European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON THE CLINICAL EVALUATION OF DIRECT ACTING ANTIVIRAL AGENTS INTENDED FOR TREATMENT OF CHRONIC HEPATITIS C (EMEA/CHMP/EWP/30039/2008)

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation:

Stakeholder No.	Name of Organisation or individual
1	EFPIA
2	IPTA (International Pediatric Transplant Organisation)
3	EATG (European AIDS Treatment Group)
4	Gilead Sciences International Ltd
5	Merck Sharpe and Dohme Ltd
6	Schering Plough Europe
7	European AIDS Treatment Network (NEAT)

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. GENERAL COMMENTS – OVERVIEW

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
1	EFPIA welcomes the opportunity to review this draft guideline for the treatment of chronic HCV using direct acting antiviral agents (DAAs) in patients receiving current standard of care (SoC). In general, the guideline is well-written, reasonably detailed, and fairly consistent with preliminary considerations for CHC trial design coming out of other regulatory agencies (e.g., FDA Advisory Committee Meeting Discussion of Clinical Trial Design Issues in the Development of Products to Treat Chronic Hepatitis C, October 19-20, 2006). However, we would like to make the following general comments: • The guideline places too much emphasis on the requirement for the initial registration program to only focus on patients who are treatment-naive. Patients who have not achieved SVR with prior therapy represent a significant unmet medical need, have few or no available treatment options and are at increased risk for progressive liver disease. This group has also become an increasingly large pool of patients available for recruitment into clinical trials. Therefore, we suggest that studies in treatment experienced patients should be initiated early and that the initial registration program for a DAA could encompass both groups. • Reference to evaluation of more than one experimental DAA is noted with recommendations to consider in Phase II exploratory studies with use of more than one DAA to optimize benefit, minimize resistance development, explore consequences of prior DAA treatment failure, etc. It should be noted that the feasibility of conducting pre-registration studies with multiple investigational agents is likely to be low. • The guideline focuses on development of new DAAs to be used in combination with the existing Standard of Care (SoC). The guideline should be expanded to include information on how to treat patients in whom SoC is contra-indicated e.g. patients with renal insufficiency etc. • The guideline should also clarify that it is a worthwhile objective to develop DAAs, or combinations of DAAs, that can improve SVR rates and / or tolerability and safety, when compared to existing SoC. Guidance on the development of combinations of unlicensed DAAs should be provided in forthcoming updates of this guideline.	See below "Summary of Outcome"

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	• The guideline does not provide guidance on the requirements for investigating subjects who have HCV genotype 2 or 3. Information in this area would be helpful. • It would be very useful to expand this to include development of combinations of DAA (ie, SOC-sparing regimens) and also for the non-responder population.	
2	The International Pediatric Transplant Association is pleased to be asked to comment on this guideline. Our comments will be limited to potential use of DAAs in pediatric populations. Thank you for allowing us to comment on this thoughtful document.	See below "Summary of Outcome"
4	Although the guidance acknowledges 'the dynamics of the field', there are several instances within the guideline that seem overly protective of the status quo offered by the current SOC. For example, there is a suggestion that efficacy in subgroups "such as…. null responders to SOC" would only be explored once the effect of "add-on" therapy has been "well described." We suggest that once initial studies of efficacy have been completed it may be possible to evaluate efficacy of new agents and draw comparisons between SOC and new therapies especially as section 1.3 the guidance acknowledges that "Tolerability and safety is also a concern with current SOC and a shortened duration of SOC is a worthwhile objective for drug development."	See below "Summary of Outcome"
5	The guideline recommends sequential development of DAAs initially for treatment-naïve subjects, followed by development in more difficult to treat populations, other populations, although comments in Section 4.4 suggest some flexibility in this position. High medical need for alternative treatments within these populations may warrant parallel rather than sequential development of novel compounds. Once efficacy has been confirmed for a given class of DAA, this may also be a rationale for parallel development approaches. In any case, clear guidance is lacking on when that studies in treatment experienced subjects could start (e.g. after a Phase-II of DAA+SOC in naives or after the Phase-III or later?)	See below "Summary of Outcome"
7	These guidelines will drive the R&D effort away from the patients at largest need for these drugs, compromising a timely understand of how to use the drugs in these setting. My suggesting is that at least one of the pivotal phase III trials should include patients at largest need of the medicine (i.e. those with genotype I, those with HIV and/or those with advanced fibrosis). Of note, the study design for	See below "Summary of Outcome"

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	patients at largest need (i.e. those at largest risk of failing current SOC) could well be to add the new medicine on top of SOC – as the failure rate is large, the sample size needed to demonstrate superiority is low. The envisioned sequence of drug development is not clearly rationalized. I would think that the main emphasize for new HCV drugs is either to replace one or both of current SOC medicines, and be added to SOC in order to abbreviate the total duration of treatment.	
7	The paper is clearly written and contains valuable guidance to design advent clinical studies on HCV-infection. This is necessary in a growing scientific field. To my opinion, the paper is comprehensive and complete - there is no need for additional changes.	
7	- The guidelines are very clear, well structured and well written. - As a general comment, I do not see however why patients with HIV-infection should be evaluated later in the development program. These are the patients in most urgent need, and I would think a parallel development would be more appropriate, especially among those with genotype 1, with relapse or non-response. - Also, if we make a parallel with HIV-infection, why not assessing these new drugs first in patients who failed current treatments, who are those at high risk of morbidity, mortality.	See below concerning revisions regarding the recommended sequence of investigations in different patient groups. In general it is considered that optimal dose of a DAA to be combined with SOC should first be characterised in patients expected to have reasonable support from SOC, mainly in order to avoid under-dosing and subsequent resistance. However, in the revised document it is clearly stated that early response data (e.g. RVR, EVR) from studies in treatment-naive or previous relapsers may guide the design of studies in patients with prior non-response, in order to minimise delay in drug development for the patients most in need. Concerning patients with HIV co-infection, it is not considered appropriate to do dose ranging trials in this population, where response to SOC is ill characterised and probably blunted. However, studies prior to licencing are strongly encouraged.
7	It is well written. My comments are ; 1. We need these drugs urgently in HIV and the fact that we can't get them early is difficult for our patients. We should stress the need for drug interaction studies to be performed early as there is always going to be concern between interaction between Hep C and HIV meds. Once these are available consideration should be given to earlier studies than are	Concerning issue 1, see above as well as the general comment below. Issue 2, the document states that either form of peginterferon may be used as SOC, and, though a standard weight based ribavirin dose in either case would be desirable (particularly if patients within a study would use different peginterferons - an option open for in the document, provided that stratification is

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	presently done - as you know one of the accepted proposal for neat was of a trial of chronic Hep C but no company would agree. 2. We need to have a standard weight based dose of ribavarin within studies. 3. As regards liver biopsy we rarely do this now because of fibroscan and lack of biopsy should not prevent entry to study.	performed), ribavirin dosing according to product label could hardly be prohibited at this stage. Issue 3: Lack of liver biopsy does not necessarily prevent study entry. The relevant passage reads: "If non-invasive methods are used as an alternative to liver biopsy, this should be justified by the applicant."

Summary of Outcome (following comments received on the draft guideline)

The new version of the HCV DAA guideline contains several changes, compared to the previous one. These are based on incoming comments and suggestions, but have also been made in the light of emerging data on DAA activity, particularly for telaprevir.

- Voiced comments and concerns, as well as results from recent studies showing high response rates in patients with previous relapse after ETR on SOC, has led us to redefine the categories of SOC-experienced patients that did not achieve SVR. Patients with ETR but not SVR are termed "relapsers", and it is suggested that such patients may safely participate in explorative studies on the same conditions as treatment-naive patients (see executive summary and sections 4.1, 4.4.1 and 4.4.2). This is likely to facilitate recruitment to such trials.
- All patients not reaching EVR or ETR on SOC (excluding the small group of patients with virological breakthrough that are not discussed) are now collectively termed "non-responders". Though recent trials has shown impressive results relative to SOC in this population too, it remains clear that this is a more difficult-to-treat population which should be considered distinct from relapsers (see section 4.4.1*: exploratory studies in specific patient populations* and section 4.4.2)
- Prompted by concerns that the document was too focussed on studies of the addition of one DAA to SOC, failing to give guidance on the development of SOC-sparing regimens, a specific heading on this (section 4.4.1: *exploratory studies of SOC-sparing regimens*) has been added, including suggestions on when to start exploratory studies of such regimens, and in what populations.
- The discussion of the use of a lead-in phase with SOC has been deleted. Though it is possible that some drugs may benefit from a lead-in phase, the potency displayed by telaprevir, and probably other DAAs, implies that use of a lead-in phase to boost therapeutic efficacy or to enrich the population to receive DAA treatment will generally not be mandated.
- The information considered necessary to initiate studies in difficult to treat patient groups such as SOC non-responders has been more specifically defined (section 4.1).
- Comments have prompted some changes in the sections on virological investigations (4.2.1 and 4.3.2).
- Concerns about the practicality of requiring a liver biopsy within 12 months of starting a trial, has led us to expand this window to 24 months, which is considered adequate given the normally slow development of fibrosis in HCV infection (4.2.3).
- It is suggested that single-arm studies (after proper drug-drug interaction studies) may be sufficient for licensure in HIV-coinfected patients, if results are sufficiently impressive; this since randomised trials vs SOC may be problematic if a very high efficacy has been demonstrated in monoinfected (section 4.4.2)
- Prompted by voiced concerns, we have included statements on DAA development in patients with genotype 2/3 infection, and on the specific value of a shortened treatment duration.

