19 December 2013
EMA/CHMP/748246/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft Guideline on clinical investigation of medicinal products in the treatment of lipid disorders' (EMA/CHMP/718840/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AESGP - Association of the European Self-Medication Industry
2	Amgen S.A.S.
3	EFPIA - European Federation of Pharmaceutical Industries and Associations
4	Pfizer Inc

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	This version as compared to the one reviewed March 2011 is much clearer and provides the sponsors with comprehensive guidance on the requirements for developing a lipid lowering agent for adults. We only have a few comments, mostly semantics.	
3	**Critical points for consideration by the EMA;**	
	Comment: 6.3.2.1 (monotherapy lipid studies): At lines 292-293 it is stated “Given the efficacy and safety of particular drugs (mainly statins) placebo controlled trials investigating products for monotherapy are no longer acceptable in large group of patients and high risk subjects.” Statin intolerant subjects represent about 10% of statin-treated patients, and guidance for studies in such a cohort is not given. **Proposed change (if any):** Add guidance for study designs in statin intolerant subjects together with a definition of statin intolerant subjects, such as; “Unable to tolerate at least two statins at the lowest approved daily dose due to skeletal muscle related symptoms, for example, pain, aches, weakness, or cramping that began or increased during statin therapy and stopped when statin therapy was discontinued”.	Partially accepted. The section is updated with a reference to statin intolerance. However, there is no consensus regarding the definition at the present time, so only general guidance is given.

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	Lines 128-130. **Comment:** We suggest adding that the requirement might also depend on the size of the population being treated (e.g. HoFH – will not be able to show a beneficial outcome on morbidity and mortality). **Proposed change (if any):** Clarification from the EMA required.	Agreed. Section is updated.
3	Line 307-318 **Comment:** "Combination of lipid-modifying agents" – is that referring to fixed-dose combinations and/or also to new add-on therapies, on top of e. g. statins? The requirement to show "benefit… ..in terms of morbidity and mortality"; is that for approval of a FDC modifying multiple lipid targets as first-line therapy? Or is it the requirement for any add-on therapy? Please compare to section 4.1.1, where "CV no harm" studies are indicated to be needed for add-on therapies targeting LDL-C lowering. **Proposed change (if any):** Clarification from the EMA required.	No further clarification is considered necessary. The section addresses combination "strategies". It is mentioned that " In principle, combination strategies are not expected to be licensed as first line therapy on the basis of their effect on LDL-cholesterol and other lipid parameters, in particular TG and HDL-C alone, unless the applicant is able to justify the benefit of such strategy in terms of morbidity and mortality."
3	Line 315 **Comment:** Statement in line 315 is narrow for a guideline applicable to the full spectrum of lipid disorders. This may be appropriate for primary	The section has been appropriately updated.

