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GUIDELINE ON THE CLINICAL EVALUATION OF DIRECT ACTING ANTIVIRAL AGENTS INTENDED FOR TREATMENT OF CHRONIC HEPATITIS C

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EXECUTIVE SUMMARY

The aim of this guideline is to provide guidance on the clinical development of compounds for the treatment of Chronic Hepatitis C (CHC). It should be read in conjunction with updated and recognised clinical treatment guidelines. The guideline focuses on direct-acting anti-viral agents (DAAs).

Due to the limited experience, thus far, with other approaches to the clinical development of DAAs, this guideline primarily addresses studies in which new DAAs are added to the available standard-of-care (SOC) treatment for CHC, where SOC refers to the combination of ribavirin and pegylated interferon (PEG-IFN) alpha 2a or 2b. However, the combination of more than one new DAA without concomitant SOC (SOC-sparing regimen) is also discussed.

The main aim of combining a DAA with SOC would be to increase efficacy, and possibly also to increase tolerability through a shorter treatment duration. A SOC-sparing regimen, most likely including more than one DAA, would, apart from putative benefits in terms of efficacy and safety, have the important advantage of allowing therapy when SOC is contraindicated or not tolerated. A special concern with respect to drug development for the treatment of CHC is the high mutation rate of hepatitis C virus (HCV), with the attendant risk of selection of drug-resistant variants leading to treatment failure. Taking this risk into account , and in order to evaluate the new DAA in a stepwise fashion, the guideline proposes that initial studies should enrol subjects with HCV genotype 1 infection that are naïve to SOC or have relapsed after achieving an end of treatment response (ETR), that do not have advanced fibrosis, and that do not have HIV co-infection. Once sufficient data are available on the effect of adding on a DAA in this group of patients, exploratory studies could be started in patients with previous non-response to SOC. Moreover, it is envisaged that the clinical development of DAAs will also encompass patient populations with special medical need, particularly transplant patients and HIV co-infected patients.

Advice is provided regarding the follow-up of patients after completion of therapy in order to determine relapse rates, and concerning the appropriate range of virological studies in patients who fail to respond from the outset, or who relapse. Such information is important in order to evaluate the potential impact of drug resistance on future therapeutic interventions.

Due to the dynamics of the field and the restricted scope of this guideline, revisions and amendments are foreseen to be necessary within a short frame of time.

1. INTRODUCTION

1.1. Epidemiology

Hepatitis C virus (HCV) is the most common infectious cause of chronic liver disease in Europe, and is globally second only to Hepatitis B virus. Worldwide, approximately 3% of the population is estimated to be infected, corresponding to around 200 million people at risk of developing serious liver related morbidity. In Europe, where the vast majority of CHC cases are reported among patients with past blood transfusion (before 1991) or with a history of intravenous drug use, the prevalence varies by geographic region, from about 0.5% in the Northern countries to 2% and higher in the Mediterranean countries and in Eastern Europe. HCV of genotype (GT) 1 is the predominant genotype globally as well as in most European regions. In Europe and in the US, approximately 30% of HIV-infected patients are co-infected with HCV, ranging up to 50% in some regions.

1.2. Natural course of HCV infection

Around 60-80% of those infected with HCV become chronic carriers. Studies in patients who acquired CHC by blood transfusion prior to the availability of HCV-screening indicate that, after 20 years of infection, around 20–30% will have progressed to cirrhosis, 5–10% will have end stage liver disease and 4–8% will have died of liver-related causes. In patients with cirrhosis, the 5-year risk of hepatic decompensation is approximately 15-20% and the risk of hepatocellular carcinoma 10%.

The prognosis of HIV infection has greatly improved due to modern antiretroviral therapy. Among those co-infected with HIV and HCV, however, liver failure due to CHC is now a leading cause of mortality. In co-infected patients, the progression of liver disease seems to be more rapid, at least in individuals with low CD4+ T-cell counts. According to biopsy studies, the proportion of patients with

cirrhosis is around twice as high in HIV/HCV co-infected middle-aged patients, compared to individuals of a similar age who have only HCV infection.

1.3. Treatment of HCV using pegylated interferon and ribavirin

The aim of currently available therapies is to achieve sustained viral response (SVR), defined as the absence of detectable virus at 6 months after end of therapy. In practice, this means cure of the viral disease, even though the risk of cirrhosis-related complications, including hepatocellular carcinoma, still remains in patients that have developed significant liver injury due to the infection.

With current SOC consisting of ribavirin and pegylated interferon (PEG-IFN) 2a or 2b, around 70-85% of patients infected with HCV GT 2 and 3 achieve SVR after a 6-month treatment course. In contrast, below 50% of the patients infected with HCV GT 1 and 4 reach SVR despite treatment for one year. Even lower SVR rates are reported in some sub-populations such as those with HCV/HIV co-infection. Therefore there is a particular need for development of new treatments for these groups. Tolerability and safety are further concerns with current SOC, and a shortened duration of SOC, or effective SOC-sparing regimens, are worthwhile objectives for drug development in the treatment of CHC.