2. SPECIFIC COMMENTS ON TEXT

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
Executive Summary Page 3	1	While guidelines focused on development of DAAs in combination with pegIFN and ribavirin are appreciated, the field will rapidly evolve towards the use of DAA combinations with the goal of reducing or eliminating the need for pegIFN and perhaps ribavirin. More flexibility for such study designs should be encompassed in this guidance.	Point taken. This issue is now discussed to some extent (see "Summary of Outcome" above).
Executive summary 2rd paragraph Page 3	1	It is stated in the Executive Summary that this guideline is focused on studies in which new DAAs are added to the available standard of care (SOC). In subsequent sections of the guideline, reduction of the duration of current SOC is stated as a potential benefit to the combination of use with DAAs. This should therefore be included in the Executive Summary. Proposed change: Due to the limited experience thus far with other approaches to clinical development of DAAs, this guideline is focused on studies in which new DAAs are added to the available standard-of-care (SOC) treatment for CHC where SOC comprise ribavirin plus a pegylated interferon (PEG-IFN) alpha 2a or 2b administered for a duration selected in accordance with the HCV genotype. <u>Reduction of the duration of current SOC however is a potential benefit to the combination of use with DAAs.</u>	Point taken, both in the summary and later in document.
Executive summary 3rd paragraph Page 3	1	Recent data suggest that the addition of a DAA to SOC could be of significant benefit in patients with a previous non-response to SOC (including null-responders). Since medical need is greater in those patients that have not responded to earlier SOC, initial development should not exclude those patients if sufficient confidence is obtained in dose-finding studies and if stringent stopping rules are in place (see comment on section 4.4.1). Proposed change: A special concern with respect to drug development for the treatment of CHC is the high mutation rate of hepatitis C virus	See "Summary of Outcome" above.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		(HCV) with the attendant risk of selection of drug-resistant variants leading to treatment failure. Taking into account this risk and in order to evaluate the new DAA in a stepwise fashion, the guideline discusses that initial studies should enrol subjects ~~naïve to SOC~~ who do not have advanced fibrosis or HIV co-infection and who have HCV genotype 1 infections. Early exploratory studies in patients with a previous non-response to SOC can be conducted if sufficient confidence is obtained from dose-finding studies and if stringent stopping rules are in place. ~~It is anticipated that sequential studies could enrol patients with genotype 1 infections who have had a sub-optimal response to SOC or relapsed.~~ Once the ~~effect~~ efficacy and safety of adding on a DAA is ~~well described~~ characterized in these types of patients later studies could evaluate efficacy in specific groups such as those with other genotypes~~,~~ and HIV co-infected patients ~~and null responders to SOC~~	
Section 1.3 1st paragraph Page 4	1	Proposal to replace 6 months by the 24 weeks (as in similar guidelines for HIV and HBV) throughout the document. Proposed change: The aim of currently available therapies is to achieve sustained viral response (SVR) defined as absence of recurrence of detectable virus at 24 weeks ~~6 months~~ after end of therapy.	Not accepted.
Section 1.3 2nd paragraph Page 4	1	This paragraph notes the need for new treatments to enhance efficacy and tolerability, noting shortening of duration of SOC, which reinforces the need to modify the Executive Summary (see comment above).	
Section 1.4 2nd paragraph Page 4	1	Cross-resistance is unlikely to occur between certain DAAs. The fact that resistance selection is reduced when the virus is exposed *in-vitro* to a combination of two DAAs opens the possibility of combining two DAAs for the treatment of CHC, with or without SOC.	Acknowledged. The revised text reads: "HCV is an RNA virus with a high mutation rate. Variants with specific mutations conferring reduced sensitivity to DAAs have generally been shown to be present prior to the initiation of DAA. Such variants are selected under drug pressure, both *in vitro* and by non-suppressive therapy *in vivo*. Available data

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		Proposed change HCV is a RNA virus with a high mutation rate and variants that demonstrate reduced sensitivity to polymerase and protease inhibitors associated with specific viral mutations have been obtained in the laboratory and from treated patients. Available data indicate that within class cross-resistance may occur. When HCV was co-exposed to two DAAs of different classes *in vitro*, however, the rate of selection of drug-resistant variants was significantly lower. This observation raises the possible advantage of combining more than one DAA with or without pegylated interferon alpha 2 and / or ribavirin ~~SOC~~ for optimal treatment of CHC	indicate that within class cross-resistance may occur. *In vitro*, the rate of selection of drug-resistant variants has been shown to be significantly lower when HCV is co-exposed to two DAAs of different classes. This observation implies that the combination of more than one DAA, with or without PEG-IFN and/or ribavirin, could be advantageous."
Section 1.4 3rd paragraph Page 4	1	Resistance mutations are present before treatment initiation and strategies can be developed to maximise the chance of a return to baseline equilibrium once resistance has developed. Therefore, we propose to delete the connotation 'harmful', since resistance does not have the same implications as AEs. The following text is proposed: Proposed change Resistance mutations present before initiation of treatment might become proportionately more prevalent than wild-type in the quasi-species following exposure to a DAA. The impact of resistance on subsequent treatment attempts is unknown. It is also not known how long selected resistant variants may persist after stopping therapy in cases of virological failure. However, resistant variants, and not wild type HCV were usually recovered from patients who relapsed after achieving an end-of treatment response (ETR) following treatment with a DAA (protease inhibitor) in combination with SOC. The ~~development of~~ selection of drug resistance ~~should therefore be regarded as potentially harmful and~~ must be taken into account in the design of clinical studies and in the benefit–risk assessment of DAAs. Strategies to minimize the risks of resistance should be explored and incorporated in the design of the clinical studies.	Partially acknowledged; however the fact that resistance is "selected" for seems self-evident. Also, if resistance developed e.g. due to viral breakthrough when treated with, perhaps an inoptimised dose of a DAA, indeed does prevent effective use of a "class" of DAAs, this could indeed, in a wider sense, be "harmful" to the prognosis of the patient. The revised text reads: "The impact of resistance on subsequent treatment attempts is unknown. It is not known how long resistant variants may persist after stopping therapy in cases of virological failure. However, resistant variants, rather than wild type HCV, have usually been recovered from patients who relapsed after achieving an end-of-treatment response (ETR) following treatment with a DAA (protease inhibitor) in combination with SOC. The development of drug resistance should therefore be regarded as potentially harmful, and must be taken into account in the design of clinical studies and in the benefit–risk assessment of DAAs. Strategies to minimize the risks of resistance should be explored, and incorporated in the design of the clinical studies."

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Section 2 2nd paragraph Page 4	1	We propose an alternative wording. Proposed change: This guideline acknowledges the constraints put on clinical drug development imposed by the high rate of mutations of HCV and therefore emphasises the importance of assessing the potential for selecting resistant variants in the design of clinical studies, including the possible use of adding more than one DAA to SOC. Once sufficiently encouraging data are available from treatment naïve subjects, drug development is encouraged in difficult-to-treat patient populations, such as HCV/HIV co-infected patients and null-responders to SOC.	The original wording better expresses our intent: that the risk of resistance development during DAA trials that may turn out to be of future clinical importance for the participating patients must indeed be considered in the design and execution of clinical trials in the field.
Section 3 Page 5	1	HCV patients with renal insufficiency are an important population - such patients are unable to use ribavirin, which is renally cleared and successful treatment with peginterferon alone is limited. Proposed change: Add "Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function (CHMP/EWP/225/02)" to the list of guidelines to be taken into account.	Acknowledged.
Section 4.1 2nd paragraph Page 5	1	The "initial clinical development program" should not be limited to patients who do not have advanced fibrosis as stated in the guidelines. Interferon and ribavirin can be safely used in patients with advanced fibrosis including compensated cirrhosis and these patients have been included in the initial registration studies for the interferon products. Medical need is high in subjects with advanced fibrosis and they should not be excluded from Phase II studies and subsequent registration trials unless there are specific safety concerns of the DAA in patients with impaired liver function. The initial clinical development programme should not be limited to naïve patients to allow for non-responders to be	The revised text reads as follows: "It is anticipated that the initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to HCV therapy or relapsed after SOC treatment, do not have advanced fibrosis and are not co-infected with HIV. Preliminary efficacy and safety data, including the characterisation of the optimal dose in this population, and an estimation of the risk of selecting for drug resistance, should be at hand prior to the initiation of studies in a wider range of patient populations. If such early data are promising, confirmatory trials may not be necessary prior to studying the DAA in more vulnerable patient groups." In patients with advanced fibrosis the efficacy/tolerability of

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		included. Proposed change: It is anticipated that the initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection~~, do not have advanced fibrosis~~ have compensated liver disease, and are not co-infected with HIV.	SOC is reduced. Also, the PK of a DAA may be different. It seems prudent to first dose-range a new DAA in patients with less severe liver injury. Of note, the document in no way precludes the inclusion of patients with compensated cirrhosis in subsequent exploratory and confirmatory studies, as stated in section 4.4.1: *"Patients with advanced fibrosis or cirrhosis:* In patients with advanced liver disease, but without contraindications to SOC, studies aiming at exploring safety and PK using an add-on DAA to SOC design should be considered. The aim should be to provide sufficient data to make it possible to include this important patient group in confirmatory studies."
Section 4.1 3rd & 4th paragraphs Page 5	1	Guidance should be included on this process. For example, use of a protocol to assess resistance for each agent. It should be possible to study combinations of DAAs in subjects unlikely to benefit from SOC (null responders) prior to or concurrent with the assessment in treatment naïve subjects given the large unmet needs for the null responder population. Clarify that use of DAAs in combination may allow a different development approach than that described in this section. Results from initial studies may indicate that the development in certain populations may not be desirable. It may not be appropriate to investigate studies in patients infected with GT 2/3 and 4 for all DAAs. Patients with a documented response are defined as > 1 log reduction at week 4, or > 2 log reduction at week 12. The definition of null-responders should mirror this definition of responders. Additional patient population not mentioned for "later" studies would include subjects with contraindications to the use of interferon and/or ribavirin. Subjects previously treated with DAAs may need to be considered as an additional subgroup in the category of those needing evaluation after initial approval of a given DAA. For instance, this patient population is described in Section 4.4.1.	See "Summary of Outcome" above. Concerning patients with contraindications to interferon or/and ribavirin, no ribavirin arms in DAA studies have generally been less efficacious, and non-interferon approaches have to our knowledge not been evaluated. In the revised document, this patient group is considered under exploratory studies of SOC-sparing regimens.

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		Proposed change: Once the DAA has been evaluated in the population above, with a preliminary assessment made of the likely safety and efficacy to be expected, risk of treatment failure and selection of resistant variants (e.g. through use of a protocol to assess for each agent), suitable agents should be studied in a larger range of patient populations. Thus, it is anticipated that later studies (which may precede or follow an initial approval for use in the above mentioned patients), if warranted, should evaluate use in: • Patients with advanced fibrosis or cirrhosis and candidates for SOC. • Patients with a documented response (e.g., > 1 log reduction at week 4 or > 2 log reduction at week 12) to a prior course of SOC who did not achieve undetectable HCV-RNA • Patients with relapse during or after completion of SOC. • Patients infected with virus of GT 2/3 and 4, as appropriate. • HIV/HCV co-infected patients. • Liver transplant patients. • Patients with a documented null-response to SOC defined as, e.g., < 1 log reduction of HCV-RNA at week 4 ~~–12~~, or < 2 log reduction of HCV-RNA at week 12. • Patients who did not achieve SVR with therapy that included an approved DAA. • Patients with contraindications to the use of interferon and/or ribavirin.	
Section 4.2 Page 5 & 6	1	The type of sequencing/sensitivity recommended should be specified whether population or clonal. If clonal sequencing is recommended the number of recommended clones should be specified. Guidelines should indicate that G1 subtype should be determined and that any differences in antiviral efficacy of DAA between	Accepted, and included in revised pharmocodynamic section (4th paragraph section 4.3.2): "For genotype 1 virus, subtype should also be determined (1a vs. 1b), and putative differences in antiviral response according to subtype should be explored."