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	hypercholesterolemia, but not, for example, for Fredrickson type IV. Even for IIb's might want to add TG lowering agent with some LDL lowering effect before maximizing statin. **Proposed change (if any):** Deletion of the sentence "Specifically, patients should be on a maximum-tolerated statin dose, before adding a second lipid-modifying agent."	
3	Line 334 to 351 **Comment:** Line 334 and following three sub-sections are extremely specific, oriented toward effects of statins. As we don't know what types of potential end organ effects new agents might display, it would be preferable to keep the statement in 333 which is sufficiently comprehensive. **Proposed change (if any):** Delete sentence "Particular attention should be paid to the following:" and then delete sub-sections and content for Liver, Muscles and Kidney.	This deletion is not agreed. These organs are known to be targets for lipid modifying agents, and it is helpful to investigators to indicate the type of data needed. The section does not exclude AE in other organs.
4	As noted in **Section 2, Specific Comments on Text**, in the introduction, there is no discussion of the clinical relevance of lipoprotein particles other than low density lipoprotein cholesterol (LDL-C) or their relatedness, even though they are mentioned later in the document, in section 4.2.2. Furthermore, there is no mention of non-high density lipoprotein cholesterol (non-HDL-C) in the document. This is an easily calculated and highly relevant marker of CV risk, that has taken on more importance in	Partly accepted. In both sections 1 and 4.2.2, lipoproteins other than LDL-C are mentioned, with the emphasis that their clinical relevance is currently limited. The text in section 4.2.2 is updated about the use of non HDL-C.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	patients with mixed dyslipidemia, e.g., diabetes and metabolic syndrome, who have only modestly elevated levels of LDL-C, but higher levels of very low density lipoprotein cholesterol (VLDL-C) and other apolipoprotein B (apoB) related, triglyceride rich lipoproteins. Non-HDL-C is also discussed in great detail, in the 2011 *ESC/EAS Guidelines for the management of dyslipidaemias that* is referenced in this draft guidance.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
58-59	1	**Comment:** Since the guidance does not firmly propose a recommendation on the use of surrogate markers this phrase should be revised to a “discussion” phrase. **Proposed change (if any):** Latterly, there is ~~an attempt to~~ a discussion on the use of imaging modalities as surrogate markers of outcome benefit with lipid modifying agents.	The sentence refers to attempts to use these modalities in clinical trials and that section of the guideline has been updated. This has been clarified.
69	1	**Comment:** Please add parentheses to the abbreviation for LDL-C when first used. **Proposed change (if any):** …lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD).	Accepted
85	1	**Comment:** Please add parentheses to the abbreviation for LDL-C when first used.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): …hypertriglyceridemia and/or low high density lipoprotein cholesterol (HDL-C).	
85-86	1	**Comment:** Please add triglycerides to the sentence to explain the abbreviation TG. **Proposed change (if any):** Although elevated triglycerides (TG) are noted as a risk factor…	Accepted
445	1	**Comment:** Please add TG to the list of abbreviations. **Proposed change (if any):** TG – Triglycerides	Accepted
118-120	2	Please consider adding “clear” to “detrimental effect on both CV and non-CV mortality and morbidity should be excluded...”. LDL-C lowering studies are not designed to definitively address this question and thus, will not be able to do this in a statistically robust manner; however, sponsors do endeavour to gather enough pt exposure and events to exclude a clear detrimental effect.	Not accepted. The addition of "clear" is not considered additive. The definition and magnitude of detrimental effect are dependent on the patient population, the comparator in the clinical studies, and therefore a subject of assessment.
131	2	Please consider adding “clear” to “detrimental effect...”.	Not accepted, see before.

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151-155 208-209	2	Kindly clarify acceptability of use of IVUS and cIMT as surrogate markers as there seems to be slight contradiction in the statements (especially lines 154-155) and lines 208 and 209.	No contradiction is noted. However, the sentence has been modified to clarify.
173	2	Please consider adding the word “exploratory” so that it reads “…risk factors is exploratory and remains to be established.”	Not accepted. The meaning of the sentence is clear and additional wording is not considered to improve clarity.
174	2	Suggest adding the phrase “if these imaging markers are included in a clinical trial” so that the statement reads “If these imaging markers are included in a clinical trial, the onus, therefore rests with the company…”	Sentence is amended to make clear the intention.
258-260	2	Studies for LDL-C can be done or designed with sufficient numbers of these subjects to allow a statistical evaluation; however, it is not typical for a sponsor to power their studies off of subgroup analyses. In general, it is expected to evaluate the various subgroups, typically done on a forest plot, to ensure consistency of effect across the various subgroups. The overall analysis is primarily based on the trend or point estimate vs achieving statistical significance. Multiplicity is not controlled when doing these subgroup analyses. They are more akin to sensitivity analyses. Importantly, a similar approach will be done by sponsors for outcomes studies. The studies are not designed (powered) to assess statistical significance of various subgroups.	Agreed. No change in the text is proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
272	2	It would be helpful to clarify with an “eg” what “dietary supplements should be recorded”. Many dietary supplements, like multivitamins contain small amounts of niacin, etc… but are seldom in a high enough conc to be pharmacologically active.	Not accepted. It is left to the investigators / sponsors to record supplement’s dose that they would consider to be clinically relevant. Attempts to provide lists of supplements is not relevant in a guideline.
288	2	Please consider changing “will” to “may”.	Accepted.
396	2	Regarding SAP for pooled CV safety data, an awareness of time for effect and drug exposure needs to be considered.	Agreed, but no change in the text is foreseen.
57-58	3	**Comments:** Latterly, there is an attempt to use imaging modalities as surrogate markers of outcome benefit with lipid modifying agents. Since the guidance do not firmly propose a recommendation on the use of surrogate markers this phrase should be revised to a “discussion” phrase. **Proposed change (if any):** Latterly, there is an attempt to a discussion on the use of imaging modalities as surrogate markers of outcome benefit with lipid modifying agents.	The sentence refers to attempts to use these modalities in clinical trials and that section of the guideline has been updated. This has been clarified.
70-71	3	**Comment:** Other drugs than HMG-Co A reductase inhibitors have demonstrated a reduction of the CHD risk, therefore the statement “In addition, clinical trials have shown that LDL-lowering therapy with HMG-Co A reductase inhibitors reduces risk for CHD” is not completely true. Indeed the first evidence of a correlation of a reduction in LDL-C with a reduction in CV morbidity was achieved with bile acid sequestrants in the LRC	The change is not additive.

