29 October 2010
EMA/CHMP/EWP/599934/2009

Overview of comments received on draft Guideline Hypertension

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

Stakeholder no.	Name of organisation or individual
1 EFPIA	
2 Servier	
3 Daiichi Sankyo 4 Novartis 5 MEB, NL 6 M. Grillo 7 E. O'Brien	

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	EFPIA welcome the revision of the existing guideline and the opportunity to provide comments. In addition, we welcome the recognition and adaptation of the CHMP guideline to consider the use of fixed dose combinations in the treatment of hypertension as first line therapy.	
1	**In addition to some few comments detailed in the below sections, we have 2 major issue:** 1. The draft revised guideline (line 284-285) states "In order to obtain a marketing authorisation for a fixed combination, it is mandatory to prove that each active component in the scheduled dosage independently contributes towards the positive evaluation of the combination drug. Concerning morbidity and mortality data the same requirements apply as to the mono-components." As to the positive effects on morbidity and mortality with a fixed combination, we suggest that on a case-by-case basis and provided justification, data from large clinical outcome trials in which the mono-agents were used as co-therapy either alone or with other agents could be sufficient to support a positive statement in labelling regarding the morbidity / mortality of the fixed combination. This is further supported by the daft FDA guidance on Hypertension Indication: Drug Labelling for Cardiovascular Outcome Claims http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075072.pdf 2. For fixed combination where one or all substances are not well known and/or the efficacy and safety of the joint application have not been established, the study design proposed for confirmatory study seems inordinately complicated and the findings of such a study could be difficult to interpret. It appears that treatment regimens are compared across study periods. How then does one separate temporal effects from treatment effects? It is suggested that a factorial design study would be preferable. If there are safety concerns with the joint administration at higher doses, the	This statement is in line with what is written in the guideline for fixed combinations in general. The comments focus on what could be accepted in "the labelling" (I interpret this as referring to the SPC). The precise wording of the SPC is something that has to be decided in each individual case. It is the task of the Sponsor to justify each claim and I my opinion there should be no statement in the guideline about this. There has been a revision of the text in the guideline in this respect.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	factorial studies could be staged to evaluate a range of low dose combinations before progressing to higher dose combinations A rewording of the section is also proposed on page 7 of this document	
	Section 1 Introduction 2nd paragraph Line 11-12 **Comments:** While the ESC guidelines does not recognize pre-hypertension as a distinct class, a patient with a usual BP of 115/70 mmHg can have an increase of 25/20 mmHg and still satisfy this criterion despite the significant elevation of BP. The guidelines could be modified to recognize this type of patient. **Proposed change (if any):** It may be more appropriate to state: "In the otherwise healthy adult population ***stable*** values below 140/90 mmHg are considered within the normal range and values of 140/90 mmHg and greater in the hypertensive range."	Not agreed.
3	**Comments:** No guidance is given regarding requirements for different dosages. **Proposed change (if any):** Add clarification that for FDC the results of higher dosages do not have to be superior to the lower dosages. Add clarification that add-on studies can be done in higher dosages and cover the dosages below.	Not agreed, higher doses should show more benefit, why else use them? Not agreed, it is important to show that also lower doses are efficacious (and safe).
4	Novartis welcomes the revision 3 of the guideline on clinical investigation of medicinal products in the treatment of hypertension to address the different development options of fixed combination beyond the standard dual fixed combination for second line therapy. With the differentiation of the three main potential indications and respective clinical data requirements, Novartis believes that it could be beneficial to define a core clinical development package as the basis for any of the potential indications. This package would be supplemented by specific confirmatory study/ies pertinent to the	I do believe that the guideline in its present form do adhere to the general comments made by Novartis.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	targeted indication(s). As suggested in the guidance, this basic program could consist of a factorial trial to demonstration the complementary mechanism of action of the individual components as well as confirmation of the dose selection. This study could be supplemented by additional (longer term) safety data as appropriate. This core package would be completed by either: • First line indication: First-line study (more severe hypertensive patients –> faster BP control) • Second/third line indication: Add-on study (patients not responding to one or more agent -> increased BP control rate) • Substitution indication: Bioequivalence study (patients already adequately treated with free combination -> improve compliance) In this new setting, Novartis does not believe that the add-on study design is appropriate to evaluate the benefit/risk of a combination for first-line therapy or substitution therapy since it targets a different patient population (non-responder) in a different treatment setting (addition of a new agent to existing, insufficient therapy). Finally, we would like to emphasise that we strongly support the introduction of the first-line indication at therapeutic dose in this guidance in line with most recent JNC 7 and ESH/ESC treatment recommendations. With regard to the study design of the confirmatory study described in the current draft, we agree with the general principles and objectives although we believe some elements should be factored in the final study design recommendation to accommodate different potential scenarios in particular medicinal product with multiple dosage strengths developed. Overall we believe this revision is positive and will be beneficial for development of optimised medicinal product to ensure better management of hypertension in patient requiring more than one drug to achieve their blood pressure targets.	
5	<u>General position</u>: The current revision to guide development of fixed combinations in therapeutic doses for first line antihypertensive therapy is supported. The proposed study design of a therapeutic confirmatory study comparing the 'traditional' add on approach versus the first line	

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	combination strategy will provide pivotal data to support a first line indication.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 1 Introduction 2nd paragraph Line 11-12	1	**Comments:** While the ESC guidelines does not recognize pre-hypertension as a distinct class, a patient with a usual BP of 115/70 mmHg can have an increase of 25/20 mmHg and still satisfy this criterion despite the significant elevation of BP. The guidelines could be modified to recognize this type of patient. **Proposed change (if any):** It may be more appropriate to state: "In the otherwise healthy adult population ***stable*** values below 140/90 mmHg are considered within the normal range and values of 140/90 mmHg and greater in the hypertensive range."	Not accepted. "Pre-hypertension" is not considered as a condition that should be treated with pharmacological methods.
Section 9.1 Fixed combinations General remarks Line 274-281 and Section 9.2.3 Substitution therapy Line 437 and onwards	1	"The joint application of the 2 components has proven to be efficacious, safe and thus, clinically useful" **Comments:** A simplification of therapy may be considered as a point to drive a combination therapy. As mentioned in the EMEA Fixed Combination Medicinal Products Guideline (CPMP/EWP/240/95 Rev. 1) http://www.emea.europa.eu/pdfs/human/ewp/024095enfin.pdf, a simplification of therapy could also be considered as a point to drive a combination therapy. In this guideline, it is stated that "**a simplification of therapy** by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and may improve patient compliance. This is also referred to as a "substitution indication". "**A simplification of therapy by decreasing the number of individual dose units to be taken by the patient, which simplifies therapy and may improve patient compliance**." **Proposed change (if any):** *(No proposals found in the answer document.)*	Not accepted. Even if no detectable change is proposed the statements in these two sections are that the combination should be among other things "clinically useful" (section 9.1) and "to reduce the number of tablets to enhance adherence". In other words "simplification of therapy" is already included in the guideline even if it is not worded in precisely that way.
Section 9.2 Clinical	1	**Comments:** The requirement to run trials with all dosages will be cumbersome and will take a lot of time.	Not accepted. In section 9.2 the wording is the following:

