Clinical Study Protocol	
Study Intervention	5 mg Rosuvastatin with a Web App (Combination Product)
Study Code	D356PL00015
Version	8.0
Date	14Sep2022

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

Sponsor Name: AstraZeneca Pharmaceuticals LP

Legal Registered Address: 1800 Concord Pike, Wilmington, DE 19805

Web App Manufacturer: Idea Evolver

Legal Registered Address: 53 Bridge Street, Suite 302, Brooklyn, NY 11201
Regulatory Agency Identifier Number(s): IND 124210

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D356PL00015

Amendment Number: Amendment 7

Study Intervention: Rosuvastatin calcium 5 mg and Web App

Study Phase: Phase III Self-selection and Actual Use for Rx-to-OTC Switch

Short Title: Technology-Assisted Consumer Trial in Cholesterol (TACTiC)

Medical Monitor Name and Contact Information will be provided separately Central Principal Investigator

PPD

National Study Chairman

PPD

CLINICAL STUDY PROTOCOL AGREEMENT

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

PROTOCOL #20030/ D356PL00015
Date: 14Dec2022

The signatures below of the Concentrics Research representative and the representatives of the Sponsor constitute their respective approvals of this protocol and provide the necessary assurances that this study will be conducted as stated in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that survey data and other pertinent data will become the property of AstraZeneca Pharmaceuticals, L.P. (AZ).

PPD

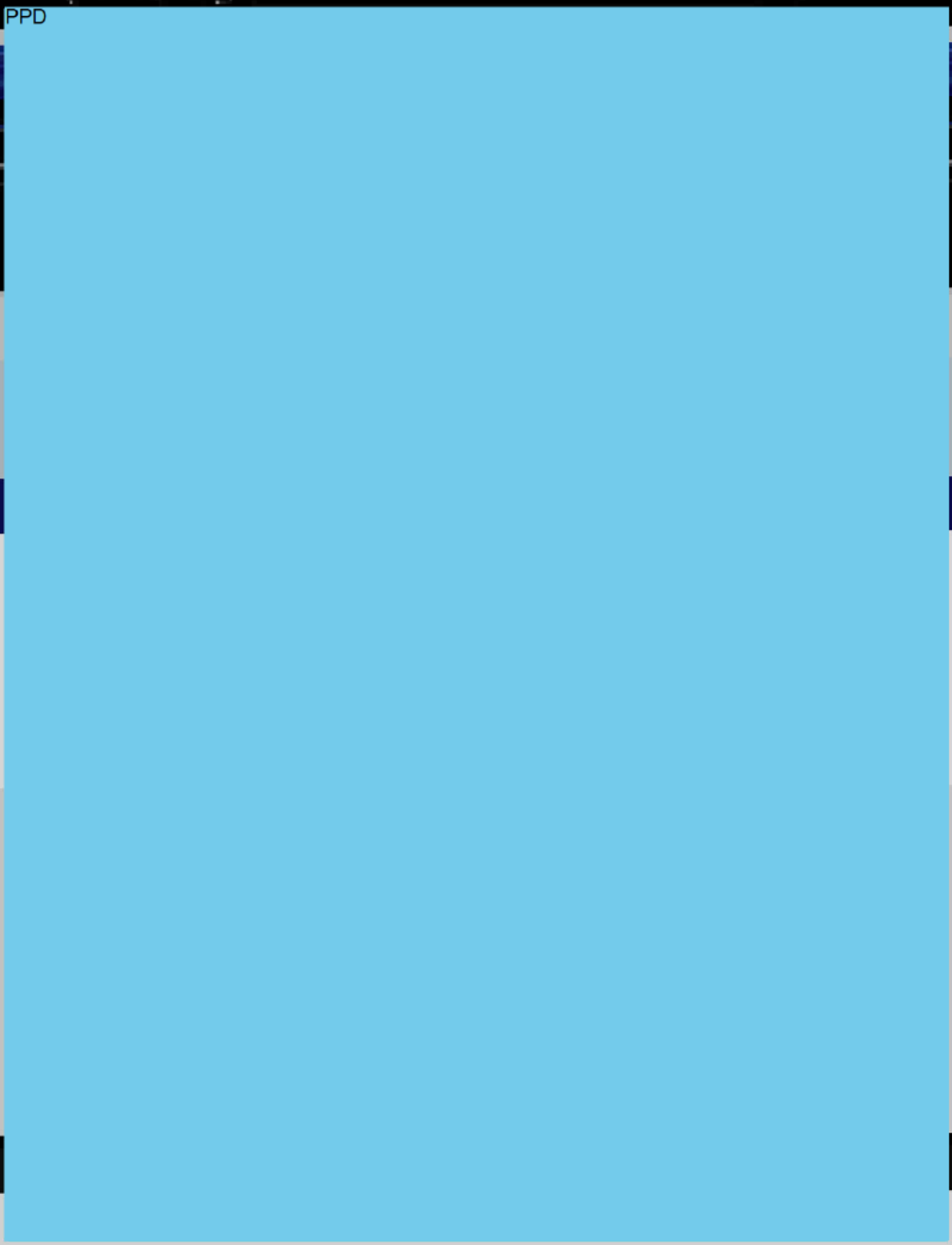

PPD

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase III, 6-Month Self-Selection and Actual Use Study for Rx-to-OTC Switch of rosuvastatin 5 mg Once-daily

Short Title: Technology-Assisted Cholesterol Trial in Consumers (TACTiC)

Rationale: For over a century, heart disease has remained the leading cause of death for both men and women in the United States and worldwide (Mercado et al 2015). Elevated cholesterol is a key risk factor for heart disease, and while lowering cholesterol with statin drugs reduces cardiovascular morbidity and mortality, only about half of the people in the United States who require therapy are currently treated (Mercado et al 2015). This represents a substantial public health issue for the United States. While there are numerous reasons why people are not treated, what is clear is that easier access to safe, effective, and affordable therapy would have a significant positive impact on public health. One way to simplify access to statin therapy would be to make it available to consumers without a prescription (e.g., Over-the-Counter [OTC]). Past attempts to achieve an OTC switch for statin treatment have failed due to concerns about the efficacy of the statins tested, and because consumers were unable to properly self-select. The Crestor OTC program addresses these concerns by using Crestor 5 mg (a safe and highly effective dose of rosuvastatin with minimal interactions [AstraZeneca Pharmaceuticals LP 2021]) with a Web App that features a Technology-Assisted Self-Selection (TASS) tool. The TASS tool ensures the medicine is only made available to consumers for whom it is safe and appropriate. Completed studies testing Drug Facts Label (DFL) comprehension, Consumer Information Leaflet (CIL) comprehension, Web App comprehension, Human Factors, Targeted Self-Selection, and All-comers Self-Selection have shown that this approach is viable. Based on the positive results from these pivotal studies, AstraZeneca is ready to proceed with the Actual Use Study (AUS).

Purpose: The purpose of this AUS is to evaluate the extent to which participants can safely and effectively self-select, purchase, and use Crestor OTC 5 mg for a 6-month period according to the label. Integral to these evaluations will be the ability of participants to correctly enter their health information into the Web App.

Objective and Endpoints

Objectives	Endpoints
Primary	
• Evaluate *initial* 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	• Percentage of participants with an Overall Correct (correct + mitigated) Initial TASS Outcome at the initial self-selection (Threshold: 85% lower bound [LB])
• Evaluate that participants are properly using nonprescription 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 TASS outcome or through the medical and medication history in those participants who fail to complete a final TASS use assessment	• Percentage of participants with an Overall Correct (correct + mitigated) Final Use Outcome at the final use assessment (Threshold: 85% lower bound [LB])
• Effectiveness in lowering LDL-C in participants regardless of final use outcome	• Percent change from baseline in verified LDL-C to Visit 2 (Threshold: -15% upper bound [UB], -20% point estimate)
Secondary	
• Compliance with cholesterol retesting within 6 months	• Cholesterol retest within 6 months of starting medication (that was verified at Visit 2, not including study mandated tests) by at least 60% of participants who are eligible for continuous treatment
• Compliance with "Stop Use" warnings	• Percentage of participants who correctly self-identify as having a "Stop Use" warning and stop medication
• Compliance with "Do Not Use" warnings	• Percentage of participants who correctly self-identify as having a "Do Not Use" warning at the final use assessment

Objectives	Endpoints
• Compliance with "Ask a Doctor Before Use" warnings	• Percentage of participants who correctly self- identify as having an "Ask a Doctor Before Use" warning at the final use assessment
• Compliance with Continuous Dosing	• Percentage of participants with overall compliance between 50% and 120% as determined by pill count (Threshold: point estimate ≥ 50%) • Percentage of participants with longitudinal compliance between 50% and 120% across all supply periods as determined using eDiary data (Threshold: point estimate ≥ 50%) • Percentage of participants who were persistent as determined by reorder data from the Web App (Threshold: point estimate ≥ 50%)
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
• CCI	

Objectives	Endpoints
	CCI
[redacted]	[redacted]

Overall Design

This is a 6-month, single-arm, technology-assisted Self-Selection and Actual Use Study to evaluate the use of rosuvastatin 5 mg in combination with a Web App; there is no comparator or control drug. The study will be conducted in a population of all-comers comprised of interested subjects who respond to an ad for a study about lowering cholesterol, complete pre-screening procedures, and complete a Web App that features a TASS tool. The TASS tool is medical device software that incorporates an algorithm based on the American Heart Association (AHA)/American College of Cardiology (ACC) cardiovascular risk calculator, the 2018 Guideline on the Management of Blood Cholesterol (Grundy et al 2018) and the Crestor OTC DFL in order to determine if a consumer would qualify for treatment with nonprescription rosuvastatin calcium, a moderate-intensity statin therapy.

Subjects are eligible to purchase nonprescription rosuvastatin calcium if they meet the requirements for safe use according to the DFL, 2018 Cholesterol Treatment Guidelines (Grundy et al 2018) and have an appropriate atherosclerotic cardiovascular disease (ASCVD) risk score.

Subjects who have a "Do Not Use" outcome or an "Ask a Doctor" outcome and do not confirm within the Web App that they spoke to a doctor will not be permitted into the home use phase of the study. CCI [redacted]

The TACTiC study will be conducted in 30-50 markets throughout the United States. All visits will be completed utilizing virtual methods such as virtual visits conducted by the Central Medical Operations Group (CMOG) study staff. The CMOG is comprised of clinicians that include registered nurses, nurse practitioners, physician assistants and medical doctors. There will be a Virtual Visit 1, 60-day and 120-day phone calls, a Virtual Visit 2 and a 30-day follow-up phone call post-study drug discontinuation to assess participants status with regard to adverse events (AEs).

Inclusion Criteria

1 Males, 20-75 years of age

2 Females, 20-75 years of age (This inclusion criterion will be applied until 50 females under the age of 50 years complete the initial TASS assessment in the Web App. After this quota of 50 females under the age of 50 years old is met, the inclusion criterion will be revised to females 50-75 years old).

3 Respond to advertising regarding a concern about high cholesterol or heart health

4 Able to read speak and understand English

Additional Criteria for Inclusion for Actual Use (at Virtual Visit 1)

1 Participant reads and signs the Informed Consent form.

Exclusion Criteria

1 The participant or anyone in their household is currently employed by any of the following:
   - A pharmacy or pharmaceutical company
   - A consumer healthcare company
   - A manufacturer of medicines
   - A managed care or health insurance company
   - A healthcare practice
   - An employee of AstraZeneca or Concentrics Research

2 The participant has ever been trained or employed as a healthcare professional (physician, nurse, nurse practitioner, physician assistant, pharmacist).

3 The participant has, or cannot recall whether he/she has, received an investigational therapy as part of a clinical trial in the previous twelve (12) months.

4 The participant is not willing to provide contact information.

5 Previous enrollment in the present study.

6 The participant has a mailing address in Alaska, or their mailing address is a Post Office (PO) Box.

7 The participant is not willing to complete an eDiary.

8 The participant is a woman of childbearing potential and is not following contraception guidelines or is not willing to follow contraception guidelines including practicing abstinence or using at least 1 of the following acceptable methods of birth control for at least 1 month prior to entry into the study and for 1 month after study completion: hormonal – oral, implantable, injectable, or transdermal; mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device; or surgical sterilization of partner.

9 The participant does not have access to the internet.

10 The participant does not have an email address or the ability to receive emails.

11 The participant responds to the Single Item Literacy Screener 2 (SILS2) question (Chew et al 2008), "How confident are you filling out medical forms by yourself?", with either 'extremely' or 'quite a bit.' (If the quota for normal literacy is met, but the limited literacy target is not met, the SILS2 exclusion will be used to help increase the percentage of limited literacy participants at Virtual Visit 1. Participants identified as normal literacy by Rapid Estimate of Adult Literacy in Medicine [REALM] testing at Virtual Visit 1 will not be excluded from entry into the treatment phase of the study.)

12 Inability to conduct interviews in a private location so that sensitive information about the participant or study would not be overheard by others not permitted to hear such information.

Additional Criteria for Exclusion from Actual Use (at Virtual Visit 1)

Confirmation by Concentrics Central Medical Operations Group (CMOG) clinician:

1 That the participant is pregnant, as determined by an approved self-administered OTC urine pregnancy test (UPT) conducted for all female participants of childbearing potential (Female participants who are not post-menopausal or surgically sterile).

2 That the participant is breastfeeding.

3 That the participant has an allergy to rosuvastatin.

Disclosure Statement: This is a 6-month, single-arm, uncontrolled technology-assisted self-selection and actual use study to evaluate the use of rosuvastatin 5 mg in combination with a Web App.

Number of Participants:

The target for this study is at least 500 evaluable participants with a goal to have 100 of limited literacy. 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. The table below summarizes the estimates and percentage drops at each step from the initial call into the Call Center through completion of the study.

Calls into Call Center	Estimated 80,000 calls
Sent the Web Link Assumes: Pre-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

Note: "Enrolled" is defined as a participant's agreement to participate in a clinical study following completion of the informed consent form (ICF) process. Subjects who are pre-screened for the purpose of determining eligibility for the study but do not sign consent, are defined as "pre-screen failures." See Section 9.3 for further detail on the definition of pre-screen and screen failures.

Intervention Groups and Duration: This is a single-arm, uncontrolled Actual Use Study. The total duration of participation is approximately 7-8 months which includes a 4-week window to use the Web App at home and complete Virtual Visit 1, 6 months for the home use period, completion of a Virtual Visit 2 after the use period, and a 30-day follow-up phone call. The protocol does not call for dose adjustments to be made by investigators or participants.

This study will evaluate self-selection and actual use including compliance with label warnings and directions. The dose is a 5 mg tablet once a day.

Data Monitoring Committee: No

Statistical Methods: The first two co-primary analyses will evaluate the percentage of participants who achieved an Overall Correct Initial TASS Outcome at initial self-selection (SS Population) and an Overall Correct Final Use Outcome at the final use assessment (Per Protocol population). For these evaluations, the outcomes obtained by the participant will be compared to the outcomes obtained by the CMOG clinician. The SS Population includes all participants who sign the ICF. The Per Protocol population includes all participants in the AUS ITT population who complete a Virtual Visit 2 and participants who have discontinued but have sufficient medical and medication history information and, when necessary, a verified low-density lipoprotein-cholesterol (LDL-C) collected prior to stopping the study to determine a final use outcome. The third co-primary analysis will evaluate percent change from baseline (PCFB) in verified LDL- C values to Visit 2 in participants regardless of their final use outcome.

There are three co-primary endpoints:

1 Percentage of participants with an Overall Correct (correct + mitigated) Initial TASS Outcome at the initial self-selection (Threshold: 85% lower bound [LB]).
2 Percentage of participants with an Overall Correct (correct + mitigated) Final Use Outcome at the final use assessment (Threshold: 85% [LB]).
3 Percent change from baseline in verified LDL-C to Visit 2 (Threshold: -15% upper bound [UB], -20% point estimate).

The sample size is based on powering the study for the co-primary endpoints. 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 LB of the 95% exact binomial confidence interval (CI) is greater than 85% with a sample of 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%

Evaluation of the second co-primary endpoint on the Overall Correct Final Use Outcome will have a sample size of at least 500 participants. A sample of 500 participants would provide at least 90% power to demonstrate that the lower bound of the 95% exact binomial CI is greater than 85% for the final use endpoint, assuming that the true correct final use outcome rate is 90%.

For each of the two co-primary endpoints assessing Overall Correct Initial TASS Outcome and Overall Correct Final Use Outcome, the following hypothesis will be evaluated:

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

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) CI is greater than 85%.

For the third co-primary endpoint, the PCFB in verified LDL-C values to Visit 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. 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: $\mu \geq -15\%$ 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%.