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		Primary Prevention Trial. Also, other drugs than HMG-Co A reductase inhibitors have demonstrated a reduction of the CHD risk (References: LRC-CPPT study: JAMA (1984) 251(3), 351-64; POSCH study: Atherosclerosis (2001) 154, 221-27). **Proposed change (if any):** Clinical trials have shown that LDL lowering therapy, primarily with HMG-Co A reductase inhibitors, reduces risk for CHD.	
75-81 Lines 76 and 80	3	**Comment:** The 4 categories of risk listed in the guideline are not exhaustive. In particular, the 2012 ESC guidelines now consider Diabetes Mellitus under 2 categories: very high risk if diabetes + one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h), high risk otherwise. This should be reflected in the guideline. Also, Euroscore stands for “EU system for cardiac operative risk evaluation”; the scoring system used for lipids is however presented in guidelines as SCORE for Systematic Coronary Risk Evaluation Project Therefore more appropriate tools like SCORE as recommended by the ESC / EAS which covers diabetes as well as other relevant co-morbidities (as CKD) should be the predominant tool to assess risk. **Proposed change (if any):** ...multifactorial level of cardiovascular risk (according to clinical guidelines). Four categories...	Section has been updated in line with the ESC guideline.

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		• Integrated global risk scoring models (e.g. Euroscore SCORE)	
77-78	3	**Comment:** It is not clear what primary and secondary prevention include overall. The CHMP guideline on the evaluation of medicinal products for cardiovascular disease prevention even states “The obvious clinical characterisation of patients at CVD risk is to select patients with symptomatic arterial diseases. Patients with a history of prior ischemic events are undoubtedly at particular risk for recurrence and this represented the “classical” secondary prevention trial populations. Although the recurrent events may be in the same arterial territory as the initial event, ‘there is also substantial risk for an event in another artery’. For example, patients with a history of ischemic stroke are at risk for not only recurrent stroke but also myocardial infarction.” In addition, as reflected in the introduction of the CHMP guideline on the evaluation of medicinal products for cardiovascular disease prevention, the terms “primary/secondary prevention” do not truly represent inherent cardiovascular risk and have yielded their place for a more comprehensive strategy aimed at treating patients at high risk of CVD adopting the intensity of preventive **Proposed change (if any):** Clarity from the EMA required	Agreed. While the points are clear, concept of primary and secondary prevention are not completely discarded. The section has been updated.

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117-120	3	**Comment:** This statement does not include a recommendation on how to exclude a “detrimental” effect, nor is defined what a detrimental effect or a signal for a detrimental effect is. To guide development of a new drug, the proposed approach is insufficient. **Proposed change (if any):** Clarity from the EMA required. Additional recommendations on how to demonstrate the lack of detrimental effect would be useful.	Not accepted. It is difficult to list all possible detrimental effects, especially with new molecules, where also rare AEs could be expected. A detrimental effect on mortality and morbidity is a general term, but not vague.
144-145	3	**Comment:** This sentence could be clarified and guidance for development of agents only lowering Lp(a) levels should be added. **Proposed change (if any):** There is limited experience with clinical studies investigating medicinal products qualitatively modify dyslipidaemias in dyslipidaemias characterised by qualitative changes in lipoproteins.	Not agreed. As there are limited clinical data in these areas, it is difficult to give appropriate guidance.
Line 146-176	3	**Comment:** It is not clear if “regression of vascular damage” could constitute an indication in its own right. If e. g. vascular imaging data indicate that the atherosclerosis burden is diminished, and this is paralleled by a significant reduction of CV clinical events in an adequately powered study, would that grant an indication? Could data from imaging studies and a separate clinical outcomes study with the same intervention be linked to grant this indication?	If a trial demonstrates a clear reproducible link between imaging markers of regression and clinical event reduction, it is possible to consider an indication. However, in the absence of such data this discussion is hypothetical and not required in the guideline. Similarly, the discussion on the need for data from one or two trials is not considered appropriate. No change to the text is thus

