

## **Chapter 12. Lipid Lowering Agents**

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## **I. INTRODUCTORY REMARKS**

Atherosclerotic cardiovascular disease is still the number one killer and the main cause of morbidity in the world. The link between high blood cholesterol, atherosclerosis and coronary heart disease (CHD) has been known for decades, but the scientific community has paid attention to this major risk factor only since powerful lipid lowering agents (LLA) were developed and commercialized about 15 years ago. The new statins (HMG Co A reductase inhibitors) can lower total and the most atherogenic LDL-cholesterol by up to 50-55% at maximum dosage. The beneficial effect of statins on plasma lipoproteins is reflected by a significant reduction in lesions progression and major cardiovascular events (by 25-40%) as demonstrated by many prospective primary and secondary prevention trials. The fibrates, another class of LLA that primarily decrease plasma triglycerides and increase the anti-atherogenic HDL-cholesterol, have also shown in angiographic and event trials a 25% reduction of major cardiovascular end points. More recently, the use of a statin to decrease LDL-C in combination with nicotinic acid to increase HDL-C in secondary prevention gave an even more spectacular 90% reduction of recurrent cardiovascular events after three years of treatment.

If the question of the benefit of treatment with LLA on cardiovascular disease is no more debatable, many issues regarding the use of LLA in clinical practice are still unresolved. For instance, in vitro and animal studies have documented various pleiotropic beneficial effects of statins on coagulation, fibrinolysis, oxidation and inflammation. Since these pathophysiological mechanisms are fundamental to atherosclerosis progression, it will be of great interest to assess whether the beneficial effect of statins is only related to lipid lowering or it is also mediated by other mechanisms. In patients with low lipid levels who are at risk of CHD because of intravascular inflammation or oxidation it remains unknown whether they would benefit from statins. Another fundamental question regards the optimal level of plasma cholesterol. It is still questioned whether the "lower is better" and whether there is a threshold effect to the lipid lowering benefit. Obviously many combination therapy trials will have to be conducted to resolve this issue.

Concerning the long term safety of LLA and recognition of adverse effects little is known. The longer these agents are used, the more we learn about subtle presentation of side effects. The neuromuscular symptoms associated with statin use or the fibrate induced fatigue are a few examples. These unrecognized side effects are also certainly involved in the problem of poor compliance to LLA. It is well documented, particularly in the elderly population, that after one year of treatment only 25% of the patients are still taking their statin. Even more worrisome is the possibility that a patient may suffer an unrecognized side effect that limits their quality of life. The issue of safety is crucial to permit the use of LLA in the paediatric population. Since statins provide effective prevention of atherosclerosis and CHD to patients with genetic diseases such as familial hypercholesterolemia in which cholesterol deposition in arteries starts in childhood, it is mandatory to establish the safety of statins at younger ages.

Some forms of morbid dyslipidemias such as hyperchylomicronemia and secondary pancreatitis are still untreated by drugs. Fortunately microsomal triglyceride transfer protein (MTP) inhibitors are in development and will need to be tested in these severe hypertriglyceridemic conditions. Other agents targeting enzymes and receptors of lipid metabolism such as cholesterol transfer protein (CETP) inhibitors, acyl transfer protein inhibitors, bile acid transporter inhibitors, LDL antioxidants etc. will also increase our arsenal of LLA in the next few years. These drugs will certainly open the way to combination therapies but may be also be the cause of lipid lowering drug interactions.

## **II. PHASE II STUDIES FOR REGISTRATION OF NEW DRUGS**

### **II.1. Outline of a typical development plan**

During this phase the lipid lowering effect of the new drug is compared to placebo in a population of moderately hyperlipidemic patients over a relatively short period of time (12-24 weeks). These controlled trials are initiated once earlier studies in normal volunteers have assessed the pharmacokinetics, optimal and

maximally tolerated dosages, dose schedule and interactions with food and other drugs. The Phase II trials are designed to evaluate the efficacy and short-term safety of the new agent. The assessment of efficacy of lipid lowering drugs is not free of ambiguity. LDL-C is an accepted surrogate for coronary heart disease, the ultimate aim of lipid lowering, and thus evidence that a drug lowers LDL-C by at least 15% is adequate for registration. However, for HDL-C raising and TG lowering drugs, not proven surrogates for CHD, it is likely that in addition to showing a benefit on lipoproteins, the demonstration of a benefit on clinical CHD outcomes will also be needed.