1.2 Schema

Figure 1 Study Design

Pre-screen Phone Call or Online Pre-screener	**Self-selection Web App (Remote Completion)**	**Virtual Visit 1 Enrollment**	**Home Use Period Study Drug Delivery**	**Phone Call**	**Phone Call**	**Virtual Visit 2 Final Visit**	**30-Day Post Use Phone Call**
Day -30 (+14)			**Day 0**	**Day 60 (+/- 7)**	**Day 120 (+/- 7)**	**Day 180 (-7 / +14)**	**Day 210 [or 30 days after study drug discontinuation] (+14 days)**

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedures	Pre-screen Phone Call or Online Pre-screener	Self-selection	Virtual Visit 1	Home Use Period			Virtual Visit 2	30-day Post Use
		Web App (Remote Completion)	Enrollment	Drug Delivery	Phone Call[g]	Phone Call[g]	Final Visit	Phone Call
	Day -30			Day 0	Day 60	Day 120	Day 180	Day 210 or 30 days after study drug discontinuation
Visit Window	+14[k]				± 7	± 7	- 7/+14	+14
Advertising (Traditional/Digital)	X							
Subject completes pre-screening[l] • Inclusion/Exclusion • Demographics • SILS2 • Privacy Acknowledgment • Study Overview • Email Link to those who qualify	X							
Subject completes Web App: • DNU = terminate • AADBU = if not OK to Use, terminate • AADBU = if OK to Use, continue • OK to Use = continue		X						
Initial purchase of drug[a]		X						
Subject contacts Call Center to schedule Virtual Visit 1		X						
Participant completes Virtual Visit 1			X					
ID check			X					
Central Assessor confirms verified diagnostic numbers if available (TC, HDL-C, LDL-C, TG, BP, hs-CRP, CAC score, and waist circumference as applicable)[b]			X				X[h]	

Procedures	Pre-screen Phone Call or Online Pre-screener	Self-selection	Virtual Visit 1	Home Use Period			Virtual Visit 2	30-day Post Use
		Web App (Remote Completion)	Enrollment	Drug Delivery	Phone Call[g]	Phone Call[g]	Final Visit	Phone Call
	Day -30			Day 0	Day 60	Day 120	Day 180	Day 210 or 30 days after study drug discontinuation
Visit Window	+ 14[k]				± 7	± 7	- 7/+14	+14
Local testing site, home test kit, and/or home BP monitor, if no verified numbers are available (TC, HDL-C, LDL-C, TG, BP, hs-CRP)[b]. Visit to be rescheduled if verified numbers are not provided.			X				X[h]	
Electronic informed consent			X					
Urine pregnancy test for women of childbearing potential[m]			X				X	
REALM Test			X					
CMOG conducts targeted medical and medication history[c]			X					
Hold on Order is released, and drug is shipped to participant			X					
Study Instructions			X					
eDiary Instructions			X					
AE reporting			X		X	X	X	X
Reorder[d]				←	—	→		
Participant completes Virtual Visit 2							X	
Central Assessor confirms verified LDL-C. Visit to be rescheduled if verified numbers are not provided.							X	
Participant completes final TASS assessment[e]							X	
Confirm medical and medication history changes[c]							X	
Diary review for AEs[f]					X	X	X	
Follow-up on incorrect TASS entries and use			X[i]				X[j]	
Drug Accountability							X	

[a] Drug will not be shipped until "OK to Use" participant completes Virtual Visit 1 and they are confirmed to enter Home Use Period.

[b] Lab and BP results must be within 12 months (+3 month window) of completing the Web App and be able to identify name of participant in order to be considered verified for Virtual Visit 1. If participant does not have verified lab test, they will be sent for study mandated testing prior to completing Virtual Visit 1 which will then be considered as verified source. LDL-C results must NOT be prior to Crestor OTC start date for Virtual Visit 2. For participants who withdraw, discontinue from study intervention or those who received a "Do Not Use" outcome or an "Ask a Doctor" outcome and never confirmed they spoke to a doctor, study mandated testing will not be performed. For males age 20 to 39, a source verified blood pressure (BP) will not be required since BP does not factor into the use assessment based on current guidelines.

[c] Once the medical assessment is complete; the CMOG clinician will use the data obtained in the medical assessment and then input that data into the Web App.

[d] Reorders shipped to participant if approved for dispensing through TASS reorder assessment in Web App.

[e] Only participants who, at their last order, received an "OK to Use" or "Ask a Doctor" (and indicated the doctor said it was OK to Use Crestor) will complete a TASS final use assessment at Virtual Visit 2.

[f] The diary will be reviewed by the CMOG for AEs at the day 60 and day 120 phone call and at the Virtual Visit 2. The diary will be used to record when the participant took study drug, if they have changes to any medications, and if they have any changes in health status. The diary will also be used for the participant to record the unique bottle ID number to confirm receipt of delivery of the study drug.

[g] Interim phones calls consist of a telephone status check on participants to assess any changes in health and/or medications as well as any additional study-related issues. At approximately Day 165, the participant's Virtual Visit 2 will also be scheduled.

[h] The only lab value verified at the Final Virtual Visit is LDL-C.

[i] Follow-up probes to understand the rationale for any discrepancies between the participant and CMOG TASS entries will be asked of any TASS question that is only asked at initial self-selection assessment as well as participants who do not meet the criteria for proceeding into the use portion of the study at Virtual Visit 1.

[j] Follow-up probes to understand the rationale for any discrepancies between participant and CMOG TASS entries will be asked for all final use assessments as well as any remaining discrepancies from the initial self-selection assessment that were not asked at Virtual Visit 1.

[k] Note that +14-day visit window extends the 30-day period (to 44 total days) and includes participant completion of the Pre-screen phone call, self-selection, and Virtual Visit 1.

[l] Subjects will either call the Call Center for pre-screening or an online pre-screener will also be available. If the online pre-screener is completed and the subject qualifies, they will be directed to call the Call Center or the Call Center will initiate an outbound call to provide the email link.

[m] If at Virtual Visit 1 or Virtual Visit 2, the pregnancy test has an inconclusive result, the participant will be rescheduled in 2 to 4 weeks at which time the urine pregnancy test will be repeated.

2 INTRODUCTION

Crestor 5 mg is a safe and highly effective moderate-intensity dose of rosuvastatin calcium to lower cholesterol, one of the key risk factors that can lead to heart disease.

2.1 Study Rationale

The partial switch of Crestor 5 mg would represent the first statin product available without a prescription to lower cholesterol in consumers who have a moderate risk of heart disease.

The Over-the-Counter (OTC) availability of Crestor 5 mg would provide an important new option to self-treat high cholesterol.

This pivotal Self-Selection (SS) and Actual Use Study (AUS) is intended to evaluate the use of rosuvastatin 5 mg in combination with a Software as a Medical Device (SaMD) (Web App that features a Technology-Assisted Self-Selection [TASS] tool). Specifically, the extent to which participants can safely and effectively self-select, purchase, and follow a 6-month regimen of Crestor 5 mg according to the Drug Facts Label (DFL) in an unsupervised environment. A Consumer Information Leaflet (CIL) will also be provided as supportive information. The TASS tool acts as a digitized, interactive version of the DFL, allowing participants to answer a dynamic and personalized set of health-related questions, in lieu of browsing/searching a DFL for information pertinent to them. During the (unsupervised) use period, participant compliance and adherence will be evaluated, including ongoing use of the Web App to report changes in health status, determine the continued suitability of the medicine, and purchase additional supply. To test our eCommerce approach, the AUS will mimic, as much as possible in a clinical trial, the in-market setting.

2.2 Background

Heart disease remains the leading cause of death for both men and women in the United States and worldwide. Elevated cholesterol is a major risk factor for heart disease, and while lowering cholesterol with statin drugs reduces cardiovascular morbidity and mortality, only about half of the people in the United States who require therapy are treated (Mercado et al 2015). There are numerous reasons for the inertia in getting people treated. What is clear is easier access to safe, effective, and affordable therapy would have a significant positive impact on public health. One way to simplify access to statin therapy would be to make them " OTC." While attempts were made in the past to switch statins OTC, the studies failed due to concerns about the efficacy of the statins that were tested and because consumers were unable to properly self-select. The Crestor OTC program addresses these two concerns by using Crestor 5 mg (a safe and highly effective dose of rosuvastatin with minimal interactions) and a TASS tool that ensures proper self-selection. Completed studies testing DFL comprehension, CIL comprehension, Web App comprehension, Human Factors, Targeted Self-Selection and All-comers Self-Selection have shown that this approach is viable. Based on the positive

results from these pivotal studies, AstraZeneca is ready to proceed with the AUS. A detailed description of the chemistry, pharmacology, efficacy, and safety of Crestor 5 mg is provided in the prescription (Rx) United States Prescribing Information (USPI) (AstraZeneca Pharmaceuticals LP 2021).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of Crestor 5 mg may be found in the Crestor Rx USPI (AstraZeneca Pharmaceuticals LP 2021).

2.3.1 Risk Assessment

The overall safety profile of rosuvastatin calcium (5 – 40 mg) was established in a large clinical trial program that included over 12,000 patients, multiple large cardiovascular (CV) outcome trials, and a post marketing experience in over 200 million patients worldwide (Yusuf et al 2016, Ridker et al 2008). Overall, Crestor was well tolerated. The most commonly reported adverse events (AEs) in controlled clinical trials were headache, myalgia, abdominal pain, asthenia and nausea. Most side effects were mild to moderate in intensity and did not lead to discontinuation. Adverse events with Crestor that are part of the Warnings and Precautions in the Crestor Rx USPI include the following: skeletal muscle effects (i.e., myopathy and rhabdomyolysis), liver enzyme abnormalities, drug interaction with coumadin anticoagulants, proteinuria and hematuria and endocrine effects. All of these adverse effects are dose related with a low frequency of observed events at the 5 mg dose (AstraZeneca Pharmaceuticals LP 2021).

Nonprescription rosuvastatin is a drug-device combination product comprised of rosuvastatin 5 mg and a Web App. The Web App helps to ensure proper self-selection during the initial purchase and reorder process by having the consumer answer a series of questions that ensure compliance with the DFL and 2018 Guideline on the Management of Blood Cholesterol (Grundy et al 2018). Consumers with any existing conditions that could result in an increased risk for AEs are either excluded from treatment or told to "Ask a Doctor" before they can order drug online.

By using the Web App, the potential for AEs with rosuvastatin 5 mg is significantly reduced, but not eliminated. CCI [redacted]

Therefore, the potential for a software error resulting in a participant who has a contraindication to therapy accessing drug is very low (e.g., pregnant woman or woman who is breastfeeding). While software errors leading to AEs are unlikely, someone could answer one of the Web App questions incorrectly leading to inappropriate access to therapy.

The primary endpoint of this study will allow us the opportunity to better understand the frequency of entry errors leading to inappropriate access to therapy.

In this AUS, we will monitor for all drug and device AEs. In addition, an email will be triggered via the Web App to the Contract Research Organization (CRO) if the participant indicates during reorder that they are pregnant, had a CV event, increased low-density lipoprotein-cholesterol (LDL-C), new muscle symptoms, liver disease and kidney disease (see Section 8.4.4 and Section 10 for further details). These findings are expected to be very rare during the course of this study.

Overall, the risk to participants from either the drug or the device in this AUS is very low. The procedures undertaken in the protocol will help to ensure the safety of participants enrolled in this study.

2.3.2 Benefit Assessment

In addition to having a well-tolerated safety profile, rosuvastatin 5 mg is highly efficacious. In a 6-week, double-blind, placebo-controlled study, rosuvastatin 5 mg lowered low-density lipoprotein-cholesterol (LDL-C) by 45% (AstraZeneca Pharmaceuticals LP 2021). Based on the Crestor Rx USPI for individual statins available in the United States, the reduction in LDL-C with rosuvastatin 5 mg is similar or greater than that reported for other statins that represent approximately 70% of all statin prescriptions in the United States today (IMS data). In the 6-week study, rosuvastatin also showed benefits on other important lipid parameters. Total Cholesterol (TC), non-high-density lipoprotein-cholesterol (non-HDL-C), ApoB and Triglycerides were reduced by 33%, 44%, 38% and 35%, respectively. HDL-C was increased by 13%. The benefits on Triglycerides and HDL-C are important since many people with abnormal LDL-C levels also have abnormal Triglyceride and HDL-C levels. The benefits of rosuvastatin 5 mg on LDL-C and other lipid parameters has been observed in numerous clinical trials evaluating short short-term and long- term treatment.

While the benefits of rosuvastatin 5 mg on cardiovascular morbidity and mortality has not been specifically evaluated in an outcome study, rosuvastatin 10 mg and 20 mg have been studied in the HOPE-3 (Yusuf et al 2016) and JUPITER (Ridker et al 2008) trials, respectively. Both of these trials enrolled a primary prevention patient population. In HOPE-3, rosuvastatin 10 mg reduced both co- primary endpoints. For the combined endpoint of CV death, myocardial infarction (MI) and stroke, the Hazard Ratio (HR) was 0.76 (CI: 0.64 – 0.91, P =0.002). For the co-primary endpoint of CV death, MI, stroke, resuscitated cardiac arrest, heart failure and revascularization, the HR was 0.75 (CI: 0.64 – 0.88, $p < 0.001$) (Yusuf et al 2016). In the JUPITER Trial, rosuvastatin 20 mg reduced the combined endpoint of MI, stroke, arterial revascularization, hospitalization for unstable angina or CV death. The HR was 0.56 (CI 0.46 – 0.69, $p < 0.00001$) (Ridker et al 2008). Importantly, while the 5 mg dose was not evaluated in an outcome trial, the LDL-lowering effects of rosuvastatin 5 mg are similar to or greater than the LDL-lowering effects seen in landmark statin trials that demonstrated benefit in primary and secondary prevention conducted over the last 2 decades (Fabbri and Maggioni 2009). Based on the data from landmark statin trials, HOPE-3 and

JUPITER, rosuvastatin 5 mg would be expected to have a significant benefit on CV morbidity and mortality.

2.3.3 Overall Benefit:Risk Conclusion

The overall assessment of benefit and risk for rosuvastatin 5 mg would support its use as a nonprescription medicine to lower cholesterol, and its evaluation in this AUS. The 5 mg dose is highly efficacious in lowering LDL-C and based on the preponderance of evidence would be expected to show a benefit in reducing CV morbidity and mortality. While no medicine is without risk, rosuvastatin 5 mg has an excellent safety profile. It has a low incidence of AEs, its metabolism is not dependent on cytochrome P450 thus minimizing the potential for drug-drug interactions, and it has no known misuse and abuse potential.

Additionally, the potential for serious AEs should be minimized by use of the Web App, which de-selects people who might be at higher risk for serious AEs.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Analysis Population (See Section 9.3_bookmark78 for definitions)
Primary		
• Evaluate *initial* 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	• Percentage of participants with an Overall Correct (correct + mitigated) Initial TASS Outcome at the initial self-selection (Threshold: 85% lower bound [LB])	• Primary: SS • Secondary: AUS ITT
• 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 TASS outcome or through the medical and medication history in those participants who fail to complete a final TASS use assessment	• Percentage of participants with an Overall Correct (correct + mitigated) Final Use Outcome at the final use assessment (Threshold: 85% LB)	• PP

Objectives	Endpoints	Analysis Population (See Section 9.3_bookmark78 for definitions)
• Effectiveness in lowering LDL-C in participants regardless of final use outcome	• Percent change from baseline in verified LDL-C to Visit 2 (Threshold: -15% UB, -20% point estimate)	• AUS ITT
Secondary		
• Compliance with cholesterol retesting within 6 months	• Cholesterol retest within 6 months of starting medication (that was verified at Visit 2, not including study mandated tests) by at least 60% of participants who are eligible for continuous treatment	• PP
• Compliance with "Stop Use" warnings	• Percentage of participants who correctly self-identify as having a "Stop Use" warning and stop medication	• PP
• Compliance with "Do Not Use" warnings	• Percentage of participants who correctly self-identify as having a "Do Not Use" warning at the final use assessment	• PP
• Compliance with "Ask a Doctor Before Use" warnings	• Percentage of participants who correctly self-identify as having an "Ask a Doctor Before Use" warning at the final use assessment	• PP

Objectives	Endpoints	Analysis Population (See Section 9.3_bookmark78 for definitions)
• Compliance with Continuous Dosing	• Percentage of participants with overall compliance between 50% and 120% as determined by pill count (Threshold: point estimate ≥ 50%)	• PP
	• Percentage of participants with longitudinal compliance between 50% and 120% across all supply periods as determined using eDiary data (Threshold: point estimate ≥ 50%)	• PP
	• Percentage of participants who were persistent as determined by reorder data from the Web App (Threshold: point estimate ≥ 50%)	• PP
CCI		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objectives	Endpoints	Analysis Population (See Section 9.3_bookmark78 for definitions)
• CCI		

Objectives	Endpoints	Analysis Population (See Section 9.3_bookmark78 for definitions)
• CCI		

3.1 Endpoint Rationale

The first co-primary endpoint for this study evaluates correct initial self-selection in participants who ultimately received an "OK to Use" outcome using the TASS tool technology. While the All-Comers Self-Selection pivotal study was designed to show that the Web App could successfully exclude participants who were not appropriate for treatment,

(i.e., 92% of participants had a "Not Right for You" outcome, which equates to a "Do Not Use" in the AUS), the AUS will only enroll participants who obtain an "OK to Use" outcome or an "Ask a Doctor" outcome and indicate the doctor gave them permission to use nonprescription rosuvastatin. Because "correct selection" is the critical starting point for treatment, the first primary endpoint in the AUS will evaluate the ability of participants to correctly select Crestor OTC for initial use.