development of a fixed combination Line 286-291		Similar data can be obtained using a low, intermediate and high dose and combining these with modelling and simulations of all intervening doses. The outcome from the modelling and simulation may be confirmed by data from the factorial Phase II trial. This approach will have the advantage of potentially providing more information on the program. **Proposed change (if any):** Dose-finding studies are necessary for identifying the appropriate dosages of the components of a fixed combination. Preferentially, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their respective components and with placebo. ***However, similar data can be obtained using a low, intermediate and high dose and combining these with modelling and simulations of all intervening doses. The outcome from the modelling and simulation may be confirmed by data from the factorial Phase II trial.***	In the situation where a combination has not yet been demonstrated to be safe and efficacious, the positive benefit/risk of the joint application of the mono-components should be demonstrated by means of a study/ies with appropriate design and dose-response data. *Preferably, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their respective components and with placebo. Ascending dosages (e.g. in a range of dose equal or superior to two) of the fixed combination could be tested in patients with insufficient response.* The results of the factorial studies should be the basis for further, confirmatory, clinical trials….. Therefore the suggested change is not accepted.
Section 9.2 Clinical development of a fixed combination Line292	1	**Comments:** Factorial design studies are preferred for identifying combination doses of interest. However, in the common situation where there is extensive clinical trial experience with the independent agents used as co-therapy, additional dose finding studies may not be necessary. In such a case we suggest that a single factorial study serves as a confirmatory study. **Proposed change (if any):** The results of the dose-finding studies should be the basis for further, confirmatory, clinical trials. ***However, in situation where there is extensive clinical trial experience with the mono-components used as co-therapy, a single factorial study could serve as a confirmatory study.***	Not accepted, see above
Section 9.2.1	1	**Comments:**	Not accepted.

Add-on therapy Line 306-308		As far as add-on therapy is considered, in addition to non-responders, it could be useful to also consider the patients who don't tolerate the initial drug. **Proposed change (if any):** **"**It is necessary to demonstrate a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond ***or tolerate*** adequately to standard therapeutic doses of one or all of the mono-components."	Patients not tolerating one or both of the mono components should not be given these drugs but instead switched to a different treatment.
Section 9.2.1 Add-on therapy Line 317-320	1	**Comments:** It is mentioned in the guideline that both "diastolic and systolic blood pressure" are required. Nowhere else in the guideline are both parameters required; usually it is only diastolic blood pressure (DBP) >2 mm Hg. **Proposed change (if any):** "In non-responders it is usually sufficient to show a clinically relevant and statistically significant superiority of the combination regarding ***a relevant greater blood pressure lowering effect (e.g. >2 mmHg with respect to DBP)***	Not accepted. It is noted that this is the only time both systolic and diastolic pressure is mentioned. However in the guideline is mentioned that it would be optimal to show significant improvement in response rate.
Section 9.2.2 1st line Line 338-340	1	**Comments:** The term 'low dose' rather than 'sub-therapeutic' combinations would be preferable as mentioned in the literature. (Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomized trials. BMJ. 2003; 326: 1427-1434)	Not accepted. The term sub-therapeutic is preferred.
Section 9.2.2 1st line Patient selection Line 380-390	1	**Comments:** The guidance mentions "it is mandatory for the Sponsor to justify that the patients considered for a first line fixed-dose combination (FDC) have a low chance to be adequately treated with a mono or by a combination in subtherapeutic doses". Why is such a mandatory request, given that several	Partially agreed. "Recommended" and "justified" could be a better wording. However, the Sponsor must be aware that it is mandatory to have ample justifications and good arguments.

		large trials, especially in the group of patients with high initial blood pressure or with risk factors for CV events, have demonstrated that blood pressure goals cannot be achieved by one drug alone? It is proposed that a FDC that is well characterized in terms of dose response for efficacy as well as for safety can be used as first line therapy for all hypertensive patients. Such an approach could facilitate the clinical practice of multidrug treatment, and encourage the selection of treatments with complimentary mechanisms of actions. In this regard, we fail to understand the justification that initial treatment should be limited to patients with high cardiovascular risk or more severe levels of hypertension. (Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: Meta-analysis of 11,000 participants from 42 trials. Am J Medicine (2009) 122, 290-300) **Proposed change (if any):** Appropriate patient selection is ***a*** key point and it is ***recommended*** for the Sponsor to justify that the patients considered for a first line fixed dose combination have a low chance to be adequately treated with mono-therapy or by a combination The inability to reach the ***therapeutic*** goal is influenced by many factors such as initial blood pressure levels, target blood pressure, concomitant diseases, target organ damage, age ***as well as the complementary mode of action of the drugs which should be taken into account***. The sponsor should also take into account demographic peculiarities, like age and gender, and concomitant illnesses, as indicated in section 4 of this document.	
Section 9.2.2 Line 407-417	1	**Comments:** As already identified in the major comments on page 2, the proposed study design seems inordinately complicated and the findings of such a study could be difficult to interpret. It appears that treatment regimens are compared across study periods. How	Partially agreed. Has been discussed in the guideline.

		then does one separate temporal effects from treatment effects? It is suggested that a factorial design study would be preferable. If there are safety concerns with the joint administration at higher doses, the factorial studies could be staged to evaluate a range of low dose combinations before progressing to higher dose combinations. **Proposed change (if any):** The therapeutic confirmatory study ***should ideally best used a factorial design***. ***If there are safety concerns with the joint administration at higher doses, the factorial studies could be staged to evaluate a range of low dose combinations before progressing to higher dose combinations.*** Depending on the need, comparative studies with other FDC may also be considered at least when these are registered for this first-line indication. Assessment of antihypertensive efficacy and its methods should be in accordance with mono-therapy (see sections 1 - 5 of this document). One additional end point could be "time until achieving target blood pressure", which is in accordance with the primary aim to achieve the BP goal in a more timely fashion.	
Section 9.2.3 Line 442-451	1	**Comments:** It is suggested that all FDC products be supported by at least one clinical trial, preferably of a factorial design.	Partially agreed, additional wording has been added to the guideline.
Line 31 § 3	2	Typing error …especially those listed in section ~~6~~ **10** (references)	Accepted.
Lines 38-39 § 4.1	2	Section 6.9 does not exist in this updated version of the Guideline. … effect on mortality and cardiovascular morbidity (see ~~6.9~~ **4.2, 5.3 and 8.9**).	Accepted.
Lines 410 & 412 § 9.2.2	2	The definition of X and Y is confusing: i.e. two different doses of the FDC?, or the two mono-components in the FDC? The recommendations that follow therefore need clarification.	Partially accepted. Changes have been made in the guideline.

