Statistical Analysis Plan	
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TACTiC- Technology-Assisted Cholesterol Trial in Consumers

A Phase III, 6-Month, Self-selection and Actual Use for Rx-to-OTC Switch of rosuvastatin 5 mg once-daily in combination with a Web App

APPROVAL PAGE

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Abbreviation or special term	Explanation
AE	Adverse event
ASCVD	Atherosclerotic Cardiovascular Disease
AUS	Actual Use Study
BP	Blood pressure
CAC	Coronary artery calcium
CMOG	Central Medical Operations Group
CSP	Clinical study protocol
DBP	Diastolic blood pressure
DFL	Drug Facts Label
HDL-C	High density lipoprotein - cholesterol
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ID	Identification
IP	Investigational product
ITT	Intent to Treat
LDL-C	Low density lipoprotein - cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
Participant	Any subject who enrolls in the study
PCFB	Percent change from baseline
PE	Point Estimate
PP	Per Protocol
PT	Preferred Term
REALM	Rapid Estimate of Adult Literacy in Medicine
REF	Risk enhancing factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SILS2	Single item literacy screener 2
SMT	Study Mandated Test(ing)
SOC	System Organ Class
SS	Self-Selection

Abbreviation or special term	Explanation
Subject	All subjects who complete the initial pre-screener either online or by calling the Call Center
TACTiC	Technology-Assisted Cholesterol Trial in Consumers
TASS	Technology-Assisted Self-Selection
TC	Total cholesterol
TG	Triglycerides
TRD	Table Requirements Document

Population Descriptions:

Subjects – All subjects who complete the initial pre-screener either online or by calling the Call Center.

Participants – Those individuals who have signed the consent form at Visit 1.

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	10/13/2021	A nominal fee for study mandated testing at Virtual Visit 1 will no longer be assessed to the participant, but rather, will be paid through a central account at CCI [redacted]	Yes	CCI [redacted]
Other	10/13/2021	Net coding will be conducted after Last Subject Last Visit.	Yes	CCI [redacted]
Other	10/13/2021	Removal of scenarios in Table 2 of Section 3.2.3	N/A	New approach does not require an LDL-C value to obtain a Stop Use criteria by the CMOG. Previously, participants with missing LDL-C values would be considered withdrawals which is an incorrect disposition for the participant.
Statistical analysis method for primary or secondary endpoints	10/13/2021	Subgroup analyses conducted for those participants who worked as a healthcare professional or were employed by a healthcare practice and non-healthcare workers has been removed from all endpoints.	Yes	CCI [redacted]
Statistical analysis method for primary endpoint	10/13/2021	Analysis of the first co-primary endpoint, Overall Correct Initial TASS Outcome, will be conducted on all participants in the Self-Selection population. Any participants with a missing CMOG TASS outcome will be imputed as "Incorrect" for the endpoint. The sensitivity analysis containing worst case imputation has been removed as this revised analysis is the same. The previously planned primary analysis conducted on the	Yes	CCI [redacted]

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		observed data has been moved to a secondary analysis of the first co-primary endpoint.		
Statistical analysis method for primary endpoint	10/13/2021	Missing outcomes for the first and second co-primary endpoints will not be programmatically determined. Any missing outcome for the Initial TASS Assessment due to incomplete medical and medication history will remain missing. For the Final Use Assessment, a TASS assessment will be conducted whenever possible. If this is not possible, the CMOG will determine the outcome based on the DFL. They will do this by following an algorithm based on the question flow of the TASS tool. This ensures a consistent process is used by all clinicians. If an outcome is not able to be determined, then the Final Use Outcome will be missing.	Yes	CCI [redacted]
Statistical analysis method for primary endpoint	10/13/2021	Details regarding inadequate LDL-C retest values entered by the participant in the TASS tool and how the CMOG should use this information when completing a TASS assessment were added.	Yes	Addresses a limitation of the Web App in the CMOG TASS Assessment when an inadequate LDL-C retest value is provided by the participant in the TASS.
Other	10/13/2021	Renumbering of tables in Appendix and text due to additional table added to Appendix.	N/A	Formatting changes.
Statistical analysis method for primary endpoint	10/13/2021	Analysis of third co-primary endpoint, Percent Change from Baseline in Verified LDL-C values to Visit 2, will be conducted on the AUS ITT population. The requirement for participants to be eligible for continuous treatment has been removed. The previously planned primary analysis conducted on participants eligible for continuous treatment has been moved to a sensitivity analysis of the third co-primary endpoint. Table 4 in the	Yes	CCI [redacted]

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		Appendix has been rearranged to account for this change.		
Statistical analysis method for primary endpoint	10/13/2021	Added categorical analysis of reduction in LDL-C for sensitivity analyses on Web App LDL-C entries.	N/A	Additional analyses for further insight into consumer behavior.
Statistical analysis method for primary endpoint	10/13/2021	Sensitivity analysis using missing data imputation was revised to be conducted on the primary analysis population for the third co-primary endpoint and imputation of missing verified LDL-C values will only be imputed. Unverified LDL-C values in this sensitivity analysis will no longer be utilized. Table 4 in the Appendix has been rearranged to account for this change.	Yes	Additional analyses for further insight into consumer behavior.
Statistical analysis method for secondary endpoint	10/13/2021	Descriptive statistics and intraclass correlation coefficient for the 10-year ASCVD Risk Score obtained through the TASS entries made by the participant and the10-year ASCVD Risk Score obtained through study mandated testing have been added. Descriptive statistics for the difference between laboratory and blood pressure data entered in the TASS tool by the participant and the data obtained through study mandated testing have been added.	N/A	CCI [redacted]
Other	01/18/2022	Updated the author.	N/A	New project statistician.
Derivation of primary or secondary endpoints	01/18/2022	Updated the CMOG final use assessment outcome for the scenario where a participant enters an LDL-C value with no change or an increase in LDL-C, there is no SMT, and participant fails to bring verification of the LDL-C that resulted in a participant DNU outcome.	Yes	CCI [redacted]

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Derivation of primary or secondary endpoints	01/18/2022	In the handling of inadequate response scenarios for LDL-C retesting, remove the procedure for CMOG clinician to redo TASS and replaced it with a mitigation process.	Yes	CCI [redacted]
Derivation of primary or secondary endpoints	01/18/2022	Clarified the handling of missing Final Use Outcomes for a participant due to unwillingness or inability to complete a final TASS assessment at Virtual Visit 2.	Yes	CCI [redacted]
Data presentations	01/18/2022	Added quartiles 1 and 3 in the set of descriptive statistics for all continuous variables.	N/A	Provide a more complete set of summary measures.
Other	01/18/2022	Added an explanation of how partial dates for a diagnostic test will be imputed.	N/A	Address scenarios where a participant's medical portal contains only the month and year of when a diagnostic test was conducted (i.e., day is missing).
Derivation of primary or secondary endpoints	01/18/2022	Added a description of how participants with multiple retests will be handled in the percentage calculations for cholesterol retest compliance.	N/A	Provide additional clarity.
Other	01/18/2022	Added additional analysis methods for the exploratory efficacy assessments of ASCVD risk scores and lab and blood pressure variability. Included corresponding literature references.	N/A	CCI [redacted]
Derivation of primary or secondary endpoints	01/18/2022	Modified scenarios for inadequate LDL-C TASS entries in the appendix (previously Appendix Table 1, renamed as Appendix A).	N/A	CCI [redacted]
Other	01/27/2022	Updated Table of Contents, List of Tables, Appendices, and overall formatting.	N/A	Provide additional clarity.

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Statistical analysis method for the primary or secondary endpoints	01/27/2022	Renamed the section on Missing Outcomes to "Management of Missing TASS Assessments" and created subheadings for participant and CMOG.	N/A	Provide additional clarity
Other	02/04/2022	Added reference to Appendix E in the in-text discussion of laboratory and blood pressure variability in Section 3.2.3.2. Clarified that the process applies to Visit 1.	N/A	Provide additional clarity
Other	03/01/2022	Add REALM vs. SILS2 Analysis Correlation comparing scores of each test. 2-way analysis of normal literacy and limited literacy categories percentage agreement between the REALM and SILS scores ROC Curve including the AUC of the ROC curve	Yes	Provide supporting analysis for use of SILS2 as literacy measure in sub-study
Data presentations	03/01/2022	Include disease background and characteristics in accordance with AZ standards. Update to include pertinent participant safety data in accordance with AZ Patient Safety Standards.	Yes	Provide additional clarity
Other	03/28/2022	Updated the definition of "eligible for continuous treatment."	Yes	Provide additional clarity
Other	03/28/2022	Updated verbiage in Section 4.2.4 to reflect "Absolute value of the relative difference," between participant TASS entries of laboratory and diagnostic data from the diagnostic form at visit 1.	N/A	Provide additional clarity
Other	03/28/2022	Updated Section 4.2.4 changed supply period compliance to those participants in 50% - 120% over all supply periods.	Yes	Provide additional clarity
Data presentations	03/31/2022	Update SAP to number the Sensitivity Analysis per outcomes.	N/A	Provide additional clarity

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	03/31/2022	Update SAP to reflect respective corresponding table, listing, and figure in the Tables Requirement Document.	N/A	Provide additional clarity
Other	04/04/2022	Update Section 4.2.1 to include order preference as one of the subgroups used in analysis. Order preference is defined as the quantity of study drug a participant orders, either 45- or 90-day supply after approval.	N/A	Provide additional clarity
Other	04/04/2022	Update Section 2.1 to define those participants who are considered "qualified refused."	N/A	Provide additional clarity
Other	04/06/2022	Update Section 3.2.2 to include additional language describing the sub-study with REALM testing and SILS2 questioning comparison.	Yes	Provide additional clarity
Other	04/18/2022	Updated Section 4.1.3.1 to include additional scenarios for imputing missing dates for participants who have incomplete data for day of event, action taken on medication, or when they spoke to a doctor. Added an additional APPENDIX.	Yes	Provide additional clarity
Other	04/25/2022	Added additional clarification for identifying select populations: pre-screen population, safety population, subjects vs. participants, and disposition population.	Yes	Provide additional clarity
Statistical analysis method for the primary or secondary endpoints	04/28/2022	Updated Section 3.2.10 for overall compliance to provide additional instructions on handling of missing IP bottles not returned by participant.	Yes	Provide additional clarity
Other	04/29/2022	Update Section 3.2.3.1 *a priori* mitigations will be performed during the course of the study. Post-study mitigations will begin after last subject completes their final visit.	Yes	Provide additional clarity

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	04/29/2022	Updated Section 3.2.3.2 to include commentary on waist circumference and measurements taken by the participant.	N/A	Provide additional clarity
Other	04/29/2022	Updated Section 3.2.3 - participants that have been in the study for less than 3 months a verified LDL-C will not be required for the CMOG to determine an outcome.	N/A	Provide additional clarity
Other	04/29/2022	Updated Section 4.2.1 to include verbiage regarding subjects with pre-screen failure population for additional insight.	N/A	Provide additional clarity
Other	04/29/2022	Updated Section 4.2.2 regarding participants in the SS population and non-missing and missing initial TASS outcomes.	N/A	Provide additional clarity
Other	04/29/2022	Updated Section 4.2.4 for overall flow and explanation regarding incorrect TASS entries.	N/A	Provide additional clarity
Data Presentations	04/29/2022	Updated SAP to include Section 4.2.6.3 for definition and description of Protocol Deviations.	Yes	To add insight for patient safety and outcomes
Data Presentations	04/29/2022	Updated SAP to include Section 6 Exploratory Analysis and 6.1 Analysis of Risk Enhancing Factors.	Yes	Introduce verbiage regarding supplementary analysis of the data
Other	05/12/2022	Updated Section 3.2.3 to articulate the CMOG's role in mimicking the participant's initial experience of the Inadequate Response Retest.	N/A	Provide additional clarity
Data Presentations	05/13/2022	Updated Appendix A - Separated into two tables Table A1 and Table A2. Table A1 provides insight into participants who enter an initial Inadequate Response LDL-C Retest into the web app and purchases an additional supply of medication during their reorder assessment. Table A2 provides insight into participants who enter an initial Inadequate Response LDL-C Retest	Yes	Provide further details regarding the potential scenarios for participants who do and do not order additional medication during their reorder assessments when they have an inadequate LDL-C response.

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		into the web app and did not purchase an additional supply of medication during their reorder assessment.		
Data Presentations	05/13/2022	Updated Appendix D - Use and Re-Selection Mitigations - describing three separate rationales for mitigation regarding participants with missing LDL-C retests.	Yes	Provide additional clarity
Data Presentations	05/20/2022	Updated Section 4.2.4 - Included language regarding the capturing and analyzing of data (input-to-input) from initial/final participant TASS inputs and the CMOG initial/final TASS inputs.	Yes	Provide additional clarity
Data Presentations	06/03/2022	Updated Section 4.2.4 – Included PP populations to be evaluated with respect to Incorrect TASS Entries.	Yes	Provide additional clarity
Data Presentations	06/15/2022	Updated Appendix B – Provided further explanation for column, “Assessment for Overall Correct Final Use Outcome”.	Yes	Provide additional clarity
Data Presentations	06/27/2022	Updated Section 8 – References – added two peer-reviewed articles to support the evidence-based study.	Yes	Provide additional clarity
Data Presentations	08/16/2022	Updated Section 4.2.4 - Data listings will be provided to explore the initial and final assessments between the participant and CMOG TASS inputs with applied mitigations, regardless of the impact on the first co-primary endpoint, for the SS populations.	Yes	Provide Additional Clarity
Data Presentations	08/16/2022	Updated Section 4.2.6.1 – Included language explaining the updated listings for capturing different populations with respect to exclusions.	Yes	Provide Additional Clarity
Data Presentations	08/17/2022	Updated Appendix A – Included a final column Is there a potential for a priori mitigation “Missing LDL-C Retest”?	Yes	Provide Additional Clarity

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	11/07/2022	Updated Section 3.2.10 – Intended Duration of Treatment formula.	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Included additional analysis requested.	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Removed analysis of "(and Self-Tested with a verified LDL-C retest within six months) plus those who received less than 3 months of treatment (and self-tested retested with a verified LDL-C retest within 3 months) regardless of outcome".	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Added Overall Compliance formula.	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Updated denominator of the percentage of participants with Overall Compliance between 50% and 120% formula.	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Updated numerator of the Supply Period Compliance formula.	Yes	Provide Additional Clarity
Other	11/07/2022	Updated Section 4.2.3 – Updated denominator of the Longitudinal Compliance Rate.	Yes	Provide Additional Clarity
Data Presentations	12/05/2022	Updated Tipping Point Analysis sections to describe figures instead of tables that will be produced.	Yes	Provide Additional Clarity
Data Presentations	12/14/2022	Updated definition of Treatment Period.	Yes	Provide Additional Clarity
Data Presentations	12/14/2022	Updated null hypotheses to represent ≥ or ≤ instead of =	Yes	Provide Additional Clarity
Data Presentations	12/14/2022	Updated the definition of "Subjects".	Yes	Provide Additional Clarity
Other	01/18/2023	Updated Overall Compliance when a participant returns fewer bottles than ordered.	Yes	Provide Additional Clarity
Data Presentations	02/14/2023	Updated Pre-Screen Population definition to Pre-Screen Eligible and Registered Population.	Yes	Provide Additional Clarity
Data Presentations	02/14/2023	Removed all TRD TLF reference numbers.	Yes	Provide Additional Clarity

* Pre-specified categories are:
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

1.1 Study Objectives

- The primary objectives of this study are as follows:
  - To evaluate initial Technology-Assisted Self-Selection (TASS) outcome for participants deemed "OK to Use" or those with an "Ask a Doctor" outcome who contact a doctor and are permitted to continue treatment compared to the TASS outcome obtained using clinician-verified medical and laboratory data
  - To evaluate that participants are properly using non-prescription rosuvastatin during the use period as assessed by their ability to correctly enter their ongoing health status into the Web App to get the correct outcome or through the medical and medication history in those participants who fail to complete a final TASS use assessment
  - To evaluate the effectiveness in lowering low-density lipoprotein-cholesterol (LDL-C) in participants regardless of final use outcome
- The secondary objectives of this study are as follows:
  - To evaluate compliance with cholesterol retesting within 6 months
  - To evaluate compliance with "Stop Use" warnings
  - To evaluate compliance with "Do Not Use" warnings
  - To evaluate compliance with "Ask a Doctor Before Use" warnings
  - To evaluate compliance with continuous dosing
- The exploratory objectives are as follows:
  - To evaluate the incorrect entries and the reasons for incorrect TASS entries for each question on the initial TASS assessment
  - To evaluate the incorrect entries and the reasons for incorrect TASS entries for each question on the final TASS assessment
  - To evaluate compliance with speak to a doctor component of the "Stop Use" warnings
  - To evaluate the timeframe for complying with "Stop Use" warnings
  - To evaluate the timeframe for complying with "Do Not Use" warnings
  - To evaluate compliance with speak to a doctor component of the "Ask a Doctor Before Use" warnings
  - To evaluate the timeframe for complying with "Ask a Doctor Before Use" warnings
  - To evaluate effectiveness in lowering LDL-C in different participant subgroups
  - To evaluate LDL-C lowering relative to level of dosing compliance

1.2 Study Design

This is a 6-month single-arm, interventional, phase III Self-Selection (SS) and Actual Use Study (AUS) using a TASS tool within a Web App. It is an open-label study using non-prescription rosuvastatin 5 mg in participants who qualify for treatment based on the medical and medication history, laboratory, and blood pressure (BP) data they enter into the Web App. A participant is considered enrolled in the study after signing the informed consent. The study will enroll

approximately 1,220 participants who will ultimately receive an "OK to Use" outcome using the Web App. Of these, an estimated 1,000 participants will ultimately be able to proceed to the use phase.

After the enrollment visit, the participant will enter a 6-month use period where they will re-purchase study drug available only through an online purchase via the Web App. Participants will be required to complete a TASS reorder assessment to confirm they are still "OK to Use" prior to re-purchase. Participants will be instructed to use an eDiary to record when they took study drug, have changes to any medications and have any changes in health status. The Central Medical Operations Group (CMOG) clinician will perform a telephone status check with participants at 60 and 120 days to assess any changes in health and/or medications as well as any additional study related issues (no instruction will be provided regarding the use of the product). A Virtual Visit 2 will be completed according to the procedures described in the Clinical Study Protocol. A 30-day follow-up phone call will be performed after study drug completion/discontinuation to assess participant status with regard to adverse events (AEs).

It is expected that a minimum of 500 evaluable participants will be assessed for the final use assessment. Evaluable means the participant completed Virtual Visit 2 or has sufficient medical and medication history information and, when necessary, a verified LDL-C collected prior to stopping the study to determine a final use outcome. The goal is to have 100 limited literacy participants in the trial.

1.3 Number of Subjects

The sample size is based on powering the study for the co-primary endpoints.

For the first co-primary endpoint, the Overall Correct Initial TASS Outcome at the initial self-selection is computed as follows:

$$\text{Overall Correct Initial TASS Outcome (\%)} = \frac{C_S + C_{AAD} + MR_{AP} + MR_{PS}}{\text{Number of participants in the Analysis Population}}$$

where:

- Correct Selector (C_S) = Obtain a correct TASS outcome that they qualify for Crestor OTC by receiving an 'OK to Use' screen in the TASS (compared to the CMOG evaluation)
- Correct AAD (C_{AAD}) = Obtain a correct TASS outcome that they must ask a doctor before qualifying for Crestor OTC by receiving an 'Ask a Doctor' screen in the TASS (compared to CMOG evaluation)
- Mitigated results *a priori* (MR_{AP})
    - MC_S = Mitigated Correct Selector
    - MC_{AAD} = Mitigated Correct Ask A Doctor
- Mitigated results post-study (MR_{PS})
    - MC_S = Mitigated Correct Selector
    - MC_{AAD} = Mitigated Ask A Doctor

The evaluation of the first co-primary endpoint on the Overall Correct Initial TASS Outcome will have a sample size of approximately 1,220; however, not all of these participants may have an Overall Correct Initial TASS Outcome. As part of the primary analysis of this endpoint, any participants with a missing Overall Correct Initial TASS Outcome will be imputed using worst case imputation (i.e., as incorrect). As such, it is unknown exactly how the true self-selection rate will be affected based on this imputation. Therefore, the resulting power assuming various true self-selection rates in order to demonstrate that the lower bound of the 95% exact binomial confidence interval is greater than 85% with a sample of approximately 1,220 participants is presented in the table below:

True Self-Selection Rate	Power	True Self-Selection Rate	Power
88.24%	90%	88.57%	95%
88.30%	91%	88.67%	96%
88.35%	92%	88.78%	97%
88.42%	93%	88.93%	98%
88.49%	94%	90.00%	>99%

That is, the sample size of approximately 1,220 provides the above varying levels of power based on various true self-selection rates to test the following set of hypotheses for the primary endpoint on the initial TASS outcome:

$$H_0: P \leq 85\% \text{ vs. } H_1: P > 85\%$$

where P is the proportion of Overall Correct Initial TASS Outcome or the proportion of Overall Correct Final Use Outcome, respectively.