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		subtype 1a vs 1b should be characterized, particularly in the case where in vitro data suggests DAA has differential antiviral activity in the genotype 1a/1b replicon system. Proposed change: In genotype 1 virus, subtype should also be determined (1a vs. 1b) and exploratory studies (see 4.4.1.) should elucidate any differences in antiviral response according to subtype as needed based on *in vitro* studies.	
Section 4.2 1st paragraph Page 5 & 6	1	"The choice of assay should be tailored to genotypes in the study population as some assays have been reported to substantially underestimate HCV RNA levels in certain genotypes." This is acceptable when comparing data from studies, which include different genotypes, but very limited data on genotype specific viral load detection by different commercial assays are available, making assessment of which assay to use complex. Proposed change: Suggest to rephrase as follows: "As some assays have been reported to substantially underestimate HCV RNA levels in certain genotypes, the choice of assay should be justified in terms of performance with those genotypes expected in the study population."	This has not been implemented. The revised version reads: "The choice of assay should be tailored to the genotypes in the study population, as some assays have been reported to substantially underestimate HCV RNA levels in certain genotypes. The same assay should be used for all samples from a single study and, whenever possible, throughout the clinical development programme."
Section 4.2.1 1st paragraph Page 6	1	Sponsors would aim to use the same assay and laboratory throughout a study, but sometimes assays are updated and laboratories have to be changed for a variety of reasons. Central/Reference labs may have more than one testing location in order to be able apply the stopping rules in an effective way. Validation of assays at different locations should ensure that results are comparable across locations. More sensitive assays (i.e. TMA) could be used to determine SVR24. Proposed change: The same assay ~~and the same laboratory~~ should be used for all	Partly accepted. Same assays should be used – that is the advice. There is no need for TMA when using the Real-time PCR assays with a lower dection limit of 15-15 IU/mL.

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		samples from a single study and, wherever possible, throughout the clinical development programme. However, a more sensitive assay (TMA) could be used to determine SVR24.	
Section 4.2.1 2nd paragraph Page 6	1	We do not agree with the statement that the method that should be systematically used for genotyping is direct sequence analysis. HCV genotypes have been delineated using a variety of methods, including amplification and direct sequence analysis, genotype-specific probe hybridization, serologic genotyping and genotype-specific primer amplification. Currently, amplification and direct sequencing of the 5' noncoding region, followed by sequence comparison and phylogenetic tree construction, is considered the gold standard. The 5'noncoding region of HCV is the most highly conserved region among HCV genotypes. This makes this region theoretically superior for sensitivity when compared to other genomic regions of HCV and using the currently available commercial assays for determination of HCV genotype mistyping is rare. However, assays utilizing analysis of the 5' noncoding region may cause mis-subtyping in 10-25% of cases. Currently these errors are of no clinical consequence, as only the HCV genotype is used for therapeutic decision making. The results obtained by analysis of the 5' noncoding region correlate well with sequence analysis of the NS5B gene for determination of genotype, with 100% concordance found in many studies. However, numerous studies have demonstrated the superiority of using sequence analysis of the NS5B gene over that of the 5' noncoding region for the discrimination of different subtypes within a particular HCV genotype. Therefore, unless a specific DAA demonstrates significant differential activity between the subtypes of a relevant HCV genotype, currently available HCV genotyping assays based on sequence analysis of the 5' noncoding region of HCV are sufficient. Currently all commercially available genotype assays are not based on the NS5B sequence but use 5' non-coding region. This could be restrictive for some sponsors as there are a limited number of laboratories available for this testing and could result	Not accepted. As is pointed out in the proposal given, 5'NC generates incorrect results for genotype 1 subtypes and probably also other genotype subtypes, and can therefore not be used. Hence, any assay based on population sequencing, reverse hybridization, or real-time PCR which has been validated for correct subtyping of at least subtypes 1a and 1b, and ideally others should be used. At the moment this means NS5B sequence+ phylogeny, or second-generation (not first-generation) line probe assays. The text has been slightly changed to clarify: *"HCV genotyping:* The method that should be systematically used for genotype determination is direct sequence analysis with either commercial or validated in-house techniques. The applicant should justify that a sufficiently large portion of the NS5B gene is sequenced. Sequence determination should be followed by phylogenetic analyses. Any assay based on population sequencing, reverse hybridization or real-time PCR, which has been validated for correct subtyping of at least subtypes 1a and 1b, and ideally also others, should be used. Presently this is accomplished using NS5B sequence + phylogeny, or second-generation line probe assays.Techniques based on the analysis of the 5' non coding region should not be used, as a too high incidence of erroneous determination of the subtype has been reported."

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		in delays to screening and study recruitment. Even though genotyping assays focusing on NS5b sequencing have greatest reliability, the acceptability of currently employed line-probe or hybridization assays or modified versions should be considered if appropriately validated for clinical use. Proposed changes: HCV genotyping: HCV genotype can be determined by various methodologies, using direct sequence analysis of the 5' noncoding region or reverse hybridization analysis using genotype-specific probes located in the 5' noncoding region. Although commercially available genotype assays are based on the 5' non coding region, it is associated with erroneous subtype determinations. It is preferred that the NS5B region is used when a validated commercial assay becomes available, unless otherwise justified. Subtype specific genotyping may be required for DAAs with subtype selective antiviral efficacy. The acceptability of currently employed line-probe or hybridization assays or modified versions may be considered if appropriately validated for clinical use.	
Section 4.2.1 3rd paragraph Page 6	1	Genotypic methods are used for subtype (1a versus 1b) determination. Please clarify what exactly is meant by 'phenotypic methods'. Proposed changes: If alternative, phenotypic methods are used for classification, this should be fully justified. It is also understood that such methods may be used in parallel in order to provide clinicians with guidance as regards the use of such methods in clinical practice.	This paragraph is flawed and has been deleted in the revised document.
Section 4.2.2 Page 6	1	Since one of the objectives of adding DAAs may be shortening of treatment duration, we propose to clarify that the SVR24 timepoint may occur at different absolute timepoints for treatment arms with differing total treatment duration.	Point taken. For the purpose of the primary analysis in confirmatory studies, it is clarified that missing SVR24 data should be considered as non-response.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		It would be good if the guideline would specify how subjects with missing W24 SVR follow-up information should be dealt with from a statistical point of view. Proposed changes: The recommended primary endpoint for confirmatory studies is sustained virological response (SVR) defined as undetectable HCV RNA ~~6 months~~ 24 weeks after completion of therapy in the specific treatment arm. ~~Subjects with less than 20 weeks of follow-up should be considered to have no response to treatment.~~	
Section 4.2.3 Page 6	1	SVR12 should be prospectively collected in phase 2 and confirmatory studies as should any other early or secondary efficacy data (inc. RVR-2, RVR-4, cEVR,) to establish a possible relationship with the primary end point during development of the DAA. Proposed changes: End-of-treatment response (ETR) and time to confirmed undetectable viral load should be reported. SVR-12 and SVR-24 should be prospectively collected in phase II and pivotal studies. Rapid viral response (RVR) at week 4 and early viral response (EVR) are currently defined in relation to the viral kinetics in patients treated with SOC. Data on virological response rates and the kinetics of changes in viral load should be generated during exploratory studies in which DAAs are added to SOC to indicate appropriate time points for describing RVR and EVR in confirmatory studies.	Point taken. The paragraph on endpoints reads as follows in the revised document: "The recommended primary endpoint for confirmatory studies is sustained virological response (SVR), defined as undetectable HCV RNA 6 months after completion of therapy, regardless of the scheduled duration of treatment. For the purpose of the primary analysis in confirmatory studies, missing SVR24 data should be considered as non-response. ETR as well as time to confirmed undetectable viral load should be reported. SVR-12 and SVR-24 should be prospectively assessed in phase II and pivotal studies. In exploratory studies other virological endpoints, such as rapid viral response (RVR: undetectable HCV-RNA at week 4), early viral response (EVR: undetectable HCV-RNA or $\geq$ 2log10 decline at week 12) and end-of treatment response (ETR: undetectable HCV-RNA at the planned end of treatment), may be used to guide the design of further studies." RVR is defined in the document as undetectable HCV-RNA at week 4
Section 4.2.4 1st paragraph Page 6	1	Given the slow rate of progression of fibrosis in the early stages and the inherent risk of liver biopsy, 12 months appears too tight a window. We propose that the time frame for liver biopsies used for the assessment of the degree of fibrosis in confirmatory trials be increased to 24 months to facilitate participation of patients and	24 month limit accepted. If cirrhosis has previously been demonstrated in a biopsy, this is considered sufficient, and no further biopsy necessary prior to inclusion in trial.

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		decrease risk associated with this specific assessment. The guidelines indicate that if cirrhosis has been demonstrated, the time window does not apply. Tighter criteria should also be applied to patients with cirrhosis with a window also specified for the prior biopsy (e.g., within 5 years). Proposed change: The main role of a histology assessment prior to enrolment is to exclude patients with advanced fibrosis from participation in early clinical trials and to enable stratification (if warranted) by degree of fibrosis in confirmatory studies. For this purpose a liver biopsy of adequate quality within 24 months prior to study entry may be employed. If cirrhosis has been demonstrated a liver biopsy of adequate quality within 5 years prior to study entry may be employed. If non-invasive methods are used as an alternative to liver biopsy this should be justified by the applicant.	
Section 4.2.4 2nd paragraph Page 6	1	Consider adding language to the last paragraph of Section 4.2.4. to indicate that an example of "specific claims" where histologic evaluation would be required for licensure would be disease suppression (maintenance) strategies. Proposed change: Evaluation of liver histology post-treatment is not foreseen as part of the assessment of the efficacy of DAA add-on to SOC regimens unless specific claims are made eg. disease suppression (maintenance) strategies**,** or hepatic safety issues make this necessary.	The possible use and evaluation of DAAs for maintenance strategies is not considered in this document.
Section 4.3.1 Pages 6 & 7	1	After the first sentence, this section focuses on drug interactions – an additional heading would make this clearer. With respect to recommendations for evaluating drug interactions, careful selection of interacting drugs (i.e., "probe" compounds) for early in vivo studies will allow for an assessment of the potential for drug-drug interactions and facilitate planning for further studies later in the development	To some extent, the section 4.3.1 has been reformulated. However, the issue of drug interactions is generally dealt with in another guideline document.

