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**ATHEROTHROMBOSIS
INTERVENTION in
METABOLIC SYNDROME with Low
HDL/HIGH TRIGLYCERIDE and
IMPACT ON
GLOBAL
HEALTH OUTCOMES**

AIM-HIGH

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TABLE OF CONTENTS

<u>Section</u>	<u>Page Number</u>
List of Abbreviations	4
1.0 Executive Summary	5
2.0 Background and Rationale	10
3.0 Study Objectives	15
4.0 Study Design	16
4.1 General Review	16
4.2 Study Committees	17
4.3 Randomization and Duration of Study Participation	18
4.4 Selection of Patients	18
4.5 Treatment Protocol	22
4.6 Assessment of Clinical Events	26
4.7 Patient Safety	29
4.8 Patient Withdrawal	30
4.9 Study Procedures	30
5.0 Statistical Considerations	35
6.0 Regulatory Standards	39
6.1 Informed Consent	39
6.2 Institutional Review Board/Independent Ethics Committee	39
7.0 Study Monitoring	39
8.0 Summary	40
9.0 References	42
Appendices	46

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
ACC	American College of Cardiology
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high TG and Impact on Global Health Outcomes
ATP III	Adult Treatment Panel III
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CK	Creatine Kinase
CRP	C-Reactive Protein
CT	Computed Tomography
CTC	Clinical Trial Coordinating Center
DM	Diabetes Mellitus
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ERN	Extended-Release Niacin
FATS	Familial Atherosclerosis Treatment Study
HATS	HDL Atherosclerosis Treatment Study
HDL	High-Density Lipoprotein
LAD	Left Anterior Descending
LDL	Low-Density Lipoprotein
Lp(a)	Lipoprotein (a)
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NCEP	National Cholesterol Education Program
NSTE	Non-ST-Segment Elevation
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
TG	Triglyceride
ULN	Upper Limit of Normal
VLDL	Very-Low Density Lipoprotein

1. EXECUTIVE SUMMARY

Title	AIM-HIGH Trial: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes
Objectives	<p>Primary:</p> <p>In patients with established vascular disease and atherogenic dyslipidemia, we plan to compare the efficacy and safety of statin monotherapy (with simvastatin) versus combination therapy (with extended-release niacin plus simvastatin), at comparable levels (<80 mg/dL [2.1 mmol/L]) of on-treatment LDL-C, in reducing the risk for the composite endpoint of coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), ischemic stroke, or hospitalization for high-risk non-ST-segment elevation (NSTE) acute coronary syndrome.</p> <p>Secondary:</p> <ul style="list-style-type: none"> • To evaluate the effect of therapy on the composite endpoint of CHD death, non-fatal MI, or ischemic stroke • To evaluate the effect of therapy on cardiovascular mortality <p>Tertiary:</p> <ul style="list-style-type: none"> • To evaluate the effect of therapy on total mortality • To evaluate the effect of therapy on the composite endpoint of, and the individual components of the composite endpoint of, CHD death, non-fatal MI, ischemic stroke, hospitalization for NSTE acute coronary syndrome, or any revascularization • To evaluate the effect of therapy for preventing clinical events, as defined above, among patients meeting current criteria for metabolic syndrome as defined by the NCEP ATP III, or future criteria for metabolic syndrome as they may evolve, or diabetes • To assess the effects of statin monotherapy versus combination therapy on lipids and lipoproteins, including, apoA-I, apoB, apoC-III, Lp(a), HDL subfractions/particle size, LDL size and subclass distribution, and their independent contribution to predicting outcomes

	<ul style="list-style-type: none"> To assess the effect of therapy on inflammatory markers such as C-reactive protein and fibrinogen, and their independent contribution to predicting outcomes
Design	This is a multicenter, prospective, randomized, double-blind, parallel-group, active comparator study.
Study Population	<p>INCLUSION CRITERIA:</p> <p>Men and women aged 45 and older with the following two criteria:</p> <p><u>1. Established Vascular Disease, Defined as One or More of the Following:</u></p> <p>a. Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):</p> <ul style="list-style-type: none"> Documented multivessel CAD (one or more $\geq 50\%$ stenoses in <i>two</i> major epicardial coronary arteries – with or without antecedent revascularization) Documented history of MI Hospitalization for unstable angina with objective evidence of ischemia (ST-segment deviation or biomarker positivity) <p>b. Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):</p> <ul style="list-style-type: none"> Documented previous ischemic stroke Symptomatic carotid artery disease with $\geq 50\%$ carotid arterial stenosis Asymptomatic carotid artery disease with $\geq 70\%$ carotid arterial stenosis History of carotid revascularization (catheter-based or surgical) <p>c. Documented Peripheral Arterial Disease (PAD; one or more of the following primary criteria must be satisfied):</p> <ul style="list-style-type: none"> ABI < 0.85 with or without symptoms of intermittent claudication History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

	<p>2) <u>Dyslipidemia defined as</u> (all 3 must be satisfied):</p> <ul style="list-style-type: none"> • The equivalent, off lipid therapy, of: <ul style="list-style-type: none"> - LDL-C of ≤ 180 mg/dL (4.7 mmol/L) - HDL-C of ≤ 40 mg/dL (1.0 mmol/L) [men] or ≤ 50 mg/dL (1.3 mmol/L) [women] - TG ≥ 150 mg/dL (1.7 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L) • For patients entering the trial on a statin: <ul style="list-style-type: none"> - the upper limit for LDL-C is adjusted according to the specific statin and statin-dose (see Table, section 4.4.1.2) - HDL-C of ≤ 42 mg/dL (1.1 mmol/L) [men] or ≤ 53 mg/dL (1.4 mmol/L) [women] - TG ≥ 100 mg/dL (1.1 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L) <p>Major Exclusion Criteria (see additional detail in protocol):</p> <ul style="list-style-type: none"> • Coronary Artery Bypass Graft (CABG) surgery within 1 year of planned enrollment (run-in phase) • Percutaneous Coronary Intervention (PCI) within 4 weeks of planned enrollment (run-in phase) • Hospitalization for acute coronary syndrome and discharge within 4 weeks of planned enrollment (run-in phase) • Fasting glucose >180 mg/dL (10 mmol/L) or hemoglobin A1C $>9\%$ • For patients with diabetes, inability or refusal to use a glucometer for home monitoring of blood glucose
	<p>Rescreening</p> <ul style="list-style-type: none"> • Patients disqualified for enrollment in the study by virtue of the above inclusion/exclusion criteria may subsequently be rescreened and considered for enrollment if at a later time they no longer fail to meet those criteria or if disqualifying exclusion criteria are corrected
<p>Total expected number of clinical centers and subjects</p>	<ul style="list-style-type: none"> • A minimum of 54 clinical centers in the United States and Canada will be involved in this study • Estimated sample size of 3,300 subjects

Participating physicians/sites	<p>The recruitment of the sites and subjects should allow an extrapolation of the results to the broadest possible population with vascular disease and atherogenic dyslipidemia. Therefore the recruitment of the sites and subjects will be done carefully in order to ensure representation of the overall population.</p> <p>To achieve this goal two rules will be followed:</p> <ul style="list-style-type: none"> • Pre-defined selection of physicians and sites • Prospective and consecutive enrollment of subjects
Main data collected	<ul style="list-style-type: none"> • Baseline demographic information, employment status, medical history, physical examination, current medical treatments • Post-randomization, clinical events including all causes of death, MI, stroke, vascular interventions and hospitalizations, with dates and detailed documentation, since last visit • Corresponding secondary and tertiary efficacy endpoint parameters, as appropriate • Fasting blood lipids and lipoproteins • Safety endpoints, including fasting blood glucose, creatinine hemoglobin A1C, thyroid function test, liver function tests
Statistical analysis	<ul style="list-style-type: none"> • Randomization will be stratified by site, gender and prior history of diabetes • Intent-to-treat analysis. • Parameters will be summarized using mean, median, standard deviation for continuous data and percentage for categorical data • Survival analysis using Cox Proportional Hazards analysis of primary efficacy outcome comparing the 2 groups (combination versus monotherapy) • Statistical analyses for the efficacy outcomes will be performed at the 2.5% significance level using 1-sided tests. All other statistical analyses will be performed at the 5% significance level using 2-sided tests. • Interim analyses are planned using group sequential methods to monitor the trial <p>The analysis is planned to:</p> <ul style="list-style-type: none"> • Describe at baseline subject characteristics, including lipids and lipoproteins, stroke history, cardiovascular risk factors, diabetes mellitus, or metabolic syndrome, among others

	<ul style="list-style-type: none">• Compare the primary, secondary, and tertiary endpoints between the patient groups receiving the combination anti-dyslipidemic therapy and statin monotherapy at corresponding follow-up time points
Timelines	3,300 qualified patients will be enrolled in a minimum of 54 clinical sites over a planned 2 year period with a mean follow-up of 4 years

2. Background and Rationale for AIM-HIGH

2.1 Vascular disease, atherogenic dyslipidemia and metabolic syndrome, statins as monotherapy and combination therapy in CHD management

2.1.1 Vascular disease

Coronary heart disease remains the leading cause of death and disability in the U.S. and the Western world. Data from the *2002 Heart and Stroke Statistical Update*, American Heart Association, indicate that there are 12.6 million individuals in the U.S. with a history of MI, angina, or both. The prevalence of stroke, transient ischemic attack (TIA) and PAD in the U.S. currently is 4.6 million, 4.9 million and 8-12 million, respectively. Aggregate direct and indirect costs for CHD in the U.S. in 2001 were \$112 billion and for stroke/TIA were \$49 billion.¹

The pathologic basis of symptomatic vascular disease including CHD, cerebral vascular disease and PAD is atherothrombosis, which is characterized by an unpredictable, sudden rupture/fissure of an atherosclerotic plaque. A rupture or large fissure of an atherosclerotic plaque typically results in a large thrombus formation, which in turn results in an acute ischemic event such as myocardial infarction or ischemic stroke. A small fissure may result in a mural thrombus, which may cause transient ischemia such as unstable angina or TIA.

2.1.2. Atherogenic Dyslipidemia and Metabolic Syndrome

Dyslipidemia is one of the major modifiable risk factor of atherosclerosis.² Elevated plasma concentrations of the apolipoprotein B (apo B)-containing low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and their remnants, and lipoprotein (a) [Lp(a)] promote the development of atherosclerotic lesions, while elevated levels of HDL-C inhibit plaque formation.³ The type of LDL particles present in the blood may also be a key atherogenic risk factor, with small, dense LDL particles more likely to be involved in the formation of plaques than larger, more buoyant ones.^{4,5}

An increasingly common dyslipidemia seen among patients with established vascular disease consists of a low HDL-C together with elevated triglycerides and preponderance of small, dense LDL particles, so-called 'atherogenic dyslipidemia.' Low-density lipoprotein cholesterol may be only minimally elevated. This phenotypic pattern is characteristic of patients with diabetes or metabolic syndrome, the presence of each of which significantly increases the risk for CHD. In fact, the great majority of patients with established vascular disease and atherogenic dyslipidemia will have at least one other component of the metabolic syndrome (BG Brown, personal communication).

