Supplements, Placebo, or RosuvastaTin Study

SPORT Trial Protocol Version 1.0

23February 2021

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Sponsor: Cleveland Clinic Investigator Initiated Trial

Funded by: Astra Zeneca

Study Chairman Protocol Approval Page

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I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice.

Study Chairman Signature:  23Feb2021

Steven Nissen, MD, MACC (Date)
Cleveland Clinic

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List of abbreviations/definitions

AE	Adverse Event
ASCVD	Atherosclerotic Cardiovascular Disease
eCRF	Electronic Case Report Form
dL	Deciliter
GCP	Good Clinical Practice
mg	milligram(s)
OTC	Over the Counter
SAE	Serious adverse event
Study Medication	Study medication refers to FDA approved rosuvastatin
Supplement	Refers to over the counter fish oil, cinnamon, garlic, turmeric, plant sterol
Sponsor	Cleveland Clinic

1 Introduction

1.1 Background

Few well-controlled trials have studied the LDL-lowering effects of dozens of marketed "cholesterol health" dietary supplements. These products combine for sales of billions of dollars annually, primarily via online marketing. The business model for the dietary supplement industry often relies on efforts to undermine FDA-approved cholesterol lowering medications in favor of "all natural" alternatives for "heart protection" and "cholesterol management." Marketing of dietary supplements (without evidence of benefit) is protected by the Dietary Supplement Health and Education Act of 1994, which assigns oversight of this industry primarily to the Federal Trade Commission, rather than the Food and Drug Administration. The supplement industry markets against prescription statins on eCommerce platforms, but rarely, if ever, perform comparative studies. Furthermore, prior research suggests most U.S. consumers believe cholesterol health supplements are safer than statins, and a majority of the public also believe supplements are as effective, or more effective, than prescription statins. Approximately one third of US adults who have been told they have elevated cholesterol are using a supplement to provide heart health protection rather than a statin. This represents a significant public health concern. [1-6]

1.2 Purpose

The purpose of this study is to evaluate the effect of select dietary supplements on cholesterol health compared with a low dose of a statin.

2 Objectives and endpoints

Primary Objective

The primary objective of this study is to compare the LDL lowering of rosuvastatin with the effect of six commonly used dietary supplements on cholesterol health

Secondary Objective

Assess the effect of each supplement on inflammatory markers compared with rosuvastatin 5 mg.

Primary Endpoint

The percent change in LDL-C for rosuvastatin 5 mg compared with dietary supplements after 4 weeks.

Secondary Endpoints

- The percent change in high sensitivity C reactive protein (hsCRP) for rosuvastatin 5 mg and dietary supplements compared with placebo after 4 weeks.
- The percent change in HDL-C, total cholesterol, and triglycerides for each supplement compared with rosuvastatin.
- The percent change in HDL-C, total cholesterol, and triglycerides for each supplement compared with placebo.

3 Study design

A randomized, single blind study design will be used to evaluate rosuvastatin 5 mg. vs. placebo and 6 commercially available over the counter supplements in a hierarchical testing order. Each participant will take study medication/supplement for a total of 4 weeks.

3.1 Rationale for duration of administration

The duration of 4 weeks is sufficient as steady-state LDL-C levels are reached for rosuvastatin 5mg within two weeks.

3.2 Risks and benefits

The risks may include a lack of effect on cholesterol health with supplements over a short duration, or an adverse effect of one of the study medication/supplements. Undeclared ingredients are a possibility with over-the-counter supplements.

The benefits may include the potential to have an effect on cholesterol health with one or more of the study medication/supplements.

4 Population

The study will randomize primary prevention patients who are considered borderline and intermediate risk for ASCVD based upon the 2018 Cholesterol Treatment Guidelines[7] and are not taking any of the studied medication/supplements at the time of randomization.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. U.S. adults with primary hypercholesterolemia, 40-75 years of age.
3. Not currently taking statins or one of the dietary supplements included in the trial. Patients willing to discontinue a prohibited supplement for 4 weeks prior to enrollment will be allowed to participate.
4. LDL-cholesterol between 70 and 189 mg/dL.
5. Patients without diabetes mellitus and a 10-year risk of ASCVD between 5 and <20% using the pooled cohort risk equation. *
   Or
   Patients with diabetes mellitus in females 50-60 years of age or males 40-50 years of age with an LDL-C between 70-189 mg/dL and with an ASCVD risk below 20%.