A multicenter, randomized, parallel group design with 2 to 4 groups receiving several drug doses, and one placebo group is generally used. Regulatory agencies require a minimum of two drug dosages and 12 weeks of active treatment for approval. A minimum of two dosages is necessary for observation of a dose *versus* effect relationship. The number of patients randomized is dependant upon the magnitude of the lipid lowering effect and the drop out rate expected. Patients with secondary dyslipidemia and a history of cardiovascular disease (secondary prevention) are excluded since the risk of placebo treatment for 3-4 months in this last group, is considered unethical. Because treatment with LLA is always additive to diet and lifestyle modifications, a pre-randomization run-in period of 4-8 weeks on diet and placebo is mandatory. Patients included in these short-term trials are usually allowed to enter subsequent long-term follow-up trials.

## **II.2. Short-term studies**

### **Monotherapy trial for treatment of primary dyslipidemia**

#### **II.2.A. Objectives**

- a. To determine the safety and efficacy as monotherapy for primary hypercholesterolemia.

#### **II.2.B. Primary endpoints**

- a. The percent change of LDL-cholesterol from baseline (randomization visit) to the end of the study.
- b. The incidence and prevalence of adverse events and clinical safety laboratory parameters abnormalities.

#### **II.2.C. Secondary endpoints**

- a. Percentage change in lipoprotein cholesterol and triglycerides (total, LDL-C, HDL-C, VLDL-C).
- b. Percentage change in apolipoproteins (apoA1, apoB, LDL apoB and Lp(a)).
- c. Percentage of patients meeting the NCEP (National Cholesterol Education Program) guidelines target lipid values at the end of the study.
- d. Percentage change in fat-soluble vitamin levels (vitamin E, A, D,  $\beta$ -carotene) and INR as a functional measure of vitamin K status (for drugs affecting lipid absorption).
- e. Quality of life assessed by the SF-12 Health Survey.

#### **II.2.D. Study design**

A multicenter, randomized, double-blind, parallel group, placebo controlled design is generally used. Study begins with a screening phase using patient's file, questionnaire, physical examination and blood tests to identify those meeting the clinical and lipids inclusion/exclusion criteria. Potential candidates then enter a 4-8 weeks lead-in, stabilization period, during which they will receive single-blind placebo medication, lifestyle and diet counselling according to NCEP guidelines. A minimum of six weeks without LLA is needed before randomization. The lead-in period is also used to monitor drug compliance. Those not taking 75-80% of their medication are usually excluded. At this point patients fulfilling the inclusion/exclusion criteria are randomized to placebo or one of two active treatment arms (with one or up to four different doses of study medication). Sometimes a short titration phase may be used within the active treatment arms. During the treatment period lasting generally 12 to 24 weeks, the dosage remains stable until the end of the study. No other lipid lowering or lipid affecting agents are allowed during the

study, and an effort is made to keep the concomitant medications stable. At the end of the study, each participant is usually invited to take part in a long term extension trial with a predetermined randomization to an active drug treatment regimen.

#### **II.2.E. Planned sample**

Assuming a dropout rate of 15 to 25% over a 24 weeks period, approximately 150 patients per group are needed to detect, with 90% power, a significant difference of 15% ( $p \leq 0.05$ ) between each treatment arm and placebo.

#### **II.2.F. Study population**

Adults (over 18 years) with primary hypercholesterolemia.