Line 417 § 9.2.2	2	In recent treatment Guidelines, 4-week evaluations are recommended	Accepted.
Line 420 § 9.2.2	2	Typing error ….(see sections 1 - ~~5~~ **7** of this document).	Accepted.
15, para 1	3	**Comments:** More recent versions of JNC are available for severity evaluation	Agreed.
31	3	**Comments:** "section 6" should be "section 10". **Proposed change (if any):** Suggest change.	Agreed.
39	**3**	**Comments:** "(see 6.9)" should be "(see 8.9)". **Proposed change (if any):** Suggest change.	Agreed.
57	**3**	**Comments:** The primary parameter is not very clear. It would be good to get advise if the DBP or the SBP can be used as a primary parameter	Accepted. SBP is the main efficacy variable.
71	**3**	**Comments:** As mercury sphygmomanometers are forbidden to use in several European countries, mercury-free sphygmomanometers should be mentioned as well. **Proposed change (if any):** Measurements with a calibrated mercury **or mercury-free** sphygmomanometer….	Agreed.
100, para 5.1 ad c)	**3**	**Comments:** Requirement to use "same recorder" for repetitive investigations. For high enrolling sites, using ≥ 1 ABPM device this may be an unfeasible requirement to keep track which recorder was used initially. **Proposed change (if any):** Repetitive investigations should be performed … using the same brand and model of recorder throughout the study.	Agreed.
100-102	**3**	**Comments:** ABPM recording intervals: recommended intervals (15 min for daytime recording; 30min for night time recording) seems to be too short. **Proposed change (if any):** It is enough to record ABPM at 30 min intervals for daytime and 1 hour	Partially agreed. This has been the subject for comments from other interested parties as well. It is greed that there is a conflict between the wish for as much data as possible and the comfort and compliance of the patient. A less precise wording could

		intervals for night time.	perhaps be used.
105-106	**3**	**Comments:** Analysis of the results of ABPM: recommended analysis (mean values (± SD) for day- and night-time periods should be evaluated separately) is not appropriate. **Proposed change (if any):** mean values (± SD) for 24 hours, day- and night-time periods should be evaluated separately.	Partially accepted. It is important that studies do demonstrate, for example, effects on circadian variations as well as night time reductions and "the early morning rise". Variations such as time of day for highest and lowest BP could be of interest and in certain situations also hourly variations. It is, however, not necessary that a particular study covers all such issues.
114-124	**3**	**Comments:** Which of these tests are necessary? **Proposed change (if any):** Add comments on necessity of the tests listed.	Not agreed. The list is an example. Whichever are chosen is up to the Sponsor to justify.
122	**3**	**Comments:** Is "Opticus" correct? **Proposed change (if any):** Suggest change.	Agreed. Have deleted "opticus".
129	**3**	**Comments:** The evaluation of cardiovascular morbidity: is "(hospitalization for) heart failure" included as the listed examples?	Heart failure is added.
125-132	**3**	**Comments:** Is it necessary for morbidity and mortality events to be adjudicated by an independent committee? **Proposed change (if any):** Clarify above question.	Mortality per se does not need adjudication, but causes of death might. Morbidity usually will be adjudicated. Clarification has been performed.
143, para 6.1	**3**	**Comments:** Can we meet the requirement that enrolment in clinical trials mimics the "frequency of prescriptions"? Number of subjects above 60 years: it is practically impossible to be proportional to the frequency of prescriptions in the clinical data package since, in general, enrolled patients in clinical studies are young in comparison to real patient populations.	Partially agreed. All too often included patients are younger that patients in general. This is a well-known fact. It is important that the patients studied mimic the patients that will be treated. However, a somewhat less precise wording could be used.
150-161, para 7	**3**	**Comments:** Can it ethically be justified, with so many good anti-hypertensive agents available, to require prolonged periods without treatment to establish baseline BP?	Partially agreed. A *wash-out* period (in treated patients) could be short and in line with the pharmacokinetic profile of the drug(s) used. However, baseline BP must be stable before the subject starts

			on the studied drug(s). Not only must the pharmacodynamic effects of drug treatment be taken into account and also the *regression-towards-the-mean* phenomenon. Therefore a more prolonged *run-in* period could be necessary.
159	**3**	**Comments: It is** not understood what's meant with 'run-in period'. The same as wash-out period or something different? Note: The wash-out period should be kept a short as possible (in accordance with half-life of the antihypertensive treatment), as ECs usually have major concerns withdrawing patients from prior antihypertensive medication – especially in the development of FDCs, where more moderate to severe patients are recruited.	Clarification will be performed, see also above.
162-168	**3**	**Comments:** Is it necessary to perform formal assessments of potential orthostatic effects? **Proposed change (if any):** Clarify above question.	Partially agreed. If there are signs or suspicions that the drug might cause orthostatic events test should be done.
162-168	**3**	**Comments:** Pharmacodynamic endpoints: please clarify "must-do" endpoints. All the listed endpoints seems not to be necessary ones.	Not agreed. The list presented in the guideline is not a minimum list but more examples. What should be done is up to the Sponsor to decide and justify. Clearly it depends on the characteristics of the drug.
205	**3**	**Comments:** "according dosing" should be "according to the dosing"? **Proposed change (if any):** Suggest change.	Agreed
212-213	**3**	**Comments:** Study duration for long-term safety evaluation: is the 6 months duration with reference treatment regulatory requirement to be fulfilled for all investigational drug? 3 months duration is scientifically enough period. **Proposed change (if any):** Controlled studies with reference agents should last even longer up to 3 months, in order to allow a comparison with respect to adverse drug reactions as well.	Not agreed. Long term safety is described in section 8.9. Efficacy could in general be assessed in studies of 3-6 months duration, but safety requires longer follow-up.
296	**3**	**Comments:** "patient" should be "patients"? **Proposed change (if any):** Suggest change.	Agreed.