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		Proposed change (if any): Clarify if "regression of vascular damage" could constitute an indication or not; if so be more specific on what the requirements are.	necessary.
Lines 162-163	3	**Comment:** Regarding Section 4.1.3. Vascular damage (target organ damage), lines 162-163 indicate that "Demonstration of regression of atherosclerotic burden is the preferred parameter or effect rather than lack of progression as the end point." This would be required in a single arm trial, but in a comparator trial, it is the difference between the drug being examined and the conventional therapy (or active comparator) that should represent the primary endpoint of the study. The change in a measure of atherosclerotic burden is a continuous parameter with a broad distribution of effects in a treatment arm. Regression, lack of progression, and progression, only represent the statistical distribution (significance of the change relative to zero) for the treatment arm as a whole, a treatment arm in which both regression and progression are likely to be observed. For example, "no change" (lack of progression) actually represents that, on average, half of the subjects progress and half of the subjects regress. Overall significant slowing of disease progression in a treatment arm, if maintained over time, would be expected to reduce subsequent cardiovascular events in a patient cohort receiving that treatment. **Proposed change (if any):** Please provide clarity on this	The comment raises some valid facts. However, it is not agreed that regression and lack of progression are simple statistical distributions. Thus far, mechanism of lack of progression or true regression have not been convincingly demonstrated or detailed. In this context, lack of progression could imply either insufficient duration of the trial to detect true progression, or lack of effect of the therapeutic intervention. The sentence as expressed is considered to have sufficient clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		statement.	
Lines 180, 409	3	**Comment:** "death, non-fatal MI and stroke" should read "death, non-fatal MI and non-fatal stroke". When you are referring to "major cardiovascular events", consider limiting the strokes to those adjudicated to be of ischemic origin. **Proposed change (if any):** Change "death, non-fatal MI and stroke" to read "death, non-fatal MI and non-fatal stroke" or "death, non-fatal MI and non-fatal ischemic stroke".	Partially agreed. The specification of the type of stroke is not supported, in the same way that all cause death is preferred to CV death.
Line 184	3	**Comment:** The trend for many contemporary registration studies to explore alternative composite endpoints than the classic triple endpoint is not acknowledged. **Proposed change (if any):** ...used in some trials for two reasons; to increase statistical efficiency and to measure clinically relevant outcomes.	Not agreed. The inclusion of softer endpoints is considered of less clinical relevance than death/MI/stroke
187-188	3	**Comment:** The guideline on the evaluation of medicinal products for cardiovascular disease prevention" (EMEA/CHMP/EWP/311890/2007), is mentioned as providing standard definitions for CV events. However, this guideline is on prevention and does not provide these definitions, but considerations on the evaluation of risk, that would be more appropriately quoted in Section 5.	Partially agreed. The section has been updated to remove reference to the prevention guideline. Applicants are encouraged to use clinically relevant definitions, as used in clinical or regulatory guidance documents.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Clarity from the EMA required	
Line 204-206	3	**Comment:** The guideline mentions qualitative abnormalities, "…that may become prime targets for new forms of lipid-modifying agents". If demonstration of such effects are currently seen as being of relevance for registration of a new product is not clear. **Proposed change (if any):** Clarify situation with respect to current impact – or absence thereof – of effects of new interventions on qualitative lipid abnormalities.	Not accepted. There is limited experience with clinical trials addressing qualitative lipid abnormalities. A statement cannot be added.
Line 209	3	**Comment:** The phrase "measure the change in thickness of the IMT either in carotid, or IVUS," is confusing. IMT refers to intima media thickness typically measured in the carotid artery by a linear array transducer (although it can be applied to other arteries). IVUS refers to an intravascular catheter containing an ultrasound transducer in its tip, that is typically employed in the coronary arteries. **Proposed change (if any):** Clarification from the EMA required. Reword the phrase to be clearer as to what is the intended meaning.	The discrepancy was noted and the section has been updated.
Line 235	3	**Comment:** The end of the cIMT section "far wall of up to 4 arterial segments" is confusing. Since line 226 refers to "12 pre-selected carotid arterial segments", this is presumed to refer to the near and far walls of the left and right CCA, bulb	Partly accepted. Read up to 6 as a minimum is acceptable. The original proposal was trying to be less restrictive. The rest is an issue of assessment.