The second co-primary endpoint is a "use" endpoint and evaluates whether participants are properly using nonprescription rosuvastatin during the use period as assessed by their ability to correctly identify changes in their health status through use of the Web App or by taking an action that complies with the DFL. This endpoint is a re-evaluation of a participant's health status not typically conducted in other Rx-to-OTC switch programs. Prior to every reorder, participants are required to enter the Web App and take an abbreviated medical assessment to ensure that they have not had a change in their health status. During this reorder assessment, participants are asked about changes in their medical and medication history that would require them to stop use and/or speak to a doctor. They are also asked about their repeat LDL-C test and to input their number to ensure they are getting an adequate therapeutic response.

Their responses will result in one of three outcomes, "OK to Use," "Do Not Use," or "Ask a Doctor." A "Do Not Use" outcome will result when the participant enters information into the app that indicates they met the *Pregnancy Alert, Do Not Use,* or *Stop Use* conditions listed in the DFL. They will also receive a "Do Not Use" outcome if their LDL-C retest shows an increase in the LDL-C or they enter two LDL-C retest results that demonstrate an inadequate response (i.e., $\geq$ 0% and < 15% reduction). For inadequate responses, the participant is instructed through the Web App and transactional emails to retest within 3 months. Note that the Web App instructs people with an initial inadequate response to take one of the following actions:

- If the participant has been compliant with dosing, they are instructed to see a doctor.
- If the participant has NOT been compliant with dosing, they are instructed to be compliant and to retest within 3 months.

Participants who have no change or an increase in LDL-C will be immediately stopped from repurchasing drug. These individuals will not be eligible for a retest.

The ability to leverage technology to re-assess consumers at the time of each purchase is unprecedented in the current OTC environment and offers an important safety check to ensure that the key requirements for continued use are met.

Because of the importance of the first co-primary endpoint in establishing that Crestor OTC can be correctly self-selected and the second co-primary endpoint showing appropriate use

without the oversight of a healthcare provider, the threshold for success for both was set at a point estimate of 90% with a lower bound of 85%. Meeting this rigorous threshold will provide a high level of confidence that the right consumers will be able to properly self-select and use Crestor OTC when it is available without a prescription.

The third co-primary endpoint was selected to evaluate the LDL-C efficacy of rosuvastatin 5 mg. Efficacy in lowering LDL-C will be evaluated as mean percent change from baseline in verified LDL-C at Visit 2. For the purposes of the statistical evaluation of this endpoint, the upper bound of the 95% confidence interval on the mean percent change from baseline (PCFB) in the overall analysis needs to be less than -15% and the point estimate needs to be less than or equal to -20%. These thresholds were chosen based on several factors: 1) 2018 AHA/ACC guidelines which state that in intermediate risk ($\geq$ 7.5% to < 20% 10-year atherosclerotic cardiovascular disease [ASCVD] risk) patients, LDL-C levels need to be reduced by 30% or more, 2) real world clinical practice results show that a 20% or greater reduction in LDL-C is a realistic, achievable goal for 5 mg rosuvastatin in a real world setting (Bullano et al 2006, Fox et al 2007) and 3) potential public health benefits for patients at increased CV risk who are not currently on any LDL-lowering therapy. Although an LDL-C lowering treatment effect of 15% to <30% is suboptimal according to the guidelines, the benefits of therapy outweigh the risks and provide an opportunity for repeated messaging to the consumer to improve their compliance with medication or to follow-up with a health care provider to optimize therapy.

The secondary endpoints were selected to evaluate compliance with retest requirements, compliance with label warnings and compliance with dosing.

The LDL-C retest success threshold was set at 60%. In the atorvastatin AUS, compliance with LDL-C retesting was 6.7% between weeks 2 and 12 and 52% over the course of the study. In the lovastatin AUS, compliance with retesting was 71% over the course of the study (Pfizer Inc 2016, Melin et al 2004). To better understand the results from these studies, AstraZeneca commissioned AETION® to conduct a study using Prognos Health and IBM MarketScan data to determine the frequency of LDL-C retesting in patients who initiated therapy with a prescription statin (refer to Appendix D). Of the 1.2M patients in this dataset, 25% had a retest within 3 months, 50% within 6 months and 75% within 12 months. These data suggest that the atorvastatin results are in line with the data from prescription statins while the Merck data was higher and most likely due to their use of an optional Mevacor OTC Self-Management System (MOTC- SMS). While all customers in our program will receive transactional emails to help ensure compliance with retesting, the ultimate impact of these emails is unknown. Therefore, the 60% threshold was set as the minimum value in this study because retesting for Crestor OTC should be at least as good as or better than what is observed currently in the real world with statin therapy.

Secondary endpoints were established to assess compliance with each specific type of DFL warning. For these endpoints, participants will be evaluated for their ability to follow the warnings based on correctly entering the information into the Web App, which would prevent a reorder from occurring, or based on the fact that they stopped therapy (regardless of whether they used the Web App). Since these situations are likely to be low frequency events, no definitive success thresholds were established for these evaluations.

Overall compliance with dosing will be assessed using three methods: pill count, diary review and number of reorders using the Web App. The first assessment for overall compliance uses the pill count or eDiary. Each participant will have overall compliance assessed and will be considered successfully compliant with dosing if they took between 50% and 120% of their pills. The target threshold for the overall compliance endpoint is an observed point estimate for the percentage of participants falling in the 50-120% range to be at least 50%. In other words, at least half of the participants need to be successfully compliant with dosing. In addition to overall compliance, a longitudinal compliance rate will be calculated to assess compliance with continuous dosing across each study drug reorder supply period. The pill use for this analysis will come from the eDiary. Finally, an additional assessment of longitudinal compliance/persistence will be performed using reorder data from the Web App. This endpoint will evaluate the percentage of users who were eligible for continuous treatment and ordered 180 days of therapy. To be eligible for continuous treatment, the participants must have received an "OK to Use" outcome or an "Ask a Doctor" outcome and indicate 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. Success is persistence $\geq$50% similar to the other compliance/persistence endpoints. The rationale for setting the compliance/persistence thresholds at 50% is based on prescription data which shows that after 180 days only about 44% of people continue to refill their prescriptions. Our intention is to show that our approach will be at least as good, if not better, on compliance and persistence than what is observed in the real world (IQVIA). Additionally, assuming an individual takes the medicine intermittently for the duration of the study, a 50% dosing compliance would equate to taking a 2.5 mg dose of rosuvastatin compared to a 5 mg dose. Based on the clinical trial data, a 2.5 mg dose gives an LDL-C lowering of approximately 35% (Olsson et al 2001). Therefore, someone taking roughly half of their pills (e.g., a 45-pill count takes about 90 days to use) would still receive excellent efficacy.

While dosing compliance will be assessed, the best measures for successful compliance will be the LDL-C lowering achieved by participants in the study and the number of participants who continue to reorder.

Following from the secondary endpoints regarding compliance with use warnings, several CCI

CCI [redacted]

[redacted]

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a 6-month, single-arm, interventional, phase III SS and 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. 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 proceed to the use phase. Note that some individuals may initially get an "Ask a Doctor" outcome because of a potential issue with treatment identified following the TASS assessment. If they ask a doctor about the potential issue, and the doctor gives them permission to order drug, they can go back into the app and retake the TASS assessment. When they confirm the doctor has given permission, they will be able to proceed to the use phase. Subjects who have a "Do Not Use" outcome or an "Ask a Doctor" outcome and do not confirm within the Web App that they spoke to a doctor will not be permitted into the home use phase of the study. CCI [redacted]

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 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). Virtual Visit 2 will be completed according to the procedures described in the Schedule of Activities (SoA), Section 1.3 and details provided in Section 8 of the protocol. A 30-day follow-up phone call will be performed after study drug completion/discontinuation to assess participants status with regard to AEs.

4.2 Scientific Rationale for Study Design

Heart disease is the leading cause of death for both men and women in the United States and worldwide (Mercado et al 2015). Elevated cholesterol is a key risk factor for heart disease, and while lowering cholesterol with statin drugs reduces cardiovascular morbidity and mortality, only about half of the people in the United States who require therapy are currently being treated (Mercado et al 2015). This represents a substantial public health issue for the United States. There are numerous reasons why people are not treated, but what is clear is that easier access to safe, effective, and affordable therapy would have a significant positive impact on public health. One way to simplify access to statin therapy would be to make it available to consumers without a prescription (e.g., OTC). Past attempts to achieve an OTC switch for statin treatment have failed due to concerns about the efficacy of the statins that were tested, and because consumers were unable to properly self-select. The Crestor OTC program addresses these two concerns by using Crestor 5 mg (a safe and highly effective dose of rosuvastatin with minimal interactions) and a TASS tool that ensures the medicine is only made available to consumers for whom it is appropriate (AstraZeneca Pharmaceuticals LP 2021). Completed studies evaluating DFL comprehension, CIL comprehension, Web App comprehension, Human Factors, Targeted Self-Selection and All-comers Self-Selection have shown that this approach is viable. Based on the success of these non-interventional behavioral studies, AstraZeneca is ready to proceed with the AUS.

The AUS is designed to test the ability of participants to input their medical data into a Web App in order to get a correct TASS outcome for the initial purchase as well as to assess their ability to correctly enter their ongoing health status into the Web App to demonstrate proper use of nonprescription rosuvastatin during the use period. Nonprescription rosuvastatin will only be available online for purchase via the Web App and direct shipment to the participant. It is intended for use by:

- Males 20-39 years of age with high LDL-C (160-189 mg/dL) plus family history of cardiovascular disease (CVD) (mother/sister younger than 65 years of age or father/brother younger than 55 years of age)
- Females 50-75 years of age with ASCVD risk score between 7.5% - <20% and LDL-C 70-189 mg/dL
- Males 40-75 years of age with ASCVD risk score between 7.5% - <20% and LDL-C 70_189 mg/dL
- Females 50-75 years of age with ASCVD risk score between 5% - <7.5% plus one risk enhancing factor and LDL-C 70-189 mg/dL
- Males 40-75 years of age with ASCVD risk score between 5% - <7.5% plus one risk enhancing factor and LDL-C 70-189 mg/dL
- Diabetics (females 50-60 or males 40-50 years of age) with LDL-C between 70-189 mg/dL and with ASCVD risk below 20%

When on the market, consumers will access the Web App through any device that has internet access. Once they access the site, they will have to answer a series of questions in order to qualify for treatment. If they qualify, they will enter an eCommerce environment where they will create a personal account and enter shipping and purchasing information. If they order drug, it will be shipped to them. Consumers will be able to purchase a limited supply (e.g., 45 or 90 days). Within a pre-specified window before their supply runs out, the consumer will be able to order additional drug through the Web App. However, before they can reorder, the Web App will ask them a limited number of health-related medical questions to ensure that they are still eligible for treatment. Consumers will also be asked to retest their cholesterol and enter their LDL-C into the app to ensure they are getting an adequate treatment effect.

Transactional emails will be sent to let them know the status of their drug orders, to remind them to retest and to take their medication daily. All customers receive transactional emails, which is a standard practice in an eCommerce environment. In-market, customers may also "opt-in" to receive additional reminders or health-related information.

To test our eCommerce approach and ensure that our approach helps to ensure the proper use of nonprescription rosuvastatin, the AUS will mimic, as much as possible in a clinical trial, the in-market setting. Subjects will see advertisements for participation in a study for a new

OTC/nonprescription medicine. If they are interested, they contact a Call Center for pre-screening and, if they qualify, receive a link to the Web App. Subjects will take the initial TASS assessment. If they receive an "OK to Use" outcome, they will be asked to contact the Call Center to set up a virtual visit to review their medical and medication history and laboratory and BP data. Subjects who receive an "Ask a Doctor" outcome may also be eligible provided they contact their doctor, retake the initial TASS assessment and confirm a doctor said it is OK to take Crestor OTC. Provided the participant does not have a significant contraindication to treatment (e.g., we learn that the participant is pregnant during Virtual Visit 1), they will be able to order a 45- or 90-day drug supply. All subsequent reorders are performed using the Web App, which requires them to confirm that they have had no significant changes to their medical and medication history. They will also be asked to retest their LDL-C and enter it into the Web App. Provided the participant meets the DFL criteria programmed into the Web App for continued use, they can reorder medication.

Because participants in the AUS will purchase nonprescription rosuvastatin calcium online, they will receive eCommerce transactional communications (emails) that one would expect to receive when making an online purchase. Transactional emails will be sent to participants during the trial to let them know the status of their orders, their eligibility to reorder, and to remind them to retest. Some transactional messages will be accompanied by secondary messages reinforcing DFL requirements (e.g., adherence reminders). There will be no "opt-in" options incorporated into this study. All participants in the AUS will have a similar eCommerce experience that will mimic, as much as possible, the in-market setting.

CCI [redacted]

4.3 Justification for Dose

The 5 mg dose of rosuvastatin was chosen for nonprescription use because it has a safety profile comparable to placebo and is highly efficacious, lowering LDL-C between 40% to 50% in controlled clinical trials. The dose planned for this study is based off the intended dose for the OTC product CCI [redacted]

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including Virtual Visit 2. Participants who discontinue with 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 and has not withdrawn from the study are also considered to have completed the study.

A 30-day follow-up phone call will be performed after study drug completion/discontinuation to assess participants status with regard to AEs. The study will end when the last phone call is completed.

5 STUDY POPULATION

The study population will include the following:

Description	# of Participants
All-comers population ages 20*-75 who self-report having concern about high cholesterol or heart health	Enrolled: 1,220 Evaluable**: At least 500 with a goal of 100 of limited literacy

* Females 20-49 will be recruited until fifty females under the age of 50 years complete the initial TASS assessment in the Web App. After this quota of fifty females under the age of 50 years old is met, the inclusion criterion will be revised to females 50-75 years old.
**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.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Recruitment Strategy

An appropriate recruitment strategy is critical for any study to successfully complete with the right participant population. As technology and digital connectedness have increased over the years, most consumers have developed a "digital footprint." This refers to the information about a particular person that exists on the internet as a result of their online activity. The potential to leverage this information for digital recruitment has grown.

During the All-comers Self-Selection study, the majority of participants met a "Do Not Use" criterion and were stopped from proceeding by the TASS. Only ~5% of the participants that completed the All-Comers SS study obtained an "Ok to Use" outcome. This was expected as the goal of this stand-alone Self-Selection study was to demonstrate that participants correctly identified if they had a "Do Not Use" condition and that TASS correctly stopped them from proceeding.

In the AUS, an all-comers population will also be recruited; however, only those who obtain TASS outcomes of "OK to Use" or "Ask a Doctor" and indicate the doctor gave them permission to use nonprescription rosuvastatin will be able to proceed to a purchase and use the product in an unsupervised OTC environment. Based on the recruitment metrics from the All- Comers SS study, it is expected that approximately 80,000 consumers will need to respond to our advertising and contact the Call Center for pre-screening into the AUS. As such, we intend to use the advantages that digital recruiting affords us to more efficiently

enroll the AUS. This will allow us to complete the study with sufficient participants to complete a robust statistical analysis.

By using a consumer's "digital footprint," advertising can be targeted more efficiently by knowing key pieces of information about a subject without directly asking for the information. Information such as age, gender, cardiac event history, or statin use can be utilized to present the advertisements specifically to those subjects. Leveraging this strategic approach in conjunction with traditional advertising will allow us to narrow the top of the recruitment funnel. At the same time, we can ensure we have not biased or influenced the subject by asking questions that might impact how they would complete the assessment in the Web App or how they would respond to the pre-screening process with the Call Center. It is important to note that we are advertising and targeting in a manner consistent with how we will advertise and target individuals in the real world when the product is launched.

Therefore, some of the tactics used in the recruitment learnings from the Self-Selection study will continue to be leveraged, such as digital advertising methods that include paid search, social media, and display advertising, traditional recruitment methods (e.g., radio, TV, print, community outreach) and supplemental methods (e.g., aggregation through existing networks and databases). However, we will also be targeting based on additional key information such as age, gender, cardiac events, and statin use which, as stated above, are similar methods that will be used when the product is commercialized.

