entry and time-updated are listed below (treated as continuous, unless a cut-point is specified).

<u>At study entry/screening:</u>

1. Age
2. Sex
3. Race
4. Screening ASCVD risk score (<2.5, 2.5-<5, 5-<7.5, 7.5-10, >10)
5. HIV-1 RNA level (≤75 vs. >75 copies/mL); given sufficient numbers of participants with detectable HIV-1 RNA at study entry *[Only a small proportion of REPRIEVE participants had HIV-1 RNA above the assay limit of quantification at entry; analysis will not be done.]*
6. CD4 cell count (≤500 vs. >500 cells/mm^3)
7. Nadir CD4 cell count (<50, 50-199, 200-350, >350 cells/mm^3)
8. Duration of ART exposure (<5 year, 5-10 years, 10+ years)
9. Any exposure to thymidine analogs, protease inhibitors, or abacavir (3 separate measures; binary)
10. BMI <30 vs. ≥30 kg/m^2
11. Fasting lipids and glucose
    a. LDL (<130 vs. ≥130 mg/dl)
    b. HDL-C
    c. TG
    d. Glucose
12. Smoking status (binary)
13. Hypertension (binary) defined as any of the following: hypertension diagnosis, use of antihypertensive treatment for elevated blood pressure, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg
14. Presence of metabolic syndrome (binary) as described by Alberti et al (*Circ*, 2009) with country- and sex-specific waist circumference cutoffs adapted to REPRIEVE (refer to the AIP for details)
15. Self-reported level of physical activity
16. Family history of premature CVD

<u>Time-updated (annually):</u>

1. HIV-1 RNA level (<LLQ; LLQ-<400; ≥400 copies/mL).
   [These limits are updated from original analysis plan and chosen to accommodate the different assays used across REPRIEVE sites.]
2. CD4 cell count (≤500; >500 cells/mm^3)

3. Fasting lipids (TC, HDL-C and LDL-C, HDL-C:LDL-C ratio, TG) and glucose.

Each baseline risk factor above will be included individually as a covariate in a Stratified Cox Regression model to estimate the cause-specific hazard of primary MACE in the ITT population. Modification of the statin effect will be assessed via covariate interaction with treatment, for the following risk factors:

- Race, sex, CD4 cell count at screening, duration of HIV-1 RNA suppression, age (<50 vs. ≥50 years), hypertension, LDL (<130 vs. ≥130 mg/dl), and non-HDL cholesterol at entry, BMI (<30 vs. ≥30 kg/m^2), metabolic syndrome, smoking status.

Continuous risk factors will be assessed for functional form using Martingale Residual plots.

To accommodate time-updated covariates, analyses will use a counting process data input. A given annual measurement will be assumed constant for the period of 6 months prior and 6 months after date of collection.

This approach will investigate associations with LDL and non-HDL levels and changes from baseline as time-updated covariates. The same approach to analysis will be used to assess the effects of other longitudinal outcomes. With respect to HIV-1 RNA levels over time, it is of particular interest to examine whether there is evidence of the modification of the effect of statins according to whether participants maintain full suppression of HIV-1 RNA levels. This will be examined in a 12-month landmarked Cox proportional hazards models assessing an interaction between continued HIV-1 RNA suppression (<400 copies/mL) over the first 12 months of the study as well as time-updated analysis.

An additional lipid analysis will be restricted to participants at risk for the first primary MACE event after 12 months and examine the association of change in LDL and non-HDL over the first year in a 'landmarked' Cox proportional hazards model.

Note: The analyses of biomarkers are planned for a secondary publication. Baseline and time-updated inflammatory and immune activation biomarkers of interest will be determined closer to the analysis, following determination of biomarker candidates per substudy findings. The analysis approach for assessment of effect of selected biomarkers for MACE will be determined based on the sampling approach to biomarker testing.

5.3.3 Secondary Efficacy Analyses: Serious Non-CV Events and AIDS-defining Illnesses

To address secondary objective 1.2.2.5 (see Section 2.2.2), Stratified Cox Regression will be used to evaluate the effect of pitavastatin on time to any (composite) or each (individual) clinical diagnosis as specified in outcome measure 4 in Section 3.2 in the ITT population, as described for the Primary Analyses above. Time to the first qualifying event will be modeled. Participants discontinuing follow-up without experiencing an event will be censored at the time of last contact on study. Deaths from other causes will be considered as competing events.

As a supporting analysis, the same Stratified Cox Regression analysis approach will be used for the START outcome measure (see Section 3.3).

5.3.4 Secondary Efficacy Analyses: Lipid Profiles Over Time

This section addresses part of secondary objective 1.2.2.3 (Section 2.2.2): to determine the effects of pitavastatin on LDL and non-LDL cholesterol in the HIV population.