*http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

4.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Age < 40 or >75 years of age
2. Women who are pregnant, plan to become pregnant within the next 6 months, or are breastfeeding.
3. Documented liver dysfunction or history of elevated LFTs indicating active liver disease
4. Documented chronic renal dysfunction within the past two years defined as an eGFR$\leq$30mL/min/m^2.
5. Known hypersensitivity to rosuvastatin or any supplement under investigation (i.e. shellfish allergy, etc.).
6. Currently taking any prescription statin, or other prescription medication/supplements to treat elevated cholesterol or triglycerides.
7. Currently taking a medication/supplement that has known interaction with rosuvastatin, including fenofibrate, gemfibrozil, HIV medications, colchicine, cyclosporine, warfarin, anti-viral medications to treat Hepatitis C, regorafenib, and darolutamide.
8. Are unwilling to discontinue prohibited dietary supplement(s) for 4 weeks prior to participation or during the course of the trial. Other non-prohibited supplements will be permitted if doses have been stable for at least 4 weeks.
9. Known cardiovascular disease including a history of prior MI, stroke/TIA, PAD or prior revascularization procedures of the heart or vasculature (e.g. CABG, stenting, PCI etc.).
10. Fasting Triglycerides >200mg/dl.
11. In the opinion of the investigator, any other condition that will preclude participation in the study.

4.3 Study medication/supplements

4.3.1 Study medication/supplement groups

Eight groups will be studied, Rosuvastatin 5 mg compared with the following:

1. Placebo (comparable to rosuvastatin 5mg)
2. Fish oil (Nature Made™ 2 soft gels / day)
3. Cinnamon (1200mg, 2 capsules / day)
4. Garlique™ (1 tablet / day)
5. Turmeric (Bio Schwartz Turmeric Curcumin, 1500mg, 3 capsules / day)
6. Plant sterol (Nature Made CholestOff™ Plus, 2 soft gels 2x / day)
7. Red yeast rice (Arazo Nutrition, Red Yeast Rice, 1200mg, 2 capsules / day)

4.3.2 Medication/supplement study groups

Eligible subjects will be randomized 1:1:1:1:1:1:1:1 to the study groups in a blinded fashion. There will be 25 subjects per study group. The total sample size will be 200 patients.

Sample Size and Power

Assuming a common standard deviation of 15 and an alpha of 0.05, enrolling a total of 25 in each group will have 90% power to detect an average difference in percent change in LDL of 15 between rosuvastatin and each study group.

4.3.3 Concomitant therapy

Medication/supplement classification used by the subject prior to randomization will be recorded in the eCRF pages.

4.3.4 Prohibited medication/supplement and therapies

New use of prescription medication/supplements for elevated cholesterol or triglycerides during participation in the trial.

New use of over the counter dietary supplements marketed for cholesterol health or triglyceride health for 4 weeks prior to or during participation in this study are prohibited. Chronic use of supplement types other than those being assessed in the trial will be permitted if doses have been stable for 4 weeks or longer.

Patients will be encouraged to maintain lifestyle habits present at the time of trial enrollment during the course of the trial. Significant dietary and physical activity modifications will be discouraged over the 4 weeks of participation. Participants are not to enroll in weight loss programs during the trial.

4.3.5 Study group assignment, randomization

Randomization will occur using REDCap Cloud electronic database platform. Study medication/supplement will be dispensed by the investigational pharmacy in a blinded fashion for in person visits to study personnel or shipped to the subjects by the investigational pharmacy following randomization. Day 1 of the study is the first day that subjects start study medication/supplement. In the event that study medication/supplement is shipped to subjects, study personnel will verify the start of study medication/supplement (Day1) for medication/supplement accountability.

The study medication/supplement will be supplied from commercially available products and administered according to the package insert. The rosuvastatin 5mg and placebo will be provided by Astra Zeneca. The over the counter supplements will be purchased and due to documented history of supplement tainting, supplements may be tested for unlabeled enhancing impurities retrospectively if deemed necessary per data findings. If we observe > 15% lowering in LDL cholesterol, we will test for impurities.