The above null hypothesis will be rejected in favor of the alternative if the lower bound of the two-sided 95% exact binomial (i.e., Clopper-Pearson) confidence interval is greater than 85%.

For the second co-primary endpoint, the Overall Correct Final Use Outcome at the final use assessment is computed as follows:

$$\text{Overall Correct Final Use Outcome (\%)} = \frac{C_S + C_{AAD} + C_R + MR_{AP} + MR_{PS}}{\begin{array}{c}\text{Number of participants in the analysis}\\ \text{population with a non-missing final use}\\ \text{outcome for both the participant and CMOG}\end{array}}$$

where:

- Correct Selector (CS) = Obtain a correct outcome that they qualify for Crestor OTC (compared to the CMOG evaluation)
- Correct AAD (CAAD) = Obtain a correct outcome that they must ask a doctor before qualifying for Crestor OTC (compared to CMOG evaluation)
- Correct Rejectors (CR) = Obtain a correct outcome that they do not qualify for Crestor OTC

(compared to CMOG evaluation)

- Mitigated results *a priori* (MR_{AP})
  - MC_S = Mitigated Correct Selector
  - MC_{AAD} = Mitigated Ask A Doctor
  - MC_R = Mitigated Correct Rejector
- Mitigated results post-study (MR_{PS})
  - MC_S = Mitigated Correct Selector
  - MC_{AAD} = Mitigated Ask A Doctor
  - MC_R = Mitigated Correct Rejector

Evaluation of the Overall Correct Final Use Outcome will have a sample size of at least 500 participants. A sample size of 500 participants would provide at least 90% power to demonstrate that the lower bound of the 95% exact binomial confidence interval is greater than 85% for the final use endpoint, assuming that the true correct final use outcome rate is 90%. That is, the sample size of 500 provides at least 90% power to test the following set of hypotheses for the primary endpoint on the final use outcome:

$$H_0: P \leq 85\% \text{ vs. } H_1: P > 85\%$$

where P is the proportion of Overall Correct Initial TASS Outcome or the proportion of Overall Correct Final Use Outcome, respectively.

The above null hypothesis will be rejected in favor of the alternative if the lower bound of the two-sided 95% exact binomial (i.e., Clopper-Pearson) confidence interval is greater than 85%.

The third co-primary endpoint is the percent change from baseline (PCFB) in verified LDL-C values to Visit 2 in participants regardless of their final use outcome. PCFB in verified LDL-C to Visit 2 is computed as follows:

$$PCFB = \frac{100*(\text{Verified LDL-C value at Visit 2} - \text{Verified LDL-C value at Baseline})}{\text{Verified LDL-C value at Baseline}}$$

where the verified LDL-C value at initial selection will serve as Baseline. The LDL-C values assessed as part of a reorder assessment and verified by the CMOG at Virtual Visit 2 will be used as the Visit 2 value. If a participant has more than one LDL-C retest during the use period, the most recent verified LDL-C value will be used in the analysis. Negative values in PCFB represent a decrease in LDL-C.

It is anticipated that at least 450 participants will be included in the evaluation of this co-primary endpoint. Assuming a true mean PCFB of -25% with a standard deviation of 25%, a sample size

of 450 participants would provide greater than 99% power to test the following set of hypotheses using a one-sample t-test at an α=0.025 of significance:

$$H_0: \mu \geq -15\% \text{ vs. } H_1: \mu < -15\%$$

where μ is the mean PCFB in verified LDL-C to Visit 2. The above null hypothesis will be rejected in favor of the alternative if the upper bound of the two-sided 95% confidence interval on the mean PCFB in verified LDL-C to Visit 2 is less than -15%.

It is expected that approximately 80,000 consumers will contact the Call Center for pre-screening in response to advertising. Traditional (i.e., television, print) and digital advertising approaches will be utilized for recruitment. Table 1 summarizes the estimates and percentage drops at each step from the initial call into the Call Center through completion of the study.

Table 1 Estimated Number of Subjects and Participants by Study Stage

Stage	Estimates
Calls into Call Center	Estimated 80,000 calls
Sent the Web Link Assumes: Screen Fail Rate = 24% Qualified Refused Rate = 8%	Estimated 54,400 subjects
Complete the Web Link (66%)	Estimated 35,900 subjects
Qualify as "OK to Use" (~5%)	Estimated 1,800 subjects
Schedule Virtual Visit 1 (85%)	Estimated 1,525 subjects
Enrolled – Complete consent at Virtual Visit 1 (80%)	Estimated 1,220 participants
Enter Use Phase of the Study (83%)	Estimated 1,000 participants
Withdrawals/Lost-to follow-up during use (~50%)	Estimated 500 participants
Evaluable participants*	Estimated 500 participants

* Evaluable for the second co-primary endpoint, Overall Correct Final Use Outcome

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

The analysis populations to be used in the study are defined as follows:

Pre-Screen Eligible and Registered Population – The Pre-Screen eligible and registered population includes all subjects who are eligible after completing the pre-screener either online or by calling the Call Center and registered for pre-screener follow-up.

Pre-Screen Failure Population – The Pre-Screen Failure population is comprised of all subjects who meet one of the following categories:

- Did not meet SS inclusion criteria or met SS exclusion criteria

- Qualified refused - Patients with OK to Use outcome but did not move forward with study
- Received Web App link but did not complete the TASS assessment
- Received Web App link and received a "Do Not Use" outcome
- Received Web App link and received an "Ask a Doctor" outcome and did not go back into the Web App and indicate a doctor said it was okay to proceed
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed but never created a Web App account
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, created a Web App account but did not make an initial purchase of study drug
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, created a Web App account, made an initial purchase of study drug but did not schedule their first visit
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, scheduled their first visit but did not sign the Informed Consent Form (ICF) (either did not show for their first visit or showed but decided not to sign ICF)

SS Population – The SS population includes all participants who sign the ICF.

AUS Screen Failure Population – The AUS Screen Failure population includes all participants in the SS population who meet the AUS exclusion criteria.

AUS Intent to Treat (ITT) Population – The AUS ITT population consists of all participants in the SS population who meet all eligibility for AUS and have investigational product (IP) delivered to their address.

Per Protocol (PP) Population – The PP population includes all participants in the AUS ITT population who complete Virtual Visit 2 or have sufficient medical and medication history information and, when necessary, a verified LDL-C value collected prior to stopping the study in order to determine a final use outcome.

Safety Population – the Safety population includes all participants in the AUS ITT population who take at least one dose of IP as determined by returning fewer pills than dispensed, including those who do not return any bottles for pill counting. As such, any participants who return all pills delivered to them are excluded.

Participant and subject disposition will be summarized using the Pre-Screened Eligible and Registered and Pre-Screen Failure populations in the study database. In addition to disposition, subject's reasons for failing the inclusion and exclusion criteria from the pre-screener will be summarized. Participant characteristics and demographics will be summarized on the SS population. The reasons for exclusion from the SS, AUS ITT and PP populations will be listed.

Analysis of the first co-primary endpoint (i.e., Overall Correct Initial TASS Outcome) will be conducted on the SS population as the primary analysis population; however, a second evaluation using the AUS ITT population and PP population will also be performed. Analysis of the second co-primary endpoint (i.e., Overall Correct Final Use Outcome) will be conducted on the PP population as the primary analysis population. Analysis of the third co-primary endpoint (i.e., PCFB in verified LDL-C to Visit 2) will be conducted on the AUS ITT population as the primary analysis population. Analyses on the secondary and exploratory endpoints will be conducted on the AUS ITT or PP populations as specified in Sections 4.2.3 and 4.2.4.

All safety analyses will be conducted on the Safety population.

2.2 Violations and Deviations

Not applicable.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Participant Disposition

Potential subjects who are screened for the purpose of determining eligibility for the study but do not sign consent in the study are defined as "pre-screen failures." Pre-screen failures are defined as all subjects who meet one of the following categories:

- Did not meet SS inclusion criteria or met SS exclusion criteria
- Qualified refused
- Received Web App link but did not complete the TASS assessment
- Received Web App link and received a "Do Not Use" outcome
- Received Web App link and received an "Ask a Doctor" outcome and did not go back into the Web App and indicate a doctor said it was okay to proceed
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed but never created a Web App account
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, created a Web App account but did not make an initial purchase of study drug
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, created a Web App account, made an initial purchase of study drug but did not schedule their first visit
- Received Web App link, received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed, scheduled their first visit but did not sign the ICF (either did not show for their first visit or showed but decided not to sign ICF)

Individuals who do not meet the criteria for participation in this study (i.e., pre-screen failures) may not be rescreened.

"Enrolled" is defined as a participant's agreement to participate in the clinical study following completion of the ICF.

Once the initial targeted medical and medication history has been gathered by the CMOG, participants may not be eligible to continue into the actual use period of the study if they are determined to be pregnant, breastfeeding, or have a severe allergy to rosuvastatin. These participants are classified as "AUS Screen Failures."

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons (e.g., continually delaying visits or interactions, refusing to use the eDiary, intoxication or under the influence of drugs). This is expected to be uncommon. Failure to comply with the dosing regimen in and of itself is not a reason for being withdrawn from the study. If a participant expresses a desire to withdraw from the study, the CMOG will attempt to obtain as much information as possible including final diary data, unused drug returned, and any information on AEs. Withdrawals, by definition, will not have completed Virtual Visit 2 or have sufficient data to determine a final use outcome. In those instances where a participant elects to withdraw, the reason for withdrawal will be documented. Withdrawals occurring after signing the ICF but prior to drug delivery to the participant will be designated as "SS Withdrawal". Withdrawals occurring following drug delivery to the participant are designated as an "AUS ITT Withdrawal".

A participant will be considered lost to follow-up if he or she repeatedly fails to complete the scheduled virtual visits and is unable to be contacted by the study team or CMOG.

A participant may be discontinued from the study intervention by the CMOG at a scheduled follow-up phone call or eDiary review if the participant has not already identified the following conditions and stopped study drug: pregnancy; severe and unexplained muscle pain, tenderness or weakness; and symptoms of liver problems (upper belly pain, dark urine, yellowing of skin or whites of eyes). Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. If such a situation occurs, the participant's disposition will be classified as "Pregnancy" for this "Stop Use" warning or "Adverse Event" for severe and unexplained muscle pain, tenderness or weakness, or symptoms of liver problems. In these instances, the participant will be scheduled for a Virtual Visit 2 and all procedures will be performed except a final TASS assessment and a study mandated test (SMT) for LDL-C. In these situations, the final TASS assessment will be considered "Incorrect" since the participant did not identify the condition and stop medication. If the participant identifies the condition and stops medication on their own, they will be scheduled for Virtual Visit 2 and all procedures including the final TASS assessment will be performed.

The PP population includes participants that have completed the study. "Completed" means the participant completed the study if he/she has completed all phases of the study, including Virtual

Visit 2. “Completed” also includes participants that have discontinued with sufficient medical and medication history information and, when necessary, a verified LDL-C value collected prior to stopping the study in order to determine a final use outcome and has not withdrawn from the study. The goal is to have 100 limited literacy participants in the trial.

3.2 Efficacy Variables

3.2.1 Diagnostic Variables

As part of the TASS assessment in the Web App, participants will be required to enter their diagnostic data. The diagnostic variables to be gathered in the Web App for the initial TASS assessment include Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C), Low Density Lipoprotein- Cholesterol (LDL-C), Systolic and Diastolic BP (SBP and DBP, respectively), and if applicable, high-sensitivity C-reactive protein (hs-CRP), Coronary Artery Calcium (CAC), and waist circumference.

Prior to Virtual Visit 1:

If a subject does not have their lab numbers prior to taking the initial TASS assessment and is unsure as to where to obtain their labs, the study staff at the Call Center will provide the subject with testing options upon request using the information provided in the Web App as a guide, but the subject will choose their preferred option. If subject wishes to go to a doctor and get a prescription for a lab test, that is acceptable. They can also order a home test kit. The study staff will not proactively tell them which testing method to use. If a subject requests assistance, the study staff will help them locate a testing site (e.g., local pharmacy, in-store clinic) for testing.

Upon completion of the initial TASS assessment and purchase, subjects will be directed to call the Call Center to schedule their Virtual Visit 1. During this call, the Call Center staff will confirm that the subject has verified diagnostic numbers (TG, TC, HDL-C, LDL-C, BP numbers) and a waist circumference measurement and if applicable, a verified hs-CRP level and CAC score in order to proceed to the use phase of the study.

The Call Center representative will mandate a lab test or BP measurement for Virtual Visit 1 if the subject states that they do not have a source document for the data entered into the Web App.

- CAC imaging results will not be verified by a SMT if a subject inputs this information into the Web App and does not have a verified source. In this instance, the subject’s TASS entry will be considered acceptable.
- The Call Center representative will help coordinate or locate a testing site (e.g., local pharmacy, in-store clinic) for testing of the TG, Cholesterol numbers and, if applicable, hs-CRP. If a subject is unable to get to one of the local testing sites, the study staff can direct them to order a home test kit. Subjects will not be required to pay for study mandated testing.
- A verified source is also required for BP numbers for Virtual Visit 1. If the subject states

they do not have verified BP numbers for their Virtual Visit 1, the study staff can help to locate a testing site for BP. If a subject is unable to get to one of the local testing sites and if they have a Food and Drug Administration (FDA) approved BP device at home, they will be allowed to use their device. If the subject cannot get to a local testing site and does not have an FDA approved BP device at home, a BP monitor will be shipped to them. General instructions on techniques to measure BP will be provided.

At Virtual Visit 1:

The diagnostic data entered into the Web App at the initial TASS assessment will be verified by the Central Assessor at Virtual Visit 1 prior to speaking with the CMOG clinician and signing informed consent. For males aged 20 to 39 years old, a source verified BP will not be required since BP does not factor into the use assessment based on current guidelines. If the diagnostic data is not verifiable, the Virtual Visit 1 will be rescheduled. Verified diagnostic numbers can include results obtained prior to completing the initial TASS assessment as long as the source type is within 12 months (+ 3-month window) and has a name that matches the subject's driver's license or other identification with a picture ID (e.g., school ID, military ID, passport, etc). If the Central Assessor is able to verify the source of the diagnostic data at Virtual Visit 1, the data is referred to as "verified source". If the diagnostic values are a result of SMT, the data is referred to as "verified by SMT." Both the "verified source" and "verified by SMT" lab and BP results will be provided to the CMOG clinician from the Diagnostic Report form for completing the CMOG clinician TASS.

During Use Phase:

Prior to every product reorder, participants are required to enter the Web App and take an abbreviated medical reorder assessment to ensure that they have not had a change in their health status. During this assessment, participants are asked about their repeat LDL-C test that they are expected to get by month 3 of treatment and to input their number to ensure they are getting an adequate therapeutic response. The LDL-C retest value is the only diagnostic lab value gathered at a reorder assessment.

At Virtual Visit 2:

The LDL-C retest value entered at a reorder assessment will be verified by the Central Assessor at Virtual Visit 2. A verified LDL-C retest value includes results from a doctor's office or health screening which must NOT be prior to the start date of Crestor OTC and have a name that matches the participant's driver's license or other identification with a picture ID (e.g., school ID, military ID, passport, etc). If the CMOG is able to verify the source of the LDL-C data at Virtual Visit 2, the data is referred to as "verified source", otherwise, the data is "unverified". Participants who fail to retest their LDL-C or do not have source documentation for the LDL-C value entered into the Web App will have study mandated testing. Study mandated lab testing

for Virtual Visit 2 will follow the same process as Virtual Visit 1 and will be performed on participants who enter Virtual Visit 2 with an "OK to Use" outcome or an "Ask a Doctor" outcome who indicated the doctor gave them permission to use the drug when the participant did not retest or did not have a source document for the LDL-C value they entered into the Web App. Participants who enter Virtual Visit 2 with a "Do Not Use" outcome or an "Ask a Doctor" outcome but they did not indicate the doctor gave them permission to use the drug or withdrew or discontinued from the study will not undergo study mandated testing. The reason that study mandated testing will not be required for these participants is that, in this virtual study design, most of these individuals will be off treatment for an extended period of time before a study mandated test can be performed. Any diagnostic data resulting from study mandated testing will be referred to as "verified via SMT." The clinicians will only use verified source LDL-C values that the participant entered into the Web App or study mandated LDL-C values when completing their assessments.

3.2.2 Rapid Estimate of Adult Literacy in Medicine (REALM)[1]

A REALM test will be administered to determine literacy for those participants who sign the ICF and attend their Virtual Visit 1. The word list will be displayed on the participant's screen and the interviewer will be able to visually see and hear the participant say each word on the video. Limited Literacy, or a $7^{th}/8^{th}$ grade reading level and below, is a REALM score less than or equal to 60. Normal literacy, or a high school reading level and above, is a REALM score greater than 60.

A sub-study of the TACTiC Trial will be performed to assess treatment-seeking behaviors in high-risk participants who failed to qualify for TACTiC. Since participants enrolled in the sub-study would pre-screen fail prior to Virtual Visit 1, a REALM test will not be available. To assess the literacy status of subjects evaluated in the sub-study, all participants who have a REALM test in TACTiC will be asked the Single Item Literacy Screener 2 (SILS2) question. The association between the SILS2 and REALM will be used to determine the SILS2 score that best corresponds to limited literacy in a primary prevention CV population.

3.2.3 TASS Outcomes

After completing the initial TASS assessment through the Web App, participants will receive one of the following initial TASS outcomes based on the information entered into the Web App:

- OK to Use
- Ask a Doctor Before Use (also referred to as "Ask a Doctor" for purposes of the protocol and this Statistical Analysis Plan (SAP))
- Do Not Use

Those participants with an "OK to Use" or "Ask a Doctor" outcome and indicated a doctor said it was okay to proceed are eligible to move forward with purchasing a supply of the product through the Web App and scheduling their Virtual Visit 1.

During the Virtual Visit 1 prior to signing the ICF, the Central Assessor will verify participants' diagnostic data (this includes source documents for the data entered by the participant into the Web App or source documents from study mandated testing). Only verified laboratory and BP data will be forwarded to the CMOG for use in their assessments.

After the ICF is signed, the CMOG will obtain a targeted medical and medication history. The CMOG will use the data obtained in the medical interview and input that data into the Web App where the following initial TASS outcomes are possible:

- OK to Use
- Ask a Doctor Before Use
- Do Not Use

The CMOG is blinded to the participant entries into the Web App in order to prevent bias in the CMOG initial TASS outcome. The participant initial TASS outcome and CMOG initial TASS outcome will be compared to determine their Overall Correct Initial TASS Outcome (i.e., first co-primary endpoint). If the CMOG clinician is unable to perform a TASS assessment through the Web App or determine a CMOG Outcome because data required to complete a specific screen is unavailable from the medical and medication history, the initial TASS outcome for the CMOG will be missing.

Prior to every drug reorder, participants are required to enter the Web App and take an abbreviated medical reorder assessment to ensure that they have not had a change in their health status. Their entries into the Web App at each reorder will result in one of three final TASS outcomes:

- OK to Use
- Ask a Doctor Before Use
- Do Not Use

Since participants are given a limited supply (i.e., 45 or 90 day) of rosuvastatin with each reorder, they are likely to have multiple reorder assessments over the duration of the trial. While this will occur, the critical reorder assessment will always be the last one taken by the participant since the corresponding TASS outcome represents their final use outcome. For the purposes of this study, a participant's *final use assessment* will refer to the last reorder assessment they received during the study which includes the final use assessment taken at Virtual Visit 2. The TASS outcome resulting from the final use assessment will be utilized as the final use outcome for the Overall Correct Final Use Outcome co-primary endpoint.