Methods of recruitment may also include the following, which can be used alone or, in combination:

Digital	Traditional	Supplemental
Keyword Searches, Age, Gender, Topics/Interests, Audience based, Geographically based, Online Behavior, Retargeting (showing ads again in the future if a consumer showed interest in the study but did not call the Call Center).	Geographically based, Specific Channels, Specific Newspapers/Magazines, Specific Radio Stations	Age, Gender, Conditions, Geographically based

5.2 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1 Males, 20-75 years of age.

2 Females, 20-75 years of age (This inclusion criterion will be applied until 50 females under the age of 50 years complete the initial TASS assessment in the Web App. After this quota of 50 women under the age of 50 years old is met, the inclusion criterion will be revised to women 50-75 years old).

3 Respond to advertising regarding a concern about high cholesterol or heart health.

4 Able to read speak and understand English.

Additional Criteria for Inclusion into Actual Use (at Virtual Visit 1)

1 Participant reads and signs the Informed Consent form.

5.3 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Exclusion Criteria

1 The participant or anyone in their household is currently employed by any of the following:
   - A pharmacy or pharmaceutical company
   - A consumer healthcare company
   - A manufacturer of medicines
   - A managed care or health insurance company
   - A healthcare practice
   - An employee of AstraZeneca or Concentrics Research
2 The participant has ever been trained or employed as a healthcare professional (physician, nurse, nurse practitioner, physician assistant, pharmacist).
3 The participant has, or cannot recall whether he/she has, received an investigational therapy as part of a clinical trial in the previous twelve (12) months.
4 The participant is not willing to provide contact information.
5 Previous enrollment in the present study.
6 The participant has a mailing address in Alaska, or their mailing address is a Post Office (PO) Box.
7 The participant is not willing to complete an eDiary.
8 The participant is a woman of childbearing potential and is not following contraception guidelines or is not willing to follow contraception guidelines including practicing abstinence or using at least 1 of the following acceptable methods of birth control for at least 1 month prior to entry into the study and for 1 month after study completion: hormonal – oral, implantable, injectable, or transdermal; mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm; intrauterine device; or surgical sterilization of partner.
9 The participant does not have access to the internet.

10 The participant does not have an email address or the ability to receive emails.

11 The participant responds to the Single Item Literacy Screener 2 (SILS2) question (Chew et al 2008) "How confident are you filling out medical forms by yourself?" with either 'extremely' or 'quite a bit.' (If the quota for normal literacy is met, but the limited literacy target is not met, the SILS2 exclusion will be used to help increase the percentage of limited literacy participants at Virtual Visit 1. Participants identified as normal literacy by Rapid Estimate of Adult Literacy in Medicine (REALM) testing at Virtual Visit 1 will not be excluded from entry into the treatment phase of the study.)

12 Inability to conduct interviews in a private location so that sensitive information about the participant or study would not be overheard by others not permitted to hear such information.

Additional Criteria for Exclusion from Actual Use (at Virtual Visit 1) Confirmation by CMOG clinician:

1 That the participant is pregnant, as determined by an approved self-administered OTC urine pregnancy test conducted for all female participants of childbearing potential (Female participants who are not post-menopausal or surgically sterile).

2 That the participant is breastfeeding.

3 That the participant has an allergy to rosuvastatin.

5.4 Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5 Pre-Screen Failures

Pre-screen failures are defined as all subjects who meet one of the following categories:

- Did not meet SS inclusion or met SS exclusion
- 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 ICF (either did not show for their first visit or showed but decided not to sign ICF).

Information on pre-screen failures will be reported. A minimal set of pre-screen failure information is required to ensure transparent reporting of pre-screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, pre-screen failure details, and eligibility criteria (Schulz et al 2010).

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention Administered

6.1.1 Investigational Products

Table 2 Investigational Products

ARM Name	Crestor 5 mg
Intervention Name	Rosuvastatin calcium
Type	Combination product (Drug and SaMD)
Dose Formulation	Tablet
Unit Dose Strength(s)	5 mg
Dosage Level(s)	1 tablet once-daily
Route of Administration	Oral
Use	Lower Cholesterol, a key risk factor for heart disease.
IMP and NIMP	IMP

Sourcing	Drug provided centrally by the Sponsor through AstraZeneca iPR Pharmaceuticals Inc. manufacturing site Software provided by AstraZeneca through Idea Evolver
Packaging and Labelling	Study Intervention will be provided in 1 or 2 45-count bottles. Each bottle will be labelled as per CFR regulations.

6.1.2 Software as a Constituent Part

The proposed Web App is being developed as a constituent part of a combination product by a third-party collaborating closely with AstraZeneca.

The Web App features a TASS tool which allows consumers to answer a select set of health-related questions in order to determine consumer suitability for self-selection, purchasing, and ongoing administration and adherence of Crestor OTC (investigational product). Crestor OTC will only be available online for purchase via the Web App and direct shipment to the consumer. The TASS tool is a specific and critical "function" of the broader Web App. The TASS tool specifically utilizes an algorithm (i.e., decision tree and business logic aligned to the DFL and treatment guidelines) that operates on consumer data input to produce an outcome regarding the appropriateness of Crestor OTC treatment for the respective consumer. The broader Web App also includes additional components such as a welcome statement, privacy statement, account setup, shopping cart checkout, and account management, which are not considered medical device functions.

The TASS acts as a digitized, interactive version of the DFL, allowing consumers to answer a dynamic and personalized set of health-related questions, in lieu of browsing/searching a DFL for information pertinent to them. It also calculates a 10-year ASCVD risk based on the Pooled Cohort Equation (PCE) to determine consumer suitability for moderate-intensity statin treatment in accordance with the 2018 Treatment Guideline (Grundy et al 2018). Potential consumers are eligible to purchase Crestor OTC if they meet the requirements for safe use according to the DFL and have an appropriate calculated ASCVD risk score.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 A detailed process flow chart for product accountability has been developed (see Appendix C). The study product will be stored at a Central Depot to prepare the product and accompanying documentation (DFL, CIL, invoice/packing slip) for shipment via a delivery service. The study product will be stored in a secure and monitored area in accordance with the labelled storage conditions with limited access to only authorized staff. The Contract Research Organization (CRO) will work with the Central Depot to ensure only enrolled and investigator-approved participants will receive study product for the initial order. Provided the participant has no changes in health as administered via the Web App, subsequent reorders will automatically trigger shipment through the Web App

to the Central Depot immediately upon online purchase by the participant. Emails will also be used to inform participants when they should reorder. They will receive a reorder email at day 25 for a 45-day supply order and at day 45 for a 90-day supply order though the Web App will allow the participant to place another order after 5 days from the last order delivered date for the AUS. This will allow an assessment of participant behaviors around reordering of drug during the AUS to best position the appropriate ordering windows in-market.

2 The investigator is responsible for final drug accountability, reconciliation, and record maintenance (i.e., reconciliation and final disposition records).

3 Further guidance and information for the final disposition of unused study interventions are provided in the Product Accountability Log.

6.3 Measures to Minimize Bias: Randomization and Blinding

Open-label, No blinding at site level	This is an open-label study; potential bias will be reduced by having participants use the medication without clinician supervision and by keeping the number of interactions with study personnel to a minimum.

6.4 Study Intervention Compliance

When participants take study drug at home, compliance with study drug will be assessed via an eDiary, pill count and reorders. Participants will be directed to ship back to Concentrics, the CRO, any unused product as well as product information during the final virtual site visit. A record of the number of Crestor 5 mg tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Once product is received at Concentrics, a final pill count will be conducted and documented on the source document and electronic case report form (eCRF).

Those participants who refuse to send back their pill bottles for a final pill count will be given the option to count the pills with the study personnel via video conference at Virtual Visit 2.

This will be recorded on source documentation and the eCRF.

Drug dispensed date (i.e., delivery date) and Drug return date will also be recorded in the Drug Accountability form.

6.5 Concomitant Therapy

Any medication that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication form along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medicine

There is no rescue medicine for this study.

6.6 Dose Modification

There will be no dose modifications as part of this study.

6.7 Intervention after the End of the Study

There is no planned intervention after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

A participant may decide to permanently discontinue study medication for any reason at any time or the CMOG clinician may decide to permanently discontinue a participant from study medication. If study intervention is permanently discontinued, the participant will be scheduled for a final Virtual Visit to complete all Virtual Visit 2 study procedures or obtain sufficient medical and medication history to determine a final use outcome if all Virtual Visit 2 assessment procedures cannot be completed. See the SoA for data to be collected at Virtual Visit 2.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

If a participant decides to permanently discontinue study medication and their last TASS assessment was "OK to Use" or "Ask a Doctor" and indicated the doctor gave them permission to continue treatment, the participant will complete a final TASS at Virtual Visit 2. However, participants will not be required to complete the study mandated LDL-C retest.

While a study participant may decide to discontinue study medication at any time, the only events that would result in study medical personnel instructing the participant to stop taking rosuvastatin are "Stop Use" criteria (which the participant has not self-identified and taken the action to stop use) as listed below:

- Pregnancy
- Severe and unexplained muscle pain, tenderness, or weakness
- Symptoms of liver problems (upper belly pain, dark urine, yellowing of skin or whites of eyes)

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 "Stop Use" warnings. The participant will be scheduled for a Virtual Visit 2. All procedures will be performed except a final TASS and a study mandated test for LDL-C.

7.2 Participant Withdrawal from the Study

- Withdrawal means anyone who signed the ICF and did not complete the study (see Section 4.4)
- 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 and will not have sufficient data to determine a final use outcome.
  - 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".

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Detailed reasons for withdrawal will be documented including participant verbatims.

7.3 Lost to Follow-up

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 staff.

The following actions must be taken if a participant fails to complete a required study visit:

- There must be an attempt to contact the participant and reschedule the missed virtual visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls [on different days and at different times] and, if necessary, a certified letter sent to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

Site personnel, or an independent third-party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of the study as a whole is handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All pre-screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., lipid profile) and obtained within 12 months (+3-month window) before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Study procedures and their timing are summarized in the SoA and described below. Protocol waivers or exemptions are not allowed. The following steps are in order of procedures:

Prior to Virtual Visit 1

1 All-comers who respond to digital or traditional ads will click on an advertisement (if digital) or visit the web page directly (if seeing/hearing traditional ad) to learn more about the study.

2 Subjects who are interested will call the Concentrics Call Center to go through pre-screening questions that are comprised of the inclusion and exclusion criteria as well as demographic information and a privacy acknowledgment or subjects can opt to complete an online pre-screener.

3 Those who meet pre-screening criteria will be sent the Web App link via email from the Call Center.

4 The subject will complete the initial TASS assessment through the Web App. If a subject does not know their lab numbers prior to taking the initial assessment and is unsure as to where to obtain their labs, the study staff 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 a 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. However, the Sponsor will not order the tests or pay for their tests in order to overcome some of the natural barriers that would be experienced by the consumer when attempting to access nonprescription rosuvastatin in-market.

5 Subjects who receive an "OK to Use" outcome or "Ask a Doctor" outcome (and confirm that their doctor says it is OK for them to use), will then be given an opportunity to purchase a 45-day or 90-day (participant's choice) supply of the product through the Web App. No drug will be shipped until the subject consents and completes Virtual Visit 1. If the subject decides not to participate or the participant is deemed not eligible to participate at the end of Virtual Visit 1, the product purchase price will be refunded.

6 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 continues to meet pre-screening criteria and has verified diagnostic numbers (Triglycerides, TC, HDL-C, LDL-C, BP numbers, and if applicable a high-sensitivity C-reactive protein [hs-CRP] level, coronary artery calcium [CAC] score and waist circumference measurement).

- Subjects will need a verified source for their laboratory values for Virtual Visit 1. Verifiable labs will be required in order to proceed to the use phase of the study (excluding CAC).

- "Verified" laboratory values are those for which the subject has appropriate source documentation (laboratory report, Doctor's office report, etc.) for the values entered into the Web App or are laboratory values resulting from a study mandated test.
- 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).
- For males ages 20 to 39, a source verified BP will not be required since BP does not factor into the use assessment based on current guidelines.
- Call Center representative will mandate a laboratory test or BP measurement for Virtual Visit 1 if the subjects states that they do not have a source document for the data entered into the Web App.
- CAC imaging results will not be verified if a subject inputs this information into the Web App and does not have a verified source. This data will be documented as "unverified," but this would not exclude them from proceeding to participate in the AUS. No study mandated testing will be required. In this instance, the subject's TASS entry will be considered acceptable.
- For study mandated tests only, the Call Center representative will help coordinate or locate a testing site (e.g., local pharmacy, in-store clinic) for testing for the triglycerides, 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 an 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.

7 A pre-study shipment will be sent to the subjects in advance of their Virtual Visit 1 and will contain pregnancy tests (if female), an eDiary and study instructions. These instructions will be reviewed with the participant at the Virtual Visit 1.

8 Subjects will receive a call ahead of their scheduled Virtual Visit to remind them of their appointment time and to have the verification of the laboratory numbers and BP they entered into the Web App with them.

At Virtual Visit 1

9 The subject will connect to the online video link, provide an ID check to the Central Assessor who will also confirm that the subject has verifiable diagnostic data, prior to speaking with the CMOG clinician and signing the informed consent. The Central Assessor will conduct this verification due to their availability at the appointment time and access to the Virtual web meeting.

- If the diagnostic data is not verifiable, the Virtual Visit 1 will be rescheduled.
- If the Central Assessor is able to verify the source of the diagnostic data, the data is referred to as "verified source." If the diagnostic values are a result of study mandated testing, 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. As noted earlier, males 20-39 will not be required to have a verified source or SMT for BP since BP does not factor into the use assessment for this age group based on current guidelines.

10 Once the diagnostic data has been verified, the participant will sign the ICF, and all use eligibility criteria will be confirmed.

11 Women of childbearing potential will take a urine pregnancy test and show the test results to the CMOG via the video.

- Participants will be identified as being of childbearing potential prior to virtual visits and a urine pregnancy test will be sent to those participants to use during this visit.
- If at Virtual Visit 1, the pregnancy test has an inconclusive result, the participant will be rescheduled in 2 to 4 weeks at which time the urine pregnancy test will be repeated.

12 All participants will be administered the REALM test to determine literacy (Davis et al 1993). The word list will be displayed on the participants screen and the interviewer will be able to visually see and hear the participant say each word on the video. This face-to-face method of obtaining the REALM is consistent with the in-person face-to-face method.

13 The CMOG clinician will conduct the targeted medical and medication history. Product shipment will be held until after the targeted medical and medication history is completed and the Investigator approves the participant to receive the investigational product.

- Once the CMOG clinician completes the medical and medication history interview and their evaluation, they will input that data along with the verified diagnostic data (including the CAC regardless of verification status) from the Diagnostics source into the TASS tool to obtain a TASS outcome. The clinicians in the CMOG and the PI are blinded to the entries made by the study participant in the Web App. The CMOG will only use lab and BP data for their TASS

assessments that has been either source verified or from a study mandated test. If the source document contains more than one value for a parameter, the CMOG will always use the most recent value for their assessment. This procedure will be used for the Virtual Visit 1 and Virtual Visit 2 TASS assessments.

- The Central Assessor will compare the self-selection outcome from the participant in Web App to the TASS entries and initial outcome from the CMOG clinician.
  - 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 TASS 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.

14 Participants will be provided with study procedure instructions and instructions on how to complete the eDiary. No instruction will be provided regarding the use of the product. See Section 8.1 for additional information on the eDiary.

15 Once the participant has been approved to use the product, the Central Principal Investigator or Sub-Investigator will authorize a release of the initial order confirmation from the Web App that is sent to the Central Depot for initial shipment of drug. The date that the drug is delivered to the address given by the participant will be Day 1.

- All participants at Virtual Visit 1 will be allowed to enter the use period of the study provided a CMOG clinician has not determined that the participant has a condition for which treatment would pose an unacceptable risk (e.g., allergy to rosuvastatin or a woman who is breastfeeding or pregnant).

Use Period

16 The use period of the study begins on the day that the product is delivered to the address provided by the participant. The use period lasts 6-months. During this period, participants have the option to purchase more product.

17 Participants will need to utilize the eDiary to record the unique bottle ID(s) received for this initial shipment and any subsequent reorder shipments received to confirm receipt of delivery of the study drug.

18 Participants will be instructed to use the eDiary to record when they took study drug, have changes to any medications and have any changes in health status. The diary will be reviewed for AEs by a CMOG clinician at the day 60 and day 120 phone call (phone calls described in Step 22 below) and at the Virtual Visit 2. AEs will be followed to resolution. See Section 8.1 for further details regarding eDiary.