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		and ICA. As such, there are 6 far wall segments and 6 near wall segments. Why would "secondary measurements" that "could be considered" be limited to only up to 4 of the 6 far wall segments? **Proposed change (if any):** Change "up to 4" to read "up to 6", indicate a minimum rather than a maximum number of arterial segments to be considered, or specify which 4 of the 6 arterial segments are permitted for consideration.	
Line 238	3	**Comment:** It is reasonable to require "a minimum of 20% luminal narrowing" within a coronary artery at baseline, because that ensures that there are discrete atheroma diffusely throughout the coronary tree that can be assessed serially to examine disease progression. However, it is overly restrictive to require that the 20% luminal narrowing be present in "the relevant coronary artery". In order to maximize the data acquired, IVUS investigators are directed to select the longest, least tortuous coronary artery to enable imaging the greatest pullback length possible. Since the presence of a minimum 20% luminal narrowing anywhere within the coronary tree ensures that there are discrete atheroma diffusely throughout the coronary tree, this approach enables the greatest baseline atheroma volume to be monitored for the effects of drug therapy. This is the standard methodology that has been successfully applied by the Cleveland Clinic in ASTEROID and SATURN studies, as well as in many other IVUS trials in which Cleveland Clinic	Not accepted. There are a number of assumptions and the luminal narrowing of 20% in the relevant coronary artery is needed in order to minimise errors of sequential measurements.

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		has served as the IVUS core laboratory. **Proposed change (if any):** .....a minimum of 20% luminal narrowing of the relevant within a coronary artery at baseline is required.	
250-253	3	**Comment:** "studies are mainly performed in patients with…moderate to very highly elevated LDL-C levels". Consideration should be given to studying patients not at LDL-C target given their level of CV risk – as these are patients likely to receive treatment (vs. basing studies solely on absolute LDL-C levels). **Proposed change (if any):** Clarification from the EMA required.	Not agreed. The introduction was updated and clarifies the different risk factors that determine the level of intervention. This is considered sufficient.
Lines 254-255, and 401	3	**Comment:** It is unclear what the Agency consider an adequate number or portion, in terms of number/portion of study subjects over >65, respectively, >75 year of age. In the light of the overall ageing population, and expectations on geriatric medicines, a clarification would be helpful for the applicant. **Proposed change (if any):** Clarification from the EMA required.	Not agreed. A specification is not endorsed, because it would vary per indication.
Line 259	3	**Comment:** The line "Patients with clinical and/or other manifestations of atherosclerosis and/or type 2 diabetes	Agreed.

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		mellitus should be represented in adequate numbers to allow statistical (sub) group evaluation." doesn't mean adequately powered to demonstrate statistically significant benefit in subgroups. **Proposed change (if any):** Rephrase with ".... in adequate numbers to allow statistical (sub) group evaluation assessment of consistency with the overall result"	
Line 272	3	**Comment:** The statement that "Dietary supplements should be recorded and remain unchanged throughout the trial duration", is very unclear. **Proposed change (if any):** Rephrase with "Dietary supplements which may affect lipoprotein levels should be recorded and remain unchanged throughout the trial duration."	Not agreed. It is preferred to keep requirement more general.
314-315	3	**Comment:** Line 314 recommends that patients are on a standard dose of background lipid-lowering therapy, whereas line 315 specifies that patients should be on a maximum-tolerated statin dose. Standard doses are usually not maximum-tolerated doses, except in rare cases (e.g. immediate post-ACS). **Proposed change (if any):** Delete sentence... "Specifically, patients should be on a maximum-tolerated statin dose, before adding a second lipid-modifying agent."	Partially agree. The sentences have been modified.

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401 - 404	3	**Comment:** It would be helpful if some context or expectations could be described for an 'adequate number of high risk patients'. If the CHMP is requiring a certain percentage of the population, this is problematic as very elderly patients, for example, may not wish to participate in clinical trials. **Proposed change (if any):** In either case and adequate number of h High risk patients […] should be included in the clinical development programme, with a discussion on the ability to gather data representing these groups in the safety summary.	Not agreed. This would be too restrictive and may differ per indication.
411-412	3	**Comment:** The sentence "Other events such as revascularisation and/or worsening of heart failure can also be evaluated" should be clarified. If the aim is, as in the previous sentence regarding hospitalisation for unstable angina, to exclude a safety signal, revascularization may not be a very adequate parameter, since its use is very depending on standard of care, with a lot of variability from a country to the other (or even between sites). **Proposed change (if any):** Clarification from the EMA required.	No change is foreseen. The aim is to exclude a safety signal and this is clear in the text.
		Editorial points for consideration by the EMA;	