The final use assessments will be determined based on the following criteria:

1. For participants who get an "OK to Use" outcome with each reorder, their final use assessment will be performed at the end of the 6-month use period during their Virtual Visit 2.
2. For participants who get a "Do Not Use" outcome as their last reorder assessment prior to the end of the 6-month use period, their Virtual Visit 2 will occur earlier. The last reorder assessment which resulted in the "Do Not Use" outcome will be used as their final use assessment.
    a. Note that a "Do Not Use" outcome occurs whenever a participant meets Drug Facts Label (DFL) or LDL-C lowering criteria that would require the participant to stop treatment. This means that a participant who meets a *Stop Use* or *Do Not Use* criterion from the DFL will receive the same "Do Not Use" outcome and be evaluated as "Do Not Use" for the purpose of the second co-primary endpoint. For the purpose of evaluating the secondary endpoints, the reasons for the "Do Not Use" outcomes will be assessed in order to place them in the appropriate category for evaluation. In other words, participants who received a "Do Not Use" outcome due to a *Stop Use* criterion in the DFL will be assigned to the *Stop Use* category for evaluation.
3. For participants who get an "Ask a Doctor" outcome during the use period, they will be given until the end of the 6-month use period to speak to a doctor. Since subjects cannot reorder drug until they speak to the doctor, the risk of continuing them in the study is low. Importantly, allowing them to continue for the full 6-months provides the opportunity to assess whether they will contact a doctor at some point.
    a. If a doctor gives them permission to continue therapy, they will take the reorder assessment and indicate that they had permission to continue therapy. They will be able to reorder medication and continue in the study. Their final use assessment will be performed at the end of the 6-month use period during their Virtual Visit 2.
    b. If they do not take another reorder assessment, they will be seen at the end of the 6-month use period and the last reorder assessment which resulted in the "Ask a Doctor" outcome will be used as their final use assessment.
4. For participants who discontinue from study intervention prior to study completion (possibly due to experiencing a "Do Not Use" or "Stop Use" criteria or another reason) and their last TASS assessment was either "OK to Use" or "Ask a Doctor" and indicated the doctor gave them permission to continue treatment, the study staff will attempt to complete all Virtual Visit 2 procedures in order to obtain a final TASS assessment for the participant and CMOG. If the participant is unwilling or unable to perform a final TASS assessment at Virtual Visit 2, the participant final use outcome will be determined by the firewalled coding team using the verbatim reason for their discontinuation from

study intervention, and this will be identified in the applicable datasets. This process is similar to that used in other actual use studies where technology is not utilized. If the participant provides an incomplete medical and medication history at Virtual Visit 2, the CMOG will attempt to complete a final TASS assessment to obtain a CMOG final use outcome. If the CMOG clinician is unable to perform a TASS assessment through the Web App because data required to complete a specific screen is unavailable from the medical and medication history, they will use the DFL and follow an algorithm based on the question flow of the TASS tool to make a determination. If the CMOG clinician is unable to determine a final use outcome, the final use outcome for the CMOG will be missing. For further details on how a missing final use outcome will be determined for the participant and CMOG, see Section 3.2.3.3.

As mentioned in Section 3.2.1, during the use phase of the study participants will be asked about their repeat LDL-C test to ensure they are getting an adequate therapeutic response. The participant's behavior with regard to retesting as well as the LDL-C value entered into the Web App contribute to their final use assessment. Participants are permitted to enter any LDL-C value into the Web App and are not told that the values will be source verified until Virtual Visit 2. If they are unable to provide a source document for a value, they will have a SMT. In contrast, the CMOG clinician will only be permitted to enter source verified LDL-C data into the Web App for their assessments. This is done to prevent a CMOG final use assessment based on an inaccurate LDL-C. Following feedback from FDA, the Web App was programmed to take specific actions based on whether a participant retested and based on the result of a retest. The actions are as follows:

- If the participant fails to enter a retest, they can continue to reorder provided they do not indicate within the Web App that they experienced another condition that would prevent them from reordering. Participants who continue to receive an "OK to Use" outcome or an "Ask a Doctor" outcome and indicate that the doctor gave them permission to use the drug, and do not voluntarily retest, will have a study mandated LDL-C test performed prior to Virtual Visit 2. This SMT will be used by the clinician for their assessment but will not be used by the participant since they did not voluntarily get tested.
- If the participant enters an LDL-C value into the Web App, the following can occur:
    - If the value demonstrates an adequate LDL-C response (i.e., ≥15% reduction), the participant will proceed in the study and will no longer be prompted to enter an LDL-C into the Web App.
    - If the value demonstrates no change or an increase in LDL-C, the participant will get a "Do Not Use" outcome and will be scheduled for Virtual Visit 2 where all procedures except a SMT will be performed. If the participant fails to bring verification of the LDL-C test that resulted in stopping drug, the CMOG clinician will leave the LDL-C field in the Web App blank. The CMOG use assessment would result in an "OK to Use" outcome. However, when a subject who has continued in the study for 3 or more months fails to obtain a verified LDL-C

retest for use by the CMOG at Visit 2, an "OK to Use" outcome by the CMOG will be coded as missing since the lack of an LDL-C value means the CMOG can never know for certain that the subject was truly "OK to Use". The need to recode the CMOG outcome in this instance is a function of the Web App being programmed to allow all subjects to complete the 6 months study regardless of whether they obtained an LDL-C retest. In those situations where the participant has been in the study less than 3 months, a verified LDL-C will not be required for the CMOG to determine an outcome since the DFL allows individuals up to 3 months to obtain an LDL-C retest.

- If the value demonstrates an inadequate LDL-C response (i.e., ≥0% and <15% reduction), the participant will get an "OK to Use" outcome and be able to order drug, but they will be asked to repeat the LDL-C test. Therefore, individuals with an inadequate response, who proceed to purchase more medication, may have more than one LDL-C value entered into the Web App during the course of the study and the second LDL-C value entered into the Web App could result in one of the following outcomes:
  - If the result is an inadequate response or an increase in LDL-C, the participant will get a "Do Not Use" outcome.
  - If the result is an adequate response, the participant will get an "OK to Use" outcome.
  - If no additional LDL-C value is entered into the Web App, the participant will continue to get an "OK to Use" outcome.

From the perspective of the CMOG final use assessment, the inadequate response scenario creates a potential for an incorrect outcome to be generated by the CMOG. This is because the CMOG's final TASS assessment was programmed to mirror the participant's TASS assessment following the entry of an initial inadequate LDL-C retest response, and the purchase of additional medication, by the participant on a reassessment. Thus, the CMOG's outcome would be the same as that obtained by the participant following the entry of a second LDL-C value into the Web App. To illustrate this point, the CMOG procedure for entering an LDL-C retest value into the Web App is always to use the most recent verified value. The CMOG is blinded to the participant's outcome as well as the LDL-C values the participant entered into the App. If the LDL-C source document shows a single verified LDL-C and that value was an inadequate response, the CMOG clinician would enter it and get a "Do Not Use" outcome for their final TASS assessment. In this example, the CMOG outcome could be incorrect since a follow-up LDL-C retest for the inadequate response might have resulted in an adequate LDL-C response or no response. To address this issue, participants who have an initial inadequate LDL-C response and prior to Visit 2 have an "OK to Use" or "Ask a Doctor" outcome (and indicate the clinician gave them permission to use the drug) will be required to have a second verified LDL-C retest. If they do not voluntarily get another LDL-C retest, they will be sent for study

mandated testing. This procedure ensures the CMOG inputs a recent second validated retest at Visit 2. If the participant with an inadequate LDL-C response for their first retest comes to Visit 2 with a "Do Not Use" outcome or an "Ask a Doctor" outcome (and they did not indicate the doctor gave them permission to use the drug), they will not be sent for study mandated testing.

Please note that for the CMOG experience to mirror the participant experience following the entry of an initial Inadequate Response Retest, the participant must also proceed to purchase drug following the initial Inadequate Response LDL-C entry. If they fail to make a purchase, the Web App will not "lock-in" the initial Inadequate Response LDL-C. In this situation, the CMOG experience will mimic the participant's initial experience (i.e., the Web App assumes the CMOG clinician is making their first LDL-C retest entry.)

See Appendix A for more details on how these scenarios of inadequate LDL-C retest values entered by the participant into the TASS tool impact the CMOG final TASS entries and how these scenarios will be identified and managed. Scenarios will be identified in the applicable datasets and listed by participant.

There may be scenarios in which some participants do not take a TASS reorder assessment, do not retest their LDL-C or do not have a final use outcome from the TASS tool but may have taken action based on the DFL or other reasons. In these instances, the participant's final use outcome will be determined based off details gathered at Virtual Visit 2 where possible. Appendix B summarizes how the Overall Correct Final Use Outcome will be managed based on potential scenarios that could be observed in this study.

During Virtual Visit 2, the CMOG will perform a medical and medication history assessment. If study mandated LDL-C retest verification is required, it will be conducted prior to Virtual Visit 2. The CMOG will use the medical and medication history and verified LDL-C data to determine a CMOG final use outcome. The participant's final use outcome obtained from their final use assessment and CMOG final use outcome will be compared to determine the Overall Correct Final Use Outcome (i.e., second co-primary endpoint).

3.2.3.1 Mitigation Plan

When assessing participants' responses to the TASS questions used to determine a TASS outcome for the co-primary endpoints, a limited number of mitigating factors will be acceptable for participants who verbalize an understanding of the label warnings or provide information that would not be considered a medical risk. Mitigating factors may be identified during the targeted medical and medication history and will be applied during the coding process for determining correct versus incorrect TASS and use. Mitigations are classified as "*a priori*" or "post study" as follows:

- *A priori* mitigations: These are anticipated responses that would be considered correct, after

a priori mitigations, usually since there is no safety risk. See Appendix_C and Appendix_D for the list of a priori mitigations.

- Post-study mitigations: While every effort is made to anticipate and document mitigations a priori, there is commonly some information that could come to light in context of reviewing all the data obtained via the Web App and the Targeted Medical and Medication History Forms from the CMOG. Therefore, an additional review will be completed post-study to assess whether any additional responses could be mitigated based on the fact that the responses are reasonable and acceptable answers to the questions and pose no medical risk.

The impact of the *a priori* and post-study mitigations on the overall co-primary endpoints will be assessed by evaluating the endpoints with and without these mitigations. The mitigations that were applied to the second co-primary endpoint will be utilized when assessing the applicable secondary and exploratory endpoints.

The mitigation process will be performed after all participants have completed the study. Coding of participant responses and application of any mitigations will be done by an independent team (i.e., firewalled) comprised of clinicians and behavioral experts. The clinicians involved in coding and mitigations are not employees of AstraZeneca or Cleveland Clinic. They are employees of Concentrics Research. Clinicians are separated into two distinct groups for the purpose of this study. The first group are CMOG Clinicians who are responsible for interviewing participants during the virtual visits in order to obtain their medical and medication histories and complete the CMOG TASS assessments. The second group of clinicians are firewalled from the CMOG and are strictly involved in the coding and mitigation process after the CMOG has completed their tasks. In other words, this second group will not be clinicians operating in the CMOG. Two trained coders will independently code the results and then compare them. In the event of a disagreement, a 3rd party adjudicator (a different trained coder) will code the results to determine the final coding assessment. This 3rd party adjudicator is an employee of Concentrics Research. Coders will apply both the clinically pre-approved *a priori* mitigations and the post-study mitigations.

The Cleveland Clinic medical team in conjunction with the AstraZeneca medical team (when requested by Cleveland Clinic) will review and approve the following mitigations:

- all post-study mitigations recommended by the firewalled coding and mitigation team,
- all remaining incorrect outcomes to confirm that no additional post-study mitigations are applicable and
- any issues related to the application of the *a priori* mitigations

The Cleveland Clinic and AstraZeneca medical teams will be blinded to the impact that post-study mitigations will have on the study results.

Approved mitigations will then be entered into the study database by the firewalled coders and data management staff.

This process follows the FDA *Guidance for Industry: Self-Selection for Nonprescription Drug Products (April 2013)*[2] which states that "reasonable predefined mitigating factors may be acceptable in certain circumstances. Mitigating factors are participant responses that would allow what appears to be an incorrect self-selection decision to be considered a correct self-selection decision. Mitigations should be clinically reasonable."

The process for coding is explained in the "Coding Process Plan." Outcomes resulting from the coding process will be part of the data listings for this study.

3.2.3.2 Laboratory, Blood Pressure and Waist Circumference Variability Process

Laboratory and BP data are entered by the participant and CMOG into the Web App to generate TASS outcomes at the initial TASS assessment. Since the CMOG will only use verified laboratory and BP data when performing their assessments, and the data used by the CMOG could be different than the data entered by the participant, different TASS outcomes could be generated. In order to address situations where small clinically irrelevant changes in laboratory or BP values lead to different TASS outcomes, acceptable levels of variability for the 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk score and for the individual laboratory and BP values were established.

The established variability criteria will only be used when assessing the first co-primary endpoint and only when the participant and clinician TASS outcomes at Visit 1 differ because of these values. In other words, if the TASS outcomes for the participant and clinician agree, the laboratory and BP values entered by the participant will be considered acceptable. Note that laboratory and BP data entered into the Web App can only result in either an "OK to Use" or "Do Not Use" outcome. There is no scenario where laboratory or BP values entered into the Web App could lead directly to an "Ask a Doctor" outcome without an "Ask a Doctor" warning being identified during the same assessment.

When applying the variability criteria, the acceptable level of variability will be determined using the CMOG verified data. If the variability in the CMOG's data encompasses the participant's data, then that value will be considered acceptable.

The laboratory and BP values determine three important elements of the TASS assessment: the 10-year ASCVD risk score, the presence of a Risk Enhancing Factor (REF) and to determine if the participant's values are within the appropriate range for treatment. The variability criteria applied when differences in outcomes are observed for each of these elements is provided in Appendix E.

While the Web App provides instructions to individuals regarding how to perform a waist circumference measurement, some variability is likely to be observed between the measurement taken by the participant and the measurement taken during the Virtual Visit 1. Pellowe, et. al. reported that waist circumference measurements can vary significantly depending on when during the respiratory cycle the measurement is taken or through volitional alteration in abdominal distension. Additionally, they observed significant alterations in waist circumference up to 6.5% when measurements are taken during different times of the day[13]. The issue of variability in waist circumference measurements has also been reported by others[12]. For the purpose of this study, a waist circumference measurement entered into the TASS tool by the participant will be considered verified if both the participant and CMOG measurements meet, or do not meet, the criterion for the metabolic syndrome (i.e., waist circumference ≥35 inches for females and ≥40 inches for males), or if waist circumference measurements are disparate for meeting the metabolic syndrome criterion, the participant value is within 6.5% of the CMOG value.

3.2.3.3 Management of Missing TASS Assessments

Missing Participant TASS Assessments

In the instances where there is a missing Final Use Outcome for a participant due to their unwillingness or inability to complete a final TASS assessment at Virtual Visit 2, a verbatim response for the reason the participant is choosing to discontinue from study intervention prior to study completion will be collected. This verbatim response will be utilized by the firewalled coders who are a part of the coding and mitigation team to determine the participant's Final Use Outcome. Since this situation can only arise when a participant has determined they no longer wish to stay in the trial and use the drug, and they have refused to perform a final TASS assessment to obtain an independent participant outcome of "OK to Use," they can only be coded as a "Do Not Use" or "Ask a Doctor" outcome. The only time the "Ask a Doctor" outcome would be coded is when the verbatim response specifically states that the participant did not want to continue in the study because they wanted to talk to a doctor. The participant Final Use Outcome determined using the participant verbatim response for discontinuing study intervention will be compared to the CMOG Final Use Outcome to determine the Overall Correct Final Use Outcome.

For those participants who experienced a Stop Use criterion, which they did not self-identify and the CMOG directed them to stop use, the final outcome for the participant will be the outcome from the most recent TASS assessment taken prior to being instructed to stop the medication. This is because the prior TASS assessment would in all likelihood have an outcome of "OK to Use" or "Ask a Doctor" indicating the participant failed to recognize the stop use criterion at the time or failed to identify it when speaking to the CMOG during a scheduled telephone call. If the participant had identified a stop use criterion, they would have had a "Do Not Use" outcome and would have been scheduled for Visit 2 to complete the study. In the

instance where a participant has not reordered study drug, and thus does not have a reorder assessment, the final use outcome for the participant used in assessing the Overall Correct Final Use Outcome will be missing. These missing outcomes will not be imputed using the participant verbatim response as these participants were directed to discontinue from treatment by the CMOG, not at their own decision. The Overall Final Use Outcome from the standpoint of the second co-primary endpoint would be coded as "Incorrect". Refer to Section 3.2.6 for details on how these subjects will be handled for the Overall Correct Final Use Outcome.

Missing CMOG TASS Assessments

When there is a missing CMOG Final Use Outcome and an outcome cannot be determined using the TASS tool due to incomplete medical and medication history, the CMOG clinician will use the DFL and follow an algorithm based on the question flow of the TASS tool to make a determination. For details on the flow of the TASS tool at the reassessments, refer to 3.2.R in the initial investigational new drug (IND) submission sequence 0032. In order to determine a final use outcome for the CMOG at the final use assessment, the outcome will be assigned in a hierarchical order based on the information supplied in the medical and medication history. The hierarchical order of the outcomes to be assigned is as follows: "Do Not Use", "Ask a Doctor" and "Ok to Use". The CMOG outcome will be determined from their corresponding responses provided in Targeted Medical and Medication History Form at Virtual Visit 2.

- For a CMOG final use outcome to be determined as "Do Not Use" (or "Stop Use"), the CMOG must have provided an answer of "Yes" to any of the questions associated with a Do Not Use warning in the Targeted Medical and Medication History Form.
- For a CMOG final use outcome to be determined as "Ask a Doctor", all answers to the questions associated with a Do Not Use warning must be answered as "No" before assessing the answers to the questions associated with an Ask a Doctor warning. In the event that there are incomplete answers to the Do Not Use associated questions, an "Ask a Doctor" outcome is not able to be determined and the CMOG final use outcome will be missing.
- For a CMOG final use outcome to be determined as "Ok to Use", all answers to the questions associated with Do Not Use and Ask a Doctor warnings must be answered as "No". By default, an "Ok to Use" final use outcome can only be obtained when the CMOG clinician has answers to all the questions that are asked in the TASS tool. This includes having an LDL-C retest with an adequate response for participants who have continued in the study for 3 or more months. Thus, all "OK to Use" final use outcomes should be coming via a TASS assessment.

In those instances where a participant, CMOG or both TASS assessments are missing such that an Overall Final Use Outcome cannot be determined, the impact of the missing information will be assessed using the prespecified sensitivity analyses (see Section 4.2.2).

Missing CMOG initial TASS assessments should be rare or non-existent. In the event the CMOG is unable to perform a TASS assessment at Visit 1, the CMOG clinician will use the

DFL and follow an algorithm based on the question flow of the TASS tool to make a determination as described above. If the CMOG is unable to make a determination, the initial outcome will be missing.

3.2.4 Incorrect TASS Entries

After a participant enters information into the Web App during the initial TASS assessment or final use assessment, the CMOG clinician will conduct a targeted medical and medication history evaluation. The clinicians in the CMOG are blinded to the entries made by the study participant in the Web App. Once this interview is complete, the Central Assessor will compare the self-selection outcome from the participant in Web App to the TASS entries from the CMOG. Information obtained by the Central Assessor is not shared with the CMOG clinician. These roles perform independent functions for purposes of this study.

- For those participants proceeding into the actual use portion of the study: follow-up probes will be asked for any discrepancies between TASS entries that are only asked at the initial self-selection assessment as well as any Web App use errors.
- For those participants who do not meet the criteria for proceeding into the actual use portion of the study: follow-up probes will be asked of a participant for any discrepancies between TASS entries as well as Web App use errors.