#### **II.2.G. Specific inclusion criteria**

- a. Adults over 18 years of age at screening.
- b. Females must not be pregnant or lactating. Females of childbearing potential, must use a medically acceptable form of contraception at least four weeks before and until four weeks after the end of the study.
- c. Documented history of hypercholesterolemia with LDL-cholesterol (a mean of the 2 values obtained at the screening and randomization visits)  $\geq 3.4$  mmol/L and  $\leq 6.2$  mmol/L and TG  $\leq 3.5$  mmol/L.
- d. Have the ability to comply with the NCEP Diet.

#### **II.2.H. Specific exclusion criteria**

- a. History of atherosclerotic vascular disease including CABG (Coronary Artery Bypass Graft), PTCR (Percutaneous Transluminal Coronary Revascularisation), clinical or symptomatic angina pectoris, myocardial infarction, stroke, or peripheral vascular disease.
- b. Uncontrolled primary hypothyroidism (as defined by TSH  $> 1.5$  times the upper limit of normal at the screening visit), nephritic syndrome, or other possible causes of secondary dyslipidemia.
- c. Hemoglobin<sub>A1C</sub>  $> 8.0\%$ .
- d. History of cancer in the past five years (excluding basal cell carcinoma).
- e. Uncontrolled hypertension as defined by a systolic BP  $\geq 160$  mmHg or diastolic BP  $\geq 100$  mmHg.
- f. Chronic renal failure or serum creatinine  $> 1.7$  times the upper limit of normal at the screening visit.
- g. Unexplained serum CK  $> 3$  times the upper limit of normal at the screening visit.
- h. Active hepatitis or cholestasis or ALT  $> 2$  times the upper limit of normal at the screening visit.
- i. History of drug or alcohol abuse within the last year (more than 21 alcoholic beverages/week).
- j. Chronic diarrhoea or malabsorption.
- k. Subjects taking one of the following medications and unable to maintain a stable dose at least four weeks prior to the screening visit and for the duration of the study: tamoxifen, raloxifene, estrogen and or progestins, thiazide diuretics, isotretinoin,  $\beta$ -blockers, thyroid hormones, androgens, fiber supplements, protease inhibitors.
- l. Subjects currently taking and unable to discontinue prior within eight weeks prior to randomization and throughout the study: Any lipid lowering agent, cyclosporine, orlistat, systemic corticosteroid, alpha-glucosidase inhibitors,
- m. Drug compliance lower than 80% of the expected tablet count during the last two weeks of the lead-in period.
- n. Have received any investigational drug within four weeks prior to the screening visit.

#### **II.2.I. Tools for assessing primary endpoints**

Blood tests.

### **II.2.J. Specific criteria for early withdrawal and discontinuation**

The criteria for discontinuation from the study are pre-specified:

- a. Failure to meet randomization criteria;
- b. Protocol non-compliance;
- c. Adverse events;
- d. Investigator judgment;
- e. Patient withdraws consent;
- f. Pregnancy;
- g. ALT  $\geq 3$  times the upper limit of normal;
- h. CK  $\geq 10$  times the upper limit of normal or CK  $\geq 5$  times the upper limit of normal with clinical signs of myopathy; on two consecutive occasions at least one week apart.

### **II.2.K. Data analysis method**

Baseline homogeneity of the variables is examined by a one way ANOVA. The analysis of efficacy is done according to the intention-to-treat principle. All statistical tests are two sided and p values  $\leq 0.05$  are considered statistically significant. The only multiplicity adjustments are the Bonferroni adjustments for the primary hypothesis tests, one for each of the active treatment arm vs. the placebo.