4.4 Study group blinding

Subjects, investigator staff, persons performing the assessments, and the clinical trial team will be blinded to assigned study group. Baseline laboratory values will not be blinded to the subjects, investigator staff, and the clinical team. Additional lipid labs will be prohibited for the 4 week participation period. The Day 28 labs will not be blinded.

It is expected that the need for unblinding of a patient's study group will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient.

5 Informed consent procedures

Eligible subjects may only be included in the study after providing IRB approved informed consent. Informed consent must be obtained before conducting any study-specific procedures. Subjects will be prescreened using historical laboratory values within 13 months of screening prior to consenting. Subjects that screen fail will not be eligible for rescreening.

6 Visit schedule and assessments

Subjects should be seen for all visits/assessments as outlined in the assessment schedule. The baseline and final visits will be completed in-person or remotely.

The fasting lipid draw and complete metabolic panel (CMP) at Day 0 and Day 28 must be obtained from a Cleveland Clinic lab. Recently acquired lipid labs and complete metabolic panel may be used in place of a Day 0 lab draw if acquired within 4 weeks of screening at a Cleveland Clinic lab and performed in the fasting state. Subjects are to remain on study medication/supplement until Day 28 labs are drawn.

Study personnel will use the following historical information to input into the ASCVD risk calculator to determine eligibility:

- Age
- Gender
- Race
- Systolic blood pressure
- Diastolic blood pressure
- Treatment for high blood pressure and diabetes
- Current smoking status

If a historical blood pressure is not found within 1 year of screening, patient reported is acceptable.

Lipid panel, hs-CRP will be collected at the initial visit and Day 28.

- Lipids: Indirect **LDL-C** (Total Cholesterol, HDL-C, and Triglycerides)
- Inflammatory markers: **hs-CRP**

Table 7-1 Assessment Schedule

	Study Day	
Activity	Day 0 [b]	Day 28[b,f] +4/-4 days
Informed consent obtained[b]	X	
Demographics	X	
Medical history	X	
Eligibility confirmed & subject randomized[h]	X	
Body weight[g]	X	
Height[g]	X	
Concomitant Medication/supplements	X	X
Hs-CRP	X	X
CMP, LDL-C, TC, HDL-C, and TGs[c, d]	X	X
Pregnancy test [a]	X	
Study medication/supplement dispensed[i]	X	
Adverse events		X
Study medication/supplement adherence[e]		X

[a] Females of child-bearing potential only, urine or serum at investigator's discretion.
[b] The baseline (0) and 28 Day visit may be completed remotely. Consent will be obtained prior to completion of the baseline visit and may be completed remotely in accordance with Cleveland Clinic guidelines
[c] Fasting lipid panel and complete metabolic panel should be drawn a Cleveland Clinic lab facility. Patients should fast for approximately 8 hours.
[d] Recently acquired lipid and complete metabolic panel labs may be used in place of a Day 0 lab draw if acquired within 4 weeks of screening at a Cleveland Clinic lab.
[e] Study medication/supplement adherence will be assessed with a pill count. The bottle will be returned to the study site to retain until the end of study.
[f] If enrolled for over 14 days and the patient discontinues study medication/supplement perform Day 28 lab work (ITT principle).
[g] Historical documented height and weight may be used. Weight to be within the last 3 months. Subject reported is acceptable.
[h] Randomization and eligibility confirmation may occur on different days from baseline pending lab results
[i] Study medication/supplement will be dispensed by the investigational pharmacy for in person visits to study personnel or shipped to the subjects by the investigational pharmacy following randomization.

6.1 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all subjects.

6.1.1 Pregnancy assessments

All pre-menopausal women who are not surgically sterile will have a urine or serum pregnancy test performed at the Day 0 visit. Pregnancy testing is not required for post-menopausal women.