437	**3**	**Comments:** The section substitution therapy leaves too much room for interpretation. It would be helpful to get more clarity.	Partially agreed. Some changes have been performed.
Line 13 to 18	**4**	**Comments:** Novartis proposes to update the introduction section on hypertension definition to include the European treatment guidance from the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). We also suggest the inclusion of an important target population of hypertensive patients which are considered as resistant to therapy. Indeed, these are the patients with the highest medical need. **Proposed change (if any):** Hypertension may be classified according to • etiology: essential or primary hypertension vs. secondary hypertension; • severity: according to WHO/ISH, JNC 7 or ESC/ESH Guidelines; • type: systolic, diastolic or both; • extent or progression (e.g. malignant hypertension) of target organ damage (heart, brain, eyes, vessels, kidney). • Resistance to therapy	This suggestion is accepted and not controversial. Partially accepted, I propose "Effects of therapy".
Line 41 to 43	**4**	**Comments:** Considering the extensive body of clinical data from large controlled clinical data and the long term clinical usage available in the field of hypertension and prevention of cardiovascular outcomes, Novartis believes that in some cases, well designed large observational studies should be appropriate to demonstrate the benefit of a medicinal product on morbidity and/or mortality outcomes. We therefore suggest the revision of the section to cover this type of studies. **Proposed change (if any):** Positive effects on mortality and cardiovascular morbidity can only be evaluated properly in large-scale and long-term controlled clinical trials. In certain situations, observational study/ies can also provide	This is not accepted, observational studies are always prone to bias in several respects and even with the most meticulously performed study this cannot be totally avoided. Effects on mortality/morbidity should be investigated in properly designed controlled clinical studies.

		relevant data. Until the results are available, it should be specifically mentioned in the SPC that beneficial effects on mortality and cardiovascular morbidity are unknown.	
Line 56 to 60.	**4**	**Comments:** This section provides important information on the main parameter, blood pressure, of clinical trials for antihypertensive agents. While the recommended secondary endpoint of BP response criteria is clearly defined, the primary endpoint on blood pressure measurement is not mentioned. Novartis suggest to complete this section by providing guidance on the acceptability of both DBP or SBP as primary endpoint. Traditionally, DBP has been used as the primary endpoint in anti-hypertensive clinical trials. However, there have been increasing evidence on the importance of SBP as mentioned in line 7 of the guidance. We therefore suggest to add a statement on the acceptability of both DBP or SBP as primary endpoint in anti-hypertensive clinical trials. **Proposed change (if any):** Blood pressure lowering effects of anti-hypertensive therapy should be documented as the pre-/post-treatment reduction of blood pressure. The primary endpoint can be the change from baseline in either diastolic blood pressure or systolic blood pressure. As a secondary endpoint these effects can also be assessed with respect to response criteria. Arbitrarily, response criteria for antihypertensive therapy include the percentage of patients with a normalisation of blood pressure (reduction SBP <140 mmHg and DBP <90 mmHg) and/or reduction of SBP ≥20 mmHg and/or DBP ≥10 mmHg.	The present wording does not specify which blood pressure, systolic or diastolic, that should be measured. However, criteria for response are given for both systolic and diastolic pressure thereby the guideline at least indirect states that both pressures should be measured. Over the years opinion has shifted whether diastolic or systolic pressure is most important from a prognostic point of view. At present there is a consensus supported by scientific evidence that SBP is the more important compared to DBP. However, measuring both is advisable and the suggestion concerning amending as statement which of the two is more important is accepted.
Line 113 to 124	**4**	**Comments:** The visco-elastic properties of the arterial tree permit generation of a forward pressure wave which travels from the heart and which superimposes with the reflected wave generated at the numerous branch points. The higher the arterial stiffness, the higher the speed of travel of forward and reflected waves (1).	Not accepted. Even if this variable seems to be interesting enough, and it could be of interest in the investigations of antihypertensive drugs, I believe that, at present, this issue needs further evaluations and that such evaluation should be performed by others interested parties and that it is at present therefore outside the scope of this guideline. If a Sponsor wishes to

		Pulse wave velocity (PWV) is traditionally considered the gold standard measurement of arterial stiffness (2). In addition, several methodologies are currently available to non-invasively estimate central aortic blood pressure from the pulse waveform recorded from a peripheral artery (1-7). Due to the superimposition of the incoming and reflected pressure waves in the arterial tree, both systolic and pulse pressure are lower in the aorta as compared with conventionally measured brachial pressure (1). Use of these methodologies in clinical trial settings have demonstrated that the effects of antihypertensive drugs seen at the brachial artery level does not invariably reflect the effects observed on central aortic systolic and pulse pressures (8-10). Non-invasive estimation of central aortic blood pressure has confined intra-arterial measurement of blood pressure to very specific studies since complicated and not applicable to large scale interventional trials. A substantial body of evidence is accumulating demonstrating the clinical value of measurements of arterial stiffness and central aortic blood pressure in assessing cardiovascular risk and predicting cardiovascular outcomes. PWV has the largest amount of epidemiological evidence demonstrating its predictive value for cardiovascular events (2). Central pressures and central indexes have also been shown to be markers and predictors of disease (11). Central systolic pressure, central pulse pressure, and the central augmentation index (AIx) obtained from peripheral pulse wave analysis have also shown independent predictive values for all-cause mortality in ESRD patients (12,13), CV events in patients undergoing percutaneous coronary intervention (14,15) and in hypertensive patients (9). Additional evidence comes from the Strong Heart Study, an observational study of prevalent and incident cardiovascular disease and their risk factors in American Indians, provides direct support to the hypothesis that central pressure is more important than brachial pressure in predicting outcomes (16). More recently, central but not brachial blood	pursue such investigations it is possible to do so. It is agreed that it could increase knowledge.

		pressure appeared predictive of cardiovascular events in an unselected geriatric population (17). The 2007 ESH/ESC Guidelines for the Management of Arterial Hypertension (18), as compared to previous version, add PWV *"to the list of factors influencing prognosis as an early index of large artery stiffness"* and acknowledge that "*the use of PWV may add further precision to the assessment of arterial damage".* The Guidelines also report that "*although pulse wave velocity is acknowledged as a valid clinical method for assessing large artery distensibility, there is a paucity of adequate studies investigating the effects of antihypertensive therapy per se and of different antihypertensive regimens on this vascular parameter. Many of the studies have been small, non-comparative or non-randomized"* In addition, although advocating large scale observational and interventional studies to confirm the prognostic role of central as opposed to peripheral blood pressure, the 2007 ESH/ESC Guidelines (18) acknowledge that "*the results obtained in a large substudy performed within a randomized trial have shown that central pulse pressure as assessed from the ''augmentation index'' is significantly related to cardiovascular events"* (9) and list central blood pressure measurement among the diagnostic procedures to evaluate the overall cardiovascular risk by searching for target organ (vascular) damage. Given the clinical and prognostic relevance in patients with hypertension of non-invasive evaluation of PWV and central aortic blood pressure as acknowledged by the 2007 ESH/ESC Guidelines for the Management of Arterial Hypertension , we believe that the EMEA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension should include the central aortic blood pressure as an additional method to evaluate blood pressure and thereby promote generation of data on this important parameter and better characterize its relevance to cardiovascular	