Metabolic syndrome was identified in 1988 and defined as a combination of insulin resistance, hyperinsulinemia, increased plasma levels of triglycerides, and decreased plasma levels of HDL-C.^{5,6} Insulin resistance in the metabolic syndrome occurs at the

level of glucose and free fatty acid metabolism, and the lipoprotein abnormalities consist of increases in plasma levels of triglycerides, apo B, and smaller denser LDL particles, with marked reductions in plasma levels of HDL-C and apo A-I.^{6,7}

Based on the Third National Health and Nutrition Examination Survey (NHANES),⁷ the estimated overall prevalence of the metabolic syndrome in the United States is 24% (43% of men and women ≥ 50 years old), which corresponds to approximately 47 million individuals. Coupled with the metabolic syndrome is a potentially increased risk for the development of diabetes and coronary artery disease.⁹⁻¹³

2.1.3. Statin monotherapy in vascular disease management

The etiologic role of elevated blood levels of LDL-C in atherosclerosis has long been established by both its strong association with CHD in well-characterized populations and the unequivocal therapeutic benefit of drug therapies that specifically reduce its concentrations. In primary and secondary prevention trials using a statin, plasma LDL-C was reduced by 25%-36% and coronary event rates were reduced by 24%-34% compared with placebo. Most recently, the Heart Protection Study (HPS) randomized over 20,000 patients with CHD, occlusive arterial disease, or diabetes to treatment with simvastatin or placebo for an average of 5 years.¹⁴ Simvastatin treatment was associated with a mean 29% decrease in LDL-C compared to placebo and relative risk reductions in non-fatal myocardial infarction (MI) or CHD death of 27% ($p < 0.0001$), non-fatal or fatal stroke of 25% ($p < 0.0001$), and coronary or non-coronary revascularization of 24% ($P < 0.0001$). Furthermore, these benefits were independent of gender, age, baseline risk status.

It is important to note that *although these trials demonstrated an approximate 30% relative reduction in cardiovascular risk, patients treated with a statin, even those who achieved on-trial LDL-C levels ≤ 70 mg/dL (1.8 mmol/L), still experienced an event rate equal to at least 60% of the rate seen in those treated with placebo.*¹⁵ For example, in the recently-reported Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT) comparing atorvastatin 80 mg versus pravastatin 40 mg in patients hospitalized for an acute coronary syndrome, the 2-year risk for a major cardiovascular event (death from any cause, MI, documented unstable angina requiring re-hospitalization, or revascularization) among atorvastatin-treated patients, who achieved a mean on-trial LDL-C of 62 mg/dL (1.6 mmol/L), was 22%. For the endpoint of death or MI, the 2-year event rate in the atorvastatin group was 8%. Extrapolated over a 10-year period, the risk for death or MI would be as high as 40% in this group, despite having a mean LDL-C of 62 mg/dL (1.6 mmol/L). These figures point to the fact that, among patients treated with statins as monotherapy for dyslipidemia, the residual risk for an event is unacceptably high. Clearly, LDL-C reduction alone is insufficient to optimize CHD management.

2.1.4. Combination Therapy in CHD management

2.1.4.1 Importance of low HDL-C in dyslipidemia

Risk assessment limited to LDL-C fails to identify a substantial number of patients at risk for coronary events and other vascular events. Patients with metabolic syndrome and most patients with type 2 diabetes have multiple lipid abnormalities: increased plasma triglycerides and apoB levels, increased number of smaller denser LDL particles and decreased plasma HDL-C levels. Most patients with CHD also have multiple lipid abnormalities. The Veterans Affairs HDL Intervention Trial (VA-HIT) group¹⁶ found that 87% of 8500 patients with established CHD had suboptimal LDL-C levels ($\geq 100\text{mg/dL}$ [2.6 mmol/L]), 33% had hypertriglyceridemia (triglycerides levels $> 200\text{mg/dL}$ [2.3 mmol/L]), and approximately 60% had low levels of HDL-C ($\leq 40\text{mg/dL}$ [1.0 mmol/L]).

Low levels of HDL-C are strong independent predictors of CHD risk. Each 1mg/dL [0.03 mmol/L] increase in HDL-C is associated with a 2% to 3% decrease in CHD risk, even after adjustment for other risk factors, and predicts coronary risk regardless of LDL-C levels.¹⁷ The NCEP III has identified HDL-C levels less than 40mg/dL (1.0 mmol/L) as a risk factor for CHD, although no goal has been set.² Subsequently, multivariate analyses of clinical trials in hypercholesterolemic patients have shown that raising HDL-C levels was associated with reductions in CHD events. VA-HIT was the first study to provide conclusive evidence that raising low levels of HDL-C, in CHD patients with normal LDL-C levels, was associated with significant reductions in coronary events.¹⁸ More recently, the HDL Atherosclerosis Treatment Study (HATS) has shown that treatment of the total lipid profile with a combination of simvastatin and niacin was associated with a significant regression of coronary atherosclerosis and further reductions in clinical events¹⁹.

2.1.4.2 Emerging role of combination therapy

The five classes of lipid-modifying agents (statins, fibrates, bile acid sequestrants, ezetimibe and niacin) produce their major effect on one lipid or lipoprotein but have only moderate or minor effects on the others.¹ Therefore, each drug as monotherapy may leave a large number of patients treated inadequately. In contrast, combination therapy can provide more effective coverage of the entire lipid profile. The clinical importance of combination therapy is underscored by the high prevalence of low HDL-C in patients with CHD, metabolic syndrome and diabetes. Review of previous trials that combined various statins with preparations of sustained- or immediate-release niacin have not only shown the beneficial effects on improving dyslipidemia^{19,20} but also on facilitating the regression of the atherosclerotic lesions and reducing clinical events including death, MI or revascularization.^{21,22} Results of recent trials of combination therapy with statins and niacin have demonstrated improved regulation of dyslipidemia.^{23,24}

2.2 Niacin and anti-dyslipidemic therapy

2.2.1 Mechanism of action

Niacin has favorable effects on all major lipids and lipoproteins. Its mechanisms of action are not completely understood. Niacin has a significant effect on HDL-C levels. The primary mechanism by which niacin increases HDL-C is by reducing the catabolic rate of apolipoprotein (apo) AI, the major protein carrier of HDL.^{25,26} Reverse cholesterol transport is thereby enhanced as cholesterol-deficient, apolipoprotein A-I-containing HDL particles are re-circulated to peripheral cells to transport additional cholesterol to the liver.

Niacin also produces large and rapid reductions in TG and inhibits its hepatic esterification, thereby reducing production of atherogenic lipoproteins³⁵. It inhibits hormone-sensitive lipoprotein lipase in fat cells reducing intracellular lipolysis and release of fatty acids into the plasma. The decrease in circulating free fatty acids reduces uptake by the liver, thereby inhibiting hepatic VLDL production. Since VLDL is converted into intermediate-density lipoprotein and then LDL, reductions in VLDL lower LDL-C.²⁶

2.2.2 Niacin in combination therapy

Several studies have evaluated the role of the combination therapy of niacin and statin. In one study using fluvastatin, combination therapy with immediate-release (IR) niacin produced greater reductions in LDL-C than did combination therapy with placebo (40% vs 25%, $p<0.001$).²⁷ In another study, the combination of IR niacin and simvastatin had no greater effect on LDL-C than simvastatin alone; however, HDL cholesterol increased by 31%, compared with 13% for the statin alone group ($p<0.05$).²⁸ In a third study, combination therapy of 1g/day once-daily niacin extended-release (Niaspan®) and statin lowered LDL-C by an additional 8% and increased HDL-C by 24%; combination therapy of 2g/day extended-release niacin and statin lowered LDL-C an additional 20% and raised HDL-C an additional 27%.²⁹ In a recent study evaluating the efficacy of the combination of the extended-release niacin and rosuvastatin, compared with rosuvastatin alone, rosuvastatin 10mg/ER niacin 2 g produced significantly greater increases in HDL cholesterol (11% vs 24%, $p<0.001$) and apolipoprotein A-I (5% vs 11%, $p<0.017$).³⁰

2.2.3 Safety and tolerability of niacin use

General population

Despite the lipid and cardiovascular benefits associated with niacin, its use has been limited in clinical practice by poor tolerability caused by dose-dependent side effects, particularly cutaneous and gastrointestinal complaints associated with immediate-release or crystalline niacin.³¹ Almost all patients who take immediate-release niacin experience flushing, which leads to medication discontinuation in approximately 10% to 20% of subjects in clinical studies.^{32,33} Elevated hepatic transaminase levels have been reported

with immediate-release niacin, usually after long-term use with high doses (>3 to 4 g/d),³⁴⁻³⁶, but hepatic failure has been rare.^{35,37}

Sustained-release preparations of niacin were developed to overcome the limitations associated with the immediate-release form.³² The different toxicologic characteristics of immediate-release and sustained-release preparations are due to the dual pathways of niacin metabolism—a low-affinity, high-capacity conjugative pathway that leads to flushing and a high-affinity, low-capacity nonconjugative pathway that may lead to hepatotoxicity. Recently, a once-daily extended-release niacin (Niaspan[®], Kos Pharmaceuticals, Miami, FL) has been formulated to distribute drug absorption over an intermediate time of 8 to 12 hours³⁸ to balance metabolism between both pathways. In one study, extended-release niacin once-daily was shown to have efficacy equivalent to immediate-release niacin three times daily and to reduce episodes of flushing by about 80%.³⁹ In a 96-week study, doses of 2000 mg/d of extended-release niacin, reduced LDL-C, triglycerides, and Lp(a) by 18%, 24%, and 36%, respectively, while increasing HDL-C by 29% from baseline.⁴⁰ Reversible elevations in liver function tests greater than 3 times upper limit of normal (ULN) occurred in <1.0% of patients, and serious hepatic toxicity was not evident.