19 The timing for reordering drug for a 45-day order and a 90-day order will be after 5 days from the date of last delivery. Emails will also be used to inform participants when they should reorder. They will receive a reorder email at day 25 for a 45-day supply order and at day 45 for a 90-day supply order. Participants will have a TASS assessment performed during the reorder. Provided they receive an "OK to Use" outcome or an "Ask a Doctor" outcome and indicate the doctor gave them permission to continue treatment, they can reorder. However, the participant does not interact with a CMOG clinician to have their medical and medication history assessed during reorders.

20 Because participants in the AUS will purchase nonprescription rosuvastatin calcium online, they will receive eCommerce transactional communications (emails) that one would expect to receive when making an online purchase; these will be consistent with the messages provided when nonprescription rosuvastatin is commercialized. Transactional messages will include confirmation that a participant's order was placed, shipped, delivered, and notification of eligibility to reorder. In addition, some transactional messages will be accompanied by secondary messages reinforcing DFL requirements which includes adherence reminders, reminders to have their cholesterol levels tested, reminders to review and be familiar with the DFL, general heart health education, and a message to participants with diabetes about the importance of having a doctor manage their blood sugars. These emails will be sent to all study participants. The number and frequency of transactional emails sent to participants will vary because they are triggered by a specific event or activity. If that transactional event or activity does not occur, the participant will not be sent the respective transactional email. All emails will comply with the 2003 Controlling the Assault of Non-Solicited Pornography and Marketing (CAN-SPAM Act) requirements.

21 If the participant is unsure where to get their LDL-C retest during the 6-month use period, the same process as described in Step 4 will be followed.

22 During the 6-month use period, the 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). At approximately day 165, participants will be called and the Virtual Visit 2 will be scheduled. During this call if a participant had an LDL-C retest, they will be asked to confirm if they have a verified LDL-C retest.

- Refer to Step 6 for definition of "verified." 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).

- Study mandated lab testing for Virtual Visit 2 will follow the same process as described in Step 6 and will be required for all participants except those who received a "Do Not Use" outcome, an "Ask a Doctor" outcome but did not indicate within the Web App that the doctor gave them permission to continue treatment, permanently discontinued study medication (participant or CMOG clinician decision) or withdrew from the study. The reason is that most of these individuals will be off-treatment for an extended period of time before a study mandated test could be performed.

At Virtual Visit 2

23 If the Central Assessor cannot verify the LDL-C value, Virtual Visit 2 will be rescheduled if the participant requires a study mandated test.

24 Women of childbearing potential will take a urine pregnancy test and show the test results to the CMOG clinician via the video.

25 Any participant who, on their last order, had an "OK to Use" or "Ask a Doctor" and indicated that the Doctor gave them permission to continue treatment will complete a TASS final use assessment during the Virtual Visit 2. Any participant who, on their last order, had a "Do Not Use" outcome or a "Ask a Doctor" outcome and did not indicate the Doctor gave them permission to continue treatment will not complete a TASS final use assessment during the Virtual Visit 2. The reorder assessment that resulted in a "Do Not Use" outcome or an "Ask a Doctor" outcome (and did not indicate the Doctor gave them permission to continue treatment) will be used as the participant's TASS final use assessment and final use outcome.

26 Any participant who, on their last order, had an "OK to Use" outcome or "Ask a Doctor" outcome and indicated that the doctor gave them permission to continue treatment will be required to have a study mandated LDL-C retest if they do not have a verified source for their LDL-C retest(s). Participants with a study mandated LDL-C retest will be instructed by the Central Assessor to answer "No" to the LDL retest question. The Central Assessor will review the TASS to ensure the participant entered "No" as instructed. If the participant still entered an LDL-C from the study mandated test, the Central Assessor will instruct the participant to repeat the TASS and reiterate to enter "No" to the LDL-C retest question. The reason for instructing participants to answer "No" to the retest question is because they were instructed to retest and did not follow the DFL or Web App instructions for retesting. Because the Web App was designed to allow individuals who do not retest to complete the study, allowing subjects to enter a study mandated test could potentially lead to incorrect outcomes and, in addition, bias the results of the retest compliance endpoint. Participants who enter an LDL-C value into the TASS assessment

that is an inadequate response to treatment will be instructed through the Web App to repeat the LDL-C retest. If these participants on their last order have an "OK to Use" outcome or "Ask a Doctor" outcome and indicated that the doctor gave them permission to continue treatment, a study mandated LDL-C retest will be required if they do not have a verified source for their repeat LDL-C retest(s). 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.

27 The CMOG clinician will then conduct a follow-up medical and medication history to determine if there were any changes in health during the study.

- Once the targeted medical and medication history interview is complete, the CMOG clinician will use the data obtained in the medical interview along with the verified LDL-C value from the Diagnostics source and input that data into the Web App to obtain a CMOG clinician use outcome. The CMOG clinician will only enter a verified LDL-C value into the TASS. If a participant has multiple verified LDL-C values during the course of the use period, the CMOG clinician will enter the most recent verified value (this can be "verified source" or "verified by study mandated test").
- The Central Assessor will compare the TASS final use outcome from the participant to the use outcome from the CMOG clinician. Follow-up probes will be asked of participants for discrepancies between TASS entries as well as any 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 or use errors.

28 The eDiary will also be reviewed at the Virtual Visit 2 for AEs as well as compliance with the Directions and Stop use warnings on the DFL. AEs will be followed to resolution. The CMOG clinician will instruct the participant to return all surplus study drug/packaging purchased during the study into the return packaging provided at the beginning of the study for shipment back to the study site. Those participants who refuse to send back their pill bottles for a final pill count will be given the option to count the pills with the study personnel via video conference at Virtual Visit 2.

29 Once all questions are complete and the participant has prepared the shipment of the study drug back to the study site, the participant will be dismissed from the study visit.

30-day Follow-up

30 Thirty days post-study drug discontinuation, study staff will complete a follow-up telephone call to assess for possible AEs. Once this post-use phone call is complete and no additional AEs have been reported, the participant will have completed all study

procedures. All AEs will be followed to resolution via additional phone call as required. Participant stipend and compensation for product purchase will be provided upon receipt of returned study drug and/or product packaging at Concentrics as well as completion of 30-day post use phone call.

8.1 eDiary

The eDiary will be used to gather minimal data in an unbiasing manner and is not used to instruct the participant on the proper use of the drug. The information gathered will include dosing (date/time and amount of drug taken), AEs (changes in health), and medication changes. The participant will record the unique ID from the study drug bottle to confirm receipt of the product.

The eDiary provider will provide a notification to the study team when they detect no activity in the eDiary for more than 7 days. This will generate a communication to the participant from the study staff to determine if (a) the participant has any questions about using the eDiary (re-training may be necessary) or (b) to understand if the participant is still participating in the study. No additional information will be provided beyond the original study instructions for the diary.

At the 60-day and 120-day planned telephone contacts, the eDiaries will be reviewed to determine if "Stop Use" criteria are present and to ask about any changes in health. If so, the CMOG clinician will discuss the entry with the participant to determine if it meets the "Stop Use" definition. Meeting the second co-primary endpoint and the secondary endpoint with regard to "Stop Use" warnings requires that the participant identify the "Stop Use" warning. Therefore, should a "Stop Use" warning be identified during the 60 or 120-day touchpoint, the participants will be managed as follows:

- If during the 60 or 120-day touchpoint, 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 Virtual Visit 2 procedures except a participant TASS and study mandated test 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. Because the study staff had to

inform the participant that they met a "Stop Use" criterion, they will be considered a failure when evaluating the second co-primary endpoint related to "use".

- Participants who the CMOG clinicians identify as having experienced "Stop Use" criteria are considered "Discontinued from Study Intervention" and not a withdrawal (refer to Section 7.1). 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.

If a participant records a "Do Not Use" warning in their eDiary, we will not contact them. Our intent in the AUS is to keep interactions with the participants to a minimum so we do not influence the participant's behaviors or bias the outcome of the study. By doing this, we allow the real-life behavior to continue into the next reorder, at which time, the TASS reorder assessment would result in a "Crestor OTC is no longer right for you" message along with a message to stop drug and contact a doctor. In the AUS, the participant will also be messaged to contact the call center to schedule Virtual Visit 2.

We approached the assessment of the "Stop Use" and "Do Not Use" warnings differently. In the DFL, the "Stop Use" warnings are related to pregnancy, acute rhabdomyolysis, myopathy and hepatitis, conditions for which stopping the drug immediately are critical. In contrast, the "Do Not Use" warnings have a much lower risk for harm if treatment is continued for a period following the event. Prescription Crestor 5 mg is actually indicated for a number of the "Do Not Use" criteria. While we want to see participants with a "Do Not Use" warning stop drug immediately, should they continue for a period of time prior to completing a TASS reorder assessment, the likelihood of harm remains low.

8.2 Efficacy Assessments

The efficacy of nonprescription rosuvastatin will be assessed as a co-primary endpoint and in CCI [redacted] During the use period of the study, participants will be told to retest their LDL-C. For those who do not retest or have unverified source for the LDL-C data inputted into the Web App, a study mandated test will be required for Virtual Visit 2 for those participants described in Section 8, Step 22. The LDL-C data will be used to assess the overall response to treatment.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

There will be no physical examinations performed as part of this study.

8.3.2 Vital Signs

Blood pressure measurement will be provided at study entry and may be performed through a local testing site (e.g., retail-based BP kiosks) if the subject did not provide a verified source. See Section 8, Step 6 for further details.

8.3.3 Electrocardiograms

No ECGs will be performed as part of this study.

8.3.4 Clinical Safety Laboratory Assessments

At Virtual Visit 1, if the subject cannot provide verification of the source of their laboratory numbers or if the source is greater than 12 months (+3-month window) prior to completing the Web App, then the subject will be sent for study mandated testing for Triglycerides, TC, LDL-C, HDL-C and, if necessary, hs-CRP. If subject is not able to get to one of the local testing sites, the Call Center can direct them to order a home test kit. Subjects will not pay for study mandated testing. Subjects also have the option of rescheduling their appointment to locate their verified source. There will be no option to obtain CAC imaging in the event a subject inputs this information into the Web App and does not have a verified source at the virtual site visit. This CAC data will be documented as "unverified" but will be considered acceptable for use by the CMOG clinician for their TASS assessment if necessary. A missing CAC score would not exclude a participant from proceeding to participate in the AUS. (Note that is highly unlikely that a participant would understand a CAC score and enter a valid score into the Web App without having had the imaging test.) Women of childbearing potential will take an over-the-counter urine pregnancy test provided by the CRO prior to the virtual visit. At Virtual Visit 2, participants will be asked to verify the LDL-C entered into the Web App. If the participants did not provide verification or did not retest, then the participant will be sent for study mandated testing. See Section 8, Step 22 for a description regarding which participants are sent for study mandated testing. Women of childbearing potential will take another over-the-counter urine pregnancy test provided by the CRO.

8.3.5 Other Safety Assessments

When the participant completes the Web App to reorder, the Web App will ask questions about certain changes in health. Changes in health will also be assessed at each interim phone call.

8.4 Adverse Events and Serious Adverse Events

The Principal Investigator (PI) is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or serious AE (SAE) can be found in Appendix B.

If the participant reports an AE, the investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from the time of signature of informed consent form, throughout the use period and 30-days after study drug completion/discontinuation. All AEs will be followed to resolution.

SAEs will be recorded from the time of signing of informed consent form.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.4.2 Follow-up of AEs and SAEs

All AEs will be followed to resolution. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Severity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.4.3 Causality Collection

The investigator should assess causal relationship between Investigational Product (both drug and software constituent) and each AE, and answer 'yes' or 'no' to the question 'AE caused by IP?'

For SAEs, in addition to assessment of causal relationship with Investigation product (both drug and software constituent), causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol (CSP).

8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any changes in health since the previous visit/you were last asked?', revealed by observation, received by CRO via email that is triggered from the Web App due to participant response during reorder to one of the TASS questions below, or recorded in the eDiary will be collected and recorded in the eCRF. Certain answers in the Web App for reorder assessment may also be collected as AEs. These include the following questions:

- Have you ever had any of the following: heart attack, stroke, operation or procedure on your heart, peripheral artery disease (PAD)?
- Have you been told by a doctor that you have kidney disease or since you started taking Crestor OTC, have you been told by a doctor that your kidney disease has gotten worse?
- Have you had any new liver problems (upper belly pain, dark urine, or yellowing of skin or whites of your eyes)?
- Have you had any new, severe, and unexplained muscle pain, tenderness, or weakness?

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Participants who report AEs with symptoms suggestive of a severe myopathy, rhabdomyolysis or liver injury will be referred to a doctor or an emergency room for immediate care.

8.4.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, should only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.6 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other study site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other study site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

All SAEs will be recorded in the EDC system. Investigators or other study site personnel will send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the USPI for Crestor - (AstraZeneca Pharmaceuticals LP 2021).

8.4.6.1 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 participants experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the Coronavirus 2019 (COVID-19) virus is the infectious organism, and the AE will be recorded accordingly. If a participant 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 AE Field.

If a test has not been performed or result is negative, additional questions will be asked about contact with someone positive for COVID-19 or with COVID 19 symptoms and timing around onset of symptoms. If either question is true, record "COVID-19 suspected" in the Adverse Event Field. If the clinician has other concurrent diagnoses for the participant's signs and symptoms (e.g., pneumonia), these will be recorded as separate AEs.

8.4.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study drug
- Pregnancies in the partner of male participants

8.4.7.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and

handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other study site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.6) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The data points required to be collected in AstraZeneca's PREGREP module and PREGOUT module will be used to report pregnancy and pregnancy outcome via the pregnancy CRF modules or a pregnancy form.

8.4.8 Medication Error

If a medication error occurs in the course of the study, then the investigator or other study site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.4.6) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.9 Software as a Constituent Part

An investigational software as a constituent part of a combination product is included in this study. Any AEs and/or any SAEs reported in this study will undergo causality assessment by the investigator for causal relationship with the investigational product, inclusive of both the drug and software constituents. If a causal relationship with the software is suspected for an AE and/or an SAE, it will be documented within the AE and/or SAE report. All SAE reports which meet the definition of an IND safety report will be submitted to health authorities according to local regulations.

8.5 Overdose

Based on data from Crestor clinical program, any dose of 80 mg or above in a 24-hour period will be considered an overdose.

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Hemodialysis does not significantly enhance the clearance of rosuvastatin.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, the investigator or other study site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hour**s of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.4.6) and within 30 days for all other overdoses.

8.6 Human Biological Samples

Participants may use a local testing site or a home test kit for labs and women of childbearing potential will take an at home urine pregnancy test. No human biological samples will be stored as part of this study. See Section 8 for further details.

8.6.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6.2 Pharmacodynamics

Pharmacodynamics are evaluated as part of the LDL-C reduction efficacy evaluations.

8.7 Human Biological Sample Biomarkers

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

There will be no mandatory collection of samples for biomarker analysis in this study.

8.7.2 Collection of Optional Biomarker Samples

There will be no collection of optional biomarkers samples in the study.

8.7.3 Other Study-Related Biomarker Research

Biomarker research is not applicable in this study.

8.8 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.9 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable to this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Statistical hypotheses will be tested for all of the co-primary endpoints for the study. These endpoints are defined in detail in Section 9.4.2.1. For each of the use co-primary endpoints, namely, the Overall Correct Initial TASS Outcome and the Overall Correct Final Use Outcome, the below 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) CI is greater than 85%.

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

For the third co-primary endpoint, PCFB in verified LDL-C to Visit 2, the below 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%.

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

where μ is the mean PCFB in verified LDL-C to Visit 2.

9.2 Sample Size Determination

The sample size is based on powering the study for the co-primary endpoints. The evaluation of the first co-primary endpoint on the Overall Correct Initial TASS Outcome will have a sample size of approximately 1220; 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 LB of the 95% exact binomial confidence interval (CI) is greater than 85% with a sample of approximately 1220 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%

Evaluation of the second co-primary endpoint on 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 CI is greater than 85% for the final use endpoint, assuming that the true correct final use outcome rate is 90%. It is anticipated that at least 450 participants will be included in the evaluation of the third co-primary endpoint of PCFB in verified LDL-C to Visit 2. 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 demonstrate that 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. The table below summarizes the estimates and percentage drops at each step from the initial call into the Call Center through completion of the study.

Table 3 Estimated Number of Subjects/Participants by Study Stage

Calls into Call Center	Estimated 80,000 calls
Sent the Web Link Assumes: Pre-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

Note: "Enrolled" is defined as a participant's agreement to participate in a clinical study following completion of the informed consent form (ICF) process. Subjects who are pre-screened for the purpose of determining eligibility for the study but do not sign consent, are defined as "pre-screen failures." See Section 9.3 for further detail on the definition of pre-screen and screen failures.