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		process, as needed. Another relevant comment could be added to the PK section. **Reference:** Katz DA, Murray B, Bhathena A, Sahelijo L. Defining drug disposition determinants: a pharmacogenetic-pharmacokinetic strategy. Nat Rev Drug Discov 2008; **7**: 293-305. Proposed changes 4.3.1 Pharmacokinetics; 4.3.2 Drug Interactions; 4.3.3 Pharmacodynamics Preclinical and early Phase characterization of drug disposition and potential DDI profile may be complemented and enhanced by pharmacogenetic studies, given that current *in vitro* functional assays cover only a small subset of drug metabolizing enzymes and transporters and are resource intensive.	
Section 4.3.1 1st paragraph Page 7	1	Substantial proof is lacking that intracellular PK is more predictive/important than plasma PK. Phosphorylation of nucleoside analogues can be very different in different human cell types and different tissues. The basis of such differences has not been fully elucidated. Further, phosphorylation patterns can be very different between animal species and humans. In vivo studies in animal species are therefore difficult to translate into predictions to human tissue effects. We propose therefore that carefully designed clinical studies should be considered if interactions between nucleosides at the in vitro level cannot be excluded. Proposed changes: For DAAs that are nucleoside analogues, the potential for interaction to occur at the level of intracellular activation by phosphorylation should be considered. If an interaction cannot be excluded based on knowledge of phosphorylation pathways, in-vitro interaction studies should be conducted. If the possibility of	This has been acknowledged.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		a relevant interaction cannot be excluded *in vitro*, then clinical studies should include an appropriate design to allow the assessment of the clinical significance of the interaction.	
Section 4.3.2 1st paragraph Page 7	1	We propose to replace 'assessment of activity against viruses other than HCV' with the broader term 'selectivity'. The assessment of activity against related human targets, cell proliferation and activity against viruses other than HCV may form part of an appropriate selectivity assessment of novel DAAs. Proposed changes: It is anticipated that an initial application dossier should include an extensive evaluation of the in-vitro activity of a new DAA including exploration of the mechanism of action, selectivity, and the risk of selection for drug-resistant variants, with assessment of the potential for cross-resistance to occur.	The main other viruses intended, for which cross-activity could be a problem, are HBV and HIV. This has been clarified.
Section 4.3.2 3rd paragraph Page 7	1	Cellular assays that assess full cycle replication including infectivity may be best to employ in the future for preclinical assessment of candidate antiviral agents.	Also for other reasons, it is foreseen that these guidelines will be revised within a short frame of time
Section 4.3.2 5th paragraph Page 7	1	We recommend to use H77 and Con1 strains as reference strains for sequencing and phenotyping analyses. These strains are widely used and easily available. Their use could improve consistency and comparability of data across laboratories. Proposed changes: "Genotypic resistance" is analysed by means of direct sequence analyses (population sequencing). H77 and Con1 strains are widely available, well characterized and should be used as gold standards for genotype 1a and 1b respectively.	Not included. At the moment it is considered premature to define golden standards.
Section 4.3.2 6th paragraph Page 7	1	It is not clear whether the samples refer to those from subjects who fail standard of care (i.e. and can be tested before first use in infected persons) or from subjects exposed to the investigational drug during the course of clinical studies. We suggest that the	Acknowledged. The revised text reads: "It is expected that sequencing and phenotyping studies will be performed on clinical isolates recovered from patients treated with the investigational agent, and that have failed to respond or

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		detailed virological studies should be limited to subjects exposed to the investigational drug. The term "fail to respond" is unclear and should be clarified. Proposed changes: "It is expected that sequencing and phenotyping studies will be performed on clinical isolates on samples recovered from those treated with the investigational agent and who fail to respond or relapse."	have relapsed."
Section 4.3.2 7th paragraph Page 7	1	"The same methods should be used throughout the development" this could provide problematic for some sponsors. Proposed changes: When presenting *in vitro* data, the assays and prototype strains used should be clearly defined, and justified. The studies should include appropriate controls to enable comparisons and bridging between studies in the context of continuous improvements in assay performance over time.	The revised text has an addition (in italics below): When presenting *in vitro* data, the assays and prototype strains used should be clearly defined and justified. The same methods should be used throughout the development, to enable comparisons between studies. *If methods are changed due to the continuous development of assays over time, appropriate controls should be included to enable comparisons and bridging between studies*.
Section 4.3.2 Last paragraph Page 7	1	Although studies of viral fitness are advisable, 'predictive value' of viral fitness analysis conducted in vitro will be limited due to difficulties in assessing the full range of genetic diversity in clinical isolates on fitness related to specific resistance mutations, as well as due to sequence-context effects from replicon systems themselves. Proposed changes: It is acknowledged that the predictive value of viral fitness analyses conducted *in vitro* is poorly understood, but it is advised that such studies are undertaken.	Acknowledged. The revised text reads: "It is acknowledged that the predictive value of viral fitness analyses conducted *in vitro* is uncertain, but it is advised that such studies are undertaken."
Section 4.2.3	1	Please add to comply with recent data Proposed changes: Sufficient data now exists with DAAs that early virologic endpoints such as RVR accurately describe the PK/PD antiviral relationship to guide dose selection for pivotal phase III trials.	Factorial designs and subsequent data analysis in confirmatory trials could not be considered a rule, but would have to be justified on a case-to case basis, in the light of available data from phase II studies.

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		On the other hand, differences in SVR between treatments are determined by the length of treatment of DAA and/or SOC. Small differences between treatments cannnot be determined in under-powered Phase II studies. In order to accelerate clinical development, once potency (dose) and safety have been demonstrated in Phase 2, the initiation of modified factorial design pivotal studies, in the absence of Phase II SVR, should be permitted provided pivotal studies are adequately designed to determine the optimum duration of DAA and/or SOC treatment	
Section 4.4 Whole section Pages 7 to 10	1	References are made in this Section to exploratory studies of treatment regimens involving combinations of DAAs, but generally little information or recommendations on the design and objectives such studies. Further guidance is requested.	See "Summary of Outcome" above.
Section 4.4 2n^{d} paragraph Page 7	1	Further guidance is requested on how compliance should be assessed.	Acknowledged. Suggestions are made in the revised text: "Adherence to therapy is of vital importance for treatment outcome, and major efforts to encourage and document compliance should be undertaken (i.e. interview and pill count)."
Section 4.4 3rd paragraph Page 7	1	Presumably a Marketing Authorisation Application can be submitted, once SVR has been achieved. In practice, SVR with SOC means cure of the viral disease. Late virological relapse, more than 6 months following treatment with SOC is rare. There is no evidence to suggest that adding an antiviral agent to SOC would impact the maintenance of response over time. In addition, it is logistically extremely difficult to follow up all patients for one year. We believe that a 6 months follow up period for patients included in efficacy studies and achieving an SVR is sufficient. If at all required, a longer follow-up could be done by setting up a "roll-over" protocol from several studies to increase the	The revised document states this issue as follows: "Patients that achieve ETR in efficacy studies should be followed for at least 6 month post treatment. At this time SVR (the primary outcome measure) should be determined. Patients exposed to DAA(s) and not achieving SVR should be monitored for at least one more year after the documentation of nonresponse, with frequent sampling (e.g., every three months) of HCV-RNA and assessment of genotypic resistance. Reversion to wild type virus and/or long-term persistence of drug-resistant variants should be documented. Where a genotypic correlate of resistance has not been observed, phenotypic resistance should also be assessed. A full dataset on the follow-up of non-responders would, however, not need to be available at the time

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		chances of success. Proposed changes: Patients included in efficacy studies and achieving SVR <u>on regimens containing SOC should be followed for 6 months</u> post treatment. Any late post-treatment relapses (or re-infection) should be carefully documented. The Marketing Authorisation Application can be submitted when SVR has been achieved and before completion of the 6-month follow-up that can be fulfilled as a post-marketing commitment	of a market authorisation application submission, but could be reported subsequently." Thus, while patients failing to reach SVR would be expected to be followed for an additional year after the determination of treatment failure, such data must not necessarily be available at the time of the MAA submission.
Section 4.4 4th paragraph Page 7	1	The main objective is to demonstrate disappearance of variants, which requires less frequent sampling than a detailed study of the kinetics of the decay. Therefore, a sampling interval of 6 months is proposed. Phenotypic methods to assess HCV resistance starting from the patient's viral sequence have a low success rate and are not easy to perform. In addition, it's not clear how much additional information these test results will provide during the follow up period after a certain level of resistant virus has emerged. Therefore, we would like to propose that population sequencing should be the method of choice to follow these patients with the potential for more sensitive genotyping methods to be used as deemed appropriate. Proposed changes: "Patients exposed to DAA(s) and not achieving SVR should be monitored with frequent sampling of HCV-RNA (e.g., every ~~three~~ <u>six</u> months) and assessment of genotypic ~~and phenotypic~~ resistance for at least one <u>year post DAA exposure</u>, <u>or less if the viral population returned to background levels or the patient started another anti-HCV treatment regimen, by population sequencing or more sensitive methods</u>. <u>Patterns of r</u>~~R~~eversion to wild-type virus and long-term persistence of drug-resistant variants should be <u>analysed</u> ~~documented~~. <u>Where a genotypic correlate of resistance has not been observed, phenotypic resistance should also be assessed</u>."	The point on the role of phenotypic resistance has been included in the revised document: "Patients exposed to DAA(s) and not achieving SVR should be monitored for at least one more year after the documentation of nonresponse, with frequent sampling (e.g., every three months) of HCV-RNA and assessment of genotypic resistance. Reversion to wild type virus and/or long-term persistence of drug-resistant variants should be documented. Where a genotypic correlate of resistance has not been observed, phenotypic resistance should also be assessed."

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Section 4.4 1st paragraph Page 8	1	"Patients exposed to SoC only, and not achieving SVR, should be managed according to clinical practice" – it would be helpful to clarify if these patients can be considered for inclusion in a study of SoC plus DAA. Proposed changes: Amend sentence to read as "Patients exposed to SoC only, and not achieving SVR, should be managed according to clinical practice, but may be considered for inclusion in a study of SoC plus DAA."	Acknowledged: The revised text reads: "Patients exposed to SOC only, and not achieving SVR, should be managed according to clinical practise, but may be considered for inclusion in a further study of SOC plus DAA."
Section 4.4.1. Dose finding, monotherapy studies 3rd paragraph Page 8	1	3rd paragraph indicates that "5-(7) days duration of monotherapy" is considered acceptable. CHMP should consider revising to remove lower limit and only indicate that up to 7 days of monotherapy is considered acceptable. We believe that FDA DAVP are now limiting DAA monotherapy to only 3 days or less in treatment-naive subjects. It is possible that a drug that selects for two amino-acid mutations that each require 1 nucleotide change may impose a genetic barrier comparable to a drug that selects for 1 amino-acid mutations requiring 2 nucleotide change. Proposed changes: ~~"5-(7)~~ ***up to 7*** days duration of monotherapy" is considered acceptable. In this context, i.e. when no *in vivo* data are available, a high genetic barrier may be defined as the need for > 2 likely key mutations (or 1 key mutation- requiring 2 nucleotide changes) to achieve IC50 values higher than expected free drug exposure *in vivo*.	Clearly, monotherapy should be as brief as possible, to yield appropriate information for dose selection. We believe this is reflected by the present wording, which is more liberal than the 3 days quoted.
Section 4.4.1. Dose finding, monotherapy studies	1	Dose ranging, monotherapy studies could include non-responders etc, who were naïve to the DAA being evaluated. Proposed changes: Amend sentence to read as "It is expected that these studies would be performed in patients who are either naïve to SoC or have not responded to SoC and are naïve to the DAA under	See "Summary of Outcome" above.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
4th paragraph Page 8		evaluation, without co-infection and without advanced fibrosis."	
Section 4.4.1 Early exploratory studies of combination therapy 1st paragraph Page 8	1	Data available today suggests that non-responders (including null-responders) can derive significant benefit of the addition of a DAA to SOC and that the addition of a DAA may lead to a restoration of the response to SOC. In addition, medical need is likely to be greater in patients who previously did not respond to a SOC regimen. Therefore, we propose to amend this section accordingly and open the possibility of studying non-responders earlier in exploratory trials. Proposed changes: Early exploratory studies of combination therapy In these studies it is anticipated that regimens with different dosages and durations of the new DAA will be added to SOC and compared to SOC alone in treatment naive patients. If sufficient confidence is obtained during monotherapy trials, early exploratory studies in patients who previously did not respond to SOC may be conducted as well (with the right stopping rules in place in order to minimize resistance evolution).	See "Summary of Outcome" above.
Section 4.4.1 Early exploratory studies of combination therapy 2nd paragraph Page 8	1	The CHMP states that consideration could be given to employing a lead-in phase of SOC before randomization to identify those treatment-naive patients that might derive most benefit from addition of the DAA and to avoid randomization of both Null-responders and Rapid virological responders. It should be noted that currently there is no data to indicate whether this approach (i.e., lead-in phase of SOC) has merit (i.e., improved SVR rate, lower resistance, etc.). In addition, exclusion of genotype 1 rapid virological responders (because they have a high chance of SVR with SOC for one year) would not be reasonable in trials evaluating durations of the new DAA that are less than current SOC.	The lead-in phase has now been deleted from the guideline. Accumulating data, not available when writing the first draft, indicates that lead-in is not generally likely to be needed, and investigations of lead-in strategies may be considered optional.