### **II.3. Long-term studies**

Following completion of the short term, double blind, placebo controlled, efficacy and safety study, subjects are often offered entry into an open-label, long term (usually 12 months), extension study. The purpose of the trial being to gather data on long-term safety and tolerability of the study drug. In monotherapy long-term trials, during the first few weeks, the lipid lowering drug is usually titrated up (when it is possible), for subjects not attaining at the end of the short-term trial, the LDL-cholesterol goal dictated by NCEP guidelines. In combination trials, it may be the combined agent that is titrated up. After the titration period, usually patients are followed less frequently (every 3 months). Still, if necessary to reach therapeutic goal, other lipid lowering agents may be added during long-term follow-up. To demonstrate safety, the ICH guidelines generally ask that 600 patients be treated for 6 months with the new agent and 100 patients studied for one year. These extension studies offer also the possibility to test the persistence of the lipid lowering effect.

## **III. PHASE III STUDIES FOR REGISTRATION OF NEW DRUGS**

### **III.1. Outline of a typical development plan**

The phase III development plan of a lipid lowering drug must include a double-blind, randomised, placebo-controlled parallel group study which replicate the short-term phase II study, but generally uses only the optimal dosage and recruits a larger number of patients. The study is performed in duplicate usually in different populations; one in North America and one in Europe for example. The U.S. Food and Drug Administration (FDA) requires that phase III studies need to recruit a significant number of women and non-Caucasian participants. The main objective of phase III studies is to test the reproducibility and the expandability of the phase II results to the general population.

The number and the nature of the other trials in the development plan will be dictated by the intended use and indication of the drug. For instance, if a strong and well tolerated hypocholesterolemic agent with a new mechanism of action is intended to be used in replacement of statins to decrease LDL-cholesterol lowering, the phase III plan will include:

- a. Trials comparing the most powerful statins on the market with the new agent, in moderately and severely hypercholesterolemic subjects.

- b. The same comparison in special populations such as patients with Heterozygous Familial Hypercholesterolemia (FH) adult or children, Homozygous FH, renal failure, sitosterolemia or aortic stenosis.
- c. Combination trials with fibrates in patients with mixed dyslipidemia.
- d. Long-term outcome trials (recurrent myocardial infarction or cardiovascular death) in secondary prevention.
- e. Trials measuring the benefit of the drug on surrogate markers of atherosclerosis such as endothelial dysfunction, intima-media thickness or coronary plaques evaluated by intravascular ultrasound (IVUS) or angiography.

Before testing the new drug in children, elderly people or patients with renal failure it is necessary to demonstrate the pharmacokinetic and pharmacodynamic equivalence in a few subjects (8-10). A trial performed in a paediatric population with Familial Hypercholesterolemia is outlined below as an example of a phase III study.

### **III.2. Short-term monotherapy studies**

#### **Monotherapy trial in children with Heterozygous Familial Hypercholesterolemia**

##### **III.2.A. Objectives**

To evaluate the efficacy and safety as a monotherapy agent in adolescents with heterozygous familial hypercholesterolemia (HeFH).

##### **III.2.B. Primary endpoints**

- a. Percentage of change of LDL-cholesterol from baseline to six months.
- b. Incidence of adverse events, ECG and clinical laboratory safety parameters.

##### **III.2.C. Secondary endpoints**

- a. Specific apolipoproteins, lipoprotein cholesterol and triglycerides.
- b. Serum steroid hormone levels
- c. Serum fat-soluble vitamin levels
- d. Serum vitamin B-12 and serum/red blood cell folate levels
- e. INR as a functional measure of vitamin K status
- f. Linear growth

##### **III.2.D. Study design**

A multi-center, double-blind, placebo-controlled, parallel group, randomized study to evaluate the safety and efficacy in monotherapy. The study consists of a five to eight week drug washout, diet stabilization lead-in period, and a twenty-six (26) weeks double-blind treatment period. At the end of the lead-in period, patients meeting the randomization criteria will be randomized to one of the two arms: Active drug at the optimal dose or placebo. An unbalanced randomization can be used such that the ratio of patients on active drug/placebo will be 2/1.

##### **III.2.E. Planned sample**

Sample size will be similar to what has been described for phase II monotherapy trials. But since the study includes adolescents, it is wise to recruit a larger number of patients to counteract a significant Lost to follow-up. With the same purpose, the number of visits should be kept minimal.