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68	3	**Comments:** add parenthesis to abbreviation for LDL-C when first used **Proposed change (if any):** lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD).	Agreed.
Lines 82-92	3	**Comment:** Suggest adding in mention of non HDL-C as a risk factor for CHD. **Proposed change (if any):** Addition of non HDL-C as a risk factor for CHD within lines 82-92.	Agreed.
84	3	**Comments:** add parenthesis to abbreviation for LDL-C when first used **Proposed change (if any):** hypertriglyceridemia and/or low high density lipoprotein cholesterol (HDL-C).	Agreed
85	3	**Comments:** add triglycerides to the sentence to explain the abbreviation TG **Proposed change (if any):** "hypertriglyceridemia and/or low high density lipoprotein cholesterol HDL-C. Although elevated triglycerides (TG) are… "	Agreed
Lines 88, 90	3	**Comment:** The abbreviation "CVD" is not defined in the text.	Agreed

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		Proposed change (if any): Define it as cardiovascular disease in the text to differentiate it from CHD.	
Line 119	3	**Comment:** The reference to 7.4 is not correct. There is no section 7.4 in the document. **Proposed change (if any):** (see also 7.2 7.4)	Agreed, changed to 7.2
Line 150	3	**Comment:** "MRI" is the last of a series of examples and should read "and MRI". **Proposed change (if any):** Change "MRI" to read "and MRI".	Agreed
Lines 160, 165, etc.	3	**Comment:** The abbreviation "CV" is not a defined term. **Proposed change (if any):** Define it as cardiovascular.	Agreed
201-202	3	**Comment:** Proposed change: A clarification to read "or apoB/apoA1 ratio" instead of "or the balance between apoB and apoA1" **Proposed change (if any):** ..or the balance between apoB and apoA1 or apoB/apoA1 ratio	Agreed
Line 246	3	**Comment:** There is only one most diseased 10 mm segment, so "segments" should be singular.	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Change wording to read “in the most diseased 10mm segment”.	
Line 247	3	**Comment:** Plaque volumes have units of cubic mm rather than “mm”. **Proposed change (if any):** Change “mm” to “mm3 ” or “mm^3”.	Should have read mm^3. This is document formatting error.
270	3	**Comment:** As some patients can be naive of any lipid-modifyng treatment, the following sentence should be modified: “Lipid-modifying therapy should be withdrawn at the start of this period, when monotherapy is studied, requiring an adequate wash-out.” **Proposed change (if any):** “For patients treated with lipid-modifying therapy, this therapy should be withdrawn at the start of this period	Accepted.
324-326	3	**Comment:** these lines in section 6.3.2.3 are difficult to understand. **Proposed change (if any):** A placebo-controlled study aimed at demonstrating superiority is ethically acceptable, if there is no established therapy for the specific target population.	Accepted.
Line 408	3	**Comment:** The A of MACE stands for adverse.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Add “adverse” so that the phrase reads “major adverse cardiovascular events (MACE)”	
66	4	**Comment:** The statement, *“Lipid disorders most often imply hypercholesterolemia,”* might be expanded further, so as to describe the range of cholesterol carrying particles and their relationship, since they are commonly reported in clinical trials as well as the summaries of pharmaceutical characteristics of lipid modifying therapies. Furthermore, these particles and their clinical significance, are discussed in detail in the **ESC/EAS Guidelines for the management of dyslipidaemias** referenced by this draft guideline (line 446) **Proposed change (if any):** Lipid disorders are commonly referred to as hypercholesterolemia. Hypercholesterolemia generally refers to elevated levels of total cholesterol, the greatest component of which comprises low density lipoprotein cholesterol (LDL-C). LDL-C is one of a family of lipoprotein particles containing apolipoprotein B (apoB), all of which carry various proportions of cholesterol and triglyceride. Apo B related lipoproteins comprise very low density lipoprotein VLDL, LDL-C, lipoprotein (a) [Lp(a)], intermediate lipoprotein (IDL), and remnant lipoproteins (RPL). Elevations in LDL-C and other apo-B related lipoproteins confer cardiovascular risk. An integrated measure of these Apo-B cholesterol carrying lipoproteins is non-HDL cholesterol (non-HDL-C). It is calculated as the difference between total cholesterol and high density	Changes are implemented in section 1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		lipoprotein cholesterol (HDL-C). HDL-C contains apolipoprotein A (apo A). Epidemiologic data shows that cardiovascular risk is inversely related to levels of HDL-C.	