In patients with diabetes mellitus (DM)

Niacin appears ideally suited to treating the atherogenic dyslipidemia associated with diabetes, but traditionally niacin use was thought to be relatively contraindicated in patients with diabetes due to adverse effects on glucose control and insulin sensitivity.^{41,42} However, due to the high prevalence of low HDL-C in diabetes and the difficulty of raising low HDL-C levels with other agents, several recent studies have re-evaluated the use of niacin in patients with controlled type 2 diabetes. The Arterial Disease Multiple Intervention Trial (ADMIT) evaluated the effect of niacin in 468 patients with peripheral arterial disease, including 125 patients with diabetes⁴³. Niacin produced small increases from baseline in average glucose levels among patients with diabetes (8.1 mg/dL [0.45 mmol/L]; $p=0.04$) and without diabetes (6.3 mg/dL [0.35 mmol/L]; $p<0.001$), but hemoglobin A1C levels were not significantly changed from baseline. These small glycemic changes did not increase niacin discontinuation or alter hypoglycemic therapy compared with placebo. Similar results were seen in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) which randomized 148 diabetic patients to treatment with an extended-release niacin (niacin ER) 1000 mg or 1500 mg or placebo.⁴⁴

Moreover, in a post-hoc analysis from the HDL Atherosclerosis Treatment Study (HATS), niacin/simvastatin combination therapy produced nearly a 50% relative reduction in major clinical events in the subset of patients with diabetes or impaired fasting glucose.⁴⁵ There was no significant difference in glycemic control between the active treatment or placebo groups. These results suggest that niacin can be used safely in diabetic patients. Although glucose levels should be monitored for potential hyperglycemia and additional glycemic control may be needed, this risk is offset by the potential cardiovascular benefits resulting from the broad improvement in the lipid triad.

Thus, niacin may be considered as an alternative to statins and fibrates when patients with diabetes cannot tolerate these agents or when their hypertriglyceridemia or low HDL-C levels do not sufficiently improve.⁴³

2.3 AIM-HIGH Rationale

The hypothesis of AIM-HIGH is that combination anti-dyslipidemic therapy (extended-release niacin plus simvastatin) will be superior to statin monotherapy alone (simvastatin) when used as secondary prevention in reducing long-term clinical events in patients with documented vascular disease and atherogenic dyslipidemia. Based on these selection criteria, the vast majority of these patients are anticipated to satisfy current NCEP ATP III criteria for a diagnosis of metabolic syndrome.

To date, there have been several large randomized controlled trials involving statin monotherapy versus placebo to reduce elevated LDL-C and clinical events in CHD patients, but only one secondary prevention randomized controlled trial to assess the role of raising low levels of HDL-C and/or lowering TG levels and its impact on favorably reducing CHD death, MI and stroke (VA-HIT). VA-HIT clearly demonstrated the superiority of gemfibrozil versus placebo in male veterans with CHD and low levels of HDL-C, but was limited in its overall generalizability because women were excluded. In addition, the increase in HDL-C in that study was quite modest (~6%) compared to what is anticipated with niacin.

Thus, while VA-HIT provides important “proof of concept” that the “HDL hypothesis” of therapeutically raising low levels of HDL-C reduces coronary and cerebrovascular events during long-term follow-up, there has been, to date, no randomized controlled trial that has evaluated prospectively the role of “combination dyslipidemic therapy” in a more geographically and demographically-diverse population of men and women with vascular disease manifested as CHD, CVD or PAD and who have the increasingly common lipid profile of low HDL-C, elevated triglycerides (with or without elevated LDL-C), and features of the insulin resistance (metabolic) syndrome. The current gaps in our scientific knowledge and contemporary therapeutics as to how such patients should be managed optimally are large, and the proposed AIM-HIGH trial seeks to address these important considerations.

3. Study Objectives

3.1 Primary Objective:

To assess, during a 3-5 year follow-up, the comparative efficacy and safety of statin monotherapy (simvastatin) versus combination therapy (niacin extended-release plus simvastatin), at comparable levels (≤ 80 mg/dL [2.1 mmol/L]) of on-treatment LDL-C, in reducing the risk for clinical events (CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk NSTEMI acute coronary syndrome) in vascular disease patients with atherogenic dyslipidemia (low HDL-C and high triglycerides).

3.2 Secondary Objectives

- To evaluate the effect of therapy on the composite endpoint of CHD death, non-fatal MI, or ischemic stroke
- To evaluate the effect of therapy on cardiovascular mortality

3.3 Tertiary Objectives

- To evaluate the effect of therapy on total mortality
- To evaluate the effect of therapy on the composite endpoint of, and the individual component of the composite endpoint of, CHD death, non-fatal MI, ischemic stroke, hospitalization for NSTEMI acute coronary syndrome, or any revascularization
- To evaluate the effect of therapy for preventing clinical events, as defined above, among patients meeting current criteria for metabolic syndrome as defined by the NCEP ATP III, or future criteria for metabolic syndrome as they may evolve, or diabetes
- To assess the effects of statin monotherapy versus combination therapy on lipids and lipoproteins, including apoA-I, apoB, apoC-III, Lp(a), HDL subfractions/particle size, LDL size and subclass distribution, and their relationship to outcome
- To assess the effects of therapy on inflammatory markers, such as C-reactive protein and fibrinogen, and their relationship to outcome

4. Study Design

4.1 General review

- Multicenter, prospective, randomized, double-blind, parallel-group, active comparator design of statin monotherapy (simvastatin) versus combination anti-dyslipidemic therapy (extended-release niacin plus simvastatin) in high-risk patients with established vascular disease (i.e., those who have a 10-year risk of an event of $\geq 20\%$) who have atherogenic dyslipidemia (low HDL-C and high triglycerides). The vast majority of these patients will qualify for a diagnosis of metabolic syndrome.

- Prospectively, eligible patients with documented vascular disease will undergo screening to establish suitability for inclusion in the trial. For patients currently treated with a statin, no drug washout will be performed. All other lipid-altering drugs (e.g., niacin, fibrates, ezetimibe) must be discontinued at least 4 weeks prior to the qualifying lipid determination. Lipid inclusion criteria are: untreated or off-therapy LDL-C ≤ 180 mg/dL [4.7 mmol/L]; HDL-C ≤ 40 mg/dL (1.0 mmol/L) [men] or 50 mg/dL (1.3 mmol/L) [women]; and TG ≥ 150 mg/dL (1.7 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L). For statin-treated patients, the upper limit for LDL-C is adjusted according to the specific statin and dose (Section 4.4.1.2). In addition, the HDL-C and TG entry criteria are modified to: HDL-C of ≤ 42 mg/dL (1.1 mmol/L) [men] or ≤ 53 mg/dL (1.4 mmol/L) [women] – assumes an average statin effect of about +5%; TG ≥ 100 mg/dL (1.1 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L) – assuming a statin effect of up to –33%.

4.2 Study committees

Executive Committee

The Executive Committee of the study is composed of a core group of investigators/academic members from participating clinical centers. A representative of the industry sponsor and the principal investigator of the central laboratory will be ex-officio members. This committee will provide scientific and strategic direction for the trial and will have overall responsibility for the design, execution, and publication. Detailed responsibilities and membership for this committee will be provided as needed. The Executive Committee of AIM-HIGH will be in charge of the logistical coordination of the different study committees.

Clinical Event Committee (CEC)

The CEC is composed of multidisciplinary academic members. This committee will be responsible for blindly validating all the primary and secondary efficacy outcome events reported by the investigators. This committee will create a charter with details on the methods and assessment of clinical events and their precise definitions.

Data and Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be instituted for this study in order to ensure its ongoing safety and to oversee the Interim Analyses. Recommendation for trial continuation will be guided by monitoring boundaries at interim analyses at which formal efficacy analysis is performed as well as safety evaluations at all safety data reviews.

Members of the DSMB will not be otherwise participating in the trial. The committee will include at least one cardiologist with expertise in atherosclerosis and inflammatory processes, one lipidologist and diabetologist as well as an independent statistician. A DSMB Charter will be drafted and approved by the DSMB, the NHLBI and the Executive Committee. The Charter will provide details regarding the interim analysis

and monitoring plan. Safety review meetings will be held approximately every 6 months. Safety data will include pre-specified evaluation of parameters for blood glucose, myopathy, hepatotoxicity as well as other possible clinical side effects such as gout, as requested by the DSMB. Formal interim analyses for efficacy data will be performed as per separate DSMB charter. Enrollment to the study will continue throughout the scheduled meetings of the DSMB.

4.3 Randomization and duration of study participation

About 3,300 patients (1,650 in each group) will be randomized to receive simvastatin monotherapy or niacin extended-release plus simvastatin. As described in Section 5.2, the estimated study duration that served as the hypothesis for sample size calculations comprises a planned 2-year enrollment and a mean 4 years of follow-up. In any case, all randomized patients will be followed until study end date, with a minimum follow-up duration of three years and a maximal follow-up duration that corresponds to the time between the first randomization and the study end date (5 years).

4.4 Selection of patients

4.4.1 Inclusion criteria:

Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia, defined in the following ways:

4.4.1.1 Established Vascular Disease

a. Documented CAD (one or more of the following primary criteria must be satisfied):

- Documented multivessel CAD, defined as one or more $\geq 50\%$ stenoses in at least *two* major epicardial coronary arteries by angiography. Patients in whom percutaneous coronary intervention (PCI) has been successfully performed on one or both coronary stenoses - even if there is no residual post-PCI stenosis - will still be considered to satisfy the trial eligibility criterion of multivessel CAD
- Documented previous MI (two of the following three criteria must be satisfied):
 - Characteristic ischemic chest pain or pain in associated referral areas
 - Elevation of CK (at least twice the upper limit of normal values) and/or CK-MB (at least twice the upper limit of normal values) and/or troponin T or I (at least twice the upper limit of normal value)
 - Development of Q waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1
- Hospitalization for NSTEMI acute coronary syndrome with objective evidence of

ischemia (ST-segment deviation or biomarker positivity) – stable for at least 4 weeks following hospital discharge. Patients must have clinical findings of ischemic symptoms consistent with angina (chest or midepigastic discomfort, dyspnea, or symptoms that represent an “anginal equivalent,” if atypical) in the judgment of the investigator

b. Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):

- Documented previous ischemic stroke (all criteria must be satisfied):
 - A focal ischemic neurological deficit persisting for more than 24 hours
 - Considered to be of ischemic origin
 - Onset within previous 5 years but not within 8 weeks prior to enrollment
 - Patients with history of ischemic stroke and atrial fibrillation do *not* satisfy the criterion for CVD, in the absence of other evidence for cerebrovascular disease. Patients with history of ischemic stroke and sinus rhythm *are* eligible

A CT scan or MRI must have been performed to rule out hemorrhage and non-ischemic neurological disease.