##### **III.2.F. Study population**

Male and female adolescents between 10 and 17 years of age with HeFH.

### **III.2.G. Specific inclusion criteria**

- a. HeFH documented by LDL-cholesterol levels consistent with FH (LDL-C > 4.2 mmol/L) or documentation of LDL-cholesterol receptor gene mutation AND a positive family history of atherosclerosis at or before 50 years of age in males, and before 60 years of age in females, OR documented family history of hyperlipidemia with LDL cholesterol levels above 95<sup>th</sup> percentile for age and sex before treatment.
- b. The participant and the parent/legal guardian must provide informed consent prior to the subject undergoing any study-specific screening procedures.

### **III.2.H. Specific exclusion criteria**

- a. As described in the monotherapy phase II trial for treatment of primary dyslipidemia.
- b. History of homozygous familial hypercholesterolemia.

### **III.2.I. Tools for assessing primary endpoints**

Blood tests.

### **III.2.J. Specific criteria for early withdrawal and discontinuation**

As described in the monotherapy phase II trial for treatment of primary dyslipidemia.

### **III.2.K. Data analysis method**

As described in the monotherapy phase II trial for treatment of primary dyslipidemia.

### **Long-term monotherapy studies**

As described in the monotherapy phase II trial for treatment of primary dyslipidemia.

## **IV. PHASE III STUDIES FOR REGISTRATION OF NEW DRUGS: ADJUNCTIVE THERAPY INDICATIONS**

### **IV.1. Outline of a typical development plan**

At the present time, the vast majority of patients treated for dyslipidemia receive only one lipid agent (monotherapy). There are numerous reasons for that: First, the NCEP has designated LDL-C reduction as the primary target of treatment to prevent atherosclerosis and statins used in monotherapy can normalize LDL-C for most of the patients. Second, most of the long-term event trials that have proven the benefit of lipid lowering to prevent CVD have been done with monotherapy. Third, combinations of certain lipid lowering agents (i.e gemfibrozil+ statin) have been proven hazardous in the past, with cases of rhabdomyolysis and acute renal failure. Fourth, in patients with mixed dyslipidemia (elevated LDL-C and TG), the hypertriglyceridemia is often secondary to overweight, a poor diet, lack of exercise or alcohol intake, and can be corrected by lifestyle modifications. Fifth, physicians are reluctant to use two different drugs in asymptomatic patients to reduce, at significant costs, a single risk factor of CVD, particularly in primary prevention.

Nevertheless, some clinical situations require combinations of lipid lowering agents to effectively treat morbid forms of dyslipidemias. A combination of a full dose statin and ezetimibe is often necessary to normalize LDL-C in HeFH patients. A statin associated with nicotinic acid can effectively take care of high LDL-C and low HDL-C, a form of dyslipidemia often encountered in survivors of myocardial infarction. High risk patients with severe mixed dyslipidemia may need a combination of a fibrate and a statin for optimal therapy.

New drugs in development may have relatively modest cholesterol lowering effect but a complementary anti-atherosclerotic mode of action on oxidation, inflammation or thrombosis. The phase III development design for such agents intended to be used as adjunctive therapy must minimally include:

- a. Two large scale, short-term, parallel group, trials in different populations comparing the effect of the optimal dose of the new drug used in combination with a statin vs the statin alone on lipid levels and surrogate markers of atherosclerosis, inflammation and oxidation.
- b. Another short-term trial using the new drug in combination with a fibrate compared with the fibrate alone in patients with mixed dyslipidemia.
- c. A long-term trial comparing in secondary prevention, the same treatment arms over cardiovascular endpoints.
- d. A long-term trial testing the effect of the combination with a statin on carotid atherosclerosis progression evaluated by measurement of intima-media thickness (the only method approved by FDA).

Some studies on LLA intended to be utilised in combination therapy have used a cross-over design where each patient is treated successively with each drug and then with the combination. In such study design each patient serves as his own control, and each of the three treatment periods has to be long enough (2-3 months) to prevent a carry-over effect of the previous treatment.