The follow-up questions are not used for adjustment of the self-selection results; this information is used to determine the root cause of any discrepancies between the medical and medication history and Web App entries. Verbatim responses to these follow-up probes will be categorized based on the reasons for the discrepancies for each TASS question.

3.2.5 Cholesterol Retesting

During the use period of the study, participants will be told through the Web App and transactional emails to retest their LDL-C within 3 months. During the reorder assessments, participants are asked to input their number to ensure they are getting an adequate therapeutic response. These LDL-C retest values will be verified at the participant's Virtual Visit 2.

Participants who should retest are those who were eligible for continuous treatment and who completed Virtual Visit 2.

3.2.6 Stop Use Warnings

Prior to every drug reorder, participants are required to enter the Web App and take an abbreviated medical reorder assessment. If a participant identifies a "Stop Use" warning, they are instructed by the Web App to both stop use and contact a doctor and will no longer be able to order drug. Stopping use can be ensured through the Web App by preventing participants from reordering medication; however, the participant must take the initiative to contact a doctor.

While the information used to assess stopping use can come from either the Web App or the Targeted Medical and Medication History Form at Virtual Visit 2, the information used to assess contacting a doctor will come from the Targeted Medical and Medication History Form completed by the clinician at Virtual Visit 2.

There are two “Stop Use” warnings for non-prescription rosuvastatin: (1) severe and unexplained muscle pain, tenderness, or weakness and (2) symptoms of liver problems (upper belly pain, dark urine, yellowing of skin or whites of eyes).

While some individuals may identify these symptoms and have treatment stopped through the use of the Web App, there is a reasonable probability that people with these symptoms will simply stop therapy and decide not to use the Web App because they do not want to reorder medication. Meeting the second co-primary endpoint and the secondary endpoint with regard to “Stop Use” warnings requires the participant to identify the “Stop Use” warning on their own. If during the planned 60- and 120-day touchpoint, following review of the eDiary, or through an unplanned contact from the participant, a “Stop Use” criterion is identified, the participants will be managed as follows:

- If during the interview with the clinician, the participant volunteers that they had a “Stop Use Warning”, they will be scheduled for Virtual Visit 2. Participants who self-identify a “Stop Use” criterion will complete all Virtual Visit 2 procedures including a TASS assessment.
- If, on the other hand, the CMOG becomes aware of a “Stop Use” criterion during the telephone call that the participant did not identify, all Visit 2 procedures except a participant TASS and SMT for LDL-C will be performed. The reason for not repeating the TASS is that the participant did not self-identify the "Stop Use" criterion. Instead, the CMOG identified the criterion and discussed with the participant, which could bias the participant’s behavior when completing the TASS. For example, a participant who did not realize they should have stopped drug because of severe muscle symptoms, may answer "yes" to this question in the TASS and be categorized as a correct selector when, in reality, they may have answered "no" to this question if they had not spoken to a CMOG clinician prior to completing the TASS. For those participants who have completed a reorder assessment, the most recent TASS reorder assessment will be used as the final TASS assessment, and the corresponding outcome will be used as the final use outcome for the participant. For those participants who have not completed a reorder assessment, the final use outcome for the participant will considered missing. As mentioned in Section 3.2.3.3, these missing outcomes will not be imputed using the participant verbatim response as these participants were directed to discontinue from treatment by the CMOG, not at their own decision. Because the study staff had to inform the participant that they met a “Stop Use” criterion, they will be considered a failure (i.e., incorrect) when evaluating the second co-primary endpoint related to “use.”
- Participants who the CMOG clinician identifies as having experienced “Stop Use” criteria are considered “Discontinued from Study Intervention” and not a withdrawal (refer to Section 3.1). In general, the only events recorded in an eDiary or communicated to the study

staff during a phone check that would result in study medical personnel instructing the participant to stop taking rosuvastatin are "Stop Use" criteria. If such a situation occurs, the participant will be classified as a discontinuation from study intervention due to "Adverse Event" or "Pregnancy" and scheduled for a Virtual Visit 2.

See Appendix B for additional details on how the participant's final use outcome would be assessed based on these different scenarios.

3.2.7 Do Not Use Warnings

The "Do Not Use" warnings for non-prescription rosuvastatin are as follows: heart attack, stroke, peripheral artery disease (PAD), an operation or procedure on your heart, liver disease, taking cholesterol-lowering prescriptions medicines, triglyceride lowering prescription medicines, cyclosporine, or warfarin. Prior to every drug reorder, participants are required to enter the Web App and take an abbreviated medical reorder assessment. If the participant identifies they have one of these warnings within the Web App, they will receive a "Do Not Use" outcome.

While one of these criteria could come to the attention of a clinician during the 60- or 120-day touchpoint, following review of the eDiary, or through an unplanned contact from the participant, the clinician will take no action in response to this information. The intent is to determine if participants can identify the "Do Not Use" warnings within the Web App during the reorder process. This is important because consumers will not have clinicians supporting their decisions when the drug is on the market. Consumers must be able to recognize these warnings on their own or identify them through the Web App so that the medication is stopped. The information regarding whether a participant stopped the medication will come from the Targeted Medical and Medication History Form completed by the clinician at Virtual Visit 2. This approach is appropriate in this study because the likelihood of harm to the participant from continuing therapy is very low. Note that Crestor 5 mg is an indicated dose for the treatment of heart attack, stroke, PAD, those with an operation or procedure on the heart or for those on cyclosporine or warfarin. While concomitant use with other statins is not a recommended treatment approach, use of Crestor with other cholesterol or triglyceride lowering medications is a common treatment approach and can be safely done with Crestor 5 mg.

It is possible that during the 60- or 120-day touchpoint or through an unplanned contact, the participant informs the clinician that they believe they met a "Do Not Use" criterion for which they stopped use of the medication and have no intention of restarting medication. If this occurs, the clinician will make no determination, but will schedule Virtual Visit 2. At Virtual Visit 2, all procedures will be performed, including a final use assessment in the Web App.

If the participant refuses to schedule a Virtual Visit 2, the clinician will attempt to obtain medical and medication history to determine if the participant experienced a "Do Not Use" warning. If

the clinician confirms the "Do Not Use" warning, the participant will have met the Do Not Use endpoints. If not, they have failed the Do Not Use endpoints.

See Appendix B for additional details on how the participant's final use outcome would be assessed based on these different scenarios.

3.2.8 Ask a Doctor Before Use Warnings

The "Ask a Doctor" warnings for non-prescription rosuvastatin during the reorder assessment are as follows: kidney disease, drink 3 or more glasses of alcohol daily, taking colchicine, HIV, AIDS or hepatitis medications. Prior to every drug reorder, participants are required to enter the Web App and take an abbreviated medical reorder assessment. If they identify an "Ask a Doctor" warning, they will no longer be able to order drug until they contact a doctor and confirm within the Web App that they can continue to order medicine.

While one of the "Ask a Doctor" warnings could come to the attention of a clinician during the 60- or 120-day touchpoint, following review of the eDiary, or through an unplanned contact from the participant, the clinician will take no action in response to this information. The intent is to determine if participants can identify these warnings within the Web App during the reorder process. This is important because consumers will not have clinicians supporting their decisions when the drug is on the market, and if they do not stop and ask a doctor on their own, it must be demonstrated that they recognize the event and can enter it into the Web App so that the appropriate action can be taken. The information regarding whether a participant contacted a doctor will come from the Targeted Medical and Medication History Form completed by the clinician at Virtual Visit 2. This approach is appropriate in this study because the likelihood of harm to the participant from continuing therapy is very low. Note that Crestor 5 mg is an indicated dose for all of the "Ask a Doctor" situations and participants will not be able to reorder drug unless they indicate the doctor gave them permission to do so.

It is possible that during the 60- or 120-day touchpoint or through an unplanned contact, the participant informs the clinician that they believe they met an "Ask a Doctor" criterion for which they stopped use of the medication and have no intention of restarting mediation. If this occurs, the clinician will make no determination, but will schedule a Virtual Visit 2. At Virtual Visit 2, all procedures will be performed and a final use assessment in the Web App will be conducted for those participants with a previous TASS outcome of "OK to Use" or "Ask a Doctor" and the doctor gave permission to proceed.

If the participant refuses to schedule a Virtual Visit 2, the clinician will attempt to obtain a medical and medication history to determine if the participant did experience an "Ask a Doctor" warning. If the clinician confirms the "Ask a Doctor" warning, the participant will have met the Ask a Doctor endpoints. If not, they have failed the Ask a Doctor endpoints.

See Appendix B for additional details on how the participant's final use outcome would be assessed based on these different scenarios.

3.2.9 Eligible for Continuous Treatment

Participants eligible for continuous therapy are defined as those with an "OK to Use" outcome or those with an "Ask a Doctor" outcome who indicated the doctor gave them permission to continue treatment, and they continued to have one of these outcomes at all assessments (initial, reorder and final use). Participants who discontinue or withdraw are not eligible for continuous treatment.

3.2.10 Pill Count

At Virtual Visit 2, all administered pill bottles will be returned, and pill count will be assessed. The total number of pills dispensed is based on the number of 45-day or 90-day supplies ordered through the Web App. The number of pills returned is the total number of pills remaining in each of the returned bottles. For those participants who refuse to send back their pill bottles for a final pill count, the option to count the pills with the study personnel via video conference will be given. For those participants who have lost one or more of their pill bottles, the eDiary data will be utilized to reconcile compliance with dosing.

Because there may be instances in which a participant continues study medication when they should not have (i.e., participant experiences "Stop Use," "Do Not Use," or "Ask a Doctor" warning) but does not stop medication, in order to properly assess compliance with continuous dosing, the intended duration of treatment will be used rather than the actual duration of treatment. The intended duration of treatment is as follows:

Intended Duration of Treatment =	(Intended Treatment Stop Date – Date Participant Received First Supply of Study Drug) + 1 Day

where the date of intended treatment stop will be the date when the medication was intended to be stopped (i.e., the date of "Stop Use" warning, the date of the "Do Not Use" warning, the date of the "Ask a Doctor" warning in situations where the participant did not confirm the doctor gave them permission to use the drug, the date of discontinuation or withdrawal, or for participants who did not receive one of the previous outcomes, the date of Visit 2).

Data listings will be provided for participants TASS initial study drug order and their overall study drug accountability.

3.2.11 eDiary

The eDiary will be used to gather minimal and unbiasing data on the participant's use of the IP. The information to be gathered will include dosing (date/time and amount of IP taken), adverse

events (changes in health), and medication changes. The participant will record the unique ID from the study drug bottle to confirm receipt of the product.

At the 60-day and 120-day planned telephone contacts, the eDiary will be reviewed to determine if "Stop Use" criteria may be present and to ask about any changes in health.

In assessing supply period compliance, the total number of pills dispensed in supply period *i* will be either 45 or 90 based on the supply ordered and the total number of pills taken is determined based on the information recorded in the eDiary. The start date for assessing compliance in the eDiary will be the first day that the participant records taking the medication. From the start date, supply periods for evaluation of the eDiary are calculated based on the supply ordered. Therefore, the first supply period will include next 45 days for a 45-day supply and the next 90 days for a 90-day supply. The next supply period will start immediately after the first supply period ends, and the duration is based on supply. This method for determining the dates in the eDiary that are assessed for dosing relative to the supply periods will continue until the subject completes Virtual Visit 2 or has an event for which early stopping of therapy is required. In other words, the duration of treatment in the supply period for evaluation in the eDiary can be less than 45 or 90 days in those situations where the participant experiences an event that requires stopping therapy. Thus, the intended duration of treatment for supply period *i* will be calculated as follows:

Intended Duration of Treatment in Supply Period *i* =	(Intended Treatment Stop Date in Supply Period *i* – Date Participant Received First Supply of Study Drug in Supply Period *i*) + 1 Day

where the date of intended treatment stop in supply period *i* will be the date when the entire supply of medication was intended to be used by the participant (assuming one tablet is taken per day) or when the medication was intended to be stopped (i.e., the end date of intended supply period based on number of pills ordered, the date of "Stop Use" warning, the date of "Do Not Use" warning, the date of discontinuation or withdrawal).

3.3 Safety Variables

3.3.1 Adverse Events

Adverse Events will be collected from the time of signature of ICF, throughout the use period and up until 30 days after study drug completion or discontinuation. AEs will be collected and documented during the treatment and 30-day follow-up periods. All AEs will be followed to resolution. Serious AEs (SAEs) will be recorded from the time of signing of informed consent form.

A treatment-period AE are those AEs with an onset date on or after drug delivery date or worsening of pre-existing AEs on or after the drug delivery date.

An SAE is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Prior to analysis, all AEs will be coded using the latest version of the MedDRA coding dictionary.

3.3.2 Reporting of AEs/SAEs in Relation to COVID-19

All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP. For patients experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism, and the AE will be recorded accordingly. If a patient presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

If the test is positive, record “COVID-19 positive” in the Adverse Event Field.

If the test is negative, record “COVID-19 negative” in the Adverse Event Field, along with the AE/SAE signs and symptoms and/or other diagnosis.

If a test was not performed or the test was negative, but the signs and symptoms, as judged by the Investigator, are suggestive of COVID-19 infection, record “COVID-19 suspected” in the Adverse Event Field. If the investigator has other concurrent diagnoses for the patient’s signs and symptoms (eg, pneumonia), these will be recorded as separate AEs.

4 ANALYSIS METHODS

4.1 General Principles

4.1.1 Types of Analyses

Analyses will consist of descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and Quartiles 1 and 3 (Q1 and Q3)) for all continuous variables. Frequency counts and percentages will be summarized for all categorical variables. Two-sided 95% confidence intervals will also be provided for the co-primary endpoints, unless otherwise stated.

4.1.2 Subgroup Analyses

Results for all endpoints will be summarized by literacy group (limited, normal) as assessed by the REALM test as well as by sex at birth, race and age group (less than 50 years old, 50 – 65 years old, >65 years old) gathered from the CMOG responses in the Targeted Medical and Medication History Form at Visit 1. Results will also be assessed relative to Order Preference (based on the participant's study drug order quantity, 45- or 90- day supply from the Order History dataset).

4.1.3 Missing Data Conventions

All primary analyses, except the first co-primary endpoint, will be conducted based on a complete case analysis (i.e., observed data).

4.1.3.1 Missing Dates

In some instances, a participant's medical portal may only reflect the month and year a diagnostic test was conducted. While this information is sufficient to assess whether a diagnostic test was conducted within the required time frame according to the study, any dates with a missing day for a diagnostic test will be imputed using the following:

Missing Date	Imputation
Missing day (ex. March 2020)	The missing day will be imputed as the first day of the month.

For the exploratory efficacy analyses where time (in days) to compliance with a "Stop Use", "Do Not Use" or "Ask a Doctor" warning is assessed, handling of missing dates will be done in accordance with the scenarios shown in Appendix F.

4.1.3.2 Missing Data Imputation

The primary analysis of the first co-primary endpoint will be based on a worst case scenario missing data imputation where all participants in the respective analysis population with a missing CMOG initial TASS outcome will be counted as Incorrect for the endpoint. In addition to the worst case scenario analysis for the first co-primary endpoint, sensitivity analyses will be performed on the participants in the SS population with a non-missing initial TASS outcome for the (Sensitivity Analysis #1) CMOG (i.e., complete case analysis) and with missing Overall Correct Initial TASS Outcome data imputed using alternative methods for use in a sensitivity analysis. For those participants in the SS population, missing data imputation methods for this endpoint are as follows:

1. Best Case Scenario: All missing data assumed to be a success for the Overall Correct Initial TASS Outcome (i.e., participants who did not complete the targeted medical and medication history at the Virtual Visit 1, and, therefore, have a missing initial TASS outcome for the CMOG will be treated as Correct for the Overall Correct Initial TASS

Outcome) (Sensitivity Analysis #2).

2. Tipping Point Analysis: Missing data will be imputed to identify the largest number of missing cases that could be incorrect and still yield statistically significant results, had the outcome of all missing cases been observed. The proportion of Overall Correct Initial TASS Outcome along with 95% exact confidence intervals will be calculated. The estimated proportions and corresponding 95% confidence intervals will be displayed graphically as a function of the number of assumed Overall Correct Initial TASS outcome among participants with missing data on the x-axis. The success threshold of 85% will be displayed as a horizontal line in the graph. (Sensitivity Analysis #2).

In addition to the complete case analysis for the second co-primary endpoint, missing data for the Overall Correct Final Use Outcome will be imputed for use in sensitivity analyses. For those participants in the AUS ITT population, missing data imputation methods for this endpoint are as follows:

1. Best Case Scenario: All missing data assumed to be a success for the Overall Correct Final Use Outcome (i.e., participants who did not complete Virtual Visit 2 or did not provide sufficient medical history to make a final use assessment, and, therefore, have a missing final use outcome for the CMOG will be treated as Correct for the Overall Correct Final Use Outcome) (Sensitivity Analysis #1).
2. Worst Case Scenario: All missing data assumed to be a failure for the Overall Correct Final Use Outcome (i.e., participants who did not complete Virtual Visit 2 or did not provide sufficient medical history to make a final use assessment, and, therefore, have a missing final use outcome for the CMOG will be treated as Incorrect for the Overall Correct Final Use Outcome) (Sensitivity Analysis #1).
3. Tipping Point Analysis: Missing data will be imputed to identify the largest number of missing cases that could be incorrect and still yield statistically significant results, had an outcome for all missing cases been observed (Sensitivity Analysis #1).

For the third co-primary endpoint, participants in the primary LDL-C efficacy population (AUS ITT) with missing verified on-treatment LDL-C values, missing data will be imputed using various missing data imputation methods. The missing data imputation methods are as follows:

1. Best Case Scenario: All participants with missing LDL-C reduction due to missing verified LDL-C values will be treated as having a 40% reduction in LDL-C from baseline to Visit 2 (i.e., PCFB = -40%) (Sensitivity Analysis #2).
2. Worst Case Scenario: All participants with missing LDL-C reduction due to missing verified LDL-C values will be treated as having no reduction in LDL-C from baseline to Visit 2 (i.e., PCFB = 0%) (Sensitivity Analysis #2).

3. Tipping Point Analysis: Missing LDL-C reduction data due to missing verified LDL-C values will be imputed over the range of 0% reduction to 40% reduction (i.e., assuming that all participants with missing data had the same reduction in LDL-C ranging from 0% to 40%) and point estimates and corresponding 95% confidence intervals will be displayed graphically as a function of the assumed reduction in LDL-C. The graph will include a horizontal line corresponding to the success threshold of a 15% reduction (Sensitivity Analysis #2).

4.2 Analysis methods

4.2.1 Analysis of Baseline Participant Characteristics and Diagnostics

For subjects who are Pre-Screen Failures:

- The categorical baseline characteristics of age group, sex at birth, education level, race, employment status, and annual household income will be summarized using frequency counts and percentages based on the data captured in the Pre-Screener. The denominator for the percentages will be the total number of subjects in the Pre-Screen Failure population overall.

Subjects can choose to complete part of the pre-screening for SS eligibility criteria via an online pre-screener or call the Call Center to complete all pre-screening questions. Anyone that qualifies after completing the online pre-screener is directed to call the Call Center to complete additional pre-screening questions. Those that do not qualify are not directed to call the Call Center to complete the additional pre-screening questions.

- Subjects who choose to complete the online pre-screener and do not qualify or subjects who qualify via the online pre-screener but do not call the Call Center to answer the follow-up pre-screening questions will have incomplete prescreening data.

The baseline subject characteristics and demographics will be summarized for the Pre-Screen Failure population overall and by each pre-screen failure category as defined in Section 2.1.

The Pre-Screen Failure population will be used to analyze the initial subject TASS outcome and reason for outcome in women under the age of 50 years old. The subject TASS entries entered by women under the age of 50 years old will be listed.

Recruitment by geographic region, based on the U.S. Census Bureau, and state for the individuals who were sent a TASS link for the pre-screen eligible and registered population will be presented. The corresponding information for the SS population is also presented.

For all participants in the SS population:

- The categorical baseline characteristics of education level, employment status, and household income will be summarized using frequency counts and percentages based on the

data captured in the Pre-Screener. The categorical baseline characteristics of sex at birth, age, and race will be summarized using frequency counts and percentages based on the data captured in the Targeted Medical and Medication History Form at Visit 1. The denominator for the percentages will be the total number of participants in the SS population. This analysis will be repeated by subgroups as defined in Section 4.1.2.