		events. *Note: the references are listed at the end of the document* **Proposed change (if any):** **5.1 Blood Pressure** […] **Ad e) Central aortic blood pressure** As non-invasive determination of central aortic blood pressure has been proven clinical relevance in patients with hypertension, these methodologies can be considered an additional approach to better characterize a patient's blood pressure profile and the effect of an anti-hypertensive treatment on blood pressure. Reviews have been published on methodological aspects. Validation of the device used is necessary. **5.2 Target Organ Damage** Compared to ECG and chest radiography, echocardiography combines a higher sensitivity for LVH with a more precise assessment of the degree of LVH (i.e. as a continuous variable reflected by magnitude of LV mass). Vascular Doppler echography and echo tracking events can be used to study LV diastolic function and arterial compliance. Changes in renal function can be assessed in terms of serum creatinine concentrations, 24-hour creatinine clearance and urinary protein excretion. The most objective method to assess renal blood flow and/or glomerular filtration rate is by using radio-isotopes, but this method is limited, among other reasons, by exposure to radioactivity. Clearance of PAH and inulin can be used as alternatives. Opticus fundoscopy can provide evidence about retinal arteries, retina, and papilla. Ultrasound of the large vessels and/or angiography can provide evidence of arteriosclerotic plaques or increased vascular mass or increased intimal-medial thickness. As non-invasive determination of arterial stiffness and central aortic blood pressure have clinical and prognostic relevance in patients with hypertension, these methodologies can be considered an additional	Not accepted. Area still under investigation. Not standard at present. Addition not accepted, see above.

		approach to better characterize vascular function.	
Line 125 to 132	**4**	**Comments:** Novartis believes that this section is currently misleading in a way that specific morbidity and mortality trial should be conducted in each of the sub-population outlined in this section. We propose to clarify the section on the fact that these sub-populations should be monitored with special attention in morbidity and mortality trials. **Proposed change (if any):** When conducting morbidity and mortality trials, special emphasis should be placed on the effects in certain populations (e.g. elderly patients, subjects with co-morbidity, e.g. diabetic patients). The very old (above 75 years) need a special attention. The evaluation of cardiovascular morbidity should especially take into account sequelae of severe organ damage (e.g. myocardial infarction, stroke, renal insufficiency), and respective therapeutic interventions (e.g. co-medication, need for bypass surgery or PTCA). When planning an all-cause mortality study, further distinction should be made with regard to cardiovascular mortality and sudden death.	Accepted.
Line 216 to 217	**4**	**Comments:** Novartis propose to revise the wording of this section to avoid potential confusion between adverse event and adverse reaction terminology. We suggest that the guidance follows the QRD recommendations and only refer to adverse events (without established causal relationship to the drug) or adverse reaction (without established causal relationship to the drug). **Proposed change (if any):** All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse reactions, drop-outs and patients who died while on therapy.	Accepted.
Line 250 to 251	**4**	**Comments:** Novartis believes that the current wording may be misleading and understood in a way that specific clinical	

		trials are required to "study" the effect on glucose and lipids. The clinical development programs of anti-hypertensive agent are usually large programs and cover a wide spectrum of hypertensive patients including patients with metabolic dysfunctions as described in section 6.1. This is considered sufficient to evaluate the safety profile of the agent in these sensitive populations and we believe that dedicated studies should not be required unless a safety signal has been detected in pre-clinical or in the pivotal clinical trials. We therefore propose to reword this section as follow. **Proposed change (if any):** As concomitant risk factors are often present at the same time, effects on glucose and lipid metabolism should be evaluated with a special attention.	Accepted.
Lines 287 to 298	**4**	**Comments:** Novartis strongly supports the approach described in section 9.2 for the standard clinical development program for fixed combination consisting of a basic platform providing the rationale for the combination (i.e. addressing the 4 key pillars mentioned in section 9.1) and supplemented by an additional clinical program based on the targeted indication(s). We believe the platform should consist of a factorial study which could be supplemented by a longer term study for safety purposes as necessary. The factorial study is considered the most appropriate design to demonstrate the contribution of each component to the efficacy of the combination and evaluate the safety profile compared to the respective monotherapies in the broad population of hypertensive patients. Specific study should then be conducted to provide the information in the appropriate population and with a design reflecting the intended clinical use: • First line indication: First-line study (more severe hypertensive patients –> faster BP control) • Second/third line indication: Add-on study (patients not responding to one or more agent -> increased BP control rate)	Partially accepted. I propose a slight change in the suggested wording to the

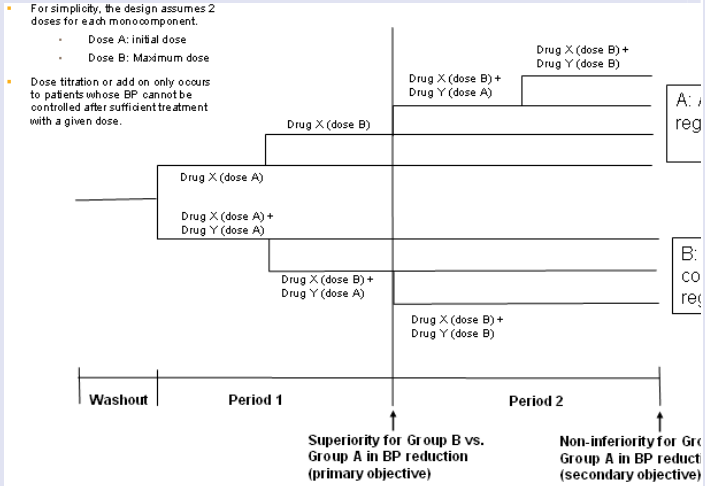
		• Substitution indication: Bioequivalence study (patients already adequately treated with free combination -> improve compliance) Novartis believes that a dose-response study should not be required in all case, in particular when the combination is considered "well known" or for substitution indication (substitute the approved doses of the monotherapy). **Proposed change (if any):** In the situation where a combination has not yet been demonstrated to be safe and efficacious, the positive benefit/risk of the joint application of the mono-components should be demonstrated and dose-response data may be necessary. Preferentially, the factorial design should be used, allowing the simultaneous comparison of various dosage combinations with their respective components and with placebo. Ascending dosages (e.g. in a range of dose equal or superior to two) of the fixed combination could be tested in patients with insufficient response. The results of the factorial studies should be the basis for further, confirmatory, clinical trials. It is important that the clinical studies should be designed in accordance with the indication claimed and the wording of the indication must state clearly whether the fixed combination should be given as 1) first line therapy in patient receiving previously neither of the substances (first-line study), 2) second-line therapy or even third-line therapy in non-responders to one or both of the mono-components (non-responder study), 3) substitution therapy in patients adequately controlled with the individual products, given concurrently, but as separate tablets at the same dose level as in the combination (bioequivalence study).	following: *In the situation where a combination has not yet been demonstrated to be safe and efficacious, the positive benefit/risk of the joint application of the mono-components should be demonstrated by means of a study/-ies with appropriate design and dose-response data could be needed as well.* Agreed. Agreed. Agree, with a minor change in the wording as follows: *2) second-line ~~therapy~~ or even third-line therapy in non-responders to ~~one or both of~~ the mono-components (non-responder study)* Agreed.
Line 300 - 308	**4**	**Comments:** This section of the guidance is related to use of fixed	Agreed to change *all* to *more.*