9.3 Populations for Analyses

The following populations are defined:

Table 4 Populations for Analysis

Population/Analysis set	Description
Pre-Screened	Pre-Screened are all subjects who complete the initial pre-screener either online or by calling the Call Center.
Pre-Screen Failures	Pre-Screen Failures are all subjects who meet one of the following categories: • Did not meet SS inclusion or met SS exclusion • 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 ICF (either did not show for their first visit or showed but decided not to sign ICF)
SS Population	Participants who sign the ICF.

AUS Screen Failures	SS population participants who meet AUS exclusion criteria.
AUS Intent to Treat (ITT) Population	SS population participants who meet all eligibility for AUS and have investigational product (IP) delivered to their address.
Per Protocol Population	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 to determine the final use outcome.
Safety	All participants in the AUS ITT who takes 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.

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be finalized prior to data base lock (DBL) and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

9.4.1.1 Subgroup Analyses

Results for all endpoints will be conducted 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 clinician 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) which will be obtained from the participant order history.

9.4.1.2 Web App Records

Whenever the subject/participant uses the Web App, a record of that interaction along with the responses to the questions are created. There is the potential for multiple records from a subject/participant since participants could enter the Web App and then exit because they do not have the information needed to complete the assessment. The rule for addressing the issue of multiple Web App records is to always use the subject's/participant's last completed record with an outcome result for analysis. A similar process will be used for the CMOG records completed at Visit 1 and Visit 2. If multiple CMOG assessments are recorded, the last record

will be used for the evaluation of the endpoints. The reason for multiple CMOG assessments will be recorded.

9.4.1.3 Mitigation Plan

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 vs incorrect TASS and use.

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. The 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.

Following the mitigation coding process conducted by Concentrics Research, 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 issue 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 be entered into the study database by the firewalled coders and data management staff.

CCI [redacted]

The mitigations that were applied to the second co-primary endpoint will be utilized when assessing the applicable secondary and CCI [redacted]

- *A Priori* mitigations: These are anticipated responses that would be considered correct, after *a priori* mitigations, usually since there is no safety risk. See Table 5 and Table 6 for 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 from the CMOG clinician. 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 a reasoned and acceptable answer to the question and pose no medical risk.

Table 5 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 does not 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 CMOG Clinician determines they are not currently taking but had taken within 7 days of completing the TASS.
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 CMOG Clinician determines that participant only smokes e-cigarettes.

Table 6 Use Period 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 does not 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.

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	CMOG 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 CMOG 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 CCI [redacted] 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.	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. 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. 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.

9.4.1.4 Managing Variability of Laboratory, Blood Pressure and Waist Circumference Data from Different Sources

In this study, subjects are required to have BP and cholesterol testing performed at a local testing site if they cannot provide verification for the data they entered into the TASS tool. If a subject/participant is unable to get to one of the local testing sites, the study staff can direct them to order a home test kit. If a subject has an FDA approved BP device at home, they will be allowed to use their device. General instructions on techniques to measure BP will be provided. See Section 8 for further details. Since the data obtained from the local testing site or the home test kit in almost all instances will not match exactly the data entered by the subject/participant in the TASS tool, rules are established to determine whether the data entered by the subject/participant should be considered a true reflection of their laboratory and BP data. Numerous factors can contribute to variability in these measurements over time. Examples include changes in diet, the time of day the sample was taken, whether the individual was fasting or non-fasting, the laboratory or person performing the analysis, and in the case of BP, white coat increases in pressure or circadian variability. Because of these

factors, setting a level of variability that would be deemed acceptable for each lab test or for a BP measurement is extremely difficult.

Based on the findings from the pivotal Self-Selection Study, the vast majority of participants entered laboratory and BP data that were an appropriate representation of their true data. Of the 500 participants in the per protocol population, 7 of the 17 incorrect rejectors and 1 of the 3 incorrect selectors were due to lab or BP data errors. In all other situations, the laboratory and BP data did not impact the primary TASS outcome assessment. Because participants in the AUS will need an "OK to Use" outcome (or permission from a doctor if they get an "Ask a Doctor" outcome) to proceed into the use period, they will need to enter precise laboratory and BP data to meet the treatment eligibility requirements. As demonstrated in the Self-Selection Study, entering fake numbers is highly likely to result in a "Not Right for You" (i.e., "Do Not Use") outcome, and if subjects try to guess numbers to get access to drug, they will get locked out of the Web App after 3 failed attempts and will have to wait for at least one hour before they can retake the assessment.

In this study, variability criteria will only be used for the assessment of the first co-primary endpoint and will only be applied when the participant and CMOG clinician TASS outcomes at Visit 1 differ because of these values. In other words, if the TASS outcomes for the participant and CMOG clinician agree, the laboratory and BP values entered by the participant will be considered acceptable. Because participants must qualify for treatment to enter the study, all of them, except young males, are required to have a 10-yr ASCVD risk score within the appropriate range. Diabetic users are required to have an ASCVD risk score of 0% to <20%, and non-diabetic users are required to have an ASCVD risk score of 5% to <20%. Since TC, HDL and systolic BP are used in the risk score calculation, these values will be considered acceptable if the CMOG clinician TASS outcome is $\geq$4% for non-diabetic users. This change from the criteria applied in the Self-Selection study is because all participants with a risk $\geq$5% are potential candidates for statin therapy. The only participants who should not be treated are those for whom the CMOG clinicians' assessments indicate they are low risk. Diabetics are excluded from this variability assessment as 0% to <5% ASCVD risk score is acceptable.

While the numerous factors described earlier can contribute to variability in laboratory measurements, establishing acceptable levels of variability that take into account both biologic and analytic sources of variability would require setting arbitrary and, in some instances, (e.g., TG levels) very large acceptability criteria. Therefore, for this study, the acceptable level of laboratory variability is based on The National Cholesterol Education Program (NCEP) analytical performance goals as shown below (Contois et al 2011).

Total Cholesterol: $\leq$ 9%

Triglycerides: $\leq$ 15%

LDL-C: $\leq$ 12%

HDL-C: $\leq$ 13%

No variability criteria will be applied to the LDL-C retest value for Visit 2 to account for differences in participant and CMOG TASS outcomes due to the retest LDL-C.

The acceptable variability for BP 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 testing site inputted BP, operator variability when using manual devices, and white coat BP effects. 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 systolic and diastolic BP at 15%.

When applying the variability criteria, the acceptable level of variability will be applied to the CMOG laboratory or BP result to determine if it overlapped with the participant's data. Further details on the process for applying the variability criteria will be found in the SAP.

The acceptable level of variability criteria for the laboratory and BP data will be used to manage the following situations:

1 The difference between the laboratory and/or BP data entered by the participant and the one obtained by the testing site was small but was enough to change the assignment of a Risk Enhancing Factor (REF) that was used to determine eligibility for treatment. This will only apply for participants with a 10-yr ASCVD risk score of 5% to <7.5% since those at higher risk do not require a REF.
2 The difference between the laboratory and/or BP data entered by the participant and the one obtained by the testing site was small but was enough to take the value outside the treatment range.

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 (Pellowe et al 2010). The issue of variability in waist circumference measurements has also been reported by others (Mason et al 2018). 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.

9.4.2 Study Endpoints

9.4.2.1 Primary Endpoint(s)

The first co-primary analysis will evaluate the percentage of participants who achieved an Overall Correct Initial TASS Outcome at the initial self-selection. The Self-Selection (SS) population will be the primary population used for this analysis; however, a second evaluation using the AUS ITT population and PP population will also be performed. The second co-primary analysis will evaluate the percentage of participants who achieved an Overall Correct Final Use Outcome at the final use assessment. The Per Protocol (PP) population will be the primary population used for this endpoint analysis (see Section 9.3 for definitions of analysis populations). For these evaluations, the outcomes obtained by the participant will be compared to the outcomes obtained by the CMOG clinician following verification of the participant's medical and laboratory data. The third co-primary analysis will evaluate percent change from baseline (PCFB) in verified LDL-C values to Visit 2 in participants in the AUS ITT population regardless of their final use outcome.

The three co-primary endpoints are evaluated as follows:

1 Percentage of participants with an Overall Correct (correct + mitigated) Initial TASS Outcome at the initial self-selection, defined as the number of participants with a correct *initial* TASS outcome divided by the number of participants in the analysis population (Threshold: 85% LB). Those participants with a missing CMOG clinician initial TASS outcome will be counted as Incorrect for the endpoint. This will be calculated as follows:

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

A 95% confidence interval will be computed using exact binomial methods (i.e., Clopper-Pearson) for the proportion of each correct outcome among the entire SS Population.

Figure 2 below provides a matrix of Correct and Incorrect Selectors or Ask a Doctor based on the participant and CMOG clinician TASS outcomes for the initial TASS assessment.

Figure 2 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**

The primary analysis for the Overall Correct Initial TASS Outcome will reported as follows:

	Analysis Population (N=XXX)		
	N	%	95% CI
Overall Correct Initial TASS Outcome	XX	XX%	(LB%, UB%)
Correct Selectors	XX	XX%	(LB%, UB%)
Correct AAD	XX	XX%	(LB%, UB%)
MR_{ap}	XX	XX%	(LB%, UB%)
MR_{ps}	XX	XX%	(LB%, UB%)

where,

- Correct Selectors (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 clinician 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 the CMOG clinician evaluation)
- MR_{ap} = Mitigated results *a priori*
- MR_{ps} = Mitigated results post-study (should there be any post-study mitigations).

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 clinician initial TASS outcome will be counted as Incorrect for the endpoint. An additional secondary analysis of this endpoint will be conducted based on the AUS ITT population. 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 CMOG clinician (i.e., complete case analysis) and with missing Overall Correct Initial TASS Outcome data imputed using best case imputation and a tipping point analysis. Further details for those participants (or CMOG clinician) with missing initial TASS outcomes and the sensitivity analyses will be described in the study SAP.

2 Percentage of participants with an Overall Correct (correct + mitigated) Final Use Outcome at the final use assessment, defined as the number of participants with a correct *final* use outcome divided by the number of participants in the analysis population with a non-missing final use outcome for both the participant and CMOG clinician (Threshold: 85% LB). This will be calculated as follows:

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

A 95% confidence interval will be computed using exact binomial methods (i.e., Clopper-Pearson) for the proportion of each correct outcome among the entire PP Population.

Figure 3 below provides a matrix of Correct and Incorrect Selectors, Ask a Doctor, or Rejectors based on the participant and CMOG clinician evaluations for the final use assessment.

Figure 3 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)

Since participants are given a limited supply (i.e., 45 or 90 day) of rosuvastatin with each order, they are likely to have multiple reorder assessments over the duration of the trial. While this will occur, the critical reorder assessment for the second co-primary endpoint will always be the last one taken by the participant because it 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, including the final use assessment taken at Virtual Visit 2. The final use assessments will be determined based on the following criteria.

1 For those 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 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 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 evaluation of 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 participants

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 gives us 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 their "Ask a Doctor" assessment will be used as their TASS final use assessment.

4 For participants who discontinue from study intervention prior to study completion 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 the Virtual Visit 2 procedures in order to have a final use assessment for the participant and the CMOG clinician. If the participant is unwilling to provide sufficient medical and medication history for the CMOG to make a final use determination, the CMOG clinician evaluation will be considered missing, and the participant deemed a withdrawal. The impact of the missing data will be assessed in the sensitivity analysis. See the Statistical Analysis Plan for further detail. All final use outcomes obtained by the participant will be compared to the use outcomes obtained by the CMOG clinician following verification of the participant's medical and medication history interview at Virtual Visit 2.

The primary analysis for the Overall Correct Final Use Outcome will be reported as follows:

	Analysis Population (N=XXX)		
	n	%	95% CI
Overall Correct Final Use Outcome	XX	XX%	(LB%, UB%)
Correct Selectors	XX	XX%	(LB%, UB%)
Correct AAD	XX	XX%	(LB%, UB%)
Correct Rejectors	XX	XX%	(LB%, UB%)
MR_{ap}	XX	XX%	(LB%, UB%)
MR_{ps}	XX	XX%	(LB%, UB%)

where,

- Correct Selectors (C_S) = Obtain a correct outcome that they qualify for Crestor OTC (compared to the CMOG clinician evaluation)
- Correct AAD (C_{AAD}) = Obtain a correct outcome that they must ask a doctor before qualifying for Crestor OTC (compared to the CMOG clinician evaluation)
- Correct Rejectors (C_R) = Obtain a correct outcome that they do not qualify for Crestor OTC (compared to the CMOG clinician evaluation)
- MR_{ap} = Mitigated results *a priori*
- MR_{ps} = Mitigated results post-study (should there be any post-study mitigations).

A sensitivity analysis for those participants with missing data for the second co-primary endpoint (i.e., those participants in the AUS ITT population but not the PP population) will be conducted. The missing data imputation methods for the Overall Correct Final Use Outcome will include best case and worst case imputation and a tipping point analysis. Further details for those participants (or CMOG clinician) with missing final use outcomes and the sensitivity analyses will be described in the study SAP.

3 The PCFB in verified LDL-C values for participants regardless of final use outcome at Visit 2. This endpoint is calculated 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. Negative values in PCFB represent a decrease in LDL-C.

The PCFB for verified LDL-C values will be summarized by subgroup and overall using descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and Quartiles 1 and 3 [Q1 and Q3]) for those participants in the AUS ITT population. 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.

To test the robustness of the third co-primary endpoint on LDL-C efficacy, several sensitivity analyses will be performed to determine the effect that various sources of LDL-C values have on the LDL-C primary endpoint. Sensitivity analyses of LDL-C efficacy will be conducted on all participants with a verified baseline and retest LDL-C who are eligible for continuous treatment, on the primary LDL-C efficacy population using various missing data imputation methods for missing verified on-treatment LDL-C values, on all participants with a baseline

and retest LDL-C regardless of verification status and Final Use Outcome, and finally, on all participants who entered a baseline and retest LDL-C into the Web App regardless of whether the test was verified. These sensitivity analyses will be further described in the SAP.

9.4.2.2 Secondary Endpoint(s)

Cholesterol Retesting

1 Percentage of participants who are eligible for continuous treatment, and have a cholesterol retest within 6 months of starting medication that was verified at Visit 2 will be calculated as follows:

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

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 Visit 2 will be summarized by subgroup and overall. 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. 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 point estimate needs to be at least 60% overall.

Compliance with Stop Use Warning

2 Percentage of participants who correctly self-identify as having a "Stop Use" warning and stop medication, calculated as follows:

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

The number and percentage of participants who correctly self-identify as having a "Stop Use" warning and stop medication will be summarized by subgroup and overall.

Compliance with Do Not Use Warning

3 Percentage of participants who correctly self-identify as having a "Do Not Use" warning at the final use assessment, calculated as follows:

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

The number and percentage of participants who correctly self-identify as having a "Do Not Use" warning at final use assessment will be summarized by subgroup and overall.

Compliance with Ask a Doctor Before Use Warning

4 Percentage of participants who correctly self-identify as having an "Ask A Doctor Before Use" warning at the final use assessment calculated as follows:

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

The number and percentage of participants who correctly self-identify as having a "Ask a Doctor Before Use" warning at the final use assessment will be summarized by subgroup and overall.

Compliance with Continuous Dosing

5 Percentage of participants with overall compliance between 50% and 120% as determined by pill count. Overall Compliance will be calculated as follows:

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

where the intended duration of treatment is calculated as follows:

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

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.

6 Percentage of participants with longitudinal compliance with continuous dosing across each study drug reorder supply period as determined using eDiary data, where supply period compliance is calculated for each supply period for each participant as follows:

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

The Longitudinal Compliance Rate, or the percentage of participants with supply period compliance between 50-120% across each study drug supply period, is calculated as follows:

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

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

7 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 by subgroup and overall on the PP population and the AUS ITT population.

9.4.2.3 CCI [redacted]

[redacted]

CCI

[redacted]

CCI [redacted]

9.4.3 Safety

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).

Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AstraZeneca/designee.

Safety data will be presented using descriptive statistics unless otherwise specified.

AEs will be presented by SOC (System Organ Class) and PT (Preferred Term) covering number and percentage of participants reporting at least one event and number of events where appropriate.

AEs will be presented as frequency count summaries by study period (treatment period and follow-up period).

An overview of AEs will present the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP, as well as AEs leading to withdrawal from study .

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, seriousness, death and events leading to discontinuation of IP.

An additional table will present number and percentage of participants with most common AEs. Most common (e.g., frequency of >x%, ≥x%) will be defined in the SAP.

CCI [redacted]

Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Treatment Period

The following events are considered treatment period related:

- 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

The 30-day Follow-up Period begins after Visit 2.

9.4.4 Evaluation of SILS2 Literacy Threshold

CCI

[redacted]

[redacted]

9.5 Interim Analyses

No interim analyses are planned for this study.