7 Study discontinuation and completion

7.1 Discontinuation

7.1.1 Discontinuation of study medication/supplement

Discontinuation of study medication/supplement for a subject occurs when the study medication/supplement is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study medication/supplement for a given subject if, he/she believes that continuation would negatively impact the subject's well-being. After study medication/supplement discontinuation, the patient should remain in the study, unless he/she withdraws consent, preferably in writing.

Study medication/supplement must be discontinued under the following circumstances:

- Subject decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the subject
- Any laboratory abnormalities that in the judgment of the investigator prevents the subject from continuing study medication/supplement administration

If discontinuation of study medication/supplement occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study medication/supplement and record this information.

Subjects who discontinue study medication/supplement or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. If discontinuation occurs after Day 14, study personnel should attempt to obtain Day 28 labs as close as possible to last dose of study medication/supplement taken.

Where possible, they should return for the Day 28 assessments indicated in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the subject/pre-designated contact per institutional guidelines to collect as much data as possible according to the visit schedule.

Patient's vital status can also be verified by the study site upon contact with patient's primary care physician or other sources according to local rules and regulations.

After study medication/supplement discontinuation, at a minimum, in the abbreviated visit, the following data should be collected either during an in person visit or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

7.1.1.1 Replacement policy

Subjects will not be replaced on study.

7.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

  And

- Does not allow further collection of personal data

It is encouraged that patient provides withdrawal of consent in writing.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Patient's vital status can be verified upon contact with patient's primary care physician or other sources according to local rules and regulations.

Study medication/supplement must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

The study will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable regulations.

7.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must continue to attempt to contact the subject until the end of the study per institutional guidelines. A subject should not be considered as lost to follow-up until the end of the study. Vital status can be determined using publically available information in accordance with institutional guidelines.

7.1.4 Early study termination by the sponsor

The study can be terminated by the sponsor at any time. Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data

In making the decision to terminate, the sponsor will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The sponsor will be responsible for informing IRB of the early termination of the trial.

7.2 Study completion

Study completion is defined as when the last subject finishes their Day 28 visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

8 Safety monitoring and reporting

8.1 Definition of adverse events and reporting requirements

8.1.1 Adverse events

An adverse event is an untoward event that affects the patient's health or safety. When reporting an adverse event, the investigator will complete the AE report form. Adverse events that require reporting include any clinical changes in condition that could possibly be attributed to:

- Any of the study medication/supplements
- Any study required procedures (lab draws)

Each adverse event will be evaluated by the investigator for relatedness and seriousness.

i) Relatedness

The relatedness of an adverse event to the study medication/supplement will be assessed by the Investigator for each submitted adverse event form.

- **Possibly Related**: An adverse event that is noted in the package insert.
- **Unknown**: An adverse event that cannot be determined to have a causal relationship with either the study medication/supplement or study procedure will be classified as unknown.
- **Not Related**: An adverse event that is determined to not have a causal relationship with either the study medication/supplement or study procedure.

ii) Seriousness

Adverse events as described above will be evaluated for serious injury. Adverse events resulting in death or serious injury are to be reported to the sponsor within 24 hours of learning of the event. An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a

life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

iii) SUSARS

All Suspected Unexpected Serious Adverse Reactions (SUSARS) related to Rosuvastatin or supplements (if required per regulatory guidelines) are to be reported to the sponsor within 24 hours of learning of the event.

8.1.2 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported by the investigator to the sponsor. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should include an assessment of the possible relationship to the study medication/supplement of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

8.1.3 Executive Committee

The Executive Committee (EC) will play an active role in providing scientific guidance and advice to the sponsor related to the design, conduct, results analysis, and publication strategy for the SPORT study. The EC will be composed of members who are experts in preventive cardiology with relevant clinical trial methodological expertise. Meeting frequency, membership, and specific responsibilities will be further described in the EC Charter.

9 Data collection and database management

9.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) within the REDCap Cloud database. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

9.2 Safety monitoring

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) which may include demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

A Medical Monitor will review safety data for the study as specified in the Medical Monitor Charter.

10 Data analysis and statistical methods

10.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

The **full analysis set (FAS)** consists of all enrolled patients. Efficacy variables will be analyzed based on the FAS as the primary population.

The **safety analysis set (SAS)** consists of all patients who received at least one dose of study medication/supplement. The safety population will be used for the analyses of safety variables.