		combination as add-on therapy in second or third line of treatment. The CHMP has revised this section of the guidance to address the situation where fixed combinations contain more than two anti-hypertensive agents. We believe that the introduction of the wording "or all" is misleading since in the case a patient is already receiving all of the mono-components of the combination no add-on is possible, only an up-titration of the components of the combination. We suggest to use more general terminology which can accommodate the different situations (dual or triple combinations). We also propose to include an opening statement with regards to fixed combination containing more than two anti-hypertensive agents since in this case, an add-on study design as described below may not be feasible. **Proposed change (if any):** *9.2.1 Second-line or third-line therapy* A fixed combination may be considered when response to one or more of the mono-components is insufficient. The following strategies in conducting confirmatory clinical studies are acceptable, but it is mandatory that at least one or two pivotal clinical study/-ies is/are performed in a population of patients whose blood pressure cannot be normalised with one or more of the mono-components. Add-on therapy Add an additional drug to non-responders to one or drug, and vice versa. Dose-titration will usually be indicated. It is necessary to demonstrate a statistically significant and clinically relevant additional blood pressure reduction of the combination in patients who did not respond adequately to standard therapeutic doses of one or more of the mono-components. Current clinical practice recommendations for the treatment of high blood pressure do not recommend forcing the dose	The wording should be the following: *Add an additional drug to non-responders to one or more drugs, and vice versa.*

		of a single antihypertensive before considering the combination of two or sometimes even three drugs. Therefore, it is not necessarily expected that the dose of the single agent is up-titrated beyond the regular maintenance dose before the second or third agent is added. In any case, the selected upper dose-titration level of each component should be adequately justified. Furthermore, it is necessary to show that any additional safety concerns (incidence/seriousness /severity/outcome of adverse events/adverse drug reactions) do not outweigh the additional benefit of the combination. In non-responders it is usually sufficient to show a clinically relevant and statistically significant superiority of the combination regarding the mean supine or sitting diastolic and systolic blood pressure, but it would be optimal, if such a trial could show a statistically significant improvement in response rates (blood pressure <140/90 mmHg) for the fixed combination, as well. Sufficient duration of time (consistent with the time-response course expected for each component of the combination) should be taken into account to ensure that blood pressure levels are stable before the second drug is added to the medication. In special situations, in particular for triple combination, alternative study design may be appropriate.	Agreed.
Line 394 to 406		**Comments:** Novartis strongly supports the concept that each intended indication requires a specific clinical development program to evaluate the benefit risk balance of the combination in the relevant target population and with a design mimicking the intended usage in the clinical setting. As mentioned in section 9.2, the factorial design is the most appropriate design for dose selection and also to provide the efficacy and safety data to fulfil the general requirement for a fixed combination described is section 9.1. The confirmatory first line study should then be	

		sufficient to provide the clinical data to establish the positive benefit/risk balance for the combination in the intended target indication of first-line therapy. The add-on study is targeting a different patient population and characterising a different usage of the combination which limits the relevance of the data when considering first-line use. We therefore propose to revise this section to include the following requirement: • Combination already well know: only first-line study • New agent and/or new combination: factorial study + first line study. **Proposed change (if any):** ***1. All substances are well known and the joint application of the two components has proven to be efficacious, safe and thus clinically useful.*** Relevant studies should be available, either as original studies or on the basis of the literature to document the benefit/risk of the combination and the doses used. In this case, in particular when the fixed dose combination is already available for the second-line indication, one therapeutic confirmatory study could be sufficient to demonstrate its benefit in terms of obtaining a more rapid and at least comparable blood pressure lowering effect compared to the dose titrating regimen. ***2. One or all substances are not well known and/or the efficacy and safety of the joint application have not been established*** In this case the benefit of the combination will need to be explored further, similar to the general requirements for fixed combination, before proceeding to the therapeutic confirmatory study. This will normally include a factorial study with comparison between the mono-components and the fixed combination.	Definition of "well known" preferably added here. My suggestion for such a definition is the following: A drug could be considered "well known" when enough patients have been exposed to the drug and for a sufficient time that it is considered possible to decide that the risk for detrimental effects caused by the drug is (very) low. Agreed.
Lines 407 to 417	**4**	**Comments:** Novartis agrees with the principles and objectives of the proposed study design of the first-line therapeutic confirmatory study proposed in the draft guidance.	

		However, the description is focussing in the particular case of fixed combination with essentially two dosage strengths which make the extrapolation difficult for the situation where more than two doses are being developed. Further, it is proposed to compare the starting dose of the combination against the maximal dose of the monotherapy which constitutes the second or the third step of an add-on algorithm. Novartis propose to consider an alternative study design to meet the main objectives outlined by the CHMP: • Demonstrate the superiority of the fixed combination use first line over the add-on regimen using the recommended titration steps for each regimen. • Use optional titration up to the maximal dose of the fixed combination. The number of period will depend on the number of doses of the monotherapy and the fixed combination. The use of optional titration force the study to have primary efficacy endpoint at the end of the first period. • Time to control is an important secondary endpoint for this design. • The duration of the periods should be based on the pharmacodynamic properties of the agents to ensure maximal effect is reached.	
		Novartis hereby enclose a schematic of the study design to illustrate the proposal:	



Proposed change (if any):
Study design therapeutic confirmatory study

The therapeutic confirmatory study should be a parallel arm design to compare the antihypertensive effects of the standard regimen of titrating one agent, before adding the second one, with the initial use of the fixed combination. The first treatment period should start with the recommended starting dose of X or Y and the recommended starting dose of the combination. In patients not achieving blood pressure control, the dose should be increased in all treatment groups until, in the monotherapy arm, the maximum dose is reached. In a second period, the second agent should be added in patients not controlled on the maximum dose of the monotherapy and subsequently be up-titrated also based on blood pressure control to reach the maximum dose of the fixed combination by the end of the study. The number of steps within the two periods will depend on the dosages of the monotherapy and the fixed combination. The duration of each titration step should be sufficient to allow a reliable treatment effect. The primary analyses should demonstrate the superiority of the fixed combination over the monotherapy at the latest time point before patients in the monotherapy

Partially agreed.
The following wording, which is an edited version of the proposal, is suggested:

The therapeutic confirmatory study should be a parallel arm study designed to compare the antihypertensive effects of titrating one agent in the approved starting dose, before adding the second drug, with the initial use of the fixed combination in the intended starting dose. In patients not achieving blood pressure control, the dose should be increased in all treatment groups until, in the mono-therapy arm, the maximum approved dose of the drug is reached.
In a second period, a second agent should be added in patients in the mono-therapy arm not controlled on the maximum dose of the initial drug and subsequently be up-titrated also based on blood pressure control to reach the maximum approved dose of that drug. In the fixed combination arm similar dose escalation should be performed until the maximal doses of the agent in the fixed combination are reached.
The number of steps within the two periods will depend on the dosages of the mono-therapy and the fixed combination. The duration of each titration step should be sufficient to allow a reliable treatment effect.