- For the initial TASS assessment entered by the participant:
    - The continuous baseline characteristics (age) and diagnostics (TC, HDL-C, LDL-C, TG, SBP, DBP, hs-CRP, CAC and waist circumference) will be summarized using descriptive statistics overall and by subgroup based on the data captured in the TASS tool at the initial assessment.
- For the initial TASS assessment entered by the CMOG:
    - The continuous diagnostics (TC, HDL-C, LDL-C, TG, SBP, DBP, hs-CRP, CAC and waist circumference) will be summarized using descriptive statistics overall and by subgroup based on the data captured in the Diagnostic Report Visit 1 iCRF. The continuous baseline characteristic of age will be summarized using descriptive statistics based on the data captured in the Targeted Medical and Medication History Form at Visit 1, which is the same value the CMOG clinician will enter into the TASS tool. REALM score is gathered from the results of the REALM test and will be summarized overall and by subgroup using descriptive statistics.
    - The SILS2 question will be used to estimate the percentage of limited literacy participants enrolled in the sub-study. The SILS2 asks, “How confident are you filling out medical forms by yourself?” Participants can respond “extremely,” “quite a bit,” “somewhat,” “a little bit,” or “not at all.”
    - The SILS2 and REALM data collected in this study will be evaluated in the SS Population to determine the optimal SILS2 threshold for the classification of participants as limited literacy or normal literacy in the sub-study. The screening question, “How confident are you filling out forms by yourself?” (SILS2) will be scored by assigning the values 0, 1, 2, 3, and 4 to the five possible responses to the question, where 0 represents extreme confidence and 4 represents no confidence in independently filling out medical forms. These numerical responses will be compared to the REALM classifications of limited literacy and normal literacy to produce a Receiver Operator Characteristic (ROC) curve. The area under the ROC curve (AUC) will also be provided. Values of sensitivity and specificity will be computed for each SILS2 threshold ($\leq 0, \leq 1, \leq 2, \leq 3, \leq 4$).

The analysis completed for the SS population will be repeated for those participants in the AUS ITT and PP populations.

Disease background and characteristics based on the targeted medical and medication history form will be presented for the SS population overall and by subgroups as well as the AUS ITT and PP populations.

The participant's order preference of the investigational product in increments of 45-day supply, 90-day supply, or mix (started 45d then switched to 90d, or vice versa) will be tabulated by number and percentage.

Additionally, the number and percentage of participants with a verified source for their diagnostic data at Virtual Visit 1 will be summarized overall and by subgroups for each diagnostic variable and source (e.g., doctor/prescription, home test kit, etc.) for those participants in the SS, AUS ITT, and PP populations.

A detailed listing of baseline characteristics and diagnostic data for each participant will also be provided as shown.

4.2.2 Analysis of Primary Efficacy Variables

The primary analysis of the first co-primary endpoint (i.e., Overall Correct Initial TASS Outcome) will be conducted on the SS population overall and by subgroups. The same analysis will also be conducted on the AUS ITT population. Additional sensitivity analyses will be conducted on the SS population.

The primary analysis of the second co-primary endpoint (i.e., Overall Correct Final Use Outcome) will be conducted on the PP population overall and by subgroups. An additional assessment of the second co-primary endpoint will be conducted based only on TASS outcomes from the Web App. Additional sensitivity analyses will be conducted on the AUS ITT population.

The primary analysis of the third co-primary endpoint (i.e., PCFB in verified LDL-C to Visit 2 regardless of final use outcome) will be conducted on the AUS ITT population. Additional sensitivity analyses will be conducted on the AUS ITT as specified below.

Initial Self-Selection

The participant initial TASS outcome and CMOG initial TASS outcome will be compared to determine their Overall Correct Initial TASS Outcome (i.e., first co-primary endpoint).

Figure 1 illustrates the possible self-selection outcomes for the initial selection.

Figure 1 Two-by-Four Table Illustrating Possible Self-Selection Outcomes for Initial TASS Assessment

		CMOG Clinician Verified Initial TASS Outcome			
		Ok to Use	AAD	Do Not Use	Missing
Participant Initial TASS Outcome	Ok to Use	**Correct Selection ($C_S + MC_S$)**	**Incorrect Selection**	**Incorrect Selection**	**Incorrect Missing**
	AAD	**Incorrect AAD**	**Correct AAD ($C_{AAD} + MC_{AAD}$)**	**Incorrect AAD**	**Incorrect Missing**

For the first co-primary endpoint, Overall Correct Initial TASS Outcome, defined as the percentage of participants with a correct initial TASS Outcome at the initial self-selection is computed as follows:

$$\text{Overall Correct Initial TASS Outcome (\%)} = \frac{C_S + C_{AAD} + MR_{AP} + MR_{PS}}{\text{Number of Participants in Analysis Population}}$$

where:

- Correct Selector (CS) = Obtain a correct TASS outcome that they qualify for Crestor OTC by receiving an 'OK to Use' screen in the TASS (compared to the CMOG evaluation)
- Correct AAD (CAAD) = Obtain a correct TASS outcome that they must ask a doctor before qualifying for Crestor OTC by receiving an 'Ask a Doctor' screen in the TASS (compared to CMOG evaluation)
- Mitigated results *a priori* (MR_{AP})
  - MC_S = Mitigated Correct Selector
  - MC_{AAD} = Mitigated Correct Ask A Doctor
- Mitigated results post-study (MR_{PS})
  - MC_S = Mitigated Correct Selector
  - MC_{AAD} = Mitigated Ask A Doctor

The denominator for the primary analysis of the first co-primary endpoint will include those participants in the respective analysis population (SS population for the primary analysis and the AUS ITT population for the secondary analysis of this endpoint). Those participants with a missing CMOG initial TASS outcome in the SS population will be counted as incorrect for the endpoint. The target threshold for this endpoint is that the lower bound of the 95% exact confidence interval needs to be greater than 85% overall.

For the initial selection, the point estimate (PE) of the Overall Correct Initial TASS Outcome will be reported and the two-sided 95% confidence interval will be computed using exact binomial (Clopper-Pearson) methods for the proportion of each correct outcome among the entire SS population overall and by subgroups. This analysis will be repeated on the AUS ITT population overall and by subgroups. For the *a priori* and post-study mitigations, the PE and the two-sided 95% confidence interval will be computed for each TASS outcome (C_S and C_{AAD}) that was mitigated.

The above analysis will be repeated for the Overall Correct Initial TASS Outcome without any mitigations overall and by subgroups and with *a priori* mitigations only for the SS population overall and by subgroups and the AUS ITT population overall and by subgroups.

For those participants with an initial TASS outcome of "Ok to Use" or "Ask a Doctor" the count and percentage of reasons for the participant outcomes will be summarized overall and by subgroups. For participants who, after completing the Targeted Medical and Medication History form at Virtual Visit 1, have an initial CMOG outcome of "OK to Use," "Ask a Doctor," or "Do Not Use," the count and percentage of reasons for the CMOG outcomes will be summarized overall and by subgroups. This analysis will be repeated on the AUS ITT and PP populations overall and by subgroups.

A separate table will be constructed to display the count and percentages of participants with a least one mitigation (*a priori* and post-study) applied to this co-primary endpoint. For those participants with at least one mitigation, counts and percentages will be reported for each mitigation descriptor for the SS population overall and by subgroups. This analysis will be repeated on the AUS ITT population and PP population overall and by subgroups.

As an additional analysis of the first co-primary endpoint (Sensitivity Analysis #1), the Overall Correct Initial TASS Outcome will be assessed with the denominator of the endpoint including only those participants in the respective analysis population with a non-missing initial TASS outcome for the CMOG. Because the SS population includes only those participants eligible for treatment and who sign the ICF, there is no possibility of the participant having a missing initial TASS outcome from the Web App for the first co-primary endpoint. The PE of the Overall Correct Initial TASS Outcome will be reported, and the two-sided 95% confidence interval will be computed using exact binomial (Clopper-Pearson) methods for the proportion of each correct outcome among the entire SS population overall and by subgroups. For the *a priori* and post-study mitigations, the PE and the two-sided 95% confidence interval will be computed for each TASS outcome (C_S and C_{AAD}) that was mitigated.

The above analysis will be repeated for the Overall Correct Initial TASS Outcome without any mitigations and with *a priori* mitigations only for the SS population overall and by subgroups.

Data listings will be provided for the participant and CMOG TASS entries at the initial TASS outcome.

While highly unlikely that a participant would come to Visit 1, sign the ICF and refuse the interview with the CMOG clinician, in the event the CMOG is not able to obtain an initial TASS outcome for a participant, the Overall Correct Initial TASS outcome will be assessed as missing. The count and percentage of reasons for a missing participant or CMOG TASS initial outcome from the Web App will be presented for the AUS ITT population overall and by subgroups.

For Sensitivity Analysis #2, missing Overall Correct Initial TASS Outcomes will be imputed using best case imputation. The PE of the Overall Correct Initial TASS Outcome will be reported, and the two-sided 95% confidence interval will be computed using exact binomial (Clopper-Pearson) methods for each of these imputation methods. For the *a priori* and post-study mitigations, the PE and the two-sided 95% confidence interval will be computed for each TASS outcome (C_S, C_{AAD} and C_R) that was mitigated on the SS population overall and by subgroups. A tipping point analysis will also be performed as part of Sensitivity Analysis #2.

Final Use Assessment

The participant final use outcome and CMOG final use outcome will be compared to determine their Overall Correct Final Use Outcome. Figure 2 illustrates the possible self-selection outcomes for the final use assessment.

Figure 2 Three-by-Three Table Illustrating Possible Self-Selection Outcomes for Final Use Assessment

		CMOG Clinician Verified Final Use Outcome		
		Ok to Use	AAD	Do Not Use
Participant Final Use Outcome	Ok to Use	**Correct Selection (C_S + MC_S)**	**Incorrect Selection**	**Incorrect Selection**
	AAD	**Incorrect AAD**	**Correct AAD (C_{AAD} + MC_{AAD})**	**Incorrect AAD**
	Do Not Use	**Incorrect Rejection**	**Incorrect Rejection**	**Correct Rejection (C_R + MC_R)**

For the second co-primary endpoint, the Overall Correct Final Use Outcome, defined as the percentage of participants with a correct final use outcome at the final use assessment is computed as follows:

Overall Correct Final Use Outcome (%) =	$C_S + C_{AAD} + C_R + MR_{AP} + MR_{PS}$ / Number of Participants in Analysis Population with a non-missing final use outcome for both the participant and CMOG clinician

where:

- Correct Selector (CS) = Obtain a correct outcome that they qualify for Crestor OTC (compared to the CMOG evaluation)
- Correct AAD (CAAD) = Obtain a correct outcome that they must ask a doctor before qualifying for Crestor OTC (compared to CMOG evaluation)
- Correct Rejectors (C_R) = Obtain a correct outcome that they do not qualify for Crestor OTC (compared to CMOG evaluation)
- Mitigated results *a priori* (MR_{AP})
    - MC_S = Mitigated Correct Selector
    - MC_{AAD} = Mitigated Ask A Doctor
    - MC_R = Mitigated Correct Rejector
- Mitigated results post-study (MR_{PS})
    - MC_S = Mitigated Correct Selector
    - MC_{AAD} = Mitigated Ask A Doctor
    - MC_R = Mitigated Correct Rejector

The denominator for the primary analysis of the second co-primary endpoint will only include those participants in the analysis population with a non-missing final use outcome for the participant and CMOG. The target threshold for this endpoint is that the lower bound of the 95% exact confidence interval needs to be greater than 85% overall.

For the second co-primary endpoint, the PE of the Overall Correct Final Use Outcome, with *a priori* and post-study mitigations, will be reported with a two-sided 95% confidence interval which will be computed using exact binomial (Clopper-Pearson) methods for the proportion of each correct outcome among the entire PP population, with mitigations, overall and by subgroups. The Overall Correct Final Use Outcome will also be evaluated without mitigations and with only *a priori* mitigations on the PP population overall and by subgroups.

An additional exploratory analysis of the Overall Correct Final Use Outcome, with *a priori* and post-study mitigations, will be performed on the PP population for those participants who had both a participant and CMOG final use assessment obtained solely from the Web App. The PE of the Overall Correct Final Use Outcome, with *a priori* and post-study mitigations, will be reported with a two-sided 95% confidence interval which will be computed using exact binomial (Clopper-Pearson) methods for the proportion of each correct outcome among the entire PP population overall and by subgroups. Overall Correct Final Use Outcome obtained

solely from the Web App TASS assessments will also be evaluated without mitigations and with only *a priori* mitigations on the PP population overall and by subgroups.

The count and percentage of participants and CMOG receiving each TASS outcome at the final use assessment along with the reasons for their outcomes will be presented on the PP population overall and by subgroups. For participants that do not have a TASS outcome at the final use assessment but have provided sufficient verbatim information for discontinuing study intervention prior to study completion that allows for an assessment of the participant final use outcome, the count and percentage of participants receiving each final use outcome at the final use assessment will be presented on the PP population overall and by subgroups. Lastly, for CMOG final use outcomes that were determined by the clinician using the DFL and the available medical and medication history the count and percentage of participants receiving either a "Do Not Use" or "Ask a Doctor" outcome by the CMOG will be presented on the PP population overall and by subgroups.

A separate table will be constructed to display the count and percentages of participants with a least one mitigation (*a priori* and post-study) applied to the second co-primary endpoint. For those participants with at least one mitigation, counts and percentages will be reported for each mitigation descriptor for the PP population overall and by subgroups.

Data listings will be provided for the participant and CMOG TASS entries and TASS outcome at the final use assessment, and overall correct final use assessment.

A sensitivity analysis will be performed for the participants in the AUS ITT population with a missing Overall Correct Final Use Outcome for the second co-primary endpoint (Sensitivity Analysis #1). As the primary analysis for the second co-primary endpoint includes all participants in the PP population, to be included in the primary analysis participants must complete the Virtual Visit 2 or provide sufficient medical history information, and in some instances a verified LDL-C value, to assess a final use outcome for the CMOG. In those cases where a participant has provided insufficient data to allow for a CMOG final use assessment, and thus, results in missing CMOG final use outcome, the Overall Correct Final Use Outcome is not able to be assessed and will be missing. The count and percentage of reasons for a missing participant or CMOG TASS final use outcome from the Web App will be presented for the AUS ITT population overall and by subgroups.

Any missing Overall Correct Final Use Outcomes will be imputed using best case and worst case imputation. The PE of the Overall Correct Final Use Outcome will be reported, and the two-sided 95% confidence interval will be computed using exact binomial (Clopper-Pearson) methods for each of these imputation methods. For the *a priori* and post-study mitigations, the PE and the two-sided 95% confidence interval will be computed for each TASS outcome (C_S, C_{AAD} and C_R) that was mitigated on the AUS ITT population overall and by subgroups (Sensitivity Analysis #1).

LDL-C

Unless otherwise specified, all LDL-C analyses are performed using source document verified or study mandated LDL-C values.

The third co-primary endpoint is the percent change from baseline (PCFB) in verified LDL-C values to Visit 2 in participants regardless of their final use outcome. PCFB in verified LDL-C to Visit 2 is computed as follows:

$$\text{PCFB} = \frac{100*(\text{Verified LDL-C value at Visit 2} - \text{Verified LDL-C value at Baseline})}{\text{Verified LDL-C value at Baseline}}$$

where the verified LDL-C value at initial selection will serve as Baseline. The LDL-C values assessed as part of a reorder assessment and verified by the CMOG at Virtual Visit 2 will be used as the Visit 2 value. If a participant has more than one LDL-C retest during the use period, the most recent verified LDL-C value will be used in the analysis. Negative values in PCFB represent a decrease in LDL-C.

The PCFB in verified LDL-C to Visit 2, along with the raw values for verified LDL-C at Baseline and Visit 2, values will be summarized using descriptive statistics and a two-sided 95% confidence interval on the AUS ITT population overall and by subgroups. The target threshold for this endpoint is that the upper bound of the 95% confidence interval on the mean PCFB in the overall analysis needs to be less than -15%, with a PE less than or equal to -20%. There will be no hypothesis testing of this endpoint in the subgroups.

The number and percentage of participants who demonstrate ≥ 0%, <0% to ≥-10%, <-10% to ≥-20%, <-20% to ≥-30%, <-30% to ≥-40%, <-40% to ≥-50%, and <-50% PCFB in verified LDL-C to Visit 2 will be summarized on the AUS ITT population overall and by subgroups. The total number of participants in the AUS ITT population regardless of participant final use outcome at Visit 2 will serve as the denominator for the percentages.

Verified Virtual Visit 2 diagnostic data will be reported by source, which includes: 1) Doctor/Prescription, 2) Employee Health Clinic, 3) Heart Health Screening, 4) Home Test Kit, 5) Local Lab, 6) Pharmacy, 7) Other and 8) Study Mandated Testing, on the AUS ITT population by count and percentages overall and by subgroups.

In order to assess the overall robustness of the LDL-C primary endpoint, additional sensitivity analyses will be conducted to determine the effect that verification status and missing LDL-C retest values have on the LDL-C primary endpoint. Because LDL-C retest values are gathered at varying times throughout the use period (e.g., at a re-order assessment, during study mandated

testing, not at all, etc.), the LDL-C values used in the primary analysis and sensitivity analyses described below will vary. Appendix G describes various scenarios for LDL-C values and which values are included in the proposed analyses of LDL-C efficacy.

In the first sensitivity analysis of LDL-C efficacy, an evaluation of verified LDL-C values for those participants who are eligible for continuous treatment at Visit 2 will be assessed (See Section 3.2.9). This evaluation was selected because it evaluates efficacy in the participants who are expected to continue treatment. The PCFB in verified LDL-C to Visit 2 in participants eligible for continuous treatment will be calculated as follows:

$$\text{PCFB} = \frac{100*(\text{Verified LDL-C value for participants eligible for continuous treatment at Visit 2} - \text{Verified LDL-C value for participants eligible for continuous treatment at Baseline})}{\text{Verified LDL-C value for participants eligible for continuous treatment at Baseline}}$$

where the LDL-C value verified by the CMOG at Virtual Visit 1 will serve as Baseline. The LDL-C values assessed as part of a reorder assessment and verified by the CMOG at Virtual Visit 2 will be used as the Visit 2 value. If a participant has more than one LDL-C retest during the use period, the most recent verified LDL-C value will be used in the analysis. Negative values in PCFB represent a decrease in LDL-C.

PCFB in verified LDL-C to Visit 2 for participants eligible for continuous treatment, along with the raw values for verified LDL-C at Baseline and Virtual Visit 2, will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and a two-sided 95% confidence interval for those participants eligible for continuous treatment on the AUS ITT population overall and by subgroups (Sensitivity Analysis #1).

The number and percentage of participants who demonstrate $< 0\%$ to $\geq -10\%$, $< -10\%$ to $\geq -20\%$, $< -20\%$ to $\geq -30\%$, $< -30\%$ to $\geq -40\%$, $< -40\%$ to $\geq -50\%$, and $< -50\%$ PCFB in verified LDL-C to Visit 2 in participants eligible for continuous treatment will be summarized overall and by subgroups (Sensitivity Analysis #1). The total number of participants eligible for continuous treatment will serve as the denominator for the percentages.

A sensitivity analysis using missing data imputation will be performed for those participants in the AUS ITT population with missing verified LDL-C data at Visit 2. Participants with missing verified LDL-C data at Visit 2 will have their PCFB in LDL-C imputed using best case and worst case imputation. The PCFB in LDL-C to Visit 2 values will be summarized using descriptive statistics and a two-sided 95% confidence interval for each of these imputation methods on the AUS ITT population overall and by subgroups (Sensitivity Analysis #2).