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		It should also be acknowledged that in studies where this strategy is employed (i.e., enriched population of patients likely to benefit from add-on therapy), SVR rates achieved with this study design cannot be compared to SVR rates achieved in other studies where DAA + SOC are started concurrently. Inclusion of a potential lead-in phase of SOC in the guidelines is considered to be theoretical and premature and suggested to be omitted. Sequential introduction of therapeutics is not a feature of treatment paradigms for either acute or chronic infectious diseases. On the contrary, the fundamental principle has always been to initiate therapy with maximum drug activity against the pathogen to ensure as rapid control as possible as well as minimise resistance or selection of resistant quasi-species especially using agents with different modes of action as being considered in these guidelines. In addition, more specifically, there is no guarantee that an initial rapid viral response to SOC might not be followed by dose reduction for intolerance when use of a triple regimen from the outset might shorten overall duration of therapy and not require undesired modification of the SOC dosing. Furthermore, there is insufficient data to be sure the use of one DAA with SOC from the outset does result in functional monotherapy in patients who in a lead-in phase might have been thought to be interferon non-responders. Indeed, there is the alternative theory that significant reduction of viral load by the DAA will make the SOC more effective than it would have been when given alone and that the therapies compliment each other. Careful early attention to the viral load can more effectively screen out those patients in both naïve and non responder populations who are actually showing a suboptimal response to the full antiviral activity available of all agents used together from the outset. Proposed changes: Section 4.4.1. should be revised to more clearly indicate that the	

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		utility of a lead-in phase of SOC before randomisation to the DAA has not been established and that additional data will be needed to validate this approach for early exploratory studies of combination therapy. The results obtained on adding a DAA after a lead-in SOC phase may be different from the effect of adding the DAA from the outset, depending on the control of viral replication achieved by SOC alone, ***therefore, studies employing the different strategies cannot be compared.***	
Section 4.4.1 Additional exploratory studies Page 8 & 9	1	It is unclear when further exploratory trials are necessary in patients with a previous partial response to SOC, and when phase III trials can be initiated without further exploratory trials in partial responders. Further guidance is also requested to clarify procedures to progress development of regimens consisting of combinations of antiviral drugs without SOC: Would it be possible to include the possibility of conducting studies with more than one DAA without SOC, provided this approach was adequately justified and based on supporting data? Is there an opportunity for a study with more than one DAA (with different MoAs) in patients who have failed previous SOC due to insensitivity to IFN or intolerance? "*European regulatory discussion is advisable prior to the initiation of confirmatory studies*". Suggest that this text is moved to section 4.4.2.	See "Summary of Outcome" above.
Section 4.4.1 Additional exploratory studies 1st paragraph Page 8	1	These studies could be initiated before previous early exploratory studies (as described in the previous paragraphs) are performed and fully analysed. Proposed changes: Additional exploratory studies - Before progressing to confirmatory studies it may or may not be considered necessary to perform further exploratory studies. This decision can only be made after	The wording has not been changed in the revised document. The guidance does not state that preliminary data cannot be used for the design of further studies (see, e.g., section 4.2.2).

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		review of the data from the first studies and with knowledge of the properties of the DAA in question and other DAA under development or licensed. <u>These studies may be started before or after the first exploratory studies are fully analysed, depending on the characteristics of the compound.</u>	
Section 4.4.1 Additional exploratory studies 2nd bullet Page 8	1	The suggestion seems to be that subjects who achieve an RVR with SOC may not benefit from a DAA. However, these subjects may be able to shorten their treatment durations significantly, (possibly to < 24 weeks), if a DAA was given. Hence it may be suggested that these are the populations to study with the aim of reducing the duration of therapy. This would deliver significant benefits to patients and public health.	See "Summary of Outcome" above.
Section 4.4.1 Early exploratory studies in specific patient populations, 1st bulleted paragraph Page 9	1	Further guidance is requested in order to clarify when separate studies in patients with advanced fibrosis or cirrhosis are indicated. In addition, please clarify if patients with compensated fibrosis or cirrhosis (Child Pugh A) could be included in the same studies as patients with less severe liver disease. Lastly, would EMEA require differentiation between patients with compensated and decompensated liver disease and justification for proceeding based on risk: benefit?	The text on this in the revised version remains unchanged, as we believe it appropriately addresses these issues: "*Patients with advanced fibrosis or cirrhosis:* In patients with advanced liver disease, but without contraindications to SOC, studies aiming at exploring safety and PK using an add-on DAA to SOC design should be considered. The aim should be to provide sufficient data to make it possible to include this important patient group in confirmatory studies." Very limited data are presently available of the use of DAAs in patients with decompensated cirrhosis, where SOC may be contraindicated. Reference is made to section 4.4.1, (headline: "exploratory studies in specific patient populations" (quoted above), and "exploratory studies of SOC-sparing regimens")
Section 4.4.1 Early exploratory studies in specific patient populations,	1	Insufficient data are available in well characterised null responders to justify using a single DAA as add-on to SOC in confirmatory studies without first undertaking exploratory studies in this sub-group of patients. We propose to update this section with the latest developments that were not available at the time of publication of this draft guideline. Available data today suggests that non-responders (including null-responders) can derive significant benefit of the	Point taken. See "Summary of Outcome" above.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
2nd bulleted paragraph Page 9		addition of a DAA to SOC and that the addition of a DAA may lead to a restoration of the response to SOC. Proposed changes: The benefit from addition of a single DAA to SOC is unproven, and may vary from agent to agent, therefore exploratory studies are needed in order to inform the design of any confirmatory studies to be undertaken in this group of patients.	
Section 4.4.1 Early exploratory studies in specific patient populations, SOC null responders Last bulleted paragraph Page 9	1	"Patients who have failed therapy with an experimental agent (A), should, if feasible, be included in a subsequent study including a DAA of different class (B). Alternative designs are foreseeable, but include a randomized trial comparing A + B + SOC with B + SOC." Proposed changes: We disagree with this concept of "functional monotherapy" . A patient may not respond to SOC, but when SOC is associated to a DAA, the effect of SOC may be modified (and improved) in several ways: (1) by the reducing effect of HCV RNA by the DAA, making SOC more effective; and (2) by the immunological effect of SOC (not antiviral effect) facilitating the antiviral effect of DAA.	In the absence of clear in vivo evidence to the contrary, assumptions of this sort of synergic effects of adding a DAA to SOC would have to be demonstrated. The risk of functional monotherapy when adding a DAA to SOC must be considered real (e.g. the less than impressive results of boceprevir+SOC in SOC non-responders).
Section 4.4.1 Page 9	1	An additional paragraph is suggested for inclusion in section 4.4.1 Exploratory studies: Exploratory secondary endpoints Persistent infections with HCV are likely to depend on inhibition of host defence mechanisms by the virus, dominated by interferon dependent signalling events[1]. Moreover, the differential susceptibility profile presented by affected individuals to resolve infection spontaneously (30%) or otherwise to chronically progress at various rates suggests that host genetic factors may play important roles in characterization of these sub-populations[2]. In support of efficacy clinical studies, bi-modal profiles and racial differences in the broad spectrum of response to peginterferon treatment indicate a possible role for	This per se interesting phenomenon is directed to interferon rather than the DAAs, and is thus not the focus of these general guidelines. The companies of new DAAs cannot be requested to perform these advanced analyses. That is rather for the academic groups to study.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		host genetic diversity in the response to anti-HCV treatment. Single marker, gene-gene and gene-environment interaction studies published in recent years suggest important roles in the pharmacogenetics of interferon treatment even after controlling for other known covariates, such as age, gender, race and viral load[3-5]. In addition to supporting and guiding drug R&D, identification of subjects prone not to respond to treatment prior to therapy initiation may serve to avoid the significant adverse events from which some of the peginterferon patients suffer. **References** 1 Gale M, Jr., Foy EM. Evasion of intracellular host defence by hepatitis C virus. *Nature* 2005; **436**: 939-945. 2 Asselah T, Bieche I, Paradis V, Bedossa P, Vidaud M, Marcellin P. Genetics, genomics, and proteomics: implications for the diagnosis and the treatment of chronic hepatitis C. *Semin Liver Dis* 2007; **27**: 13-27. 3 Rhodes SL, Erlich H, Im KA, Wang J, Li J, Bugawan T et al. Associations between the human MHC and sustained virologic response in the treatment of chronic hepatitis C virus infection. *Genes Immun* 2008; **9**: 328-333. 4 Su X, Yee LJ, Im K, Rhodes SL, Tang Y, Tong X et al. Association of single nucleotide polymorphisms in interferon signaling pathway genes and interferon-stimulated genes with the response to interferon therapy for chronic hepatitis C. *J Hepatol* 2008. 5 Lin E, Hwang Y, Chen EY. Gene-gene and gene-environment interactions in interferon therapy for chronic hepatitis C. *Pharmacogenomics* 2007; **8**: 1327-1335. Proposed changes: <u>Exploratory secondary endpoints</u> It is recommended that exploratory analyses of host factors be	

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		conducted to characterize the various responder populations and safety profile across the different treatment arms.	
Section 4.4.2 Page 9	1	It should be clarified whether, if sufficiently justified, for example in SOC null responders, it would be possible for studies to be conducted using a combination DAA approach without SOC?	See "Summary of Outcome" above.
Section 4.4.2 1st paragraph Page 9	1	First paragraph requires clarification. In the first sentence, it appears that CHMP is indicating that either enhanced efficacy or overall reduction in the duration of therapy (with non-inferiority to SOC) is an acceptable approach for registration. The second sentence of the first paragraph appears to be contradictory and the concept of reduced overall duration is not included later in this section in the various scenarios envisaged for the design of confirmatory studies.	Acknowledged. See "Summary of Outcome" above.
Section 4.4.2 2nd paragraph Page 9	1	This guidance suggests that in most cases the first confirmatory studies have to be conducted in naïve patients infected with HCV genotype 1. However, we want to emphasize that if the phase 2 data justify it, a parallel development in both naïve and non responder patients could be considered as both patient subgroups require an optimization of treatment outcome. Proposed changes: "In most cases, it is foreseen that first confirmatory studies are conducted in treatment naïve patients infected with HCV genotype 1, although the range of patients to be included in the confirmatory studies should be decided on a case by case basis depending on accumulated data with the new DAA."	Acknowledged. See "Summary of Outcome" above.
Section 4.4.2 2nd bulleted point Page 9	1	It would be helpful to indicate the expected approach for the non-inferiority assessment of the DAA being evaluated compared to the approved DAA (e.g. non-inferiority based on a fixed margin or a synthesis method). The current wording suggests that sponsors subsequent to the first DAA approval should conduct non-inferiority studies may be problematic for several reasons. One being, that confidence	An attempt has been made to clarify this, and the revised text reads as follows: "When at least one DAA has been approved prior to initiating confirmatory studies of the new agent, it will have to be considered whether a comparison of the investigational DAA with the approved DAA is appropriate, whether this comparison should be conducted with a superiority or non-inferiority design, and, if the latter, what is an appropriate non-inferiority margin."