- Symptomatic carotid artery disease with $\geq 50\%$ stenosis established by angiography or color-coded duplex ultrasound on the basis of recognized criteria (see Appendix 2 for method of evaluation)
- Asymptomatic carotid stenosis $\geq 70\%$ established by angiography or color-coded duplex ultrasound on the basis of recognized criteria (see Appendix 2 for method of evaluation)
- History of carotid revascularization (surgical or catheter-based)

c. Documented PAD (one or more of the following primary criteria must be satisfied):

- ABI < 0.85 , with or without symptoms of intermittent claudication (see Appendix 3 for measurement method)
- A history of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

And

4.4.1.2 Atherogenic Dyslipidemia defined as:

- Off therapy, the following criteria must all be met:
 - LDL-C of ≤ 180 mg/dL (4.7 mmol/L)
 - HDL-C of ≤ 40 mg/dL (1.0 mmol/L) [men] or ≤ 50 mg/dL (1.3 mmol/L) [women]
 - TG ≥ 150 mg/dL (1.7 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L)

- For patients entering the trial on a statin, the equivalent lipid criteria must be met as follows:
 - the upper limit for LDL-C is adjusted according to the specific statin and statin-dose in the table below
 - HDL-C of ≤ 42 mg/dL (1.1 mmol/L) [men] or ≤ 53 mg/dL (1.4 mmol/L) [women]
 - TG ≥ 100 mg/dL (1.1 mmol/L) and ≤ 400 mg/dL (4.5 mmol/L)

No patient currently receiving a statin will be required to discontinue their statin therapy prior to obtaining baseline laboratory tests or beginning the open-label run-in. All other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils, combination therapy drugs (e.g., niacin extended-release/lovastatin [Advicor®] or simvastatin/ezetimibe [Vytorin®]) must be washed out for at least 4 weeks prior to the baseline.

In eligible patients who are receiving a statin at enrollment, the LDL-C upper limit for qualification will be modified as follows:

Statin	10 mg	20 mg	40 mg	80 mg
None	(≤ 180 mg/dL)	(≤ 180 mg/dL)	(≤ 180 mg/dL)	(≤ 180 mg/dL)
Atorvastatin	≤ 113 mg/dL	≤ 101 mg/dL	≤ 92 mg/dL	≤ 87 mg/dL
Pravastatin*	≤ 141 mg/dL	≤ 129 mg/dL	≤ 117 mg/dL	≤ 110 mg/dL
Simvastatin	≤ 129 mg/dL	≤ 117 mg/dL	≤ 110 mg/dL	≤ 97 mg/dL
Fluvastatin	--	≤ 141 mg/dL	≤ 135 mg/dL	≤ 115 mg/dL
Rosuvastatin**	≤ 97 mg/dL	≤ 87 mg/dL	≤ 81 mg/dL	--

*or Lovastatin

**for Rosuvastatin 5 mg use 113 mg/dL

Statin	10 mg	20 mg	40 mg	80 mg
None	(≤ 4.7 mmol/L)	(≤ 4.7 mmol/L)	(≤ 4.7 mmol/L)	(≤ 4.7 mmol/L)
Atorvastatin	≤ 2.9 mmol/L	≤ 2.6 mmol/L	≤ 2.4 mmol/L	≤ 2.3 mmol/L
Pravastatin*	≤ 3.7 mmol/L	≤ 3.3 mmol/L	≤ 3.0 mmol/L	≤ 2.8 mmol/L
Simvastatin	≤ 3.3 mmol/L	≤ 3.0 mmol/L	≤ 2.8 mmol/L	≤ 2.5 mmol/L
Fluvastatin	--	≤ 3.7 mmol/L	≤ 3.5 mmol/L	≤ 3.0 mmol/L
Rosuvastatin	≤ 2.5 mmol/L	≤ 2.3 mmol/L	≤ 2.1 mmol/L	--

*or Lovastatin

**for Rosuvastatin 5 mg use 2.9 mmol/L

4.4.2. Exclusion (Non-Inclusion) Criteria:

- Hospitalization for acute coronary syndrome and discharge within 4 weeks prior to planned enrollment (run-in phase)
- Coronary Artery Bypass Graft (CABG) surgery within 1 year of planned enrollment (run-in phase), unless there has been a new, intercurrent acute coronary syndrome event or recurrent angina, associated with angiographic evidence of disease progression ($\geq 50\%$ stenosis) in 1 or more native vessels or bypass grafts, regardless of whether subsequently treated with PCI/stenting
- Planned percutaneous coronary intervention (PCI) within 4 weeks prior to planned enrollment (run-in phase)
- Stroke within 8 weeks prior to planned enrollment (run-in phase)
- Fasting glucose >180 mg/dL (10 mmol/L) or hemoglobin A1C $>9.0\%$
- Inability or refusal to use a glucometer for home monitoring of glucose
- CHD associated with unstable angina and symptoms refractory to maximal medical therapy (i.e., persistent Canadian Cardiovascular Society [CCS] Class IV)
- Post-MI course complicated by persistent rest angina, shock, or persistent congestive heart failure (CHF), etc., or if the need/likelihood of urgent revascularization is high
- Patients with left main coronary disease $\geq 50\%$ and no prior CABG
- Ejection fraction $<30\%$
- Cardiogenic shock, pulmonary edema or CHF unresponsive to standard medical therapy
- Concomitant valvular heart disease likely to require surgery or adversely affect prognosis during follow-up period
- Congenital or primary cardiomyopathy likely to adversely affect prognosis during follow-up period
- Resuscitated out-of-hospital sudden death or symptomatic sustained or non-sustained ventricular tachycardia without an implantable cardioverter-defibrillator (ICD)
- Significant systemic hypertension (blood pressure $>200/100$ mmHg) unresponsive to medical therapy
- Active peptic ulcer disease
- AST or ALT > 2 times upper limit of normal or active liver disease
- Recent history of acute gout. (For patients with baseline uric acid > 7.0 mg/dL [415 $\mu\text{mol/L}$], treatment with allopurinol is recommended but not mandated)
- Chronic renal insufficiency with creatinine ≥ 2.5 mg/dL (220 $\mu\text{mol/L}$)
- Patients who cannot discontinue the following excluded concomitant medications:
 1. Drugs with a high probability of increasing the risk for hepatotoxicity or myopathy, such as those predominantly metabolized by cytochrome P450system 3A4, including, but not limited to: cyclosporine, gemfibrozil, fenofibrate, itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, verapamil, amiodarone

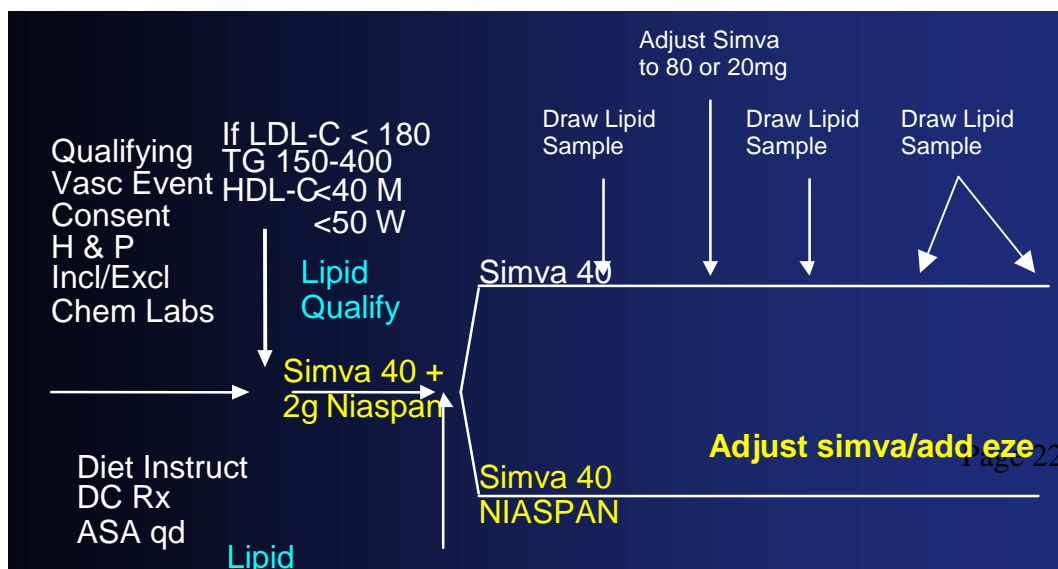
2. Lipid-lowering drugs (other than the investigational drugs), such as statins, bile-acid sequestrants, fish oils, cholesterol absorption inhibitors (e.g., ezetimibe, *but see section 4.5 on Treatment Protocol for use of ezetimibe to achieve treatment goals*), fibrates
 3. High-dose, antioxidant vitamins (vitamins C, E, or beta-carotene) that can interfere with the HDL-raising effect of niacin
- Pregnant (or likely to become pregnant) women or pre-menopausal women not using adequate contraception
 - Significant co-morbidity likely to cause death in the 3-5 year follow-up period
 - Patients with AIDS/active HIV infection, due to potential confounding drug interactions
 - Significant active history of substance abuse within the previous 5 years
 - Unwillingness/inability to give informed consent or follow study protocol
 - Current participation in another clinical study or trial that involves a study drug or intervention
 - Unwillingness of patient's physician to allow participation in the study

4.5 Treatment Protocol (See Study Flow Charts on page 23 and 34)

- The study drugs will be supplied by Kos Pharmaceuticals, Cranbury, NJ
 - Simvastatin: 10mg, 20 mg, 40 mg and 80 mg tablets
 - Extended-release niacin: 500mg and 1000mg tablets and matching placebos containing 50mg immediate-release niacin
 - Ezetimibe 10 mg
- The maximum doses permitted in this trial are:
 - Extended-release niacin 2000 mg
 - Simvastatin 80 mg
 - Ezetimibe 10 mg

See Manual of Operations for further details on dosing.

Written informed consent must be obtained before any study-specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.



Conversion factors, mg/dL to mmol/L: cholesterol, multiply by 0.0259; for triglyceride, multiply by 0.0113. Entry lipid levels to qualify are modified as described above in 4.4.1.2 for patients on a statin.