Next, a sensitivity analysis of LDL-C values regardless of participant final use outcome (i.e., "OK to Use," "Do Not Use," and "Ask a Doctor" (regardless of doctor permission)) at Visit 2 and the verification status of the LDL-C values will be assessed. The PCFB in LDL-C to Visit 2 values, along with the raw values for verified LDL-C at Baseline and verified or unverified LDL-C at Visit 2, will be summarized using descriptive statistics a two-sided 95% confidence interval on the AUS ITT population overall and by subgroups (Sensitivity Analysis #3). PCFB will be calculated as follows:

$$\text{PCFB} = \frac{100*(\text{Verified or Unverified LDL-C value at Visit 2} - \text{Verified LDL-C value at Baseline})}{\text{Verified LDL-C value at Baseline}}$$

where the LDL-C value verified by the CMOG at Virtual Visit 1 will serve as Baseline. In order to enroll in the AUS portion of the study, verified diagnostic data is required at Virtual Visit 1. Therefore, the baseline LDL-C value will always be verified. The LDL-C values assessed as part of a reorder assessment will be used as the Visit 2 value. In the instance where a participant has both unverified and verified LDL-C values taken while on-treatment, the verified value will be used. If a participant only has an unverified LDL-C value taken on-treatment, this unverified value will be used. If a participant has more than one unverified LDL-C retest during the use period and no verified values, the most recent unverified LDL-C value will be used in the analysis. If a participant has more than one verified LDL-C retest during the use period, the most recent verified LDL-C value will be used in the analysis. Negative values in PCFB represent a decrease in LDL-C.

The number and percentage of participants regardless of final use outcome who demonstrate ≥ 0%, < 0% to ≥-10%, <-10% to ≥-20%, <-20% to ≥-30%, <-30% to ≥-40%, <-40% to ≥-50%, and <-50% PCFB in LDL-C entered into Web App to Virtual Visit 2 will be summarized on the AUS ITT population overall and by subgroups. The total number of participants in the AUS ITT population regardless of participant final use outcome at Visit 2 will serve as the denominator for the percentages.

In the final sensitivity analysis of LDL-C efficacy, an evaluation of the LDL-C values entered into the Web App by the participant at the initial selection and at a reorder assessment will be assessed. In cases where more than one retest is entered into the Web App, the most recent LDL-C value will be used for this analysis. The verification status of the LDL-C values for this analysis is not relevant. Any verification testing performed for the purposes of validating the data entered into the Web App will not be utilized or required for the purposes of this assessment.

The PCFB in LDL-C values, along with the raw LDL-C values entered into Web App at Baseline and the raw LDL-C values entered into Web App during the Treatment Period, will be

summarized using descriptive statistics and a two-sided 95% confidence interval on the AUS ITT population overall and by subgroups (Sensitivity Analysis #4). PCFB will be calculated as follows:

$$\text{PCFB} = \frac{100*(\text{LDL-C value entered into Web App during Treatment Period} - \text{LDL-C value entered into Web App at Baseline})}{\text{LDL-C value entered into Web App at Baseline}}$$

where the LDL-C value entered by the participant at initial selection will serve as Baseline. Negative values in PCFB represent a decrease in LDL-C.

Additionally, the number and percentage of participants regardless of final use outcome who demonstrate ≥ 0%, <0% to ≥-10%, <-10% to ≥-20%, <-20% to ≥-30%, <-30% to ≥-40%, <-40% to ≥-50%, and <-50% PCFB in LDL-C entered into Web App to Virtual Visit 2 will be summarized on the AUS ITT population overall and by subgroups.

4.2.3 Analysis of Secondary Efficacy Variables

Secondary efficacy analyses will be conducted on the AUS ITT or PP populations as specified below.

Cholesterol Retesting

During the use period of the study, participants will be told through the Web App and transactional emails to retest their LDL-C within 3 months. Participants who should retest are those were eligible for continuous treatment. The percentage of participants who are eligible for continuous treatment and have a cholesterol retest within 6 months of starting medication that was verified at Virtual Visit 2 will be calculated as follows:

$$\text{Percentage} = \frac{100* \text{ (Number of participants who are eligible for continuous treatment and had a cholesterol retest within 6 months after starting medication that was verified at Visit 2)}}{\text{Total number of participants who are eligible for continuous treatment}}$$

The number and percentage of participants who are eligible for continuous treatment and have a cholesterol retest within 6 months of starting medication that was verified at Virtual Visit 2 will be summarized on the PP population overall and by subgroups. Those participants with an unverified cholesterol retest value at Visit 2, and thus required study mandated testing, will not be included in the numerator for this endpoint. Participants with multiple retests will be included in the numerator for this endpoint if at least one of the retests is a non-study mandated verified retest. That is, at least one of the retests has a Source Type equal to “Verified source” on the

Visit 2 Diagnostic Report. The total number of participants who are eligible for continuous treatment will serve as the denominator for the percentages.

The target threshold for this endpoint is that the observed PE needs to be at least 60% in the overall analysis. There are no target thresholds for the subgroup analyses.

An additional analysis of cholesterol retesting will be conducted on those participants in the AUS ITT population. The percentage of participants who had a cholesterol retest within 6 months of starting medication that was verified at Virtual Visit 2 will be calculated as follows:

$$\text{Percentage} = \frac{100^* \text{ (Number of participants who had a cholesterol retest within 6 months after starting medication that was verified at Visit 2)}}{\text{Total number of participants in the AUS ITT Population}}$$

The number and percentage of participants who had a cholesterol retest within 6 months of starting medication regardless of final use outcome that was verified at Virtual Visit 2 will be summarized on the AUS ITT population overall and by subgroups (Sensitivity Analysis #1). Those participants with an unverified cholesterol retest value at Visit 2, and thus required study mandated testing, will not be included in the numerator for this endpoint. Participants with multiple retests will be included in the numerator for this endpoint if at least one of the retests is a non-study mandated verified retest. That is, at least one of the retests has a Source Type equal to "Verified source" on the Visit 2 Diagnostic Report. The total number of participants in the AUS ITT population will serve as the denominator for the percentages. There are no target thresholds for this analysis. Another table will be produced with this information based on duration of time in the study (i.e., ≤2 months, ≤3 months, ≤4 months, ≤5 months, 6+ months).

An additional analysis to assess the percentage of participants who had a cholesterol retest within 6 months after starting medication that was verified at Visit 2 in the population of participants that reordered medication at least once will be conducted and summarized on the AUS ITT population overall and by subgroups (Sensitivity Analysis #2).

Lastly, an analysis to assess the percentage of participants who had a cholesterol retest within 6 months after starting medication that was verified at Visit 2 in those participants in the AUS ITT population who received at least 3 months of treatment will be conducted and summarized overall and by subgroups (Sensitivity Analysis #3).

Compliance with Stop Use Warning

The percentage of participants who correctly self-identify as having a "Stop Use" warning and stop medication will be calculated as follows:

$$\text{Percentage} = \frac{\text{100* (Number of participants who correctly self-identify as having a “Stop Use” warning and stop medication)}}{\text{Total number of participants who CMOG identify as having a “Stop Use” warning}}$$

The number and percentage of participants who correctly self-identify as having a “Stop Use” warning and stop medication will be summarized on the PP population overall and by subgroups.

Compliance with Do Not Use Warning

The percentage of participants who correctly self-identify as having a “Do Not Use” warning at the final use assessment will be calculated as follows:

$$\text{Percentage} = \frac{\text{100* (Number of participants who correctly self-identify as having a “Do Not Use” warning at the final use assessment)}}{\text{Total number of participants who CMOG identify as having a “Do Not Use” warning}}$$

The number and percentage of participants who correctly self-identify as having a “Do Not Use” warning at the final use assessment will be summarized on the PP population overall and by subgroups.

Compliance with Ask a Doctor Before Use Warning

The percentage of participants who correctly self-identify as having an “Ask a Doctor Before Use” warning at the final use assessment will be calculated as follows:

$$\text{Percentage} = \frac{\text{100* (Number of participants who correctly self-identify as having an “Ask a Doctor Before Use” warning at the final use assessment)}}{\text{Total number of participants who CMOG identify as having an “Ask a Doctor Before Use” warning}}$$

The number and percentage of participants who correctly self-identify as having an “Ask a Doctor Before Use” warning at the final use assessment will be summarized on the PP population overall and by subgroups.

Compliance with Continuous Dosing

Compliance will be assessed in three ways, using pill counts, the eDiary and the number of reorders. The data from these three methods should provide a robust assessment of compliance in this study.

Overall Compliance will be calculated for each participant using pill counts as follows:

$$\text{Overall Compliance} = \frac{100^* \text{ (Total Number of Pills Taken)}}{\text{Intended Duration (in days) of Treatment}}$$

The intended duration of treatment is defined in Section 3.2.10.

If a situation occurs in which a participant returns fewer bottles than ordered, the convention for counting pills taken (i.e., the numerator for Overall Compliance) will be to take the total number of pills taken during the use period of the study using the electronic data capture (EDC) drug accountability data and the eDiary data to determine the number of pills taken during the supply period corresponding to the missing bottle(s).

Each participant will have overall compliance assessed and will be considered successfully compliant with continuous dosing if overall compliance is between 50% and 120%. The target threshold for the overall compliance endpoint is that the observed point estimate for the percentage of participants falling in the 50-120% range needs to be at least 50% overall. That is, at least half of the participants need to be successfully compliant with continuous dosing. A lower bound of 50% was chosen because published clinical studies have reported intermittent dosing with as little as 5 mg to 10 mg once weekly can provide significant reductions in LDL-C[3,4,5,6,7].

Overall Compliance will be summarized using descriptive statistics on the PP population overall and by subgroups.

The number and percentage of participants with >0-<50%, 50-120% and >120% overall compliance will be summarized on the PP population overall and by subgroups.

A Longitudinal Compliance Rate will be calculated to assess compliance with continuous dosing across each study drug reorder supply period. In order to derive the longitudinal compliance rate, supply period compliance will first be calculated for each supply period for each participant as follows:

$$\text{Supply Period Compliance} = 100^* \text{ (Total Number of Pills Taken in Supply Period } i \text{ based on the eDiary)}$$

Intended Duration (in days) of Treatment in Supply Period *i*

The intended duration of treatment in supply period *i* is defined in Section 3.2.11.

Missing e-diary entries will be treated as missed dosing.

Each participant will be considered successfully compliant across all supply periods if each supply period compliance is between 50% and 120%. The Longitudinal Compliance Rate will then be assessed as:

$$\text{Longitudinal Compliance Rate (\%)} = \frac{100^* \text{ (Number of participants with 50-120\% Supply Period Compliance across all supply periods)}}{\text{Total number of participants in PP population for whom supply period compliance was assessed across all supply periods}}$$

The target threshold for the Longitudinal Compliance Rate endpoint is that the observed point estimate needs to be at least 50% overall. That is, at least half of the participants need to be successfully compliant with continuous dosing across all supply periods.

Longitudinal Compliance Rate, along with the number of participants with 50-120% supply period compliance across all supply periods, will be summarized on the PP population overall and by subgroups.

An additional assessment of longitudinal compliance will be performed using reorder data from the Web App. Percentage of participants who were persistent as determined by reorder data from the Web App will be calculated as follows:

$$\text{Percentage} = \frac{100^* \text{ (Number of participants who were persistent)}}{\text{Total number of participants eligible for continuous treatment}}$$

Persistence is defined as participants eligible for continuous treatment and delivered the full 180 days or more of treatment. The number and percentage of participants who were persistent will be summarized on the PP population and AUS ITT population overall and by subgroups.

The target threshold for this endpoint is that the observed point estimate needs to be at least 50% overall.

4.2.4 Analysis of Exploratory Efficacy Variables

Exploratory efficacy analyses will be conducted on the PP population unless otherwise specified.

Incorrect TASS Entries

For the initial TASS assessment, the number and percentage of incorrect TASS entries entered into the TASS tool by the participant, along with the reasons for incorrect TASS entries, will be summarized for each TASS question on the SS population overall and by subgroups. Additionally, data listings will be provided for reasons for incorrect participant TASS entries at the initial TASS assessment, and the central assessor discrepancy probes at Visit 1. A similar evaluation will be made on the final use assessment entries in the SS population.

There may be instances when a participant will be required to have a study mandated test at Visit 1, or at final use visit. For example, the LDL-C value entered by the participant may not be verified at Visit 1. The number and percentage of participants requiring a SMT will be analyzed overall and by subgroup for laboratory tests and blood pressure at Visit 1and for LDL-C at the Final Use Visit.

Descriptive statistics will be provided for the absolute difference between the laboratory and BP data that was unable to be verified at Virtual Visit 1 but was entered into the TASS tool by the participant and the laboratory and BP data resulting from study mandated testing and entered into the TASS tool by the CMOG. These data will be summarized on the SS population overall and by subgroups.

Additionally, the number and percentage of laboratory or BP TASS entries between the participant and CMOG with absolute value of the relative differences that are ≤1x, >1x to ≤2x, >2x to ≤3x, >3x to ≤4x, >4x to ≤5x and >5x the variability for each parameter as defined in the Laboratory and Blood Pressure Variability Assessments section of the Appendix will be summarized on the SS population overall and by subgroups.

Variability in the absolute difference in 10-year ASCVD risk scores calculated in the TASS tool based on the participant and CMOG entries will be summarized on the SS population overall and by subgroups. The intraclass correlation coefficient (ICC) (Watson and Petrie, 2010)[9] will be computed to evaluate the agreement between these two scores on the population SS overall and by subgroups. Bland-Altman plots will be generated to show the difference in risk scores on the y-axis and the mean of the risk scores on the x-axis (Altman and Bland, 1983)[8] on the SS population overall and by subgroups. A scatterplot will be constructed using the ASCVD risk scores calculated in the TASS tool based on the entries made by the participant and those made by the CMOG on the SS population overall and by subgroups. Lin's concordance correlation coefficient (Lin, 1989)[10] will be calculated between the two ASCVD risk scores on the SS population overall and by subgroups.

For the initial participant TASS assessment, the number and percentage of incorrect TASS entries entered into the TASS tool by the participant will be summarized for each TASS question along with the number and percentage of incorrect TASS entries that resulted in incorrect outcomes. The number and percentage of incorrect TASS entries that resulted in incorrect TASS outcomes that could be mitigated *a priori* and post-study will also be summarized. This information will be summarized in the SS population overall and by subgroups. A similar evaluation will be made on the final participant TASS assessment entries in the PP population overall and by subgroups. Mitigations are further assessed based on whether the mitigation was performed *a priori* or post-study for the initial participant TASS assessment in the SS population overall and by subgroups and repeated using the AUS ITT population and PP population. A similar evaluation will be conducted for the final participant TASS assessment in the PP population overall and by subgroups.

An exploratory analysis of the number and percentage of participants with incorrect TASS entries which could be mitigated, regardless of whether the entry impacted the first or second co-primary endpoint, will be summarized for each TASS question on the SS, AUS ITT and PP populations overall and by subgroups for the initial assessment and the PP population overall and by subgroup for the final use assessment. Data listings will be provided to explore the initial and final assessments between the participant and CMOG TASS inputs with applied mitigations, regardless of the impact on the first co-primary endpoint, for the SS populations.

The number and percentage of participants with incorrect TASS entries into the TASS tool, along with the reasons for incorrect TASS entries, during the initial assessment will be summarized for each TASS question on the SS population overall and by subgroups. The number and percentage of participants with incorrect TASS entries, along with the reasons for incorrect TASS entries, at the final use assessment will be summarized for each TASS question on the PP population overall and by subgroups. A data listing will be provided for reasons for incorrect TASS entries at the final TASS assessment.

Discrepancies between TASS entries by the participant and participant responses to the same questions asked by the CMOG and recorded on the medical and medication history form will be summarized overall and by subgroups for the SS population at Visit 1 and for the SS population at the final use visit.

Compliance with Speak to a Doctor Component of Stop Use Warning

The percentage of participants who correctly self-identify as having a "Stop Use" warning and speak to a doctor will be calculated as follows:

$$\text{Percentage} = \frac{100^{*} \text{ (Number of participants who correctly self-identify as having a "Stop Use" warning and speak to a doctor)}}{\text{Total number of participants who correctly self-identify as having a "Stop Use" warning}}$$

The number and percentage of participants who correctly self-identify as having a "Stop Use" warning and speak to a doctor will be summarized on the PP population overall and by subgroups.

Timeframe for Complying with Stop Use Warning

As discussed in Section 3.2.6, the data for assessing the Stop Use timeframe will come from the Targeted Medical and Medication History Form at Visit 2. For those participants who correctly self-identify as having a "Stop Use" warning and stop the medication, the date from when a participant identifies a "Stop Use" warning to the date the medication was stopped will be calculated, in number of days, as follows:

$$\text{Time from having a "Stop Use" warning to stopping the medication (in days)} = \text{(Date medication was stopped – Date of "Stop Use" warning)} + 1 \text{ Day}$$

Descriptive statistics for time (in days) from having a "Stop Use" warning to stopping the medication will be summarized on the PP population overall and by subgroups.

For those participants who correctly self-identify as having a "Stop Use" warning and contact a doctor, the date from when a participant identifies a "Stop Use" warning to the date their doctor was contacted will be calculated, in number of days, as follows:

$$\text{Time from having a "Stop Use" warning to contacting a doctor (in days)} = \text{(Date doctor contacted – Date of "Stop Use" warning)} + 1 \text{ Day}$$

Descriptive statistics for time (in days) from having a "Stop Use" warning to contacting a doctor will be summarized on the PP population overall and by subgroups.

Timeframe for Complying with Do Not Use Warning

As discussed in Section 3.2.7, the data for assessing the "Do Not Use" timeframe will come from the Targeted Medical and Medication History Form at Visit 2. For those participants who correctly self-identify as having a "Do Not Use" warning and stop the medication, the date from when a participant identifies a "Do Not Use" warning to the date the medication was stopped will be calculated, in number of days, as follows:

Time from having a "Do Not Use" warning to stopping the medication (in days)	=	(Date medication was stopped – Date of "Do Not Use" warning) + 1 Day

Descriptive statistics for time (in days) from having a "Do Not Use" warning and stopping the medication will be summarized on the PP population overall and by subgroups.

Compliance with Speak to a Doctor Component of Ask a Doctor Before Use Warning

The percentage of participants who correctly self-identify as having an "Ask a Doctor Before Use" warning and speak to a doctor will be calculated as follows:

$$\text{Percentage} = \frac{100^* \text{ (Number of participants who correctly self-identify as having an "Ask a Doctor Before Use" warning and speak to a doctor)}}{\text{Total number of participants who correctly self-identify as having a "Ask a Doctor Before Use" warning}}$$

The number and percentage of participants who correctly self-identify as having a "Ask a Doctor Before Use" warning and speak to a doctor will be summarized on the PP population overall and by subgroups.

Timeframe for Complying with Ask a Doctor Before Use Warning

As discussed in Section 3.2.8, the data for assessing the Ask a Doctor timeframe will come from the Targeted Medical and Medication History Form at Visit 2. For those participants who correctly self-identify as having an "Ask a Doctor Before Use" warning and contact a doctor, the date from when a participant identifies an "Ask a Doctor Before Use" warning to the date their doctor was contacted will be calculated, in number of days, as follows:

Time from having a "Ask a Doctor Before Use" warning to contacting a doctor (in days)	=	(Date doctor contacted – Date of "Ask a Doctor Before Use" warning) + 1 Day

Descriptive statistics for time (in days) from having a "Ask a Doctor Before Use" warning and contacting a doctor will be summarized on the PP population overall and by subgroups.

Evaluations of Effectiveness in Lowering LDL-C in Different Participant Subgroups

For participants determined to be eligible for continuous treatment at Visit 2, the difference in PCFB in LDL-C between participants who had a retest LDL-C value during the course of the study with a verified source and those who did not retest but had a SMT completed at Virtual Visit 2 will be assessed. PCFB will be calculated for each of these participant subgroups in the same manner as the primary LDL-C endpoint. The absolute difference in PCFB between these two subgroups will be calculated and descriptive statistics will be summarized on the PP and AUS ITT population overall and by subgroups.

Evaluation of LDL-C Lowering Relative to Level of Dosing Compliance

Descriptive statistics for PCFB in verified LDL-C at Visit 2 for those participants eligible for continuous treatment will be summarized by level of overall compliance (>0 - <50%, 50-120%, and >120%) in the PP population overall and by subgroups, and for those participants with supply period compliance between 50% and 120% across all supply periods, in the PP population overall and by subgroups. The calculations for overall compliance and supply period compliance will be calculated using the same method as previously described in Section 4.2.3.