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		intervals for the first approved DAA may be very wide, presenting a challenge in establishing an acceptable margin of non-inferiority to support approval of a new DAA drug. Any differences in study populations may also be problematic in establishing a non-inferiority evaluation. If a sponsor has already initiated a Ph III program vs current SOC prior to approval the first DAA, clarification should be provided regarding the potential requirement to conduct an additional phase III non-inferiority study once the first DAA is approved. In this situation it may be pertinent to amend the wording to enable subsequent sponsors to conduct a superiority vs peg-INF/RBV followed by a smaller non-inferiority vs peg-INF/RBV/DAA for initial approval in treatment naïve populations. Addition of new DAA to an existing DAA may not be warranted.	Once a DAA has been approved, it seems likely that the new "standard of care" will include this agent. When a phase III program is initiated after this, case-specific decisions will have to be made concerning study design (populations studied, relevant comparators, superiority vs non-inferiority). Given the anticipated size of confirmatory trials, this should per se not pose a problem for the definition of a non-inferiority margin. If a phase III program comparing a DAA+SOC with SOC has already been initiated at the time of approval of the first DAA, the demonstrated efficacy/safety profile vs SOC would determine whether further comparisons with the approved DAA is mandated or not, prior to licensure. At present, the questions on the statistical design of these studies cannot be fully answered. However, other guidelines (e.g. on non-inferiority studies in general) will be of relevance.
Section 4.4.2 3rd paragraph Page 10	1	We agree that SOC (pegylated interferon alfa 2 / RBV) cannot be regarded as a proper reference regimen. Nevertheless, since there are currently no approved alternatives for this patient population, and although we acknowledge that a SOC comparator arm should not be a requirement in studies in null-responders, studies with an SOC comparator arm that include null-responders could be acceptable on the condition that proper and stringent stopping rules are in place to protect both patients in the SOC and the DAA+SOC arms. Proposed changes: Patients with null-response to SOC constitute a patient population where currently no evidence-based guidance as regards the proper design of confirmatory studies can be provided. SOC, however, could be considered as best supportive care at this moment on the condition that stringent stopping rules are in place to avoid unnecessary treatment burden for patient	Acknowledged. See "Summary of Outcome" above.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		both in the SOC and the DAA+SOC arm. ~~cannot be viewed as a proper reference regimen.~~ It is foreseen that dual or triple DAA constitute putative treatment options.	
Section 4.5.1 2nd paragraphe Page 10	1	Given the unmet medical need in these patients, therapy with combinations of unlicensed DAAs should be acceptable. Proposed changes: "At least dual therapy with DAAs is foreseen as warranted, including combinations of unlicensed DAAs, with appropriate justification."	Acknowledged.
Section 4.5.2 Page 10	1	The wording of this section implies that a deferral of performing studies in paediatric patients would be granted until comprehensive safety and efficacy data have been accumulated in adults. Given the current regulations regarding provision of a Paediatric Investigational Plan even for a deferral, guidance on paediatric study design through expansion of this section should be given top priority. This should include the importance of *avoiding monotherapy* in this population. The initial version of the guidance should indicate that a deferral should be sought for studies with a DAA plus SOC until such time that approval of SOC has been granted in paediatrics.	Given the natural course of HCV infection, treatment is very seldom urgent, and can often be deferred. The revised document suggests that pharmacokinetic studies might be initiated in children prior to licensure.
Definitions and Abbreviations Page 10	1	Can the guideline also define "intolerant" patients to SOC? How long at least should the subject have received SOC to be considered intolerant? Should a non-responder be considered a patient who failed SOC (pegIFN/RBV) and not just a person who failed only IFN/RBV or IFN alone or pegIFN alone?	According to the document, a non-responder is someone that failed SOC (peg-IFN + ribavirin), as this is how SOC is defined in the document.
Definitions and Abbreviations Last entry "SOC"	1	The guideline should clarify whether the two currently available forms of pegylated interferon alpha 2 can be used interchangeably, or that additional studies are necessary to bridge the efficacy and safety for the use of the DAA with each form of pegylated interferon alpha 2. The guidance should clearly state if approval of a DAA in combination with SoC will apply to either form of pegylated interferon. If data is required to demonstrate safety or efficacy with each form of SoC this should	Acknowledged.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
Page 10		be stated and the types of bridging studies required should be described. Proposed changes: SOC: Standard of care: Pegylated interferon alpha 2a or 2b, plus ribavirin Both forms of pegylated interferon alpha can be used interchangeably.	
4.5.2	2	IPTA is in agreement with Section 4.5.2 (Studies in Children) and its statements 1. that hepatitis C is not an issue of the same magnitude in children as it is in adults and 2. that clinical efficacy and safety studies in children should be deferred until after data from trials in adults are available. However, it is important to realize that, if data from adult trials are encouraging, once DAAs are available for the indication of treating hepatitis C in adults, then they will undoubtedly be employed in children as well. Thus, IPTA recommends consideration be given to initiating pharmacokinetic and safety studies in paediatric population after completion of phase III studies in adults, but prior to final approval of a drug with indications for adult usage.	This has been acknowledged and included in the revised version of the document.
Page 5, section 4.1., line 2	3	Include strong recommendation regarding adherence to updated and generally acknowledged clinical treatment guidelines. Proposed changes: With respect to diagnostic criteria, indications for therapy and clinical follow-up, adherence to updated and generally acknowledged clinical treatment guidelines is **strongly** recommended.	Acknowledged.
Page 5, section 4.3.1., line 9	3	Drug-drug interaction studies, in particular in HIV/HCV coinfected patients, should be performed before initial approval is granted and as soon as data on efficacy and safety of the drug are available from monoinfected patients. Proposed changes:	The need for interaction studies with antiretrovirals is clearly stated in the document.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		Thus, it is anticipated that later studies (which should precede an initial approval for use in the above mentioned patients) should evaluate use in:	
Page 6, section 4.2.3, line 2	3	Definition of RVR and EVR should be stated. Proposed changes: Rapid viral response (RVR) defined as undetectable HCV RNA 4 weeks of therapy and early viral response (EVR) defined as undetectable HCV RNA 12 weeks of therapy …	All abbreviations are defined at the end of the document
Page 6, section 4.2.3	3	In secondary endpoints inclusion of clinical endpoints should be also considered for certain populations and in patients with decompensated liver disease. Proposed changes: In secondary endpoints include: - demonstrated improvement in mean MELD score in subjects with decompensated cirrhosis. -Improvement of life expectancy in transplant recipients	Though we recognise that endpoints other than virological are of interest, this is somewhat outside the scope of the document.
Page 6, section 4.3.1., line 4	3	Drug-drug interaction studies, in particular in HIV/HCV coinfected patients, should be performed before initial approval is granted and as soon as data on efficacy and safety of the drug are available from monoinfected patients. Proposed changes: The prioritisation of clinical drug-drug interaction studies (performed pre- approval) should take into account the possible mechanisms of interactions and the clinical need for co-administration of specific agents with the DAA.	The need for interaction studies with antiretrovirals is clearly stated in the document.
Executive Summary - Fourth paragraph	4	Although it is appropriate for studies to include 'follow-up of patients after completion of therapy to determine relapse rates and to perform an appropriate range of virological studies in those who fail to respond from the outset or who relapse', the guidance does not provide advice regarding the duration of post-treatment follow-up that is appropriate at the time of initial registration (in order not to delay access to life saving new	Hopefully this is clarified in the revised section 4.4. SVR (six months following end-of-treatment) is standard.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		therapies) versus data that may reasonably be provided as a Follow Up Measure or a Condition of Approval.	
Section 1.4. Direct acting antivirals and resistance Second Paragraph 2nd sentence	4	It would be helpful to define 'class' more clearly. There appears to be significant cross-resistance among all protease inhibitors, however non-nucleoside polymerase inhibitors as a 'class' are different since there are multiple binding pockets and in many cases a possible lack of cross-resistance or partial cross resistance. Proposed changes: Available data indicate that within some drug classes cross-resistance is likely to occur.	Statement rephrased: "Within-class cross resistance *may* occur". A general definition of "class", however, is not provided.
Section 2. SCOPE, Second Paragraph	4	We suggest that the unmet medical need is such that development and availability of new therapies need not be restricted to SOC naïve or "null-responders to SOC" patients; as stated elsewhere in the guidance, reduction of SOC duration or proof of the value of add-on therapy are equally worthwhile objectives. Although unlikely to have been the intent, the implication of the second sentence in this paragraph is that new therapies would automatically be positioned as 2nd line therapy, behind pegylated interferon and ribavirin. In addition, studies in patients that are difficult to treat should be encouraged, and may be conducted in parallel (with other populations) rather than in series. Proposed changes: Replace the second sentence in this paragraph with 'As appropriate to the mechanism of action and contingent on proof of concept, drug development is encouraged in difficult-to-treat patient populations, such as HCV/HIV co-infected patients and null-responders to SOC.	See "Summary of Outcome" above. Also, the wording of the paragraph in question has been modified in the revised document.'
Section 3.LEGAL BASIS	4	We note that the draft HCV guideline cross-refers to the 'Non-Clinical Development of Fixed Combinations of Medicinal Products'. It would be helpful if the HCV Guideline could comment upon any additional considerations from a non-clinical perspective, and in particular provided confirmation that	The focus of the document is the clinical development, and the extent of preclinical data necessary in these situations have not been considered beyond the principles delineated in the document on non-clinical development of fixed combinations.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		combination toxicology studies would not be required with a new DAA and SOC where there is not overlapping toxicity, but may be necessary for new fixed dose combinations of DAAs.	
Section 4. 1 Subject charac-teristics and selection of patients 2nd paragraph	4	It is agreed that initial studies should be conducted in a clearly defined patient population e.g. HCV genotype 1 etc, however given the potential for new therapies to reduce or substitute for current SOC, especially in SOC relapse patients, and the importance of studying difficult to treat patients, further clarification could be added to paragraph 2. Proposed changes: Propose an additional sentence be added at the end of the 2nd paragraph: '<u>However, therapeutic approaches that might decrease the length of SOC therapy or treat patients with HCV genotype 2, might be of benefit.</u>'	See "Summary of Outcome" above.
Section 4.1 Subject charac-teristics and selection of patients 3rd paragraph	4	Suggest that the words 'Preliminary assessment' be further clarified to indicate the amount of safety/efficacy data , or any requirement for prior CHMP consultation that would be considered appropriate prior to initiating studies in other patient groups.	Hopefully this is more clear in the revised section 4.1
Section 4.1 Subject charac-teristics and selection of patients 4th paragraph	4	We suggest that the wording that implies that these studies may 'precede or follow an initial approval' be deleted because initiating the study of these additional patient groups need not be constrained or delayed based on the marketing approval status of the compound in treatment naïve patients. Proposed changes: Revise 4th paragraph to 'Thus it is anticipated that later studies may evaluate use in: …'	The text is not changed, since no such constraint is implied.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
Section 4.2.2 Primary endpoint	4	We agree with the primary endpoint 'for confirmatory studies is sustained virological response (SVR) defined as undetectable HCV RNA 6 months after completion of therapy'. However, further clarification and greater flexibility would be helpful regarding the appropriate primary endpoint for exploratory studies. For instance, delays while awaiting Phase 2b trial SVR data prior to progression to Phase 3 trials may delay significantly the availability of life-saving therapies. We suggest that the Guidance allow for RVR/EVR data sets to be acceptable for progression in clinical trials, provided these data are supported by adequate safety and tolerability data.	Guidance does allow for this, which has been clarified in the revision of the document.
Section 4.2.3 Secondary endpoints Second paragraph	4	RVR and EVR are well defined in the draft HCV guideline itself, and thus we do not understand why the time points for assessing these measures should be redefined during the course of exploratory studies. However, we do recognize the value of gathering the virological response rates and kinetics of changes in viral load at more frequent intervals during exploratory studies than in confirmatory studies. Therefore, we propose the final sentence of the second paragraph be amended by replacing RVR and EVR with 'new virological response rates' as shown in the opposite column. Proposed changes: We propose the following amendment: 'Data on virological response rates and the kinetics of changes in viral load should be generated during the exploratory studies in which DAAs are added to SOC to indicate appropriate time points for describing new virological response rates in confirmatory studies.	This paragraph has been reworded in accordance with the intent of this suggestion.
Section 4.3.2 Pharmacodynamics 1st paragraph	4	We suggest that the guideline be more specific as to which viruses are of concern here (i.e. is there anything beyond HIV & HBV that was being considered?) Proposed changes: For example the following addition could be made:	Amended.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
		…mechanism of action, activity against viruses other than HCV (i.e. HIV and HBV)…	
Section 4.3.2 Pharmacodynamics 4th paragraph	4	Request further clarification as to whether "in vivo" refers to clinical studies or preclinical animal studies.	The use of in vivo would refer to either, but the clinical situation is of relevance. In the paragraph in question, no experimental recommendation is given. All that is stated is that in vitro data may be significantly different from the in vivo effect (regardless of viral host).
Section 4.3.2 Pharmacodynamics 6th paragraph	4	Suggest additional clarification is added to avoid unnecessary or impractical analyses for non-compliant patients. Proposed changes: Suggest the following amendment: It is expected that detailed virological studies of clinical isolates recovered from those who fail to respond or relapse will be performed, except in documented cases of non-compliance.	We disagree. Compliance may vary from 0-100%, and less than optimal compliance is an important real life phenomenon.
Section 4.3.2 Pharmacodynamics 7th paragraph	4	Genotypic and phenotypic resistance analyses are currently performed in-house by most Sponsors because of lack of commercial available assays and small sample size. However, commercial assays may be used in later studies e.g. Phase 3, if available. Proposed changes: Suggest the following amendment: When presenting in vitro data…The same methods should be used throughout the development where feasible – to enable comparisons between studies.	The principle is that the same methods should be used. In the revised text it is stated that, if different methods are used, appropriate controls should be used to enable comparisons.
Section 4.4 Clinical efficacy studies 3rd Paragraph	4	While we agree that 'Patients included in efficacy studies and achieving SVR should be followed post treatment' and 'any late post-treatment relapses (or re-infection) should be carefully documented', we do not consider that one-year post-treatment data need be available from all clinical efficacy studies at the time of MAA submission. Duration of post-treatment follow up per the usual SOC provision should be sufficient and these data could be provided during CHMP review, or post-approval as a follow up measure, or addressed in a separate long term follow-up registry.	The revised document prescribes a 6 months follow up (to SVR) post treatment, and a further one year for virology studies in patients that fail to reach SVR. In the revised document, section 4.4., it is clarified that full long-term follow up data on non-responders would not have to be available at the time of MAA submission.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
Section 4.4 Clinical efficacy studies 4th Paragraph	4	We agree that follow-up post treatment will provide important long term efficacy data. However, there is a risk for delay in bringing new drugs forward for a chronic disease in need of better therapies. Therefore, we suggest that follow-up data be provided during MAA review or as a follow up measure.	See above.
Section 4.4.1 Exploratory Studies Early exploratory studies of combination therapy First paragraph	4	While we agree that the primary goal of exploratory studies with new agents should be to explore 'regimens with different dosages and durations of the new DAA added to SOC and compared to SOC alone in treatment naive patients', the remainder of Section 4.4.1 appears to address only one possible approach to investigating an add-on regimen such as SOC+DAA. It may be possible to consider A + B + SOC for earlier studies. Further, the CHMP may agree that one long term goal of antiviral drug development is the creation of multi-drug oral antiviral regimens that will not require PEG and RIBA. Therefore, exploration of PEG-free treatment regimens should not only be allowed early in development, but encouraged. Studies in special populations (at greatest need for new therapeutics), including treatment experienced patients and those ineligible for PEG therapy due to advanced liver disease, should be encouraged early in development.	See "Summary of Outcome" above.
Section 4.4.1 Exploratory Studies Early exploratory studies of combination therapy Second paragraph	4	There are a number of disadvantages associated with the proposed study design: point 1 makes the assumption that monotherapy with a DAA will always be inferior to SOC; and point 2 effectively 'raises the bar' for new therapies i.e. it maintains the status quo for SOC and sets the scene for DAAs to be second line therapy.	See "Summary of Outcome" above.