9.6 Data Monitoring Committee

There is no Data Monitoring Committee for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

CCI [redacted]

11 APPENDICES

Appendix A. Regulatory, Ethical, and Study Oversight Considerations

Appendix B. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Appendix C. Cutter Evaluation of Drug Accountability Compliance

CCI [redacted]

Appendix E. Abbreviations & Definitions

Appendix F. Protocol Amendment History

Appendix G. References

CCI [redacted]

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (World Medical Organization 1996)
  - Applicable ICH Good Clinical Practice (GCP) Guidelines (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use 1996)
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs) and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the USPI and will notify the IRB, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (US Food and Drug Administration 2018), local regulations, ICH guidelines (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use 1996), Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- The source must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A 4 Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject/participant records or datasets that are transferred to the sponsor will contain the identifier only; subject/participant names or any information which would make the subject/participant identifiable will not be transferred.
- The subject/participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her study documents including the Targeted Medical and Medication History form may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

A description of this clinical study will be available on https://astrazenecaclinicaltrials.com and https://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use 1996), and all applicable regulatory requirements.
- Records and documents, including e-signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed with the CMOG.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

A 8 Study and Study Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the date the advertising is placed which is the first day a subject can call for pre-screening and will be the study start date.

The sponsor designee reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support

publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), 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.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity rating scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Appendix C Cutter Evaluation of Drug Accountability Compliance

To better improve public health, AstraZeneca is developing an innovative approach in healthcare through use of a Technology Assisted Self-Selection tool (TASS). This allows qualified statin-eligible consumers who are not Rx-treating their high cholesterol to self-treat and improve their health. Our approach requires a standard e-commerce solution to drug delivery. Therefore, in our Actual Use Study (AUS), we will follow a real-world e-commerce approach for access and delivery of drug.

The Technology-Assisted Cholesterol Trial in Consumers (TACTIC) is a self-selection (SS) and AUS that will be conducted as part of the Rx-to-OTC Switch program for rosuvastatin 5 mg to lower cholesterol, one of the key risk factors that can lead to heart disease. This study fully leverages innovative approaches that include technology-assisted self-selection and reselection using a Web App access that will block the purchase of drug if "Do not use" criteria are inputted by the consumer. The goal of AstraZeneca is to design the AUS to mimic, to the best of our ability in a clinical trial, the "real-life" consumer experience ordering and using non-prescription rosuvastatin.

Nonprescription rosuvastatin will ONLY be available through an online purchase. It will not be available on shelves at retail stores. Because the purchase of the drug will be done outside of a retail setting, AstraZeneca proposes that self-selection, purchase, and acquisition of the product be conducted in a similar manner in the AUS. This means that consumers would use the Web App to answer self-selection questions, and if eligible to receive the product, they are permitted to complete an online purchase and have the drug delivered to the address they provided upon purchase.

Our proposed approach to product delivery requires a thorough evaluation of the steps we would need to take to ensure the integrity of the product accountability process while at the same time ensuring minimal impact to the naturalistic aspect of the study. As summarized below, during the AUS, AstraZeneca will have a carefully designed and executed process for managing product accountability. However, one step during the online delivery process that we will not incorporate into our process is the requirement for a signature from the consumer upon delivery of drug. Given that shippers routinely deliver products during the day, people may not be interested in participating in the study due to the added burden of needing to be home at the time of delivery for signature. In addition, if they do participate, they may end up missing days of therapy if they are not home to sign for their delivery. Since subjects are required to re-order drug every 45 or 90 days during the course of the study, this issue is a real possibility. While a signature is not required, delivery of medication will be confirmed by the delivery company as outlined below. Note that in our current e-commerce environment, consumers are not required to sign for medications that come from an online pharmacy.

As previously stated, AstraZeneca is committed to maintaining the integrity of product accountability, and the following safeguards and accompanying documentation demonstrate control of investigational product through the entire process:

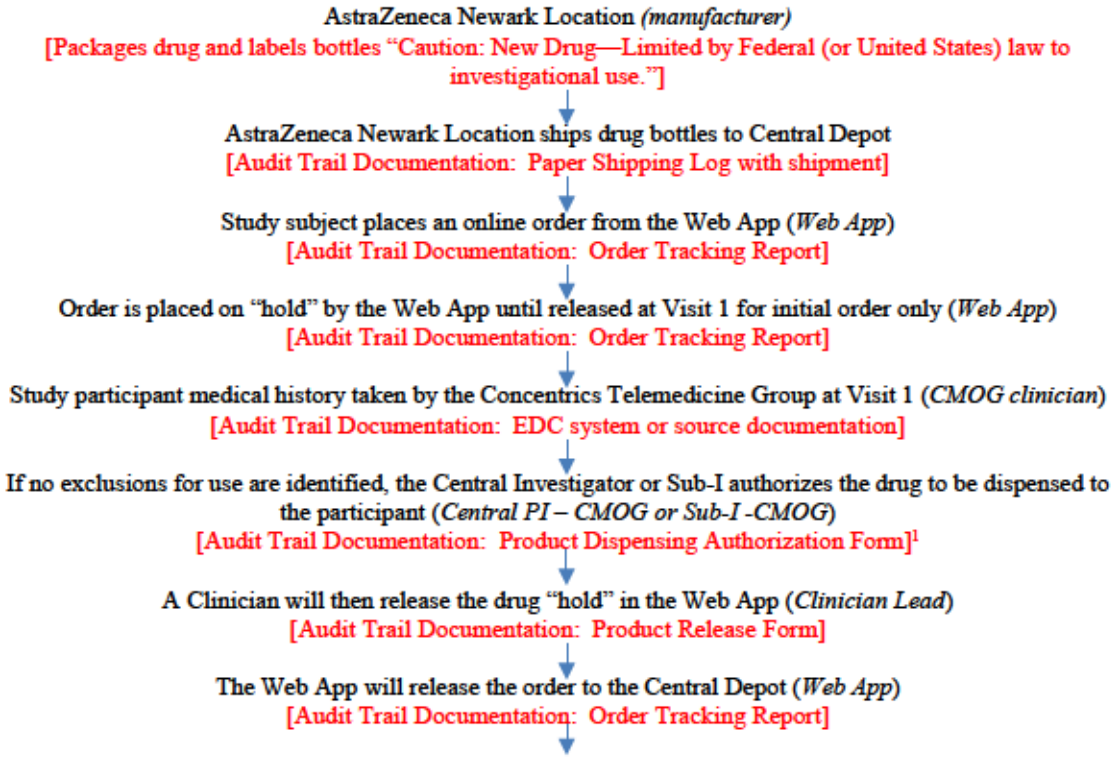
- The AstraZeneca Newark packaging site will be responsible for packaging the bottles of drug which will be shipped to a packaging and distribution vendor, Hibbert. Hibbert acts as a Central Depot to prepare the drug and accompanying documentation (Drug Facts Label (DFL), Consumer Information Leaflet (CIL), invoice/packing slip) for shipment via a delivery service. This service, for example FedEx or USPS, will provide an audit trail via a tracking number which will confirm the location of the drug during transit and arrival at the delivery address provided by the participant at the time of purchase. Inventory will be configured as a regulated product in Hibbert's Inventory Management System. Regulated is defined as encompassing product that is lot controlled, and/or has an National Drug Code (NDC), and/or is governed by Prescription Drug Marketing Act guidelines. This configuration triggers added quality control checks in the Hibbert inventory system and processes.
- Upon completion of an online purchase by the subject, the Web App has a control using Ship Engine® technology to ensure the subject is inputting a valid mailing address.
- In the AUS, the initial shipment will be held by the Web App until the participant completes virtual Visit 1 online with the study staff, to consent and verify that they are not pregnant/breastfeeding and/or has severe allergy to the medication. Once Visit 1 is completed, the central investigator or sub- investigator will authorize a release of the initial order confirmation from the Web App that is sent to the Central Depot. Provided the participant has no changes in health as administered via the Web App, subsequent re-orders will automatically trigger shipment through the Web App to the Hibbert Central Depot immediately upon online purchase by the participant. Emails will also be used to inform subjects when they can reorder. They will receive a reorder email at day 25 for a 45-day supply order and at day 45 for a 90 day supply order. Participants will be told at Visit 1 and at the time Visit 2 is scheduled, to return all unused drug product as well as empty, used bottles after Visit 2 for drug accountability. During the virtual Visit 2, the participant will provide a visual confirmation of the packaging of study material to the study staff and confirm it is ready for returns shipment. Those participants who refuse to send back their pill bottles for a final pill count will be given the option to count the pills with the study personnel via video conference at Virtual Visit 2. This will be recorded on source documentation and the eCRF.
- The Hibbert system integrates with the Web App.
  - The Order Shipped notification will include the following shipment data comprised of information from both the Web App and Hibbert:
    - Full participant name and address

    - Participant ID
    - Carrier and Shipping Method used for Shipping
    - Quantity of Crestor 5mg Bottle shipped
    - Lot Number
    - Date Shipped
    - Date Clinician Released (initial order only)
    - Date Order Cancelled (if applicable)
    - Tracking Number
  - The Order Delivered notification will update shipment data with the following details:
    - Participant ID
    - Date Delivered
    - Tracking Number
- In addition to the aforementioned product controls, AstraZeneca will send transactional emails to participants notifying them that their drug is being shipped and that it is has been delivered to the address they provided at the time they placed the order. The delivery email will also contain a telephone number to call if they did not receive their order. These emails will support identification of an issue with product accountability. If the participant did not receive their drug supply, Hibbert will initiate the manual override process described below.
- Upon notification of any missing shipments or product damage, Hibbert will manually initiate a replacement order to ship to participant. A manual order placement check is in place for maximum of two (2) per participant based on the participant ID. If the participant requests a third replacement order, the request will be elevated to AstraZeneca and Concentrics for further evaluation and a decision on next steps. Any approved replacement order will be tracked via Hibbert's systems and the new delivery date will be entered into the Study Admin Portal once received from Hibbert. While missing shipments will be a rare occurrence, the replacement order process was put in place to ensure continuity of treatment, and to prevent potential abuse of the online ordering process.

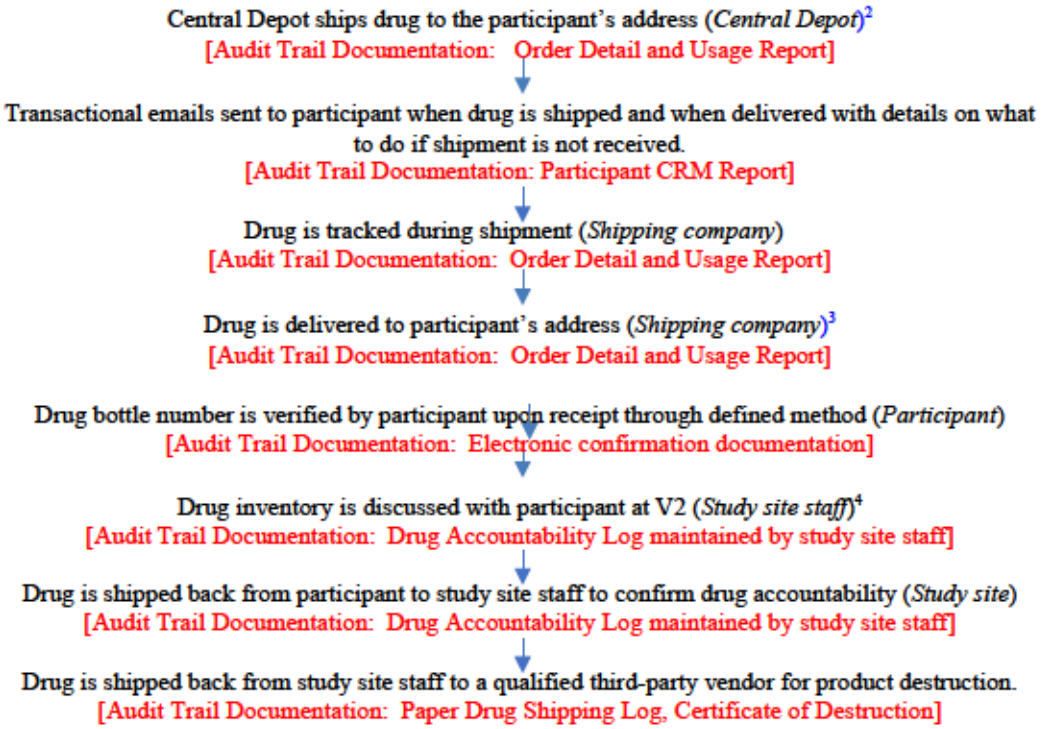
Documentation and appropriate audit trails will be in place to ensure traceability of product from Sponsor to Central Depot, Web App to Central Depot, and Central Depot to the delivery address provided by consumer. See attached Flowchart for Management of Investigational Product in the AUS (Figure 1).

AstraZeneca is requesting feedback from the Agency about the interpretation and application of 21 CFR 312.40 and 21 CFR 312.57, 312.59, 312.61 and through 312.62 as it relates to this novel AUS design and no requirement for a signature for this product upon arrival at the delivery address.

FIGURE 1: Management of Investigational Product in the AUS



[1] If exclusions are identified, the Central Investigator or Sub-I does NOT authorize the drug to be dispensed [Audit Trail Documentation: Product Dispensing Authorization Form, Documentation of Deactivation of Accounts, Documentation of Cancelled Orders] – no drug dispensed



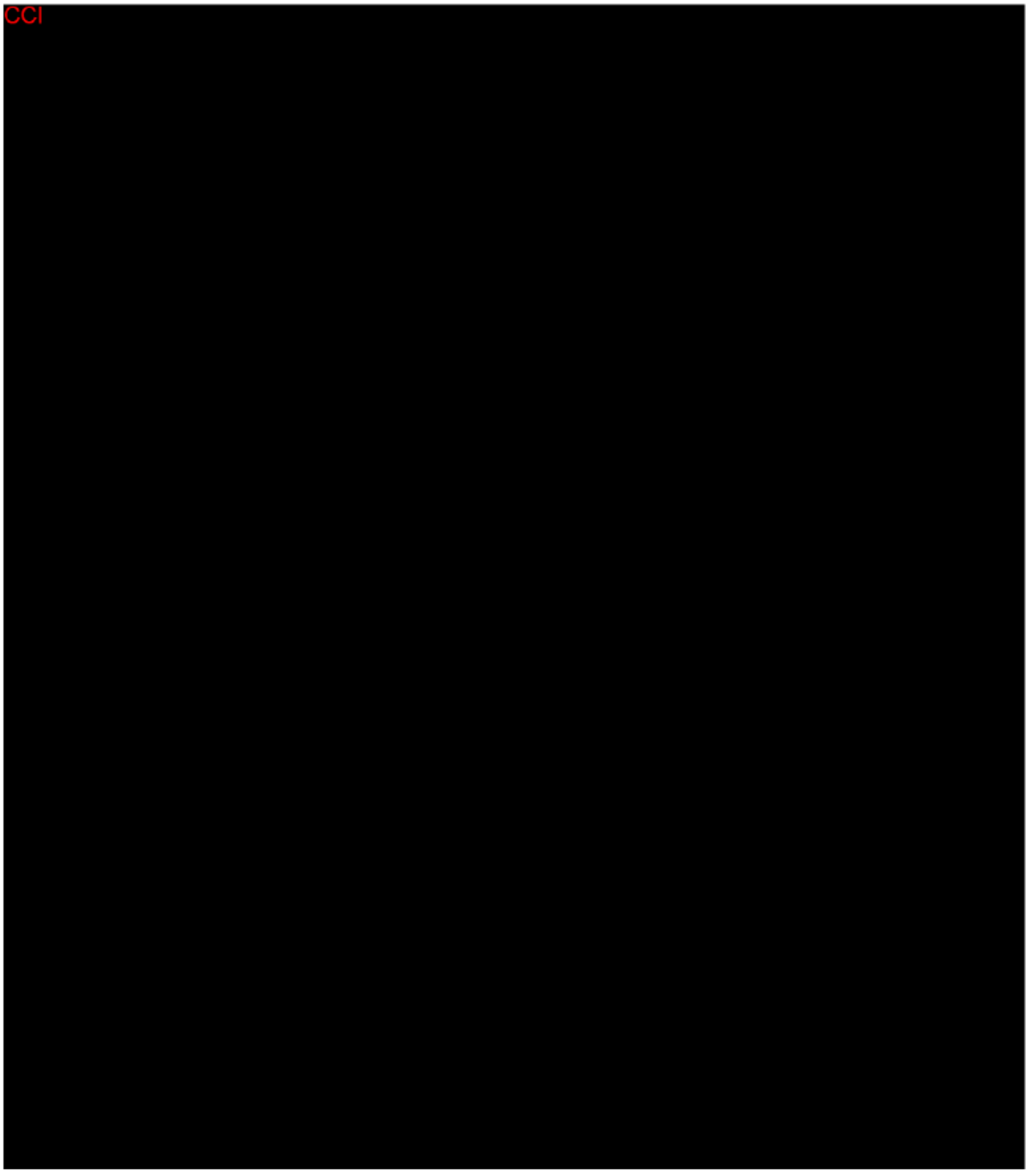
[2] Central Depot System will integrate with the Web App. The Order Shipped notification will include the following shipment data comprised of information from both the Web App and Central Depot: Full participant name and address, Participant ID, Carrier and Shipping Method used for Shipping, Quantity of Crestor 5 mg Bottle shipped, Lot Number, Date Shipped, Date Clinician Released (initial order only), Date Order Cancelled (if applicable), Tracking Number. The Order Delivered notification will update shipment data with the following details: Participant ID, Date Delivered, Tracking Number