4.2.5 Analysis of Safety Variables

All safety analyses will be conducted on the safety population (i.e., all participants in the AUS ITT Population except those who return all pills delivered).

Duration of Treatment

Summary statistics for duration of treatment by days for the investigational product will be presented by overall and categorized by days of treatment 0-<30d, 30 - <60d, 60 - <90d, 90 - <120d, 120 - <150d, 150 - <180d, and those equal to or greater than 180 days.

Adverse Events

All AEs will be documented and recorded during the treatment period of the study, and during the follow-up period of the study. These two distinct time periods will be annotated in their respective tables.

Treatment Period:

Adverse events will be considered Treatment Period related if they fulfil one of the following criteria:

- Adverse events with an onset date on or after drug delivery date through Visit 2 or, if Visit 2 is not available, date of last contact
- Worsening of pre-existing events on or after drug delivery date
- Adverse events starting during treatment period and extending into 30-day follow-up period

Follow-Up Period:

Adverse events will be considered Follow-Up Period related if they occur after Visit 2.

For each time period, a summary table will be constructed to display the number of participants with at least one AE, the number of AEs by severity, the number of AEs possibly related to study drug, the number of serious AEs possibly related to study drug, the number of participants experiencing at least one serious AE, the number of participants with an AE leading to withdrawal from study, the number of participants with an AE leading to discontinuation of IP, and the number of AEs with outcome of death, and AEs by common terminology criteria for adverse events (CTCAE), along with key subject information.

The number and percentage of participants with at least one AE will be summarized by system organ class (SOC) and by preferred term (PT) within SOC.

The number and percentage of participants with at least one AE will be summarized by decreasing frequency on PT.

In addition, tables will be constructed to summarize AEs by severity.

Additionally, the number and percentage of participants with most common AEs, defined as those PTs with frequency ≥ 5%, will be summarized by SOC and by PT within SOC during the treatment period. This analysis will be repeated for the follow-up period.

All AEs will be listed.

4.2.6 Other Relevant Data Analysis/Summaries

4.2.6.1 Subject and Participant Disposition

A subject and participant disposition table will be constructed to show the various populations that will be evaluated in this study. The pre-screen failure population will be assessed based on the various categories of pre-screen failures possible. The subject disposition in the Pre-screen failure population will be presented based on the category of pre-screen failure. The reasons for pre-screen failures will be presented for those categories where data is available (i.e., inclusion/exclusion failures, qualified but refused to participate and subjects who failed TASS assessments).

The number of AUS screen failures, withdrawals, and discontinuations from study treatment in the SS population will be presented along with the associated reasons. Additionally, the number of participants who are lost to follow-up will be provided.

4.2.6.2 Concomitant Medication

All concomitant medications will be coded with the WHO Drug Dictionary. Tables will be constructed with counts and percentages of participants by anatomical therapeutic chemical ATC level 4 and preferred term at baseline (overall and by subgroups), in the treatment period and follow-up period.

4.2.6.3 Protocol Deviation

Protocol deviations will be summarized using all participants in the study database. The following criteria will be reported by count and percentages: participants with at least one important protocol deviation; related to the inclusion or exclusion criteria; discontinuation criteria and deviations related to study procedure.

5 INTERIM ANALYSES

Not applicable.

6 EXPLORATORY ANALYSES

6.1 Analysis of Risk Enhancing Factors

REFs will be evaluated based on the ASCVD and presence of these factors. These analyses will be a part of the Supplemental Statistical Analysis Plan.

7 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

8 REFERENCES

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9 APPENDIX A - TABLE OF SCENARIOS FOR INADEQUATE LDL-C TASS ENTRIES ENTERED BY PARTICIPANT THAT COULD IMPACT CMOG TASS ENTRIES

For participants who 1) come to Visit 2 with an “OK to Use” outcome or an “Ask a Doctor” outcome and indicate the physician gave them permission to use the drug, 2) entered an initial retest that resulted in an Inadequate Response LDL-C and 3) made a purchase at the time they entered their initial Inadequate Response LDL-C retest, a second verified LDL-C retest will be required. If the participant does not obtain a second verified LDL-C retest or does not obtain a repeat LDL-C retest through SMT, their final use outcome will be “Missing” in situations where the CMOG receives a DNU outcome due to an “Inadequate Decrease on Follow-Up LDL-C Retest.”

For participants who come to Visit 2 with a “Do Not Use” outcome or an “Ask a Doctor” outcome and does not indicate their clinician gave them permission to use the drug, a second verified LDL-C retest will not be required following an Inadequate Response retest. In these instances, the CMOG will also be unable to determine an “OK to Use” outcome due to the lack of a verified LDL-C retest with an adequate response.

The following Table illustrates the potential scenarios where the participant enters an initial Inadequate Response LDL-C Retest into the Web App and purchases an additional supply of medication during their reorder assessment.

TABLE A1

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
1a	IR (v)	-	OK to Use	Y	Y	SMT	<u>If SMT is IR:</u> DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest <u>If SMT is NR</u>: DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	Same as CMOG TASS Outcome	No

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
							If SMT is AR: OK to Use or Ask a Doctor		
1b	IR (v)	-	OK to Use	Y	N	IR (v) - Value 1	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	Yes
2a	IR (v)	-	Ask a Doctor and Doctor Confirmed it is OK to Continue	Y	Y	SMT	If SMT is IR: DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest If SMT is NR: DNU	Same as CMOG TASS Outcome	No

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
							Kickout Reason: Increase or No Decrease in LDL Cholesterol If SMT is AR: OK to Use OR Ask a Doctor		
2b	IR (v)	-	Ask a Doctor and Doctor Confirmed it is OK to Continue	Y	N	IR (v) - Value 1	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	Yes
3a	IR	-	OK to Use	Y	Y	SMT	If SMT is IR: DNU **Kickout Reason:** Inadequate	DNU outcome for IR result coded to Missing due to lack of two verified IR LDL-	Yes

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
							Decrease on Follow Up LDL Cholesterol Retest If SMT is NR: DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol If SMT is AR: OK to Use or Ask a Doctor	C values to determine final outcome Otherwise, same as CMOG TASS Outcome	
3b	IR	-	OK to Use	Y	N	No verified retest can be entered	OK to Use	"OK to Use" outcome coded to Missing due to a missing verified LDL-C retest value	Yes
4a	IR	-	Ask a Doctor and	Y	Y	SMT	If SMT is IR: DNU	DNU outcome for IR result coded to Missing due to lack of two verified IR LDL-	Yes

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
			Doctor Confirmed it is OK to Continue				**Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest If SMT is NR: DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol If SMT is AR: OK to Use or Ask a Doctor	C values to determine final outcome Otherwise, same as CMOG TASS Outcome	
4b	IR	-	Ask a Doctor and Doctor Confirmed it is OK to Continue	Y	N	No verified retest can be entered	Ask a Doctor and Doctor Confirmed it is OK to Continue	" Ask a Doctor and Doctor Confirmed it is OK to Continue " outcome coded to Missing due to a	Yes

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
								missing verified LDL-C retest value	
5	IR (v)	IR	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	N	-	IR (v) - Value 1	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	No
6	IR	IR (v)	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	N	-	IR (v) - Value 2	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	No
7a	IR (v)	AR	OK to Use	Y	Y	SMT	<u>If SMT is IR:</u> DNU **Kickout Reason:** Inadequate Decrease on	Same as CMOG TASS Outcome	No

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
							Follow Up LDL Cholesterol Retest If SMT is NR: DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol If SMT is AR: OK to Use or Ask a Doctor		
7b	IR (v)	AR	OK to Use	Y	N	IR (v) - Value 1	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	Yes

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
8	IR (v)	NR	DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	N	-	IR (v) - Value 1	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	DNU outcome coded to Missing due to lack of two verified IR LDL-C values to determine final outcome	No
9a	IR	AR	OK to Use	Y	Y	SMT	<u>If SMT is IR:</u> DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest <u>If SMT is NR</u>: DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	DNU outcome for IR result coded to Missing due to lack of two verified IR LDL-C values to determine final outcome Otherwise, same as CMOG TASS Outcome	Yes

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
							If SMT is AR: OK to Use or Ask a Doctor		
9b	IR	AR	OK to Use	Y	N	No verified retest can be entered	OK to Use	"OK to Use" outcome coded to Missing due to a missing verified LDL-C retest value	Yes
10	IR (v)	IR (v)	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	N	-	IR (v) - Value 2	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	Same as CMOG TASS Outcome	No
11	IR	IR	DNU **Kickout Reason:** Inadequate Decrease on Follow Up LDL Cholesterol Retest	N	-	No verified retest can be entered	OK to Use	"OK to Use" outcome coded to Missing due to a missing verified LDL-C retest value	No

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
12	IR	AR (v)	OK to Use	N	-	AR (v) - Value 2	OK to Use	Same as CMOG TASS Outcome	No
13	IR (v)	AR (v)	OK to Use	N	-	AR (v) - Value 2	OK to Use	Same as CMOG TASS Outcome	No
14	IR (v)	NR (v)	DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	N	-	N (v) - Value 2	DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	Same as CMOG TASS Outcome	No
15	IR	NR (v)	DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	N	-	N (v) - Value 2	DNU **Kickout Reason:** Increase or No Decrease in LDL Cholesterol	Same as CMOG TASS Outcome	No
16	IR	NR	DNU **Kickout Reason:** Increase or No	N	-	No verified retest can be entered	OK to Use	"OK to Use" outcome coded to Missing due to a missing verified LDL-C retest value	

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest"?
	Value 1 (1st retest)	Value 2 (2nd retest)							
			Decrease in LDL Cholesterol						No

IR – Inadequate LDL-C Response; AR – Adequate LDL-C Response; NR – No Response (i.e., Zero Percent lowering or increase in LDL-C); v – verified source; DNU – Do Not Use; SMT – Study Mandated Test; UTD – Unable to Determine
*The CMOG will always enter the most recent verified LDL-C retest from the Diagnostic Form for their TASS assessment.

The following Table illustrates the potential scenarios where the participant enters an initial Inadequate Response LDL-C Retest into the Web App and **does not** purchase an additional supply of medication during their reorder assessment. In these situations, the clinician Web App experience will be the same as the participant experience at the time they entered the inadequate LDL-C response value into the Web App.

TABLE A2

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest – Rationale #3"?
	Value 1	Value 2							
1**	IR (v)		OK to Use	N	-	IR (v)	OK to Use	Same as CMOG TASS Outcome	No
2**	IR		OK to Use	N	-	No verified retest can be entered	Ok to Use	Same as CMOG TASS outcome	No
3	IR (v)	-	Ask a Doctor and Doctor **DOES NOT** Confirm it is OK to Continue	N	-	IR (v) - Value 1	Ask a Doctor and Doctor **DOES NOT** Confirm it is OK to Continue	Same as CMOG TASS Outcome	No

Scenario	Participant LDL-C		Participant Final TASS Outcome	SMT Required (Y/N)	SMT Obtained (Y/N)	LDL-C (v)* input by CMOG	CMOG TASS Outcome	Coded Outcome	Is there a potential for *a priori* mitigation "Missing LDL-C Retest – Rationale #3"?
	Value 1	Value 2							
4	IR	-	Ask a Doctor and Doctor **DOES NOT** Confirm it is OK to Continue	N	N	No verified retest can be entered	Ask a Doctor and Doctor **DOES NOT** Confirm it is OK to Continue	"Same as CMOG TASS Outcome	No

IR – Inadequate LDL-C Response; AR – Adequate LDL-C Response; NR – No Response (i.e., Zero Percent lowering or increase in LDL-C); v – verified source; DNU – Do Not Use; SMT – Study Mandated Test; UTD – Unable to Determine
*The CMOG will always enter the most recent verified LDL-C retest from the Diagnostic Form for their TASS assessment.
**Scenarios 1 and 2 are discontinuation scenarios.

10 APPENDIX B - SCENARIOS FOR ASSESSING OVERALL CORRECT FINAL USE OUTCOME

Scenario	Action	Analysis Population	Study Disposition	Assessment for Overall Correct Final Use Outcome*
Participant has "Stop Use and Ask a Doctor" warning and discontinues from study intervention	Participant identifies the "Stop Use and Ask a Doctor" warning on their own or through TASS and completes all assessments associated with Virtual Visit 2	PP	Discontinuation from Study Intervention/ Completed	Correct, Incorrect or Mitigated
Participant has "Stop Use and Ask a Doctor" warning and discontinues from study intervention	Participant identifies the "Stop Use and Ask a Doctor" warning on their own or through TASS and completes sufficient medical and medication history to obtain a final use outcome	PP	Discontinuation from Study Intervention/ Completed	Correct, Incorrect or Mitigated
Participant has "Stop Use and Ask a Doctor" warning and withdraws from study	Participant identifies the "Stop Use and Ask a Doctor" warning on their own or through TASS and does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess Clinician final use outcome is "Missing"
Participant has "Stop Use and Ask a Doctor" warning and asks a doctor	Participant identifies the "Stop Use and Ask a Doctor" warning on their own or through TASS, speaks with a doctor and completes sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Completed	Correct, Incorrect or Mitigated

Scenario	Action	Analysis Population	Study Disposition	Assessment for Overall Correct Final Use Outcome*
Participant has "Stop Use and Ask a Doctor" warning and asks a doctor and withdraws from study	Participant identifies the "Stop Use and Ask a Doctor" warning on their own or through TASS, speaks with a doctor and does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess Clinician final use outcome is "Missing"
Participant has "Stop Use and Ask a Doctor" warning and does not stop use	Participant does not identify "Stop Use and Ask a Doctor" warning on their own or through TASS and completes all assessments associated with Virtual Visit 2	PP	Completed	Incorrect
Participant has "Stop Use and Ask a Doctor" warning and CMOG identifies and discontinues from study intervention	Participant does not identify "Stop Use and Ask a Doctor" warning but CMOG identifies at 60/120-day call and completes sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Discontinuation from Study Intervention/ Completed	Incorrect
Participant has "Stop Use and Ask a Doctor" warning which CMOG identifies and withdraws from study	Participant does not identify "Stop Use and Ask a Doctor" warning but CMOG identifies at 60/120-day call and participant does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess??
Participant has "Ask a Doctor" warning and discontinues from study intervention	Participant identifies "Ask a Doctor" warning from DFL or through TASS and completes sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Discontinuation from Study Intervention/ Completed	Correct, Incorrect or Mitigated

Scenario	Action	Analysis Population	Study Disposition	Assessment for Overall Correct Final Use Outcome*
Participant has "Ask a Doctor" warning and withdraws from study	Participant identifies "Ask a Doctor" warning from DFL or through TASS but does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess Clinician final use outcome is "Missing"
Participant has "Ask a Doctor" warning and does not stop use	Participant does not identify "Ask a Doctor" warning and completes sufficient medical and medication history, or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Completed	Incorrect
Participant has "Do Not Use" warning and discontinues from study intervention	Participant identifies "Do Not Use" warning on their own or through TASS and completes sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Discontinuation from Study Intervention/ Completed	Correct, Incorrect or Mitigated
Participant has "Do Not Use" warning and withdraws from study	Participant identifies "Do Not Use" warning from DFL or through TASS but does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess Clinician final use outcome is "Missing"
Participant has "Do Not Use" warning and does not stop use	Participant does not identify "Do Not Use" warning and completes sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	PP	Completed	Incorrect

Scenario	Action	Analysis Population	Study Disposition	Assessment for Overall Correct Final Use Outcome*
Participant has an "OK to Use" outcome which CMOG cannot confirm because of the lack of a verified LDL-C retest and participant has been in study <3 months	Because participant has up to 3 months to obtain an LDL-C retest, the CMOG can obtain an "OK to Use" outcome without the need for a verified LDL-C retest value	PP	Completed	Correct, Incorrect or Mitigated
Participant has an "OK to Use" outcome which CMOG cannot confirm because of the lack of a verified LDL-C retest and participant has been in study >3 months	A CMOG final use outcome cannot be obtained due to the lack of a verifiable LDL-C value	AUS ITT	Withdrawal	Insufficient data to assess If CMOG obtains "OK to Use" outcome, the CMOG outcome will be changed to "Missing". An *a priori* mitigation for missing LDL-C is possible in this situation
Participant decides to withdraw from study	Participant does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Withdrawal	Insufficient data to assess Participant and Clinician final use outcomes are "Missing."
Participant is Lost to Follow-Up (LTF)	Participant does not complete sufficient medical and medication history or all assessments associated with Virtual Visit 2 to obtain a final use outcome	AUS ITT	Lost to Follow-Up	Insufficient data to assess Participant and Clinician final use outcomes are "Missing."

*The mitigation process is the same as the overall mitigation process for the study.

11 APPENDIX C - INITIAL SELF-SELECTION MITIGATIONS

Label Reference	Rationale for Mitigation
Pregnancy alert: Do not use if you are pregnant or breastfeeding. If you become pregnant, stop taking and call your doctor. Participant enters “no” in the Web App but learns at a later date that they were pregnant.	Participant did not know they were pregnant at the time they used the Web App. Participants who demonstrate they had knowledge of a pregnancy are not mitigated.
Do not use if you are taking: - any cholesterol lowering and/or triglyceride lowering prescription medicine - cyclosporine (a medicine for your immune system) - warfarin/ COUMADIN® (a blood thinner) Ask a Doctor before use if you are taking: - colchicine (a medicine to treat gout) - HIV/AIDS or hepatitis medicines (such as lopinavir, ritonavir or atazanavir) Participant enters “no” in the Web App.	Participant was not on a medicine at the time they took the TASS assessment but started a medicine subsequently, or the participant was prescribed a medicine but had no intention of taking the medicine.
Do not use if you are taking cyclosporine (a medicine for your immune system). The participant enters “no” into the Web App.	In the instance where the participant doesn’t realize that an eyedrop medicine they are using has cyclosporine, they may enter “no” into the Web App. A “no” response will be mitigated to correct because the low concentration and very low systemic absorption of cyclosporine from an eyedrop formulation will not significantly impact rosuvastatin exposure, and therefore not pose a risk to the participant.
Ask a doctor before use if you take: - colchicine (a medicine to treat gout)	Participant answers ‘yes’ in TASS to taking colchicine but Clinician determines they are not currently taking but had taken within 7 days of completing the TASS.

Label Reference	Rationale for Mitigation
Male 20-75 – Take 1 tablet every day Female 50-75 – Take 1 tablet every day Participant enters an age within 12 months of their correct age.	A Participant who enters an age within 12 months of their correct age will be mitigated to a correct response since the benefit risk profile of rosuvastatin will not be impacted.

Web App	Rationale for Mitigation
Are you currently taking a prescription medicine for high blood pressure (also known as “hypertension”)? Participant enters “no” into the Web App.	Participant was not on a BP medicine at the time they took the TASS assessment but started a BP medicine subsequently, or the participant was prescribed a BP medicine but had no intention of taking the medicine.
Do you smoke cigarettes? Participant enters “yes” into the Web App.	Participant says “yes” in the Web App to smoking cigarettes, but Clinician determines that participant only smokes e-cigarettes.

12 APPENDIX D - USE AND RE-SELECTION MITIGATIONS

Label Reference	Rationale for Mitigation
Pregnancy alert: Do not use if you are pregnant or breastfeeding. **If you become pregnant, stop taking and call your doctor.** Participant becomes pregnant during the study but does not stop taking the drug and/or does not call doctor.	Participant did not know they were pregnant while using the product.
Pregnancy alert: Do not use if you are pregnant or breastfeeding. If you become pregnant, stop taking and call your doctor. Participant enters “no” in the Web App but learns during the final visit that they were pregnant.	Participant did not know they were pregnant at the time they used the Web App.
Do not use if you had a heart attack, stroke, peripheral artery disease (PAD) or an operation or procedure on your heart. Participant enters “yes” in the Web App.	While the participant believes, based on their history, that they had one of these events, the CMOG physician determines that it was not a true event. The “yes” response will be mitigated to correct because the participant believed they were giving a correct response and their response was a conservative response, which results in them not qualifying for Crestor OTC. In this case, no medical harm can come to the participant based on this response.
Do not use if you are taking: - any cholesterol lowering and/or triglyceride lowering prescription medicine - cyclosporine (a medicine for your immune system) - warfarin/ COUMADIN® (a blood thinner) Ask a Doctor before use if you are taking: - colchicine (a medicine to treat gout) - HIV/AIDS or hepatitis medicines (such as lopinavir, ritonavir or atazanavir) Participant enters “no” in the Web App.	Participant was not on a medicine at the time they took the TASS assessment but started a medicine subsequently, or the participant was prescribed a medicine but had no intention of taking the medicine.
Do not use if you are taking cyclosporine (a medicine for your immune system). The participant enters “no” into the Web App.	In the instance where the participant doesn’t realize that an eyedrop medicine they are using has cyclosporine, they may enter “no” into the Web App. A “no” response will be mitigated to correct because the low concentration and very low systemic absorption of cyclosporine from an eyedrop formulation will not significantly impact rosuvastatin exposure, and therefore not pose a risk to the participant.