- Baseline blood sampling for fasting blood glucose, hemoglobin A1C, thyroid function tests (e.g., TSH), liver function tests (ALT, AST) and other relevant blood chemistries will be obtained and monitored at periodic intervals, as deemed appropriate. (See Appendix 4, page 53.)
- Blood samples for frozen storage will be obtained at baseline and at specified points during therapy.
- After patients are deemed to have met inclusion and non-inclusion criteria and informed consent has been obtained, eligible subjects will first undergo an unblinded 4-week run-in period during which they will receive extended-release niacin once-daily in the evening, titrated by 500 mg daily at weekly intervals, beginning with 500 mg once-daily in the evening to a maximum of 2000 mg, together with simvastatin 40 mg, to establish tolerability of this combination. Administration of aspirin 325 mg up to 30 minutes prior to dosing will be encouraged. ***In order to proceed to randomization, a patient must tolerate a minimum of 1500 mg extended-release niacin.*** The titration period may be extended up to 8 weeks in order to establish tolerability. (See Manual of Operations for further detail.)
- Patients who successfully complete the unblinded, open-label run-in period and tolerate this combination therapy will be then be randomized to receive study medication once-daily with either statin monotherapy, beginning with simvastatin 40 mg, or combination therapy with niacin extended-release /simvastatin at a dose of 2000/40 (or 1500/40, if 1500 mg was the highest tolerated dose of extended-release niacin during the run in), for 8 weeks. After 8 weeks (2 months), the dose of simvastatin will be increased to 80 mg for patients in either treatment group if LDL-C is > 80 mg/dL (2.1 mmol/L) based on a sample drawn at 1 month. If

LDL-C is < 40 mg/dL (1.0 mmol/L), the dose of simvastatin will be decreased to 20 mg. Values for LDL-C will be provided to the investigators throughout the trial; however, values for other lipid parameters such as HDL-C and triglycerides will *not* be provided.

At 12 weeks (3 months), a fasting lipid sample will also be drawn. If a patient's LDL-C is > 80 mg/dL (2.1 mmol/L), the patient should be contacted to come into the clinic. If he or she is currently taking simvastatin 40 mg, the dose of simvastatin should be increased to 80 mg. If he or she is currently taking simvastatin 80 mg, then ezetimibe 10 mg should be added to their treatment regimen. ***In patients who are given ezetimibe at this point, the dose of simvastatin should be simultaneously decreased back to 40 mg. In either case, changes to the treatment regimen should be done no later than 16 weeks (4 months).***

At 24 weeks (6 months), fasting lipid samples will again be obtained. At this visit, the following titrations/dose adjustments should be made, preferably in the clinic at or just before 9 months, in lieu of the 9-month telephone contact (see Table page 34), since it may be necessary to dispense additional or different simvastatin tablets, or ezetimibe.

- If the LDL-C is > 80 mg/dL (2.1 mmol/L) but < 100 mg/dL (2.6 mmol/L), and the patient is receiving 40 mg of simvastatin and 10 mg of ezetimibe, no adjustment in the dosage of either drug will be made based on the LDL-C result.
- If LDL-C is > 80 mg/dL (2.1 mmol/L) but < 100 mg/dL (2.6 mmol/L), and the patient had been receiving only simvastatin 40 mg, the dose of simvastatin should be doubled to 80 mg.
- If LDL-C is > 80 mg/dL (2.1 mmol/L) but < 100 mg/dL (2.6 mmol/L), and the patient had been receiving simvastatin 80 mg, then ezetimibe 10 mg should be added to their treatment regimen. ***In patients who are given ezetimibe at this time, and the dose of simvastatin had been 80 mg, the dose of simvastatin should be simultaneously decreased back to 40 mg.***

- Only in patients whose LDL-C remains \geq 100 mg/dL despite therapy with simvastatin 40 mg and ezetimibe 10 mg, may the dose of simvastatin be increased to 80 mg in combination with ezetimibe.

At 12 months and at 36 months, fasting lipid samples will again be obtained. However, the only simvastatin/ezetimibe dose adjustments permitted, based on these sample results, will be for LDL-C > 100 mg/dL [2.6 mmol/L] or < 40 mg/dL [1.0 mmol/L]. See Manual of Operations for further details about dose titration and addition of ezetimibe.

Dose adjustment of both simvastatin, niacin extended-release, and ezetimibe is also allowed throughout the trial, as needed, to manage possible adverse events such as muscle aches or weakness, marked fatigue, nausea, or intolerable flushing, as described in the Manual of Operations

Because of the possibility that cutaneous flushing in the combination therapy arm could potentially unmask the identity of blinded therapy to both patients and study personnel, each placebo tablet for extended-release niacin will include a small, sub-therapeutic dose of crystalline (immediate-release) niacin 50 mg.

- All patients will be encouraged to take aspirin 325 mg (or ibuprofen or other non-steroidal anti-inflammatory) up to 30 minutes prior to dosing with the investigational drug to alleviate flushing, to take the investigational drug with a lowfat snack at bedtime, and to avoid hot or spicy food/drink around the time of dosing.
- Excluded concomitant medications
 - Drugs with a high probability of increasing the risk for hepatotoxicity or myopathy, such as those predominantly metabolized by cytochrome P450 system 3A4, including: cyclosporin, gemfibrozil, fenofibrate, itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, verapamil, amiodarone
 - Lipid-lowering drugs (other than the investigational drugs), such as statins, bile-acid sequestrants, fish oils, cholesterol absorption inhibitors (e.g., ezetimibe, except for its use as described above to achieve study protocol treatment goals for LDL-C), fibrates

- Treatment adherence

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drugs for the duration of the trial. Patients should be counseled in particular about the possibility of flushing and ways in which to manage or mitigate it. Any interruptions of therapy should, if possible, be brief (e.g., < 4 weeks) and for only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons. For every patient, an assessment of study drug adherence must be obtained at each scheduled visit.

4.6 Assessment of clinical events

All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be

found in the Clinical Events Committee charter.

4.6.1 Primary Efficacy Endpoints

The first occurrence of any of the following major adverse cardiovascular events, as validated by the CEC in concert with the core ECG laboratory:

- CHD death
- Non-fatal MI (including silent MI)
- Ischemic stroke
- Hospitalization for high-risk NSTEMI acute coronary syndrome

4.6.2 Definitions of components of the primary efficacy endpoints

4.6.2.1 Coronary Heart Disease Death

Defined as any death with a clear relationship to underlying coronary heart disease (including death secondary to acute MI, sudden death, unobserved and unexpected death, and other death not definitely attributed to a nonvascular cause).

4.6.2.2 Myocardial infarction (MI)

Based on ACC definitions for measuring outcomes²⁷, the following situations will be considered:

- For patients with no recent cardiac intervention within 24 hours, at least one of the following must be present :
 - CK-MB elevation ≥ 2 times upper limit of normal (ULN)
 - Troponin elevation ≥ 2 times ULN

With at least one of the following:

- Ischemic symptoms within 48 hours
 - New ST depression ≥ 0.5 mm in 2 contiguous leads or T wave inversion ≥ 1 mm in leads with predominant R wave or R/S ratio > 1.0 in 2 contiguous leads
 - LBBB (new)
 - ST elevation (new ST elevation in at least 2 contiguous leads ≥ 0.2 mV in V1, V2, or V3 or ≥ 0.1 mV in other leads)
 - New R wave ≥ 40 ms with R/S ≥ 1 in V1 and R/S ≥ 1.5 in V2
 - New Q waves ≥ 30 ms in 2 contiguous leads
- Patient who underwent recent PCI/CABG (within 72 hours)
 - PCI: CK-MB ≥ 3 times ULN or development of new Q wave
 - CABG: either CK-MB ≥ 5 x ULN and new Q waves, or CK-MB ≥ 10 times ULN (with or without Q wave)

Silent MI detected on routine ECG will be included in the definition of MI.

4.6.2.3 Stroke

Defined as an acute neurological vascular event with focal signs lasting more than 24 hours *and* considered to be of ischemic origin. If a previous deficit has worsened, it must have lasted more than one week, or more than 24 hours if accompanied by an appropriate new CT or MRI finding.

CT scan or MRI should be performed and provided to the CEC to allow exclusion of non-vascular causes.

4.6.2.4 Non-ST-Segment Elevation Acute Coronary Syndrome

Defined as the onset of characteristic ischemic chest pain in the precordium or associated referral areas (occurring in an accelerating tempo in the prior 48 hours or prolonged (at least 20 minutes) rest pain, presumed to be ischemic. Presence of ischemia must be documented by ECG changes (e.g., new or additional ST depression [at least 0.5 mm in 2 contiguous leads]), or biomarker positivity. Biomarker positivity is defined as cardiac troponin or CKMB above the ULN but < 2 times ULN in at least one blood sample.

4.6.3 Secondary Efficacy Endpoints

- To evaluate the effect of therapy on the composite endpoint of CHD death, non-fatal MI, or ischemic stroke
- To evaluate the effect of therapy on cardiovascular mortality

4.6.4 Tertiary Efficacy Endpoints

- To evaluate the effect of therapy on total mortality
- To evaluate the effect of therapy on the composite endpoint of, and the individual components of the composite endpoint of CHD death, non-fatal MI, ischemic stroke, hospitalization for NSTEMI acute coronary syndrome, or any revascularization
- To evaluate the effect of therapy for preventing clinical events, as defined above, among patients meeting current criteria for metabolic syndrome as defined by the NCEP ATP III, or future criteria for metabolic syndrome as they may evolve, or diabetes

- To assess the effects of statin monotherapy versus combination therapy on lipids and lipoproteins, including apoA-I, apoB, apoC-III, Lp(a), HDL subfractions/particle size, LDL size and subclass distribution, and their relationship to outcome
- To assess the effects of therapy on inflammatory markers, such as C-reactive protein and fibrinogen, and their relationship to outcome

4.6.5 Definitions of components of secondary and tertiary efficacy endpoints

- 4.6.5.1 Hospitalization

Defined as at least one overnight stay (or admission to emergency room \geq 23 hours)

- 4.6.5.2 Revascularization procedure

Defined as any of the following procedures:

- Coronary revascularization: PCI (includes percutaneous transluminal coronary angioplasty [PTCA], coronary stenting, and others such as brachytherapy, atherectomy, laser, and rotational ablation) or CABG.
- Cerebrovascular revascularization: carotid endarterectomy, carotid percutaneous transluminal angioplasty (with or without stent).
- Peripheral revascularization: peripheral arterial bypass surgery, or any therapeutic intervention for critical leg ischemia (including thrombolysis)

4.7. Patient safety

4.7.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have causal relationship with this treatment.

All adverse events, regardless of seriousness or relationship to study drug, are to be recorded on the Case Report Form devoted to recording adverse events. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the adverse events was caused by the study drug.

4.7.2 Serious adverse events

Serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

In the case of a serious adverse event, the investigator must immediately fax the signed and dated case report form, accompanied with photocopy of all examinations, to the representative of the monitoring team.

4.7.3 Follow up of adverse events and serious adverse events

The investigator should take all appropriate measures to ensure the safety of the patients. The outcome of any adverse events (clinical signs, laboratory values or others) should be followed up until they return to normal or until stabilization of the patient's condition.