## **IV.2. Short-term adjunctive therapy studies**

### **Combination-therapy trial in subjects with primary hypercholesterolemia at high-risk of cardiovascular disease not controlled by a starting dose of a statin alone**

#### **IV.2.A. Objectives**

To evaluate the efficacy and the safety of the investigational drug administered in combination with a statin in subjects with primary hypercholesterolemia and at high risk of cardiovascular disease, who do not reach the target value of LDL-C (2.5 mmol/L) on starting dose of the statin alone.

#### **IV.2.B. Primary endpoint**

- a. The proportion of subjects achieving target LDL-C (according to NCEP ATP-III guidelines) after 12 weeks of treatment (the aim is to show that a greater number of patients will reach the LDL-C target by combining the investigational agent to the statin rather than by increasing the dosage of the statin).

#### **IV.2.C. Secondary endpoints**

- b. The proportion of subjects achieving target LDL-C at weeks 2, 4 and 8.
- c. The percent change of LDL-C, TG, VLDL-C, HDL-C, apolipoprotein B, apolipoprotein A1, apolipoprotein C III, apolipoprotein E and Lp(a) after 12 weeks of treatment.
- d. Change in quality of life, evaluated by the SF-36 questionnaire, after 12 weeks of treatment.
- e. Adverse events and laboratory abnormalities occurring during the active treatment phase.

#### **IV.2.D. Study design**

A multi-center, randomized, double-blind, parallel group study.

Subjects with primary hypercholesterolemia and at high risk of cardiovascular event because of CHD history or diabetes mellitus or presence of other risk factors (absolute risk greater than 20% at 10 years according to Framingham tables) will be recruited. After a four weeks wash-out period of any lipid lowering agent (eight weeks for fibrates and one year for probucol), candidates will receive a starting dose of statin for another four weeks (open-label). At the end of the open-label period, they will be randomized to continue on statin therapy and placebo or to the combination of statin and the investigational drug at a

fixed dose for 12 weeks. In each group, the statin dosage is doubled after 4 and 8 weeks of treatment if LDL-C remains greater than 2.5 mmol/L. Diet therapy will be followed for the duration of the study.

#### **IV.2.E. Planned sample**

To show a 15% difference in the percentage of subjects achieving the target LDL-C level, with a power of 90% and a significance level of 0.05; a total sample of approximately 500 participants (250 per treatment arm) is needed.

#### **IV.2.F. Study population**

Men and women with primary hypercholesterolemia as well as with cardiovascular disease or well controlled diabetes mellitus or a cardiovascular risk greater than 20% at 10 years according to Framingham tables (NCEP ATP-III)

#### **IV.2.G. Specific inclusion criteria**

- a. Age 30 to 70 years.
- b. Primary hypercholesterolemia with an LDL-C  $\geq$  2.5 mmol/L and TG  $\leq$  3.5 mmol/L after the four weeks run-in period of open label statin therapy.
- c. Documented history of cardiovascular event (acute coronary syndrome; coronary, cerebral or peripheral revascularization; stroke or transient ischemic attack).

AND/OR

Well controlled and stable diabetes mellitus ( $Hb_{A1C} \leq 7.0\%$  at baseline and no change in treatment later than 3 months before screening).

AND/OR

A risk of CHD greater than 20% at 10 years, according to the modified Framingham tables of the NCEP ATP-III.

#### **IV.2.H. Specific exclusion criteria**

- a. Medical condition likely to limit life span to less than one year
- b. Women of child bearing potential who do not agree to practice an effective method of birth control until one month following study completion
- c. Lactating women
- d. Postmenopausal women on hormone replacement therapy
- e. Patients with homozygous familial hypercholesterolemia
- f. Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (thyroid hormone substitution must be stable for at least 3 months prior to screening)
- g. Chronic renal insufficiency or nephrotic syndrome
- h. Active or chronic hepatobiliary or hepatic disease
- i. Treatment with agents with known interactions with the statin or the investigational drug used in the study
- j. Any other lipid-altering agents (drug or food supplement) administered during the study

#### **IV.2.I. Tools for assessing primary endpoints**

Blood tests and questionnaire about quality of life (SF-36 Acute, Chapter 25, Appendix B).