Summary statistics (means and quantile distributions) will be provided to describe the distributions of LDL and non-HDL cholesterol from study entry and 12 month intervals over time. At each annual post-entry time point, the mean difference in levels between treatment groups will be estimated with 95% confidence interval. Mixed Effects Models adjusted by sex at birth and screening CD4 cell count will be used for repeated measurements of LDL and non-HDL cholesterol over time with time as a class covariate to allow for estimation of annual treatment group differences. Similar summaries and analyses will be provided for supporting lipid outcome measures specified in Section 3.3 (#4 – #7).

6 Report Contents

The key report contents are listed below. Further details and descriptions of tables and figures are provided in the AIP.

- [Final analysis only] CONSORT Diagram
- Screening, Enrollment and Eligibility (during accrual period):
    - Overall Status including total screenings; total enrollment; screening failures; status pending; days since last enrollment; days since last screening overall and by network.
    - Accrual Benchmarks: observed vs. target accrual benchmarks
    - [Interim Only] Screening Disposition by Site
    - [Interim Only] Enrollment by Week
    - [Interim Only] Reasons for Screening Failure
    - Violations of eligibility criteria
    - [Interim Only] Site enrollment status
- Baseline Characteristics:
    - Stratification, Demographics and ASCVD Risk including screening CD4 count, sex at birth, age, 10-year ASCVD risk score, history of statin use, race.
    - CVD History and Risk Factors including systolic blood pressure, weight, BMI, waist circumference, smoking status, years smoked and family history of premature CVD; final analysis will also include alcohol use, physical activity and diet.
    - Fasting Lipids/Glucose including fasting status (for screening lipids only), total cholesterol, triglycerides, LDL-C, HDL-C and HDL-C:LDL-C ratio.
    - HIV-Related Medical History including years since HIV diagnosis, risk for acquiring HIV and nadir CD4.
    - CD4 cell count and HIV-1 RNA.
    - ARV Regimen History including total duration of ARV use, individual ARV history and duration of exposure for each of abacavir, protease inhibitor, thymidine analog, tenofovir; ARV classes (NRTI+NNRTI, NRTI+INSTI, NRTI+PI, Other NRTI-containing, NRTI-sparing) and choice of NRTI, NNRTI, PI, INSTI.

- Study and Treatment Status:
    - Overall summary:
        - Number on-study and on-treatment, on-study and off-treatment, deceased, off-study.
        - Reasons of off-study (prematurely).
    - Additional Study and Treatment Status Summaries:
        - All off-treatment reasons.
        - Time to treatment initiation.
        - Time to off-treatment.
        - Cumulative probability of study discontinuation (Kaplan-Meier analysis).
        - Cumulative probability of treatment discontinuation (Kaplan-Meier analysis).
    - Disposition Benchmarks:
        - Incidence rate of premature study discontinuation
        - Incidence rate of premature treatment discontinuation
        - Incidence rate of treatment crossover
    - Treatment Adherence:
        - Adherence self-rating
        - [Interim Only; Closed Report] LDL cholesterol levels
    - Duration of Follow-Up:
        - Duration of follow-up on study (months)
        - Total person-years of follow-up on study
        - Study year of latest clinic visit on study
        - Time to latest contact on study
        - Years to latest contact on study
    - Currency of Follow-Up
        - Visit currency
        - Currency by visit year
- **Vital Status and Endpoint Follow-Up:**
    - **Duration of follow-up**
    - **Currency of follow-up**
- Safety
    - All-Cause Mortality
        - Mortality Summary by category of: cardiovascular event, HIV-associated clinical diagnosis, non-AIDS cancer, accidental, suicide, homicide, other sudden death of unknown etiology, or other (with possible additional subcategories, as adjudicated by CEC)
        - Death Details including weeks on study at time of death, baseline and most recent HIV-1 RNA and CD4 count, weeks since the last dose of randomized treatment, weeks since the last dose of other ART treatment (if applicable), last ART regimen, site's reports of primary cause of death (text, categorization and diagnosis), and site's determination of relatedness to study treatment.
    - Adverse events
        - Summary of Serious Adverse Events (SAE) by term and grade

        - Summary of related and possibly related adverse events by term and grade
        - Summary not related adverse events by term and grade
        - Adverse events that resulted in study treatment withdrawal by term and grade
        - Incidence rates of death (all-cause), SAEs, targeted events and protocol-reportable AEs
    - Myalgia Assessment
        - Muscle Weakness by Grade
        - Muscle Aches by Grade
- Efficacy (see Section 5.3)
    - Primary efficacy analyses
        - Time to first primary MACE, supporting and sensitivity analyses
        - [Final Analysis only] Time to Each MACE Component
        - [Final analysis only] Time to All-Cause Death
        - Time to MACE or All-Cause Death
    - Secondary efficacy analyses
        - [Final analysis only] Prognostic Factors of MACE
        - [Final analysis only] Serious non-CV Events and AIDS-defining Illnesses
        - [Final analysis only] Lipid Profiles Over Time
    - Exploratory Analyses:
        - [Final analysis only] Time to Heart Failure