[3] If a shipment is missing or product is damaged, Central Depot will manually initiate a replacement order to ship to the participant. This will only be permitted X2

[4] Those participants who refuse to send back their pill bottles for a final pill count will be given the option to count the pills with the study personnel via video conference at Virtual Visit 2. This will be recorded on source documentation and the eCRF

CCI

CCI



CCI

CCI

[redacted]

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix E Abbreviations & Definitions

Abbreviation or special term	Explanation
AAD	Ask a Doctor
AADBU	Ask a Doctor Before Use
ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
ASCVD	Atherosclerotic Cardiovascular Disease
AUS	Actual Use Study
BP	Blood Pressure
CAC	Coronary Artery Calcium
CAN-SPAM	Controlling the Assault of Non-Solicited Pornography and Marketing
CFR	Code of Federal Regulations
CI	Confidence Interval
CIL	Consumer Information Leaflet
CMOG	Central Medical Operations Group
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
CVD	Cardiovascular Disease
DBL	Data Base Lock
DFL	Drug Facts Label
DNU	Do Not Use
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HDL-C	High-Density Lipoprotein - Cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
Hs-CRP	High-sensitivity C-reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation or special term	Explanation
IMS	Intercontinental Medical Statistics
iPR	iPR Pharmaceuticals (a manufacturing site for AstraZeneca)
IRB	Institutional Review Board
ITT	Intent to Treat
LB	Lower Bound
LC	Label Comprehension
LDL-C	Low-Density Lipoprotein - Cholesterol
medDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Myocardial Infarction
NCEP	National Cholesterol Education Program
OTC	Over-the-Counter
PAD	Peripheral Artery Disease
Participant	Any subject who enrolls in the study
PCE	Pooled Cohort Equation
PI	Principal Investigator
PO	Post Office
PT	Preferred Term
REALM	Rapid Estimate of Adult Literacy in Medicine
REF	Risk Enhancing Factor
Rx	Prescription
SAE	Serious Adverse Event
SaMD	Software as a Medical Device
SAP	Statistical Analysis Plan
SMT	Study Mandated Testing
SoA	Schedule of Activities
SOC	System Organ Class
SS	Self-Selection
Subject	All subjects who completes the online pre-screening either online or by calling the Call Center
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASS	Technology-Assisted Self-Selection
TC	Total Cholesterol
TG	Triglycerides
TOC	Table of Contents
UPT	Urine Pregnancy Test
USPI	United States Prescribing Information
Web App	Web Application

Appendix F Protocol Amendment History

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	*14Dec2022*
Amendment 6	*01Sep2022*
Amendment 5	*11Apr2022*
Amendment 4	*14-Oct-2021*
Amendment 3	*22-Jul-2021 (never implem5ented)*
Amendment 2	*16-Jun-2021*
Amendment 1	*11-Mar-2021*
Original Protocol	*17-July-2020*

Amendment 7 (14Dec2022)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 and Section 3 Synopsis and Objectives and Endpoints	Added "correctly self-identify" to the endpoint description	Provide clarity	Non-substantial
Section 1.1 and Section 3 Synopsis and Objectives and Endpoints	Added "(i.e. participant who are longitudinally compliant)"	Provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1, Section 5, and Section 5.2 Synopsis, Study Population, Inclusion Criteria	Clarified Inclusion Criteria #2 – removed reference to "enrolled" to achieve our quota on females under 50 years of age	In order to achieve the quota of n=50 of females under 50 years of age, subjects had to complete the initial TASS assessment which occurs before enrollment. As such, to achieve the quota, it was not necessary to enroll the participant which means signing the ICF.	Substantial
Section 1.1 and Section 5.3 Synopsis and Exclusion Criteria	Added the full SILS2 question being asked	Provide clarity	Non-substantial
Section 1.1 and Section 9.1 Synopsis and Statistical Hypotheses	Null hypotheses equations updated from "=" to "≤" and "≥" respectively	Provide clarity. The updating of the equation doesn't change the testing of the statistical hypotheses.	Non-substantial
Section 1.1 and Section 9.4.2.1 Synopsis and Primary Endpoint(s)	Updated "where the LDL-C value entered by the participant at initial selection and verified by the CMOG will serve as Baseline" to "where the verified LDL-C value at initial selection will serve as Baseline"	Provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 3.1 Endpoint Rationale	Updated from "uses the pill count" to "uses the pill count or eDiary" for overall compliance with dosing	Participant may not return pills but have been highly compliant with completing the eDiary or a participant may not have been as compliant with eDiary but returned all pills. This will allow us to use whichever has the most data for the compliance calculation	Non-substantial
Section 4.4 End of Study Definition	Updated definition of "completing the study"	To provide clarity that participants who discontinue with sufficient medical and medication history to determine a final use outcome (and do not withdraw) are considered to have completed the study	Non-substantial
Section 7.2 Participant Withdrawal from the Study	Categorized withdrawals as SS withdrawals or AUS ITT withdrawals	Provide further clarity	Non-substantial
Section 8.4.3 Causality Collection	Updated question asked on causality to reflect how it is asked on source	Provide clarity	Non-substantial
Section 8.6.2 Pharmacodynamics	Updated from "Pharmacodynamics are not evaluated in this study" to "Pharmacodynamics are evaluated as part of the LDL-C	Provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	reduction efficacy evaluation"		
Section 9.3 Populations for Analyses	Updated definition of pre-screened population	Provide further clarity	Non-substantial
Section 9.3 and Section 9.4.3 Populations for Analyses, Statistical Analyses	Updated definition of safety population	Provide further clarity as it is unknown as to when a participant took a first dose so we defined that first dose to be the date drug was delivered	Non-substantial
Section 9.4.1.3 Mitigation Plan	Added wording to confirm that AZ and Cleveland Clinic are blinded to the impact that post-study mitigations will have on the study results	CCI [redacted]	Non-substantial
Section 9.4.1.3 Mitigation Plan	Added mitigation on missing LDL-C retests to Table 9-4 that was added to SAP	Ensure the a priori mitigation on missing LDL-C retest was captured in the CSP after being identified in the SAP v4.0	Substantial
Section 9.4.1.4 Managing Variability of Lab, Blood Pressure, and Waist Circumference from Different Sources	Added how waist circumference variability would be handled	Provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4.1.4 Managing Variability of Lab, Blood Pressure, and Waist Circumference from Different Sources	Added that diabetics are excluded from variability assessment for 5% to <20% ASCVD risk score as they can have a 0% to <20% ASCVD risk score	Provide clarity	Non-substantial
Section 9.4.2.1 Primary Endpoint(s)	Updated Figure 2 to include Missing column	Provide clarity	Substantial
Section 9.4.2.1 Primary Endpoint(s)	Updated Figure 3	Provide clarity	Substantial
Section 9.4.2.2 Secondary Endpoint(s)	Updated equation for overall compliance	Simplified for clarity but analysis itself did not change	Non-substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
Section 9.4.3 Safety	Updated definition of treatment period and added definition of follow-up period	Provide clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
General	Updated to correct formatting and align style	Ensure consistency	Non-substantial

Appendix G References

AstraZeneca Pharmaceuticals LP 2021
AstraZeneca Pharmaceuticals LP. CRESTOR (rosuvastin calcium) [Prescribing Information]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/spl/data/08039402-2a60-4599-83b5-1c63b85ead70/08039402-2a60-4599-83b5-1c63b85ead70.xml

Bullano et al 2006
Bullano MF, Wertz DA, Yang GW, Kamat S, Borok GM, Gandhi S, et al. Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. Pharmacotherapy. 2006;26(4):469-478.

Chew et al 2008
Chew LD, Griffin JM, Partin MR, Noorbaloochi S, Grill JP, Snyder A, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. J Gen Intern Med. 2008;23:561-6.

Contois et al 2011
Contois JH, Warnick GR, Sniderman AD. Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurement. J Clin Lipidol. 2011 Jul-Aug;5(4):264-72.

Davis et al 1993
Davis TC, Long SW, Jackson RH, Mayeaux EJ, George RB, Murphy PW, et al. Rapid estimate of adult literacy in medicine: a shortened screening instrument. Family Medicine. 1993;25(6):391-395.

Fabbri and Maggioni 2009
Fabbri G and Maggioni AP. Cardiovascular risk reduction: what do recent trials with rosuvastatin tell us? Adv Therapy. 2009;26(5):469-487.

Fox et al 2007
Fox KM, Gandhi SK, Ohsfeldt RL, Blasetto JW, Bays, HE. Effectiveness of rosuvastatin in low-density lipoprotein cholesterol lowering and National Cholesterol Education Program Adult Treatment Panel guideline III LDL-C goal attainment compared to other statins among diabetes mellitus patients: a retrospective study using an electronic medical records dataset in the United States. Curr Med Res Opin. 2007;23(9):2125-2133.

Grundy et al 2018
Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report on the American College of

Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;139(25):e1082-e1143.

International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use 1996
International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use. Topic E6 Note for Guidance on Good Clinical Practice: Consolidated Guideline, CPMP/ICH/135/95. 1996. Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

IQVIA
IQVIA longitudinal patient prescription database (LRx).

Mason et al 2018
Mason C, Katzmarzyk PT. Variability in waist circumference measurements according to anatomic measurement site. Obesity (Silver Spring). 2009 Sep;17(9):1789-95. Epub 2009 Apr 2. Erratum in: Obesity (Silver Spring). 2018 Nov;26(11):1815.

Melin et al 2004
Melin JM, Struble WE, Tipping RT, Reynolds JM, Vassil TC, Levy SJ, et al. A consumer use study of over-the-counter lovastatin (CUSTOM). Am J Cardiol. 2004;94:1243-8.

Mercado et al 2015
Mercado C, DeSimone AK, Odom E, Gillespie C, Ayala C, Loustalot F. Prevalence of cholesterol treatment eligibility and medication use among adults – United States, 2005-2012. Morb Mortal Wkly Report. 2015;64(47):1305-1311.

Olsson et al 2001
Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol. 2001;88:504-8.

Pellowe et al 2010
Pellowe E, Salako K, Snelling S, Urdaibay C, Weston C. Daily variability in waist circumference. Heart. 2010 Apr;96(7):550.

Pfizer Inc 2016
Pfizer Inc. Actual Use Trial of Atorvastatin Calcium 10 mg. 2016. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01964326.

Ridker et al 2008
Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195-2207.

Schulz et al 2010
Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

US Food and Drug Administration 1990
US Food and Drug Administration, Division of Metabolic and Endocrine Drug Products. Guidelines for the clinical evaluation of lipid-altering agents in adults and children. 1990. Available from: https://www.fda.gov/media/71165/download (Withdrawn).

US Food and Drug Administration, Center for Drug Evaluation and Research 2013
US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry – Self-Selection Studies for Nonprescription Drug Products. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM272122.pdf.

US Food and Drug Administration 2017
US Food and Drug Administration. Software as a medical device (SAMD): Clinical evaluation guidance for industry and Food and Drug Administration staff. 2017. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/software-medical-device-samd-clinical-evaluation.

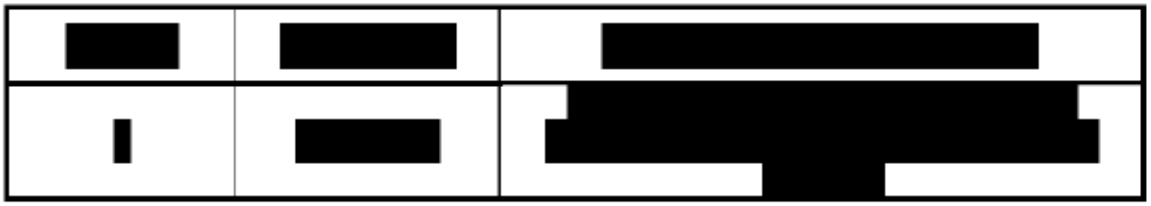
US Food and Drug Administration 2018
US Food and Drug Administration. Code of Federal Regulations – Protection of Human Subjects. 2018. 21 C.F.R. § 50. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50.

World Medical Organization 1996
World Medical Organization. Declaration of Helsinki. BMJ. 1996;313(7070):1448-1449.

Yusuf et al 2016
Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al for the HOPE-3 Investigators. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016;374:2021-2031.

CCI

[redacted]



2	CCI [redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CCI

CCI

[redacted]


CCI

CCI

[redacted]

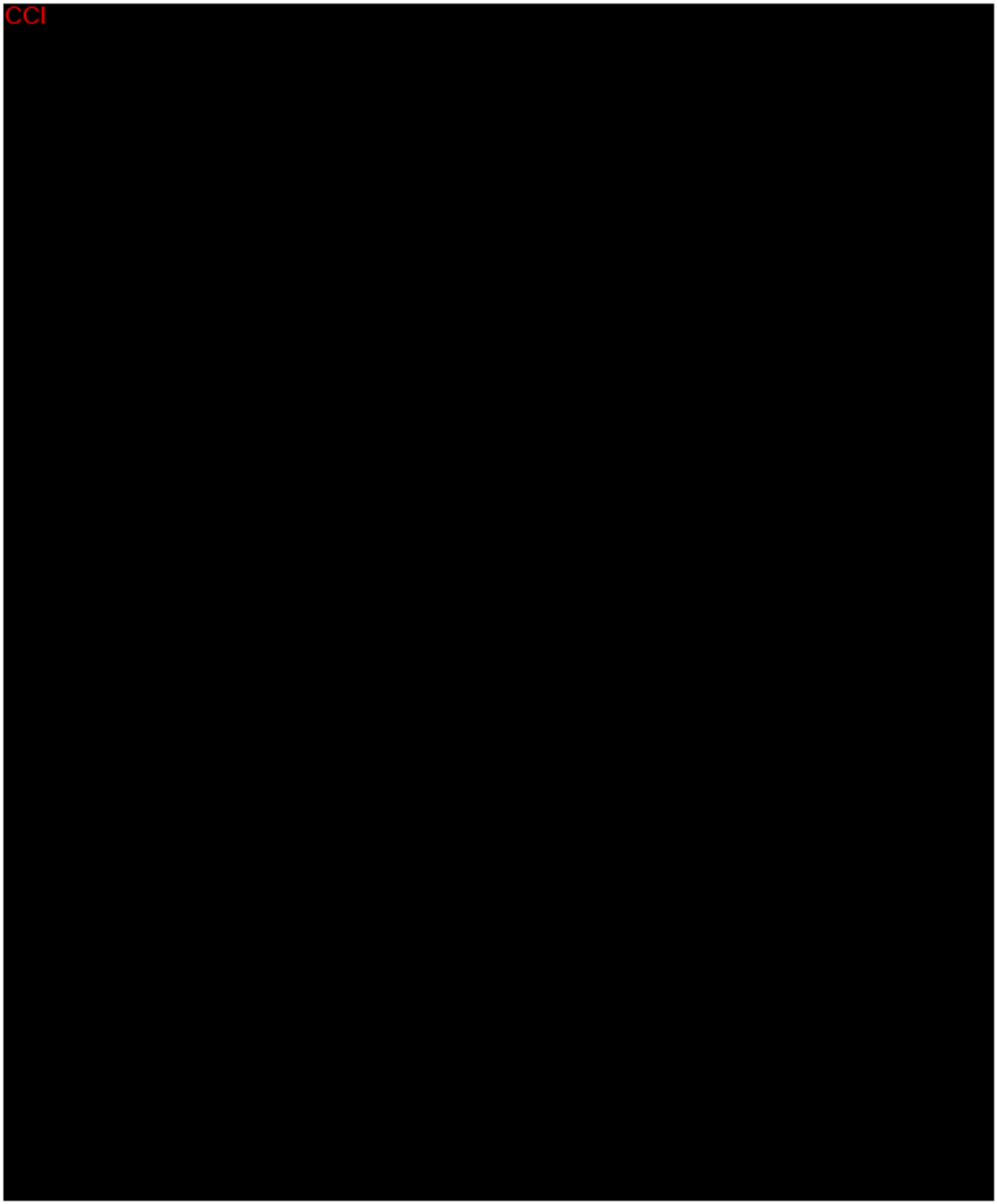

CCI

CCI

CCI

CCI

[redacted]


CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]


CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] XX

CCI [redacted]	[redacted]

CCI [redacted]