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
Section 4.4.1 Exploratory Studies Early exploratory studies of combination therapy Last paragraph	4	We agree that the primary goal of exploratory studies with new agents should be to explore 'regimens with different dosages and durations of the new DAA …added to SOC and compared to SOC alone'; but, why should this be limited to treatment naïve patients? Doesn't this population, with, by definition, more severely limited treatment options, need new therapeutic interventions? We believe that early exploratory studies of combination therapy, safely conducted, should be allowed in the populations with greatest need. Additionally, the paragraph describing the lead-in-phase of SOC to identify selected patients who would benefit from addition of another agent is a good example of a point where the guidance seems to suggest that the current SOC (PEG/RIBA) will remain the SOC over time. This language seems overly protective of the status quo.	This critique is acknowledged. The discussion of lead-in phase has been deleted in the revised document. For the other points, see "Summary of Outcome" above.
Section 4.4.1 Exploratory Studies Additional exploratory studies	4	We agree that progression into confirmatory studies should not occur until: • Data from the first studies have been reviewed • The dose has been optimised based on safety and efficacy considerations • Proper stopping criteria have been identified However we do not consider that the other issues listed need to be fully explored prior to advancing the development of a single agent in this area of unmet medical need. Some of the questions, while interesting and worthy of further study in an academic or Phase IIIB setting, need not be fully addressed prior to initiating confirmatory studies with a promising new therapy. In particular we suggest that the final bullet point be deleted as it is not immediately relevant to the registration of a new product. The guideline includes a mixture of terminology and guidance on development that is appropriate to monotherapy and add-on therapies (SOC+one DAA) as well as advice that is appropriate to development of new combinations of DAAs. To prevent	This section has been revised, in line with this critique. See also "Summary of Outcome" above.

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		confusion it would be helpful if all guidance associated with development of combinations of multiple DAA experimental agents (and the role of SOC in the use of these combinations) be presented in a separate section.	
Section 4.4.1 Exploratory Studies Exploratory studies in specific patient populations	4	We agree that further study of specific patient populations is appropriate and that patients with advanced fibrosis or cirrhosis, SOC null responders and HCV/HIV co-infected patients should be included in the clinical development program. The timing of these studies should vary, based upon the characteristics of the molecules in question, their resistance thresholds and evolving standards of care for the patient population in question. Some of these studies could be conducted post-approval and results submitted as follow up measures; others should be permitted early in development.	See "Summary of Outcome" above.
Executive Summary	5	While guidelines focused on development of DAAs in combination with pegIFN and ribavirin are appreciated, the field will rapidly evolve towards the use of DAA combinations with the goal of reducing or eliminating the need for pegIFN and perhaps ribavirin. More flexibility for such study designs should be encompassed in future guidelines	See "Summary of Outcome" above.
4.1: Subject characteristics	5	Subjects previously treated with DAAs may need to be considered as an additional subgroup in the category of those needing evaluation after initial approval of a given DAA. For instance, this patient population is described in Section 4.4.1.	This group is mentioned in 4.1 and 4.4.1
4.2.1: HCV genotyping	5	Even though genotyping assays focusing on NS5b sequencing have greatest reliability, the acceptability of currently employed line-probe or hybridization assays or modified versions should be considered if appropriately validated for clinical use.	The paragraph in question reads as following in the revised document, and thus is open for alternative approaches if thoroughly justified: *HCV genotyping:* The method that should be systematically used for genotype determination is direct sequence analysis with either commercial or validated in-house techniques. The applicant should justify that a sufficiently large portion of the NS5B gene is sequenced. Sequence determination should be followed by phylogenetic analyses. An assay based on population sequencing, reverse hybridization or real-time PCR, which has been validated for correct subtyping of at least

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			subtypes 1a and 1b, and ideally also others, should be used. Presently this is accomplished using NS5B sequence + phylogeny, or second-generation line probe assays. The dynamics of this field are acknowledged; *yet, if other methods are used, this should be fully justified*. Techniques based on the analysis of the 5' non coding region are currently not recommended, as a too high incidence of erroneous determination of the subtype has been reported.
4.3.1: Pharmacokinetics	5	With respect to recommendations for evaluating drug interactions, careful selection of interacting drugs (i.e., "probe" compounds) for early in vivo studies will allow for an assessment of the potential for drug-drug interactions and facilitate planning for further studies later in the development process, as needed.	Point taken and included in revised text: "It is foreseen that some new DAAs will have a significant drug interaction potential. Since an important target population is HIV/HCV co-infected patients, an extensive interaction programme is likely to be needed. The prioritisation of clinical drug-drug interaction studies (e.g., performed before or after initial approval) should take into account the possible mechanisms of interactions and the clinical need for co-administration of specific agents with the DAA. A careful selection of interacting drugs (i.e., "probe" compounds) for early *in vivo* studies will allow for an assessment of the potential for drug-drug interactions and facilitate planning for further studies later in the development process, as needed."
4.3.2: Pharmacodynamics	5	Cellular assays that assess full cycle replication including infectivity may be best to employ in the future for preclinical assessment of candidate antiviral agents	Also for other reasons, it is foreseen that these guidelines will be revised within a short frame of time
4.3.2: Pharmacodynamics	5	Clarity is needed on the scope of "detailed virological studies of clinical isolates recovered from those who fail to respond or relapse", as it is not clear why phenotypic analysis of resistance mutations would not be sufficient.	The revised text is, hopefully, more clear on this point: "It is expected that sequencing and phenotyping studies will be performed on clinical isolates recovered from patients treated with the investigational agent, and that have failed to respond or have relapsed"
4.3.2: Pharmacodynamics	5	Although studies of viral fitness are advisable, 'predictive value' of viral fitness analysis conducted in vitro will be limited due to difficulties in assessing the full range of genetic diversity in clinical isolates on fitness related to specific resistance mutations, as well as due to sequence-context effects from	This is recognised in the revised text. "It is acknowledged that the predictive value of viral fitness analyses conducted *in vitro* is uncertain, but it is advised that such studies are undertaken."