4.8 Patient Withdrawal

4.8.1 Withdrawal criteria

Occurrence of an outcome event according to the judgement of the investigator is not considered as a reason for study drug discontinuation. Permanent study drug discontinuation is only clearly justified for an adverse event or when a patient or his or her physician insists on withdrawing from study drug treatment, generally for clinical reasons. Study drug discontinuation should be avoided as far as possible. The reason for study drug discontinuation will be recorded on the Case Report Form.

4.8.2 Reasons for Withdrawal

The patients may withdraw from the study drug at any time and for any reason, or this may be at the investigator's discretion. (See above.) In any case, follow-up for efficacy and safety endpoints should be continued.

4.8.3 Follow-up After Withdrawal

- Patients who prematurely discontinue study drug are not to be replaced
- All randomized patients must be followed up according to the study flowchart until study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.
- In order to follow the medical status of the patients, especially when they withdraw after having experienced an adverse event, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their stroke or MI status, and thus avoid lost to follow-up for the efficacy assessment.
- If patients are lost to follow-up, the Case Report Form must be completed up to the last visit or contact.

4.9 Study Procedures

4.9.1 Visit schedule (See Flow Chart below, page 34)

4.9.2 Screening and run-in procedures

Potentially eligible patients will be identified from all relevant in-patient and out-patient sources, including coronary care units, stroke centers, invasive and noninvasive laboratories, office practices and specialty clinics. Patients referred from other physicians or other sources will also be screened. The patient will receive complete information about the study both orally and in writing. Written informed consent must be obtained prior to performing any study related procedures, including phlebotomy to obtain screening laboratories, withdrawal of current lipid-modifying drugs, electrocardiograms, chest X-rays, etc.

As described above, eligible subjects will first undergo an unblinded 4-week run-in period to establish tolerability of the combination therapy. This will ensure a higher likelihood of long-term adherence, once randomization to the double-blind phase of the trial is initiated. Key baseline patient characteristics will be recorded in the Case Report Form. Eligible subjects will receive extended-release niacin once-daily in the evening, titrated by 500 mg daily at weekly intervals, beginning with 500 mg once-daily in the evening to a maximum of 2000 mg, together with simvastatin 40 mg, to establish tolerability of this combination. Administration of aspirin 325 mg up to 30 minutes prior to dosing will be encouraged. In order to proceed to randomization, a patient must tolerate a minimum of 1500 mg

extended-release niacin. The titration period may be extended up to 8 weeks, if necessary, to establish tolerability. (See Manual of Operations.) The number of patients failing to proceed to randomization, and the reason(s) why, must be documented.

4.9.3 Randomization

After successful completion of the unblinded, open-label run-in period with the combination therapy, patients will then be randomized to receive blinded study medication with either simvastatin monotherapy, or combination therapy (simvastatin plus niacin extended-release). Randomization will be stratified by site, gender and history of diabetes. All patients who are randomized will be included in the intent-to-treat analyses, whether or not they are subsequently found to be eligible or actually receive the allocated treatment. All randomized patients will be followed until the study end date or death. Study drug administration should be initiated as soon as possible after randomization.

4.9.4 Clinical follow-up visits (See Flow Chart below and Manual of Operations)

4.9.4.1 Screening, baseline visit and run-in period

- Baseline visit:
 - Demographic information, medical history, physical examination, current medical treatments, and ECG
 - Fasting blood lipids and lipoproteins (See study flow chart on page 34 and Appendix 4, page 53)
 - Fasting blood glucose, hemoglobin A1C, thyroid function tests, uric acid, CK, liver function tests (See study flow chart on page 34 and Appendix 4, page 53)
 - Blood samples for frozen storage
 - Other laboratory tests, as described in Appendix 4 and Manual of Operations
- Run-in period:
 - Adverse events occurring during the run-in period and adherence with study drug(s) will be recorded at -2 weeks (by telephone) and at the end of the run-in

4.9.4.2 Randomization (Day 0)

Patients tolerating the combination therapy during the run-in period will be randomized. All patients will receive simvastatin open-label. Patients will be randomized to blinded therapy with either extended-release niacin or placebo matching extended-release niacin.

4.9.4.3 Follow-up (See Flow Chart on page 34 and Appendix 4, page 53)

- 1-month follow-up visit (Day 30 ± 7)
 - Fasting blood sample for lipids

- Fasting blood sample for chemistries
- Record of efficacy endpoints, if any
- Record of adverse events, if any
- Study drug adherence
- Record of interventions, if any
- 2-month follow-up visit (Day 60 ± 7)
 - Increase or decrease dose of simvastatin as needed, based on achieving LDL-C target ≤ 80 mg/dL (2.1 mmol/L) but ≥ 40 mg/dL (1.0 mmol/L)
 - Record of efficacy endpoints, if any
 - Record of adverse events, if any
 - Study drug adherence
 - Record of interventions, if any
- 3-month follow-up visit (Day 90 ± 10)
 - Fasting blood sample for lipids
 - Fasting blood sample for chemistries
 - Record of efficacy endpoints, if any
 - Record of adverse events, if any
 - Study drug adherence
 - Record of interventions, if any
 - *If required, within 1 month of this visit, increase or decrease dose of simvastatin and/or add ezetimibe 10 mg, as described above in section 4.5*
- 6-month follow-up visit (Day 180 ± 10)
 - Fasting blood sample for lipids
 - Fasting blood sample for chemistries
 - Record of efficacy endpoints, if any
 - Record of adverse events, if any
 - Study drug adherence
 - Record of interventions, if any
 - *If required, patient returns at 9 months to increase or decrease dose of simvastatin and/or add ezetimibe 10 mg, as described above in section 4.5*
- Subsequent 6-month visits (every 180 Days ± 10)
 - Fasting blood determinations for lipids and chemistries, as per protocol (Appendix 4, page 53)
 - Record of efficacy endpoints, if any
 - Record of adverse events, if any
 - Study drug adherence
 - Record of interventions, if any
 - Electrocardiograms will be obtained at year 1 and annually thereafter
 - *At 12-months and again at 36 months, dose adjustments for simvastatin/ezetimibe will be permitted, but only for LDL-C > 100 mg/dL [2.6 mmol/L] or < 40mg/dL [1.0 mg/dL]*

- Telephone follow-up contact with patient at 2 weeks (± 4 days), 36 weeks (± 7 days), and, thereafter, every 24 weeks (6 months, ± 10 days)
 - Screen for possible efficacy endpoints or adverse events
 - Patients will be asked to return to the clinic to assess for any endpoints or events identified

- Final follow-up visit (study end date): visit may occur within 30 days after the study end date; however, only events occurring up to and including the scheduled actual study end date will be included in the primary efficacy analysis
 - Record of efficacy endpoints, if any
 - Record of adverse events, if any
 - Study drug adherence
 - Record of interventions, if any
 - Electrocardiogram

Every attempt should be made to complete the follow-up visits during the defined window periods. A final follow-up visit is required for all patients. In the rare cases a final follow-up visit cannot occur within the 30-day timeframe following study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

Flow-Chart*

Visit	Baseline visit or prior	-2 wk phone FU		2 wk phone FU	1mo visit FU	2mo visit FU	3mo visit FU	6mo visit FU	9mo phone FU	12mo visit FU	15mo phone FU	18mo visit FU	21mo phone FU	24mo visit FU	27mo phone FU	30mo visit FU	33mo phone FU	36mo visit FU	39mo phone FU	42, 48, 54mo visit FU	45, 51, 57mo phone FU	60mo visit FU	
Day	Run-in period		D 0		D 30±7	D 60±7	D 90±10	D 180±10		D 360±10		D 540±10		D 720±10		D 900±10		D 1080±10		D 1260 1440 1620 ±10		From study end date to 30 days after	
Medical history	x																						
Previous medications	x																						
Inclusion/exclusion criteria	x																						
Informed consent/patient demography	x																						
Vital signs	x		x		x	x	x	x		x		x		x		x		x		x		x	
ECG (annually)*	x									x				x				x		x		x	
Lab tests (blood lipids, glucose, etc)** - see lab chart Appendix 4	x				x		x	x		x	(x)	x		x		x		x		(x)	x		x
Randomization			x																				
Study drug allocation	x		x		x	x	x	x		x		x		x		x		x		x		x	
Adherence		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Primary efficacy endpoints				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

*ECG at baseline and annually
FU = follow up D = Day

**See separate schedule of laboratory tests in Appendix 4 (Page 53)
(X) = check AST in clinic if dose adjustments made previously at months 12 or 36

5. Statistical Considerations

5.1 General Statistical Approach

AIM-HIGH is a randomized, multi-center controlled clinical trial in patients with established vascular disease and atherogenic dyslipidemia. Patients will be randomized in a 1:1 proportion to a combination of simvastatin and extended-release niacin or simvastatin alone. General issues concerning the statistical analyses are:

- Primary and secondary efficacy analyses will be performed under the principle of intention-to-treat.
- Safety and some exploratory secondary analyses will be restricted to treated patients.
- All statistical analyses of efficacy outcomes will be performed at the 2.5% significance level using 1-sided tests
- Primary and secondary efficacy endpoints will be analyzed using Proportional Hazards survival analysis techniques and a Wald Chi-square statistic to test the difference between the two treatment groups
- A formal interim analysis plan will be drafted and approved prior to the start of the trial. Group sequential methods will be used to monitor the trial for efficacy and harm.

Additional details concerning the final and interim analysis plans are given below. Further details will be provided in a detailed statistical analysis plan that will be finalized prior to any analysis of trial data.

5.2 Outcome Parameters and Analysis Datasets

The primary outcome is the time from randomization to the first occurrence of any of the following events: coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for high-risk NSTEMI acute coronary syndrome.

The secondary outcomes are:

- cardiovascular death, nonfatal MI or ischemic stroke
- cardiovascular mortality

The tertiary outcomes are:

- the composite endpoint of, and the individual components of the composite endpoint of, CHD death, non-fatal MI, ischemic stroke, hospitalization for NSTEMI acute coronary syndrome, or any revascularization
- clinical events, as defined above, among patients who meet the current criteria for metabolic syndrome as defined by the NCEP ATP III, or future criteria for metabolic syndrome as they may evolve, or diabetes
- lipids and lipoproteins, including lipoprotein subclasses, and inflammatory markers (e.g., fibrinogen, hs-CRP), analyzed in terms of therapy effects and clinical outcomes

As noted, the primary efficacy analyses will be performed based on the intention-to-treat principle, including all randomized patients analyzed according to their treatment assignment.

The Statistical Analysis Plan will present additional details concerning the planned analyses.