		arm are allowed to receive add-on treatment with the second agent i.e. the end of the first period. At the end of the study, the initial combination therapy regimen should be at least non-inferior to the add-on regimen.	Regarding the primary vs the secondary objectives, I have some doubt which should be which. As primary objective I would prefer to have non-inferiority for the fixed combination over the free at end of study.
Lines 417 to 420	**4**	**Comments:** Novartis does not believe that comparative study with other fixed combination is appropriate to evaluate the benefit of a specific combination as first-line therapy. Indeed, the choice of the individual component of a combination is often driven by underlying condition(s) or concomitant disease(s) and not only based blood pressure reduction potential. This is particularly true between the different classes of anti-hypertensive products. We therefore believe that the comparison should focus on the combination versus the respective monotherapy and suggest to remove the statement from the guidance. **Proposed change (if any):** Both treatment periods should be of sufficient duration to allow a reliable treatment effect. Assessment of antihypertensive efficacy and its methods should be in accordance with mono-therapy (see sections 1 - 5 of this document). One additional end point could be "time until achieving target blood pressure", which is in accordance with the primary aim to achieve the BP goal in a more timely fashion.	Partially agreed. I propose the following wording: *Both treatment periods should be of sufficient duration to ascertain that a reliable treatment effect is detected.* The suggested deletion could be accepted.
Line 424 to 436	**4**	**Comments:** The paragraph on safety assessment appears to be located in the wrong sub-headings since it refers to products with "well-know" agents although it is located in the section for not "well known" agents. We suggest it is moved up to line 401. Novartis believes that Diabetic patients without additional complication are not at higher risk of developing hypotension, however, they may develop autonomic dysfunction which is an acknowledged risk. **Proposed change (if any):** *1. All substances are well known and the joint*	

		application of the two components has proven to be efficacious, safe and thus clinically useful. Relevant studies should be available, either as original studies or on the basis of the literature to document the benefit/risk of the combination and the doses used. In this case, in particular when the fixed dose combination is already available for the second-line indication, one therapeutic confirmatory study could be sufficient to demonstrate its benefit in terms of obtaining a more rapid and at least comparable blood pressure lowering effect compared to the dose titrating regimen. When all substances are known and the value of the combination of the mono-components has been documented sufficiently, in particular when the FDC is already available for second-line indication, long term safety demands could be satisfied to a large extent by bibliographic data. The completed studies should, however, supply a large enough sample for safety assessments and a safety extension may be necessary. This could be performed with an open label design and/or comparative studies with other FDC. *[…]* *Safety* Any fixed combination for first line treatment should not raise new safety concerns other than encountered with the mono-components. Special attention should be paid on dose-dependent side effects, including symptoms and signs of organ damage (e.g. renal dysfunction). Particular caution is necessary in patients at higher risk for orthostatic hypotension for example those with autonomic dysfunction (caused by diabetes mellitus or other diseases) or elderly patients. Special attention should also be given to the occurrence of "first dose hypotension". Safety assessment should be made initially (e.g. 1-2 weeks) and after each dose titration step.	Accepted. It is suggested that the second paragraph under subheading "Safety" is moved to the section above with subtitle: 1. *All substances are well known…* No changes in the wording are proposed.
Line 437 to 457	**4**	**Comments:**	Partially accepted.

		The CHMP foresee that the clinical development of a combination should be based on the status of the individual components and whether they are considered "well-know" or not. This is a new criterion and we believe that the guidance should clarify what data and what extend of data is required to be considered "well-know".	A definition of "well-known" will be added.
Line 437 to 457		**Comments:** This section addresses the clinical requirement for registration of a fixed combination as substitution therapy. By definition, a substitution therapy is only applicable for components which are already approved as monotherapy and for use in free combination. To be granted a Marketing Authorisation, an anti-hypertensive product has to demonstrate a positive benefit risk balance in broad patient population including sensitive patients (e.g. elderly patients, patients with co-morbidities, various stages of hypertension etc.) as described in section 1 to 5 of the present guidance. It is also required to provide comparative efficacy/safety data against acknowledged standard anti-hypertensive agent and at least one combination studies. In this context, Novartis believes that a anti-hypertensive medicinal product approved as monotherapy for treatment of hypertension satisfies the "well-known" criterion. Further, the recent update of the Pharmacovigilence requirements for Marketing Authorisation renewal, confirms that the extend of clinical data generated for the approval of product and confirm within the first years of commercialisation is considered enough by the legislator to consider the product well-known and its benefit/risk well-characterised and to dispense the Marketing Authorisation Holder of future renewal after the first 5-year period is over unless clear safety concerns have arisen. The substitution therapy is only intended in patients already adequately treated with the free combination (positive benefit/risk demonstrated in this patient in the clinical practice) with the aim to improve patient's	

		compliance. We therefore believe that in all cases the pivotal registration studies should be the Bioequivalence study which guarantees that the switch in medication from free to fixed combination will not alter the positive benefit/risk balance in those patients. In this context, the clinical development program requirements should be primarily driven by the data available on the joint application of the approved monotherapy: 1/ The combination use is considered well-known: In case a combination is considered well-know, we agree with CHMP proposal that only BE studies would be required. 2/ The combination use is <u>not</u> considered well-known: As mentioned in a previous comment, Novartis believe that the factorial design is the appropriate design to establish the benefit/risk of a combination in the broad population of hypertensive patient and to address the general requirements to support the scientific and medical rationale of combinations as set up in section 9.1. In the case of substitution therapy, no additional efficacy study beyond the factorial study should be required since the demonstration of the positive efficacy of the free combination in the patients is a pre-requisite for the substitution. In particular, the add-on study is not considered an appropriate design since it target a different population (non-responders). However, it may be appropriate in some cases to supplement the factorial study data with additional safety data on the combination in particular with longer term safety. **Proposed change (if any):** Requirements will vary depending on which substances are used in the fixed combination. The following situations are possible: *All substances are well known and the joint application of the two or more components has proven to be*	Editorial change, accepted. Accepted. Accepted. Accepted. Partially accepted. My proposal is the following:

		efficacious, safe and thus clinically useful. This should be documented on the basis of relevant clinical studies, either as original studies or on the basis of the literature. In this case, the pivotal data are the bioequivalence study comparing the drugs in free combination with the fixed dose. A comparative pharmacokinetic data, demonstrating that the two components of the fixed combination do not affect each others respective pharmacokinetic patterns should also be performed. *One or all substances are not well known and/or the efficacy and safety of the joint application have not been established* In this case, the pivotal data are also the bioequivalence study comparing the drugs in free combination with the fixed dose. However, the benefit/risk of the combination will need to be explored further, before a substitution indication can be considered. This will normally include factorial study with comparison between the mono-components and the fixed combination. Specific attention should be paid to the doses, as used in the fixed combination tablet. Additional safety data, in particular long term safety, may be required.	*In this case, additional safety data, in particular long term safety, is required.*
	5	In the section on safety assessment for fixed combinations in first line therapy page 11 specific attention should be given to monitoring electrolyte levels and specifically hyponatreamia.	Accepted.
	5	1) With respect to elderly throughout the guideline the MEB would suggest using a cut-off of 75 years of age. In the document it is suggested to pay specific attention for elderly using different terms; subjects above 60, elderly, the very old, and patients in the age range of 70 – 90 years. It is suggested to use only the category of 75 years and above (elderly patients) and drop the upper age limit. This as in our ageing society patients over 75 more appropriately reflect the elderly patient seen in clinical practice. An upper limit of patients in need of antihypertensive treatment is defined by a complete clinical picture, not only age.	Accepted.

		2) The last sentence of the first paragraph of the introduction seems somewhat outdated; "Recent data underscore the importance of elevations in SBP,…" This is established already for a considerable period and the sentence would preferably be deleted.	
	6	**5.2 Target organ damage** … Changes in renal function can be assessed in terms of serum creatinine concentrations, 24-hour creatinine clearance and urinary protein excretion. … *Proposed change.* ... Changes in renal function should be assessed in terms of serum creatinine concentrations, of estimates of glomerular filtration rate (eGFR) calculated by equations using readily availbale variables (e.g., serum creatinine, gender, and age), and of urinary albumin (or protein) excretion measured as urinary albumin (or protein) to creatinine ratio.	Partially agreed. I do not think that it is wise to be too precise regarding the exact way to estimate glomerular filtration rate. However, I agree that eGFR is a valuable variable, and therefore I suggest the following: *Changes in renal function should also be assessed by estimated glomerular filtration rate (eGFR), using properly evaluated equations.*
	6	**5.1 Blood pressure** Proposal This expert suggests that the clinical trials on antihypertensive drugs should include the systematic collection of the outdoor temperature when blood pressure is measured. This is a low cost and readily available information which might reduce the confounding of the seasonal effect. This inclusion could be added in Section 5 – 5.1 Blood pressure – ad a) Sphygmomanometry before the last sentence as follows: *Present version* " … Blood pressure should be measured under standardised conditions, as nearly as possible at the same time each day, on the same arm, by the same personnel, with the same apparatus. Blood pressure measurement during exercise may provide supportive evidence for efficacy." *Proposed change* " … Blood pressure should be measured under standardised conditions, as nearly as possible at the same time each day, on the same arm, by the same	Not accepted. Even if the outdoor temperature has an effect on blood pressure, it is difficult to see how the differences in temperature should be used when the results are assessed. Moreover, most examinations will probably anyway take place in an air conditioned or otherwise well ventilated room. Therefore I prefer not to include this statement.

		personnel, with the same apparatus. Data collection should include information on outdoor temperature to control for the seasonal effect on blood pressure. Blood pressure measurement during exercise may provide supportive evidence for efficacy."	
	7	**5.1 Blood pressure** The recommendation highlights the importance of blood pressure measurement at peak and trough points but is somewhat ambivalent in that it gives support to the conventional measurement but in practice such measurement would be redundant by the recommendation: "ABPM is required for the evaluation of new antihypertensive agents" (vide infra). ABPM will, of course, give a much better assessment of trough and peak levels. **ad a) Sphygmomanometry** The point made above in relation to ABPM makes this section largely irrelevant except that conventional measurement will remain as part of the assessment and must comply with the above recommendations. **ad b) Intra-arterial measurements** The recommendation that intra-arterial measurement should NOT be used is indeed correct, not only on methodological grounds but also on ethical grounds. **ad c) Non-invasive ambulatory blood pressure monitoring** This recommendation makes ABPM mandatory for the evaluation of new antihypertensive agents. It should be noted that in the re-evaluation of older drugs ABPM may not be mandatory but presumably would be seen as at least desirable.	Not or only partially accepted. Even if ABPM is a valid tool it should not replace casual BP measurements. That was never the intention of this guideline. However, it is acknowledged that the statement that ABPM is requested might be too far fetching. A revision has been made in the guideline to the following: *ABPM is a valuable tool for the evaluation of new antihypertensive agents, therefore studies employing such devices should be performed at least in a subgroup of patients or during phase II studies.*
	7	The recorders used must fullfil international acknowledged validation procedures (AAMI/BHS). This statement fails to acknowledge that the European Society of Hypertension International Protocol is the most-used validation protocol.	Agreed. ESH-IP is added.
	7	Recorders using auscultation and oscillometry as combined methods should be preferred since the numbers of errors can be reduced.	Agreed. The following change has been added. *Well validated ABPM-recorders should be employed.*

		There is only one such instrument listed on the www.dableducational website – the Nissei DS-250 which is given a questionable recommendation. Therefore, in practice, there are no such instruments available for ABPM.	
	7	Repetitive investigations should be performed on a comparable (work-) day using the same recorder. During daytime (06.00 hrs - 22.00 hrs) readings should be done at least at 15-minute intervals and during night-time (22.00 hrs - 06.00 hrs) at 30 minute intervals. One might argue that 15 minute intervals during the day can be counter-productive in that the patient has difficulty in being 'ambulant' because of the frequency of measurement but this has to be balanced against the advantage of the number of recordings available for analysis.	Partially agreed. The following has been added: Repetitive investigations should be performed on a comparable (work-) day using the same recorder. During daytime (06.00 hrs - 22.00 hrs) readings should be done *as frequent as possible but with due considerations taken to the fact that too short intervals between measurements might compromise the ambulatory nature of the investigation. However, a desirable goal could be measurements* at least 15-minute intervals and during night-time (22.00 hrs - 06.00 hrs) at 30 minute intervals.
	7	For evaluation purposes at least 64 readings/24 hours have to be evaluable, including at least 52 readings during day-time and 12 readings at night. In day-time at least 2 readings and during night-time at least 1 reading/hour have to be available. Regarding the analysis of the results, mean values (± SD) for day- and night-time, periods should be evaluated separately. Special problems (e.g. trough-to-peak ratio, early morning rise) may be worked out by calculating hourly blood pressure or using time series analysis, respectively. Many more indices may be analyzed using the dabl ABPM system.	Agreed. The statement should be regarded as examples. The Sponsor is free to perform other measurements, but must be prepared to justify the choices.
		ad d) automatic self (home) measurement Self (home) measurement of blood pressure with the help of automatic devices…*not recommended until validated.* Agree – the evidence is simply not available.	Accepted. I am of the same opinion.