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		replicon systems themselves.	
Section 4.4: Clinical Efficacy Studies	5	There are references made in this Section of the guideline to exploratory studies of treatment regimens involving combinations of DAAs, but generally little information or recommendations on the design and objectives such studies.	See "Summary of Outcome" above.
Section 4.4.1: Exploratory studies	5	The efficacy endpoints that are required during exploratory studies involving combinations of DAAs with SOC are not described. It is not clear for instance if endpoints such as early viral response or end-of-treatment response can be accepted in such studies.	This has, hopefully, been clarified under revised section 4.4.2: "The recommended primary endpoint for confirmatory studies is sustained virological response (SVR), defined as undetectable HCV RNA 6 months after completion of therapy, regardless of the scheduled duration of treatment. ETR as well as time to confirmed undetectable viral load should be reported. SVR-12 and SVR-24 should be prospectively assessed in phase II and pivotal studies. In exploratory studies other virological endpoints, such as rapid viral response (RVR: undetectable HCV-RNA at week 4), early viral response (EVR: undetectable HCV-RNA or ≥ 2log10 decline at week 12) and end-of treatment response (ETR: undetectable HCV-RNA at the planned end of treatment), may be used to guide the design of further studies."
section 4.1 para 2	6	***Subject Characteristics and Selection of Subjects*** *"It is anticipated that the initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection, do not have advanced fibrosis and are not co-infected with HIV:"* The subject characteristics and selection of subjects should not be too restrictive in the sequential approach. Current compounds are most active against HCV 1 but future compounds may have high activity against other genotypes and should not be excluded as initial targets.	See "Summary of Outcome" above.
Section 4.1 para 4 bullets 2 & 7	6	***Subject characteristics and selection of subjects*** *"Patients with a documented response (e.g., > 1 log reduction at week 4 or > 2 log reduction at week 12) to a prior course f SOC who did not achieve undetectable HCV-RNA."* and	See "Summary of Outcome" above.These categories have been redefined in the revised document.

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		"Patients with a documented null-response to SOC defined as, e.g., < 1 log reduction of HCV-RNA at week 4-12." These are two separate patient populations both of whom are considered for "later" studies. However, by separating the two populations the patients with equal to 1 log are not included.	
Section 4.2.1 para 1	6	***Determination of HCV RNA levels*** *"HCV RNA levels must be determined with a standardised, CE-marked quantitative assay based on real-time PCR technology with a lower limit of detection of the order of 10-15 IU/ml. The choice of assay should be tailored to genotypes in the study population as some assays have been reported to substantially underestimate HCV RNA levels in certain genotypes. The same assay and the same laboratory should be used for all samples from a single study and, preferably, throughout the clinical development programme."* Multi-national studies may use assays that are not CE-marked but have been validated. We would suggest that assays used be validated against a CE-marked assay.	The assay should be CE-marked, and deviations from this should be thoroughly justified.
Section 4.2.1 para 2	6	***HCV Genotyping*** *"The method that should be systematically used for genotype determination is direct sequence analysis with either commercial or validated in-house techniques. The applicant should justify that a sufficiently large portion of the NS5B gene is sequenced. Sequence determination should be followed by phylogenetic analyses. The simplest and currently most reliable method is to use a distance matrix based on Kimura-2 parameter and neighbour-joining analysis for phylogenetic tree building. Techniques based on the analysis of the 5' non coding region should not be used as a too high incidence of erroneous determination of the subtype has been reported."* For genotyping, the guidance recommended to sequence the NS5B gene instead of 5' non-coding region, the latter being the most widely used method. Is the incidence of erroneous determination high enough to justify a complete switch given the	This is what is currently viewed as the reference method, but the guidelines opens for justified alternative approaches

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		lack of available laboratories to reliably conduct the sequencing? Is it possible to implement a two-step procedure: majority of the samples can be genotyped by 5' non-coding region, followed by NS5B sequencing for the undetermined ones?	
Section 4.2.2 para 1	6	***Primary Endpoint*** *"The recommended primary endpoint for confirmatory studies is sustained virological response (SVR) defined as undetectable HCV RNA 6 months after completion of therapy"* The guidance recommends the primary endpoint as sustained virological response defined as undetectable HCV RNA 6 months after completion of therapy. The 12 week follow-up for SVR has not been validated with the DAAs although it will most likely also be valid. For the present, 6 months is the gold standard.	Agreed.
Section 4.2.4 para 1	6	***Liver History*** *"The main role of a histology assessment prior to enrollment is to exclude patients with advanced fibrosis from participation in early clinical trials and to enable stratification (if warranted) by degree of fibrosis in confirmatory studies. For this purpose a liver biopsy of adequate quality within 12 months prior to study entry may be employed. If cirrhosis has been demonstrated, the time window does not apply. If non-invasive methods are used as an alternative to liver biopsy this should be justified by the applicant."* Conducting a liver biopsy within 12 months prior to study entry will be difficult as the medical community within the EU does not conduct liver biopsies. Many centers in the EU use non-invasive markers to determine fibrosis and a liver biopsy is no longer the standard of care. For patients without cirrhosis, patient should have a previous liver biopsy within 3 years, if more than 18 months fibrosis markers should be obtained. We recommend that the guidance 12-month biopsy be replace with an 18 month or 3 year marker test.	In the revised document, a 24 month limit is suggested.

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Section 4.3.2, para 1	6	***Pharmacodynamics*** *"It is anticipated that an initial application dossier should include an extensive evaluation of the in-vitro activity of a new DAA including exploration of the mechanism of action, activity against viruses other than HCV, and the risk of selection for drug-resistant variants, with assessment of the potential for cross-resistance to occur."* We agree that it is important to test activity against viruses other than HCV, especially for compounds without clear biochemical/structural evidence of defined targets. It would helpful to have a standard panel of viruses that the agency would like to counter screen.	The revised document clarifies that this primarily concerns HBV and HIV.
Section 4.3.2, para 6	6	***Pharmacodynamics*** *"It is expected that detailed virological studies of clinical isolates recovered from those who fail to respond or relapse will be performed."* It would be difficult to carry out traditional virological studies of clinical isolates for HCV, given the lack of a reliable system to culture clinical isolates in vitro. Instead, one may have to use surrogate assays, such as purified NS3 protease (for protease inhibitors) and chimeric NS5B replicons (for polymerase inhibitors) using sequences from clinical isolates.	This paragraph has been rephrased: It is expected that sequencing and phenotyping studies will be performed on clinical isolates recovered from patients treated with the investigational agent, and that have failed to respond or have relapsed.
4.2.2.	7	Definition of SVR should be revised. These new compounds will hopefully abbreviate the time of using SOC drugs – hence many pivotal RCT's will be designed in such a way that various will have different duration of treatment. Proposed changes: Hence, SVR should be defined as 6 months from time when the treatment with the longest duration of anti-HCV therapy has been completed.	Not accepted. While it is agreed that patients ought to be followed for the full duration of the longest treatment arm, including its follow-up period, SVR has by convention been defined as undetectable HCV-RNA 6 months post end-of-treatment, regardless of treatment duration. The likelihood of relapse after 24 weeks post EOT when SOC+DAA are studied at the presently relevant shorter durations (12-48 weeks) is considered very slim.
4.2	7	1. No mention of the place of non invasive tests for the evaluation of fibrosis in the pretreatment workup of HCV + patients. (section 4.2)	This is mentioned. Liver biopsy remains gold standard; however: "If non-invasive methods are used as an alternative to liver biopsy, this should be justified by the applicant."

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome (if applicable)
1.2	7	2. No mention of the recent change in epidemiology of HCV infection among HIV patients: increase of incidence of acute HCV infection. (section 1.2)	Not accepted The treatment of acute HCV infection, as well as present trends in HCV epidemiology, is beyond the scope of the present document
4.4.1 &/or 4.5	7	3. No mention of the outcome in case of treatment during acute of subacute phase (few data available but scientifically sound to mention it). (sections 4.4.1 &/or 4.5)	See above.
4.1	7	"It is anticipated that the initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection, do not have advanced fibrosis and are not co-infected with HIV. Once the DAA has been evaluated in the population above, with a preliminary assessment made of the likely safety and efficacy to be expected, risk of treatment failure and selection of resistant variants, suitable agents should be studied in a larger range of patient populations." Proposed changes Regarding HIV-coinfected patients, I don't think that it is reasonable to wait until the " DAA has been evaluated in the population above"- This will ensure years of delay for HIV-HCV coinfected patients, without valid reasons. Would suggest this wording: "It is anticipated that the initial clinical development programme will focus on patients who are infected with HCV genotype 1, are naïve to any treatment of their HCV infection, do not have advanced fibrosis and are not co-infected with HIV. *Once interaction studies with common anti-HIV are complete enough for guidance on dosages and drug interactions, evaluation of HIV/HCV co-infected patients should begin in parallel."*	Though dose ranging studies should not be performed in co-infected patients, the document strongly encourages early development in co-infected patients. Under section 4.4 it is stated: *"HCV/HIV co-infected patients:* The primary aims of exploratory studies in co-infected patients include safety and confirmation that doses predicted from interaction studies result in proper exposure to the experimental compound and interacting HIV medicinal products. If not otherwise justified, these data should be available at time of drug approval." An important change in the revision of this document after incoming comments, is the recognition that randomising co-infected patients to SOC only, if SOC+DAA has been proven clearly more efficacious in the monoinfected may be problematic. Therefore the strict demand for RCTs in the con-infected population has been moderated as follows: "If a considerably increased effect relative to SOC has been demonstrated in monoinfected patients, randomised controlled trials in the co-infected population may not be mandated. In such a scenario, single-arm studies in co-infected patients may be sufficient for licensure, if these demonstrate convincingly enhanced efficacy compared to historical controls. A further important aim of such studies would be to demonstrate safety in this patient population, as well as the efficacy and safety of putative adjusted doses due to drug interactions."

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Page 8	7	Design of the trials for combination therapy: I am not sure the lead in phase of SOC is appropriate. We would not support such a design in HIV-infection. We might miss the benefit of early combination of the 3 drugs. I would think at least this design should be tested against a more classic design before making a rule. Also, it is going difficult to know how many patients to enroll since a lot of them will not be randomized.	Accepted. See "Summary of Outcome" above.