5.3 Statistical Analyses

Primary Endpoint

AIM-HIGH is designed to compare the time-to-event distributions of the simvastatin versus the simvastatin+niacin treatment groups; the null hypothesis is that the hazard ratio for the two survival distributions is equal to one. The primary test of the null hypothesis will be based on the Wald Chi-square statistic from a Cox Proportional Hazards model with treatment arm as the only covariate, including gender and history of diabetes as strata and using a one-sided hypothesis with a 0.025 significance level. Cumulative event rate estimates will be used to describe the survival probabilities for each treatment group at pre-specified clinically significant time points. Non-CHD deaths will be treated as competing risks and patients with these events will be censored at the time of death.

An estimate of the hazard ratio, along with a 97.5% confidence interval, will be derived from a Cox proportional hazards model. The assumption of proportional hazards for the treatment group factor will be assessed visually using log-cumulative hazard plots and by including a time-by-treatment interaction in the Cox model. Any indication of departures from the proportional hazards assumption will be investigated more formally and discussed in the presentation of the results.

Secondary endpoints will be examined in a similar manner.

Tertiary analyses may be stratified based on metabolic syndrome status at baseline or other demographic or clinical parameters. Subgroup analyses to explore potential variation in the treatment effect will utilize Cox proportional hazards models including treatment-by-subgroup interaction terms. Significance levels will not be adjusted in the subgroup analyses, as these analyses are exploratory in nature and are to be interpreted descriptively. Further details of the exploratory analyses will be presented in the Statistical Analysis Plan.

5.4 Interim Analyses and Sample Size Adjustment

Interim analyses based on a group sequential design that includes early stopping rules for benefit and futility while preserving the overall Type I error rate (O'Brien-Fleming)⁴⁶ will be incorporated into the AIM-HIGH study design. The DSMB will review unblinded data reflecting the local investigator's assessment of endpoint (i.e., non-adjudicated data) at pre-specified times (for example, every six months). Interim analyses will be performed with significance levels determined using the alpha-spending rule of Lan and

Demets.⁴⁷ Sequential boundaries will be designed to assess both unexpectedly large benefit or futility. Approximately 890 events will be observed during the trial, based on sample size calculation assumptions. The first interim analysis will occur after at least 100 events have been observed, with additional interim analyses triggered by occurrence of a pre-specified total number of events. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Analysis Plan document prior to the randomization of the first subject.

5.5 Sample Size Determination:

In AIM-HIGH, qualified patients will be enrolled in at least 54 clinical sites over a planned 2 year period; follow-up will be completed with a mean of at least 4 years and a minimum follow up of 3 years. For the current study, the goal is that the study population will comprise 30% women. The lipid inclusion criteria and focus on high-risk vascular disease patients will ensure that the vast majority of patients will have metabolic syndrome (85% of patients in HATS with atherogenic dyslipidemia had metabolic syndrome).

Sample size calculations were based on estimates of untreated 4-year event rates derived from the ongoing CHARISMA trial (personal communication: William E. Boden, MD, member of the Steering Committee), due to the similarities of the patients enrolled in this study and the patient population proposed for AIM-HIGH (i.e., high-risk patients with established vascular disease and lipid abnormalities). CHARISMA examines a secondary endpoint including cardiovascular death, non-fatal MI, stroke and hospitalization for an acute ischemic event; this is the primary endpoint proposed for AIM-HIGH. To date, CHARISMA has observed a 9.13% annual event rate for the secondary endpoint. We assumed that 68% of the CHARISMA population is using a lipid-lowering drug with an associated 30% decrease in annual event rate. This results in an estimated 11.5%/year event rate in untreated patients and an 8.0%/year event rate in patients treated with lipid-lowering drugs. These annual event rates correspond to 4-year event rates of 39% and 28% in the untreated and lipid-lowering groups.

The event rate estimates were further adjusted for presence of metabolic syndrome. Approximately 75% of the CHARISMA population have metabolic syndrome; it is expected that 90% of the AIM-HIGH population will fall into this category and have an associated 60% increased risk. With additional assumptions that there will be a 50% decrease in risk in the niacin + simvastatin group compared to placebo, and that 10% of both treatment groups will stop using all drugs and 10% of the combination treatment group will stop using niacin but continue with simvastatin only, the estimated 4-year AIM-HIGH primary endpoint event rates based on CHARISMA data are 30% in the simvastatin treatment group and 23% in the combination therapy treatment group.

Based on these 4-year estimates and an assumption of exponential survival time,⁴⁸ a one-sided test with an alpha-level of 0.025, 2 years for patient accrual and a minimum of 3 years of follow-up, a total sample size of 3,300 patients will result in 99% power to detect

a difference between hazard rates of 0.089 and 0.067 (hazard ratio=1.33) in the simvastatin and simvastatin + niacin therapy groups, respectively. With the above assumptions, it is expected that approximately 890 events will be observed during the trial.

AIM-HIGH power estimates based on data from other comparable clinical trials and using similar calculations to those described above are:

Study	CHAR-3	CHAR-4	CHAR-4*	VA-HIT	VA-HIT	HATS	HATS	4S
N=3000	.64	.98	.90	.85	.96	.88	.99	.94
N=3300	.68	.99	.93	.88	.97	.91	.996	.96
N=3800	.74	.996	.96	.92	.99	.94	.999	.98

CHAR: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)⁴⁹, and unpublished data (personal communication, CHARISMA Steering Committee).

CHAR* This column assumes that the CHARISMA quadruple composite endpoint, which is currently unadjudicated, is 33% lower after adjudication.

VA-HIT¹⁸

HATS¹⁹

4S (Scandinavian Simvastatin Survival Study)⁵⁰

5.6 Sample Size Conclusions:

The current design with a sample size of 3,300 results in a well-powered trial for detecting the specified difference in the primary endpoint proposed for AIM-HIGH. This will result in 99% power to detect a difference between hazard rates of 0.089 and 0.067 (hazard ratio=1.33) in the simvastatin and simvastatin+niacin therapy groups, respectively. Moreover, there is 68% power to detect a difference in the secondary AIM-HIGH efficacy endpoint (the primary endpoint in CHARISMA CHAR-3) with this sample size.

6. Regulatory Standards

6.1 Informed consent

The investigator, or a person designated by the investigator, should fully inform the patient of all pertinent aspects of the clinical trial including the written information approved by the Ethics Committee.

Prior to a patient's participation in the clinical trial, the Informed Consent Form should be signed and personally dated by the patient or by the patient's legally acceptable representative.

The Informed Consent Form must be reviewed and approved by the sponsor prior to submission to the appropriate Ethics Committee for approval.

6.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The investigator must submit this protocol to the appropriate IRB/IEC, and is required to forward to the Sponsor a copy of the written and dated approval opinion by the Chairman with IRB/IEC composition.

The study (study number, protocol title and version number), the document reviewed (protocol, Informed Consent Form, Investigator's Brochure, etc.) and the date of the review should be clearly stated on the written IRB/IEC approval opinion.

During the clinical trial, any amendment or modification to the protocol should be sent to the IRB/IEC. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety and all updates to the Investigator's Brochure will be sent to IRB/IEC.

7. Study Monitoring

7.1 Responsibilities of the Investigator(s)

The investigator(s) undertake(s) full responsibility to perform the study in accordance with this protocol, Good Clinical Practice and the applicable regulatory requirements.

The investigator is required to ensure adherence with the visit schedule and procedures required by the protocol. The investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner.

7.2 Responsibilities of the Clinical Trial Coordinating Center

The Clinical Trial Coordinating Center (CTC) for the study is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the

Case Report Forms, in keeping with established Good Clinical Practice (GCP) standards. Therefore, the main duty of the Monitoring Team is to help the investigator and the CTC maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the clinical centers will be contacted, through site visits, letters, or telephone calls, by a representative of the Monitoring Team to review study progress, investigator and patient compliance to protocol requirements and any emergent problems. During monitoring visits, the following points will be scrutinized with the investigator: patient informed consent, patient recruitment and follow-up, study drug allocation, patient compliance with the investigational medicine, investigational medicine accountability, concomitant therapy use, adverse event documentation and reporting, and quality of data.

8. Summary

Advances in dyslipidemic therapy, which have contributed to the decline in incident CHD over the past 30 years, have been largely attributable to the statins. However, despite these impressive gains, CHD remains the most frequent cause of death in the United States and the Western World. Although large-scale clinical trials with statins have found that reducing LDL-C decreases mortality and coronary events by 25 – 35%, event rates in these trials remain unacceptably high, in the range of 70% to 75% of those observed among placebo-treated patients. Furthermore, nearly 30 years ago, results from the Coronary Drug Project showed the benefits of niacin treatment in decreasing cardiovascular events, also by 25 – 35%, in patients with previous myocardial infarction. This benefit has been attributed to, among other effects of niacin, changes in HDL-C and triglycerides. More recently, the accumulated clinical evidence has led many to suggest that low HDL-C should be considered a target for therapy, particularly in patients with multiple risk factors, established CHD, or its equivalent. Therefore, now is the time to capitalize on the potential to achieve an additive event rate reduction through combination therapy and test this hypothesis in a long term, large scale clinical outcomes trial.

Raising HDL-C levels has been shown to reduce coronary events in CHD patients at or near LDL-C goals. Niacin controls multiple lipid and lipoprotein abnormalities and is presently the most effective agent for raising low levels of HDL-C. Combination therapy using niacin and a statin can provide complementary benefits to the serum lipid profile. Since patients with vascular disease (CHD, cerebrovascular disease, or PAD) who have so-called mixed dyslipidemia are at very high risk for developing subsequent MI, stroke or ischemic limb loss, The AIM-HIGH Trial may shed important light on defining optimal lipid management for these patients. Such multidimensional dyslipidemic therapy may provide clinicians with a powerful approach to treating patients whose risk for developing CHD, cerebrovascular disease, or PAD may not be mitigated by lowering LDL-C alone, especially in those individuals who have residual low levels of HDL-C and/or elevated levels of triglycerides.

As noted previously, no randomized clinical trial to date has addressed systematically the dyslipidemic management of patients with symptomatic vascular disease, including patients with CHD, cerebrovascular disease, and PAD as expressions of diffuse systemic atherothrombosis. The inclusion of patients with diabetes, metabolic syndrome and the atherogenic dyslipidemic triad of low HDL-C, elevated TG and increased small, dense LDL particles, many of whom are obese and at significant risk for subsequent vascular complications, provides a compelling rationale for configuring a therapeutic strategy aimed at reducing the high-risk associated with these overlapping atherothrombotic conditions.