Label Reference	Rationale for Mitigation
Stop Use and Ask a Doctor if you: - get severe and unexplained muscle pain, tenderness or weakness - get symptoms of liver problems (upper belly pain, dark urine, yellowing of skin or whites of eyes)	While the participant believes, based on their history, that they had one of these events, the CMOG physician determines that it was not a true event. The "stop use" will be mitigated to correct because the participant believed they were taking the correct action and it was a conservative action, which results in them not continuing to take Crestor OTC. In this case, no medical harm can come to the participant based on this action.

Other	Rationale for Mitigation
Lost Opportunity	Clinician determines it was ok for someone to take the drug but based on responses in the Web App, participant got a "Do Not Use" (DNU) or "Ask a Doctor" (AAD). Participant decides to stop taking study medication and discontinues from the study, but clinician determines that they were "OK to Use".
Missing LDL-C Retests - Given consumers can only purchase non-prescription rosuvastatin through the Web App, we can stop shipping medication to individuals who fail to retest after a period of time agreed with FDA. Thus, for participants who qualify for treatment (i.e., have an "OK to Use" outcome or an "Ask a Doctor" outcome and indicates the doctor gave them permission to use the drug) but fail to obtain the necessary verified retest(s) (whether it is an initial retest or a second retest in those with an inadequate response), an *a priori* mitigation allowing these individuals to be mitigated to a "correct" response is appropriate. This mitigation can only be applied in situations where the CMOG's outcome was "coded" as "missing" because of a missing LDL-C value, and the CMOG's TASS outcome would have matched the Participant Outcome if not for the missing LDL-C retest.	1. CMOG final TASS assessment is "OK to Use" or "Ask a Doctor", but is coded as "Missing" because the participant failed to obtain a verified LDL-C retest or an SMT. 2. CMOG final TASS assessment is "OK to Use" but coded as "Missing" because the participant failed to retest and the SMT was an Inadequate Response, or the participant self-tested with a verified inadequate response result that was used for their Visit 2 reassessment. 3. Participant enters an initial Inadequate Response LDL-C retest into the Web App (verified or unverified), has an "OK to Use" outcome or "Ask a Doctor" outcome, indicates the doctor gave them permission to use the drug and makes a purchase. CMOG final TASS assessment is coded as "Missing" because only one or no verified LDL-C retest value was available for use, but otherwise would have matched the participant outcome. (Table XX, scenarios 1b, 2b, 3a, 3b, 4a, 4b, 7b, 9a, 9b)

13 APPENDIX E - LABORATORY AND BLOOD PRESSURE VARIABILITY ASSESSMENTS

10-year ASCVD Risk Score Assessment:

Total Cholesterol, HDL-C and SBP values are used to calculate a 10-year ASCVD risk score, which is part of the initial TASS assessment to determine initial treatment eligibility. Since participants will only be eligible for treatment if their 10-year ASCVD risk score is 5% to <20%, no participant at Virtual Visit 1 will have a 10-year ASCVD risk score outside of this range with the exception of diabetics. A diabetic was required to have an ASCVD risk score of 0% to <20%. When using verified laboratory and BP data that is different from the data the participant entered into the Web App, the 10-year ASCVD risk score generated by the CMOG is highly likely to differ from the value generated by the participant. For the purpose of evaluating the first co-primary endpoint of the AUS, if the CMOG's initial TASS outcome is "Do Not Use" because the CMOG's 10-year ASCVD risk score is <5% or >20%, and no other "Do Not Use" warnings were identified, the participant's 10-year ASCVD risk score will be considered acceptable if the CMOG ASCVD risk score is 4% or greater. Diabetics are excluded from this variability assessment as 0% to <5% ASCVD risk score is acceptable. The rationale for not imposing an upper risk level is that all participants with a risk >5% are potential candidates for statin therapy. The only participants who should not be treated are those for whom the clinicians' assessments indicate they are too low risk. The lower risk for acceptability was set at >4% to account for variations in laboratory or blood pressure data that lead to a risk score slightly lower than 5%.

REF Assessment:

A REF is generated from the laboratory or BP values if one of the following criteria are met:

- TG and LDL-C REF criteria:

Lab	Values for a REF
TG	≥175 mg/dL
LDL-C	≥160 mg/dL
hs-CRP	≥2.0 mg/L

- Metabolic syndrome is also a potential REF and requires the laboratory and BP values to reach pre-specified thresholds. To obtain a REF for metabolic syndrome, 3 out of 4 of the following criteria need to be met:

Criteria (3 out of 4 must be met)	Value
Low HDL-C	Males: 20-39 mg/dL Females: 20-49 mg/dL
Elevated Triglycerides	150 - 174 mg/dL
Elevated Blood Pressure	Systolic blood pressure 130-180mmHg* OR Diastolic 85-120mmHg* OR Use of blood pressure medications ("yes")
Increased waist circumference	Males 40" and greater or Females 35" and greater - The waist circumference input is a yes/no response

*If SBP is 130-180mmHg AND DBP is 85-120mmHg, this only counts as a 1 of the 3 flags required to trigger a REF (not 2 separate flags).

The 2018 Cholesterol Treatment Guidelines outlines the different REFs and how they should be used when making treatment decisions. As previously stated, the laboratory and BP variability criteria for REFs will only be applied if the participant and CMOG initial TASS outcomes are different. Since the participant is only eligible for treatment following a "OK to Use" or "Ask a Doctor" (and indicated a doctor said it was okay to proceed) initial TASS outcome, this would require the CMOG to obtain a "Do Not Use" initial TASS outcome because of the lack of the REF generated by the participant. If this occurs, the variability criteria will be applied to the CMOG laboratory or BP value that generated a REF for the participant. If application of the variability criteria results in the laboratory or BP value meeting the REF criteria, the participant's REF will be considered acceptable.

Treatment Range Assessment:

Predefined laboratory and BP treatment ranges are part of the TASS assessment. The following values will result in a "Do Not Use" outcome by the TASS Tool:

Laboratory Parameter	Values for "Do Not Use" Outcome
TC	<130 or >320
TG	≥500
LDL – Male age 20-39	<160 or ≥190
LDL - Male age ≥40 to ≤75 Female age <50 or >75	<70 or ≥190
HDL	<20 or >100
SBP	<90 or >180
DBP	<50 or >120

Should the CMOG get a "Do Not Use" initial TASS outcome because a lab value was "out-of-range," the variability criteria will be applied to the "out-of-range" value(s). If the variability criteria result in a value within the appropriate treatment range, it will be considered acceptable.

The following reference was used to establish the acceptable level of variability between the laboratory parameters (Contois JH, et.al. Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurements; Journal of Clinical Lipidology (2011) 5, 264–272.[11]) for the evaluation of REFs and Range differences within the outcome assessments. The values were based on The National Cholesterol Education Program (NCEP) analytical performance goals for these tests.

Laboratory Parameter	Acceptable Level of Variability for Laboratory Values
Total Cholesterol	≤9%
Triglycerides	≤15%
LDL-C	≤12%
HDL-C	≤13%

No variability criterion will be applied for hs-CRP results.

Multiple factors can contribute to variability in these laboratory measurements over time. Examples include changes in diet, the time of day the sample was taken, whether the individual was fasting or non-fasting, and the laboratory or person performing the analysis. However, because of the difficulty in trying to account for these factors in addition to the analytical factors in the assessment of variability, we will rely solely on the analytical variability.

The acceptable variability for blood pressure measurements is more difficult to ascertain based on a review of the literature. Important factors that could impact variability include the timing of the BP measurement because of the circadian variability in BP, the use of a different device for the participant's inputted BP versus the clinical sites inputted BP, and operator variability when using manual devices. In light of these factors and taking into account that a normal circadian change is BP over the course of 24 hours could be 10% to 20%, we set the acceptable variability for BP at 15%.

Laboratory Parameter	Acceptable Level of Variability for Blood Pressure Values
Systolic Blood Pressure	≤15%
Diastolic Blood Pressure	≤15%

Procedure for Applying Laboratory and Blood Pressure Variability Criteria for Evaluation of the Overall Correct Initial TASS Outcome

If the participant and CMOG initial TASS outcomes agree, the laboratory and blood pressure variability is acceptable. If the initial TASS outcomes do not agree, it will be assessed whether this is due to laboratory or blood pressure variability using the following approach:

1. Assess whether the difference in initial TASS outcomes is due solely to a CMOG laboratory or blood pressure value being out-of-range. If this is true, the variability criteria will be applied to the CMOG laboratory or BP value to determine if the variability results in a value in the treatment range.

    a. If the established variability is within treatment range, then the CMOG value is acceptable.

    b. If the established variability is outside the treatment range, then the CMOG value is not acceptable.

2. Assess whether the difference in initial TASS outcomes is due solely to the CMOG 10-year ASCVD score being out of range. If this is true, apply the variability criteria to the CMOG 10-year risk score.

    a. If the ASCVD risk score is within the designated range, then the CMOG total cholesterol, HDL-C and SBP values are acceptable.

    b. If the ASCVD risk score is outside the designated range, then the CMOG total cholesterol, HDL-C and SBP are not acceptable.

3. Assess whether the difference in initial TASS outcomes is due solely to the CMOG laboratory or blood pressure data not generating a REF. If this is true, apply variability criteria to the CMOG laboratory or BP value to determine if the REF is generated.

    a. If REF generated, then the CMOG values are acceptable.

    b. If REF not generated, then the CMOG values are not acceptable.

14 APPENDIX F – IMPUTATION OF MISSING KEY DATES FROM THE TARGETED MEDICAL AND MEDICATION HISTORY FORM.

Scenarios	Day of Event [1]	Date Stopped Medication [2]	Date Spoke to the Doctor [2]	Imputation
Missing Date for Day Action Taken (Stopped Medication or Spoke to Doctor)	Yes	Only Month and Year	Yes	Date Stopped Medication imputed as the date halfway between date of the event and the end of the month
	Yes	Only Month and Year	Only Year	Date Stopped Medication imputed as the date halfway between date of the event and the end of the month. No imputation for Date Spoke to Doctor
	Yes	Only Year	Yes	No imputation for Date Stopped Medication
	Yes	Yes	Only Month and Year	Date Spoke to Doctor imputed as the date halfway between date of the event and the end of the month
	Yes	Yes	Only Year	No imputation for Date Spoke to Doctor
	Yes	Only Month and Year	Only Month and Year	Date Stopped Medication imputed as the date halfway between date of the event and the end of the month. Date Spoke to Doctor imputed as the date halfway between date of the event and the end of the month
	Yes	Only Year	Only Month and Year	No imputation for Date Stopped Medication Date Spoke to Doctor imputed as the date halfway between date of the event and the end of the month
	Yes	Only Year	Only Year	No imputation for Date Stopped Medication No imputation for Date Spoke to Doctor
Missing Date of the Event	Only Month and Year	Yes	Yes	Date of Event imputed as the date halfway between the beginning of the month and earliest date of action (i.e., earliest of the date medication stopped or spoke to doctor)
	Only Month and Year	Only Month and Year	Yes	Date of Event imputed as the date halfway between the beginning of the month and the date spoke to doctor. Date Stopped Medication imputed as the date halfway between date of

Scenarios	Day of Event [1]	Date Stopped Medication [2]	Date Spoke to the Doctor [2]	Imputation
				the event and the end of the month.
	Only Month and Year	Yes	Only Month and Year	Date of Event imputed as the date halfway between the beginning of the month and the date medication stopped. Date Spoke to Doctor imputed as the date halfway between date of the event and the end of the month
	Only Month and Year	Only Month and Year	Only Month and Year	Date of Event imputed as beginning of the month. Date of each action imputed as end of the month.
	Only Year	Yes	Yes	No imputation for Date of Event
	Only Year	Yes	Only Month and Year	No imputation for Date of Event Date Spoke to Doctor imputed as the date halfway between date of the stopped medication and the end of the month
	Only Year	Only Month and Year	Yes	No imputation for Date of Event Date Stopped Medication imputed as the date halfway between date of spoke to doctor and the end of the month.

[1] Event dates will be obtained from the Targeted Medical and Medication History Form or from the AE form of the respective AE. AE dates will be start dates of the event.
[2] Action dates only imputed if the participant took the respective action.

15 APPENDIX G - SCENARIOS FOR LDL-C VALUES AND INCLUSION OF VALUES IN PROPOSED ANALYSES OF LDL-C

Scenario	Primary LDL-C Analysis	Sensitivity Analyses			
		#1	#2	#3	#4
*An LDL-C retest will be performed at Visit 2 and used for this analysis. ^ Missing LDL-C value will be imputed according to missing data imputation method.					
"OK to Use" Outcome Scenarios					
1. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) and has entered an LDL-C value into the Web App during a reorder assessment verified by source document for Visit 2	X	X	X	X	X
2. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) and has entered an LDL-C value into the Web App during a reorder assessment **NOT** verified by source document for Visit 2	X*	X*	X*	X*	X
3. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) with an *inadequate* LDL-C response value entered into the Web App during an early reorder assessment but at a subsequent reorder assessment enters an adequate LDL-C response value into the Web App verified by source document for Visit 2	X	X	X	X	X
4. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) with an *inadequate* LDL-C response value entered into the Web App verified by source document for Visit 2	X	X	X	X	X
5. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) with a single *inadequate* LDL-C response value entered into the Web App **NOT** verified by source document for Visit 2	X*	X*	X*	X*	X
6. Completes 6-month trial with an "OK to Use" outcome (based on participant's outcome) and has **NOT** entered an LDL-C value into the Web App during a reorder assessment	X*	X*	X*	X*	-
7. Has an "OK to Use" outcome with an LDL-C value entered into the Web App during an early reorder assessment verified by source document for Visit 2, but at a later reorder gets a "Do Not Use" or "Ask a Doctor" outcome	X	-	X	X	X
8. Has an "OK to Use" outcome with an LDL-C value entered into the Web App during an early reorder assessment verified by source document for Visit 2, and subsequently	X	-	X	X	X

Scenario	Primary LDL-C Analysis	Sensitivity Analyses			
		#1	#2	#3	#4
*An LDL-C retest will be performed at Visit 2 and used for this analysis. ^ Missing LDL-C value will be imputed according to missing data imputation method.					
withdraws from trial prior to study completion 9. Has an "OK to Use" outcome with an LDL-C value entered into the Web App during an early reorder assessment **NOT** verified by source document for Visit 2 and subsequently withdraws from trial prior to study completion	-	-	X^	X	X
10. Has an "OK to Use" outcome with an LDL-C value entered into the Web App during an early reorder assessment **NOT** verified by source document for Visit 2, but at a later reorder gets a "Do Not Use" or "Ask a Doctor" outcome	-	-	X^	X	X
11. Has an "OK to Use" outcome with an LDL-C value entered into the Web App during an early reorder assessment **NOT** verified by source document for Visit 2 and refuses a study mandated retest at Visit 2	-	-	X^	X	X
12. Has "OK to Use" outcome without an LDL-C value entered into the Web App during an early reorder assessment, but gets a "Do Not Use" or "Ask a Doctor" outcome at a subsequent reorder assessment	-	-	X^	-	-
13. Has "OK to Use" outcome without an LDL-C value entered into the Web App during an early reorder assessment and subsequently withdraws from trial prior to study completion	-	-	X^	-	-
"Do Not Use" Outcome Scenarios 1. Has "Do Not Use" outcome with an LDL-C value entered into the Web App during a reorder assessment verified by source document for Visit 2	X	-	X	X	X
2. Has "Do Not Use" outcome with an LDL-C value entered into the Web App during a reorder assessment verified by source document for Visit 2 and subsequently withdraws from the trial prior to study completion	X	-	X	X	X
3. Has "Do Not Use" outcome with an LDL-C value entered into the Web App during a reorder assessment **NOT** verified by source document for Visit 2 and subsequently withdraws from the trial prior to study completion	-	-	X^	X	X
4. Has "Do Not Use" outcome without an LDL-C value entered into the Web App during a reorder assessment	-	-	X^	-	-
5. Has "Do Not Use" outcome without an LDL-C value entered into the Web App during a	-	-	X^	-	-

Scenario	Primary LDL-C Analysis	Sensitivity Analyses			
		#1	#2	#3	#4
*An LDL-C retest will be performed at Visit 2 and used for this analysis. ^ Missing LDL-C value will be imputed according to missing data imputation method.					
reorder assessment and subsequently withdraws from the trial prior to study completion					
"Ask a Doctor" Outcome Scenarios					
1. Has an "Ask a Doctor" outcome with an LDL-C value entered into the Web App at the 6-month final use assessment verified by source document for Visit 2	X	X	X	X	X
2. Has an "Ask a Doctor" outcome with an LDL-C value entered into the Web App at the 6-month final use assessment **NOT** verified by source document for Visit 2	X*	X*	X*	X*	X
3. Has "Ask a Doctor" outcome (participant indicates doctor gave permission to use drug) with an LDL-C value entered into the Web App during a reorder assessment verified by source document for Visit 2 and completes the 6-month trial	X	X	X	X	X
4. Has an "Ask a Doctor" outcome without an LDL-C value entered into the Web App at the 6-month final use assessment	X*	X*	X*	X*	-
5. Has "Ask a Doctor" outcome (participant indicates doctor gave permission to use drug) without an LDL-C value entered into the Web App during a reorder assessment and completes the 6-month trial	X*	X*	X*	X*	-
6. Has "Ask a Doctor" outcome (participant does not indicate doctor gave permission to use drug) with an LDL-C value entered into the Web App during a reorder assessment verified by source document for Visit 2	X	-	X	X	X
7. Has "Ask a doctor" outcome with an LDL-C value entered into the Web App during a reorder assessment verified by source document for Visit 2 and subsequently withdraws from the trial prior to study completion (regardless of whether or not participant had indicated doctor gave permission to use drug)	X	-	X	X	X
8. Has "Ask a doctor" outcome with an LDL-C value entered into the Web App **NOT** verified by source document for Visit 2 during a reorder assessment and subsequently withdraws from the trial prior to study completion (regardless of whether or not participant had indicated doctor gave permission to use drug)	-	-	X^	X	X
9. Has an "Ask a Doctor" outcome with an LDL-	-	-	X^	X	X

Scenario	Primary LDL-C Analysis	Sensitivity Analyses			
		#1	#2	#3	#4
*An LDL-C retest will be performed at Visit 2 and used for this analysis. ^ Missing LDL-C value will be imputed according to missing data imputation method.					
C value entered into the Web App at the 6-month final use assessment **NOT** verified by source document for Visit 2 and refuses a study mandated retest at Visit 2					
10. Has an "Ask a Doctor" outcome without an LDL-C value entered into the Web App at the 6-month final use assessment and refuses a study mandated retest at Visit 2	-	-	X^	-	-
11. Has "Ask a Doctor" outcome (participant indicates doctor gave permission to use drug) without an LDL-C value entered into the Web App during a reorder assessment and completes the 6-month trial and refuses a study mandated retest at Visit 2	-	-	X^	-	-
12. Has "Ask a Doctor" outcome (participant does not indicate doctor gave permission to use drug) without an LDL-C value entered into the Web App during a reorder assessment	-	-	X^	-	-
13. Has "Ask a doctor" outcome without an LDL-C value entered into the Web App during a reorder assessment and subsequently withdraws from the trial prior to study completion (regardless of whether or not participant had indicated doctor gave permission to use drug)	-	-	X^	-	-