#### **IV.2.J. Specific criteria for early withdrawal and discontinuation**

Threatening of health or well-being of a participant by their continuation in the study, in the opinion of the investigator.

#### **IV.2.K. Data analysis method**

The analysis of the primary efficacy variable is based on the intention-to-treat and performed using chi-square test. Analysis at each time point (4, 8 and 12 weeks) is provided.

### **IV.3. Long-term adjunctive therapy studies**

#### **Combination-therapy trial in subjects with mixed dyslipidemia**

##### **IV.3.A. Objectives**

To demonstrate that the fixed combination of a new triglyceride lowering agent (TLA) with a cholesterol lowering agent (CLA), titrated to the NCEP ATP-III guidelines, can slow the progression of atherosclerosis when compared to the cholesterol lowering agent alone, in subjects with mixed dyslipidemia after 24 months of treatment.

##### **IV.3.B. Primary endpoint**

- a. Annualized rate of change in intima-media thickness (IMT).

##### **IV.3.C. Secondary endpoints:**

- b. Annualized rate of change in IMT of each anatomical site (internal carotid, bifurcation and common carotid).
- c. Change in lipid parameters and biochemical markers of vascular inflammation and insulin resistance.
- d. Cardiovascular events (combination of coronary death, non-fatal myocardial infarct, stroke and revascularization procedures).
- e. Adverse events and abnormalities of clinical laboratory parameters.

##### **IV.3.D. Study design**

A multi-center, double-blind, randomized, parallel group, carotid ultrasound study of the fixed combination compared to the cholesterol lowering agent alone administered to subjects with mixed dyslipidemia. Potential subjects will undergo a 4-week lead-in period when they will receive diet and lifestyle counselling only (no LLA), as described in the NCEP ATP-III clinical guidelines or equivalent to establish screening lipid levels. This is especially important in patients with mixed dyslipidemia since diet and lifestyle has great impact on triglyceridemia. At the end of the lead-in period, eligibility for entry into the study is determined. All eligible subjects will enter a run-in period of treatment with the cholesterol lowering agent alone. The dosage will be titrated-up every four weeks to a target LDL-C level as per NCEP ATP-III guidelines. Once the target LDL-C is reached, subjects will then be randomized to continue on the CLA alone or to the combination with the TLA at fixed dose. Carotid ultrasonography will be performed at baseline and every six months for 24 months of treatment. Clinical safety and/or lipid efficacy assessments will be performed at each visit.

##### **IV.3.E. Planned sample**

It is estimated from similar studies that the standard deviation of the annualized rate of IMT change is 0.06 mm/yr. With a sample size of 340 subjects in each treatment group and a two-sided alpha level of 0.05, the study will have 90% power to detect a difference of 0.015 mm/yr. With a dropout rate of 20%, 850 subjects will be randomized.

##### **IV.3.F. Study Population**

Men and women with mixed dyslipidemia persisting after diet and lifestyle modifications. Patients with dysbetalipoproteinemia (Type III) should be excluded because they are particularly responsive to TLA.

##### **IV.3.G. Specific inclusion criteria**

- a. Age 30 to 65 years
- b. Mixed dyslipidemia defined by LDL-C  $\geq 4.2$  mmol/L and  $\leq 6.2$  mmol/L AND TG  $\geq 2.3$  mmol/L and  $\leq 6.5$  mmol/L.