If the AIM-HIGH Trial can prove the hypothesis that combination dyslipidemic therapy directed toward multiple lipid targets improves significantly cardiovascular and cerebrovascular events compared to statin monotherapy, it will provide a scientifically-important and clinically-meaningful approach to optimizing event-free survival in a large and growing population of high risk patients for whom treatment, at present, is less than adequate.

In summary, both the healthcare consequences (morbidity and mortality) as well as the economic consequences (rising healthcare expenditures and spiraling direct/indirect costs) of this therapeutic challenge in dyslipidemic management have profound healthcare delivery—and potentially healthcare policy—implications for government organizations in the U.S., Canada, and worldwide.

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APPENDICES

Appendix 1. Intima-Media Thickness Measurement

Carotid intima-media thickness (IMT) is a marker of early arterial change of the arterial walls including atherosclerosis and/or vascular hypertrophy, detected by B-Mode ultrasonography.

1. Recommendations for the ultrasonographic examinations:

- Machines equipped with 5 or 7 MHz transducers
- Subjects in the supine position
- ECG signal used for synchronizing the image analysis to the end of the diastole
- Doppler ultrasound used for vessel identification (and information on blood flow velocity)
- Carotid artery scanned at the level of the bifurcation, with the head turned to the opposite side (e.g. to the right for left carotid artery)
- Examined region:
 - 30 mm of the common carotid artery
 - carotid bulb
 - 10 mm each of the internal and external carotid arteries
- Regions scanned with both longitudinal and transverse projections, in order to assess the occurrence of plaques
- Three “frozen” images recorded for assessment of intima-media thickness and lumen diameter
- Optimal image projection considered to be achieved when ultrasound beams are perpendicular to the far vessel wall

2. Recommendations for assessment of intima-media thickness (defined as the distance from the leading edge of the lumen—intima interface to the leading edge of the media-adventitia interface of the arterial wall) and lumen diameter (defined as the maximal distance between the leading edges of the intima-lumen interface)

- Ultrasonographic images analyzed with a computerized system
- Intima-media thickness measured in a 10-mm long segment just proximal to the carotid bulb in the common carotid artery
- Calculation by the computer program of the minimum, maximum and mean values of intima-media thickness from three separate images

3. Assessments of plaques

- **A plaque is defined as a distinct area with an intima-media thickness exceeding twice that of the neighboring sites**
- Classification of plaques, according to a four-graded semi-quantitative scale of their size/severity:
 - Grade 0: no plaque
 - Grade 1: small localized plaque/wall thickening

- Grade 2: moderate plaque with <50% lumen diameter stenosis
 - Grade 3: circumferential and/or large plaque with $\geq 50\%$ lumen diameter stenosis
- Plaques detection must be focused on the distal part of the common carotid artery, the carotid bulb or in the proximal parts of the internal or external carotid artery.

Appendix 2. Criteria for Carotid Stenosis \geq 70%

1. Ultrasound

- Technique
 - Color duplex ultrasound scanners equipped with 5 or 7 MHz linear-array probe
 - Examination in transverse and longitudinal section using B-mode grey-scale imaging, then with color Doppler ultrasound, of the following:
 - Common carotid artery (CCA)
 - Carotid bifurcation
 - Extracranial internal carotid artery (ICA)
- Doppler waveforms obtained from
 - The base of the CCA
 - The Bulb of the ICA
 - The distal end of the extracranial ICA
 - And at the sites of suspected significant stenosis
- Criteria used for classifying the degree of stenosis

Category	Diagnostic Criteria
Normal	No visible plaque and normal waveforms
Stenosis	
1-29%	Visible plaque causing < 30% diameter stenosis and/or spectral broadening/flow disturbance on waveform
30-49%	Visible plaque causing 30-49% diameter stenosis, peak systolic velocity (PSV) < 1.2 m/s
50-69%	PSV \geq 1.2m/s
70-99%	PSV \geq 3m/s and end-diastolic velocity > 1.2m/s or very narrow lumen with damped flow distally
Total Occlusion	No flow detected

2. Intra-arterial digital subtraction angiography (IADSA)

- Technique
 - 5F catheter introduced via the femoral artery under local anesthesia
 - Selective catheterization of the CCA (contrast medium injected in the innominate artery or the aortic arch, in case of proximal vessel occlusion)
 - IADSA images acquired at 2/s
 - Two views of the carotid bifurcation (anteroposterior oblique and lateral)
 - Three views of the intracranial circulation (Towne's, Towne's oblique and lateral)

- Measurement of degree of stenosis
 - Degree of ICA stenosis measured on magnified hard copy films of either the oblique or the lateral image, whichever shows the most severe stenosis
 - Diameter of the residual lumen compared with the original diameter of the normal carotid bulb extrapolated on the angiogram
 - Percentage stenosis = $(\text{normal lumen} - \text{residual lumen}) / \text{normal lumen} \times 100$
 - Grading systems:
 - Normal
 - Mild (1-29%)
 - Moderate (30-69%)
 - Severe (70-99%)
 - Total occlusion

Appendix 3. Ankle-Brachial Index Measurement

- Measure highest systolic reading in both arms
 - Record first doppler sound as cuff is deflated
 - Record at the radial pulse
 - Use highest of the two arm pressures

- Measure systolic readings in both legs
 - Cuff applied to calf
 - Record first Doppler sound as cuff is deflated
 - Use Doppler ultrasound device
 - Record dorsalis pedis pressure
 - Record posterior tibial pressure
 - Use highest ankle pressure (DP or PT) for each leg

- Calculate ratio of each ankle to brachial pressure
 - Divide each ankle by highest brachial pressure

Schedule of Laboratory Assessments

Appendix 4

**Appendix 4. Schedule of Laboratory Assessments
(See Laboratory Manual of Operations for Additional Detail)**

	Screen	Base-line	1 mo	3 mo	6 mo	9 mo	1Yr	18 mo	2 Yr	30 mo	3Yr	42 mo	4 yr	54 mo	Final +	Clinically Suspected Toxicity					
																Myopathy			Hepatic		
																Init.¶ Samp	1 st F/U	2 nd F/U	Init.¶ Samp	1 st F/U	2 nd F/U
DBQ (1)	all		all	all	all		all				all				all	-	-	-	-	-	-
HDL2,3	all		-	-	-	-	all				all				-	-	-	-	-	-	-
ApoB (2)		all	-	-	-	-	all				all				-	-	-	-	-	-	-
ApoA-I		all	-	-	-	-	all				all				-	-	-	-	-	-	-
ApoCIII (3)		15%	-	-	-	-	15%				15%				-	-	-	-	-	-	-
ApoCIIIhp		15%	-	-	-	-	15%				15%				-	-	-	-	-	-	-
LDLbuoy(11)		15%	-	-	-	-	all				all				-	-	-	-	-	-	-
Lp(a)		all	-	-	-	-	all				-				-	-	-	-	-	-	-
TSH		all	-	-	-	-	-				-				-	-	-	-	-	-	-
CK (4)	all		-	5%*	-	-	5%				-				-	5%*	5%*	5%	3%*	-	-
Fibrinogen		15%	-	-	-	-	15%				-				-	-	-	-	-	-	-
Uric Acid (5)	all		-	5%	-	-	5%				-				-	-	-	-	-	-	-
Insulin (6)		all	-	30%	-	-	45%				-				-	-	-	-	-	-	-
HGB A1c (7)		all	-	30%	-	-	45%				45%				-	-	-	-	3%*	-	-
Glucose (8)	all		30%	30%	-	-	45%				-				-	-	-	-	-	-	-
Homocyst (9)		all	-	10%	-	-	10%				10%				-	-	-	-	-	-	-
AST (10)	all		20%	all	all	-	all	all	all	all	all	all	all	all	3%*	-	-	3%*	3%*	3%*	3%*
hsCRP (12)		15%	-	-	-	-	all				all				-	-	-	-	-	-	-
Creatinine (13)	all		-	5%	-	-	5%				5%				-	-	-	-	-	-	-
Retained samples (14)		all					all				all										

Table footnotes:

+ Final sample is that obtained at close-out visit just before therapy is discontinued (3-5 yr).

* All of those with baseline elevation > lab ULN or with suspect symptoms on-therapy (assume 3% of 3300 population).

¶ An initial sample of CK and AST will be drawn at the first presentation with symptoms consistent with hepatic or myotoxicity and, if abnormal, will be repeated at least twice with frequency to be determined by the judgement of the investigator and the patient's primary physician.

- (1) – Derived beta quant is measured TC, TG, HDL-C by precipitation, and LDL computed by Friedewald.
- (2) – ApoB and ApoAI to be measured in all patients at baseline, 1 year, and 3 years.
- (3) – ApoCIII total and that in the heparin-precipitate (hp) fraction (apoB-associated) in estimated 15% of patients not on statins at baseline.
- (4) -- CK measured at baseline in all, at 1 month on-therapy and at 1 yr in asymptomatic subgroup with CK >2x ULN at baseline (assume 5% of 3300), and in all with new onset muscle aches (assume another 5%), and also, initially, with suspected hepatotoxicity.
- (5) – Uric acid measured at baseline and in an assumed 5% with initial levels >7.5 mg/dL (445 umol/L) at 1 year or any with new gout symptoms.
- (6–8) - Insulin, HbA1C, and glucose measured in all at baseline, and (in an estimated 30% with abnormal HgbA1C levels at baseline) early post-randomization and at 1 year, along with a representative 15% sample of those with normal levels at baseline; plus HgbA1C at 3 yr in this estimated 45% cohort.
- (9) – Homocysteine at baseline in all, and in an estimated 10% of those with baseline >15 mg/dL (110 umol/L) at 1 and 3 yr.
- (10) – AST in all at baseline, 3 months and every 6 months thereafter, and within 3 months after starting combination of simvastatin + ezetimibe in conjunction with blinded therapy or after starting 80 mg simvastatin, and also in initial sample for all with suspected myopathy and all samples with suspected hepatic toxicity.
- (11) – LDL size/buoyancy will be determined by a variant of density gradient ultracentrifugation (VAP = vertical autoprofile) and by other techniques as may be arranged in the future, in estimated 15% of patients not on a statin at baseline, and in everyone at years 1 and 3.
- (12) – hsCRP should be measured by the Dade-Behring reagent, or its equivalent. Measurement will be made in estimated 15% of patients not on a statin at baseline, and in everyone at years 1 and 3.
- (13) – Creatinine will be measured at baseline, and at 1 and 3 yrs in an estimated 5% with creatinine \geq 1.5 mg/dL (133 umol/L) at baseline. Patients are excluded for baseline creatinine 2.5 mg/dL (220 umol/L) or greater
- (14) – Samples to be frozen and stored. See laboratory Manual of Operations for additional detail.