10.2 Subject disposition

The number of patients screened will be presented by study group and overall for the screened set. In addition, the reasons of screen failures will be provided for screened set as well. The number and percentage of patients who completed the study, who discontinued the study and the reason for discontinuation will be presented for each study group and all patients. The frequency (%) of patients with major protocol deviations will be presented in separate tables.

10.3 Subject demographics and baseline characteristics

All demographic and baseline characteristics summaries will be based on the FAS. They will be presented in summary tables by study group. Continuous data will be summarized by descriptive statistics, and categorical data will be summarized by frequency distributions. Finally, the number of enrolled patients by site will be presented descriptively.

10.4 Study evaluations

10.4.1 Study medication/supplement

The duration of the study medication/supplement use will be computed as the time from the first dose to the patient's study completion visit during the study close-out period.

The duration of the study medication/supplement use will be summarized for the full analysis set and safety set by study group descriptively including by duration categories.

The safety set will be used for the above analyses unless otherwise specified.

10.4.2 Prior and concomitant therapies

Prior or concomitant medication/supplements will be summarized for the safety set in separate tabulations based on a predetermined list of medication/supplements. Prior medication/supplement are defined as any medication/supplement a subject was taking prior to randomization in the study. Concomitant medication/supplements will include any medication/supplements taken during the study period.

10.5 Analysis of the primary endpoint

To control the overall alpha of the study, the primary endpoint will be evaluated hierarchically. Each comparison to rosuvastatin will use an alpha of 0.05. Once a comparison is not met (2-sided p-value ≥ 0.05) all subsequent comparisons will be considered exploratory with nominal p-values. The change in LDL-C for rosuvastatin will be compared with the other 7 study groups using ANCOVA in a hierarchical fashion in the following order:

- Rosuvastatin 5 mg compared with the following:
    1. Placebo (identical to rosuvastatin 5mg)
    2. Fish oil (Nature Made™ 2 soft gels / day)
    3. Cinnamon (1200mg, 2 capsules / day)
    4. Garlique™ (1 tablet / day)
    5. Turmeric (Bio Schwartz Turmeric Curcumin, 1500mg, 3 capsules / day)
    6. Plant sterol (Nature Made CholestOff™ Plus, 2 soft gels 2x / day)
    7. Red yeast rice (Arazo Nutrition, Red Yeast Rice, 1200mg, 2 capsules / day)

If the percent change in LDL has a non-normal distribution (graphically assessed), median values will be used to summarize the endpoints and compared with a non-parametric test. At a minimum, adjustments for baseline LDL and age will be used in summarizing the endpoints. Other adjustments may be warranted if differences in factors across study groups are statistically significant. The primary endpoint will be analyzed in the FAS.

10.6 Analysis of secondary endpoints

The following secondary endpoints will be analyzed in the FAS:

- Percent change in high sensitivity C reactive protein (hsCRP) for each study group compared with rosuvastatin 5 mg
- The percent changes in HDL-C, total cholesterol, and triglycerides for each study group compared with rosuvastatin 5 mg

- The percent changes in HDL-C, total cholesterol, and triglycerides for each study group compared with placebo

The comparisons of each study group to placebo will utilize placebo-subtracted changes from baseline. Percent change from baseline for each study group and placebo will first be calculated. The difference found in the placebo arm will then be subtracted from each study group. The mean and 95% confidence intervals will be used to summarize the effect of each study group.

No hierarchical testing of the secondary endpoints will be conducted. Since the study was not powered to test secondary endpoints, all testing and p-values will be considered exploratory. No adjustments will be made for multiplicity.

10.6.1 Adverse events

All information obtained on adverse events will be summarized by study group. A subject with multiple adverse events of the same type is only counted once towards the total of that event. Serious adverse event and deaths resulting from an adverse events will be tabulated. All adverse events, deaths and serious adverse events will be provided in patient listings.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator will obtain approval/favorable opinion from the Institutional Review Board (IRB) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures and any other written information to be provided to subjects.

The protocol will be registered in a publicly accessible database *clinicaltrials.gov*. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results in *clinicaltrials.gov.*

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