#### **IV.3.H. Specific exclusion criteria**

- a. Women who are pregnant or lactating.
- b. Patients with dysbetalipoproteinemia (Type III)
- c. Patients with symptomatic cardiac or cerebrovascular disease (within the last 3 months prior to the screening visit)
- d. Patients who do not have a satisfactory baseline carotid ultrasound.
- e. Patients requiring specific lipid lowering therapy different from the CLA used in the study.
- f. Subjects taking any drugs known to interact with the medications used in the study.
- g. Subjects with uncontrolled hypertension (>140/90 mmHg), diabetes or hypothyroidism.
- h. Subjects with history of acute pancreatitis, malignancy, hepatobiliary disease (active), nephrotic syndrome, chronic renal failure or malabsorption.
- i. Subjects with alcohol consumption of more than 14 alcoholic beverages per week.
- j. Subjects with severe obesity or body mass index > 35 kg/m<sup>2</sup>.
- k. Subjects with poor compliance during the run-in period (< 80%) as assessed by tablet count.

#### **IV.3.I. Tool for assessing primary endpoints**

Quantitative ultrasonography.

#### **IV.3.J. Specific criteria for early withdrawal and discontinuation**

Finding of severe atherosclerotic carotid stenosis requiring surgery or adverse event requiring discontinuation of treatment.

#### **IV.3.K. Data analysis method**

The analysis of safety and efficacy data is done on the intention-to-treat population. But to be included in the efficacy analysis a participant needs to have at least both a valid baseline and a valid follow-up carotid IMT evaluation performed at least one year post baseline. The primary endpoint comparison between the two treatment groups needs to include analysis of time by treatment interaction.

### **V. OTHER STUDIES (SPECIAL INDICATIONS)**

#### **V.1. Hyperlipidemia in the elderly**

Since the benefit of treating hyperlipidemia to prevent cardiovascular events in elderly men and women (70-80 years) at high cardiovascular risk has been demonstrated in large scale randomized trials; the population involved in new drug trials should include a significant proportion of older patients. The number of drugs susceptible to be prescribed unilaterally to older people for secondary prevention of CVD is growing every year (aspirin, ACE inhibitors, beta-blockers, clopidogrel, statins, etc.). As a consequence, pharmacokinetic and interaction studies should be performed in elderly subjects. New drug phase III trials should not be restrictive in terms of concomitant medication in order to represent a “real life” situation and obtain valuable information on the safety of the new agent in this segment of the population. It may also be judicious in the future to include systematically in every long term trial involving subjects older than 70 years an evaluation of cognitive functions in order to detect subtle beneficial or deleterious effects.

#### **V.2. Hyperlipidemia in dialysis and renal transplant patients**

Total cholesterol level is inversely associated with survival in dialysis patients, a group at high risk of cardiovascular disease. The nephrotic syndrome is associated with high plasma levels of total and LDL-C, thus can promote atherogenesis and the risk of CHD. Chronic renal failure is characterized by hypertriglyceridemia, and decreased levels of HDL-C in approximately 30% of patients. Patients with kidney transplantation exhibit variable patterns of hyperlipidemia; some patients are purely hypertriglyceridemic while others present with hypercholesterolemia or mixed dyslipidemia. Unfortunately, the risk of myotoxicity and of interaction between cyclosporine and many of the currently available lipid lowering drugs (statins or fibrates), and the lack of large scale trials, has hampered their

utilization in this subgroup of patients. Thus, new drug development projects should include phase III short and long term studies to examine the efficacy and safety to reduce hyperlipidemia and CVD in patients with renal disease.

## **VI. EXAMPLES OF LANDMARK WELL DESIGNED TRIALS**

### **Monotherapy, short-term trials**

1. Nawrocki JW, Weiss SR, Davidson MH, Sprecher DL, Schwartz SL, Lupien PJ, Jones PH, Haber HE, Black DM. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-Co A reductase inhibitor. *Arterioscler Thromb Vasc Biol* 1995;15:678-682.
2. Holdaas H, Hartmann A, Stenstrom J, Dahl KJ, Borge M, Pfister P. Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporine. *Am J Cardiol* 1995;76:102A-106A.

### **Monotherapy, long-term trials**

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