1.4. Direct acting antivirals and resistance

A large number of direct acting antivirals (DAAs) from different pharmacological classes (nucleos(t)ide analogues, various families of non-nucleoside polymerase inhibitors and protease inhibitors) are currently under development for the treatment of CHC.

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 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. The impact of resistance on subsequent treatment attempts is unknown. It is not known for 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.

2. SCOPE

Guidance is provided on the design of exploratory and confirmatory clinical studies considered to be of relevance for the evaluation of direct-acting anti-HCV compounds.

This guideline acknowledges the constraints on clinical drug development imposed by the high rate of mutation of HCV. It emphasises the importance of considering the risk of selecting for resistant variants when designing clinical studies. This includes the possible addition of more than one DAA to SOC. Once sufficiently convincing data on the efficacy, safety and optimal dose are available from treatment naïve subjects/relapsers, drug development is encouraged in difficult-to-treat patient populations such as HCV/HIV co-infected patients and previous non-responders to SOC.

The scope of this guideline reflects the limited experience with DAA in the field of drug development for the treatment of CHC. Sponsors planning modes of drug development that are not covered in this guideline, are advised to consult with EU Regulators early in the clinical development programme, and at least prior to initiating confirmatory studies.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and parts I and II of the Annex I to Directive 2001/83 as amended.

Pertinent elements outlined in current and future EU and ICH guidelines, should also be taken into account, especially those covered by:

- Dose-Response Information to Support Drug Registration (ICH E4);
- Statistical Principles for Clinical Trials (ICH E9);
- Choice of Control Group in Clinical Trials (ICH E10);
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A);
- Pharmacokinetic Studies in man (3CC3A);
- "Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function (CHMP/EWP/225/02);
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95);
- Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02);
- Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06);
- Note for Guidance on the clinical development of medicinal products for the treatment of HIV infection (CHMP/EWP/633/02);
- Clinical Evaluation of Medicinal Products intended for Treatment of Hepatitis B (CPMP/EWP/6172/03);
- Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).

4. MAIN GUIDELINE TEXT

4.1. Subject characteristics and selection of subjects

With respect to diagnostic criteria, indications for therapy and clinical follow-up, adherence to up-dated and generally acknowledged clinical treatment guidelines is strongly recommended.

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.

Thus, it is anticipated that later studies (which may precede or follow an initial approval for use in the abovementioned patients) should evaluate use in:

- Patients with advanced fibrosis or cirrhosis who are candidates for SOC.
- Patients with a documented non-response (failure to reach >1 $\log_{10}$ reduction at week 4, ≥2 $\log_{10}$ reduction at week 12, or who did not achieve undetectable HCV-RNA) to a prior course of SOC.
- Patients infected with virus of GT 2/3 or 4.
- HIV/HCV co-infected patients.
- Liver transplant patients.
- Patients who did not achieve SVR with therapy that included an approved DAA.

4.2. Methods to assess efficacy

4.2.1. HCV genotyping and viral load

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 in the order of 10-15 IU/ml. 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.

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 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.

4.2.2. Endpoints

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. In the primary efficacy 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 ≥ 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 and 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, in order to find appropriate time points for describing viral kinetics, as well as possible DAA-specific stopping rules in confirmatory studies.

Biochemical response: Normalised ALT at end of therapy and at 6 months after end of therapy.

4.2.3. Liver histology

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, taken no more than 24 months prior to study entry, may be employed. If cirrhosis has been demonstrated, this time window does not apply, and there is no need for a new biopsy prior to study entry. If non-invasive methods are used as an alternative to liver biopsy, this should be justified by the applicant.

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 efficacy claims are made or hepatic safety issues necessitates it.

4.3. Clinical pharmacology studies

4.3.1. Pharmacokinetics

The general principles laid down in current CHMP guidelines on pharmacokinetics are applicable.

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.

In designing the programme, priority should be given to studies of co-administration with other drugs used in the management of HCV, HIV, liver transplantation, depression and substance abuse. Within these areas, essential drugs (for which reasonable therapeutic alternatives are lacking) that have a foreseen potential for interaction, should be prioritised for study. The aim should be to provide sufficient data to support recommendations for adjustment of dose and/or dose intervals, if necessary, for the experimental compound and the interacting essential drug(s).

For DAAs that are nucleoside analogues, the potential for drug interactions 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 a relevant interaction cannot be excluded *in vitro*, clinical studies should include an appropriate design to allow for an assessment of the clinical significance of the putative interaction.

This guidance document foresees that DAAs will be used as add-on to SOC, which includes the nucleoside analogue ribavirin. The very long elimination half-life and the toxicity of ribavirin have to be considered in the design of interaction studies.

4.3.2. Pharmacodynamics

It is anticipated that an initial application dossier should contain an extensive evaluation of the *in vitro* activity of a new DAA, an exploration of its mechanism of action, its activity against viruses other than HCV (HIV, HBV), the risk of selection for drug-resistant variants, and the potential for cross-resistance with other agents.

Whenever there is a suspicion, based on theoretical considerations, that a certain combination of compounds could be antagonistic, combination studies *in vitro* should be performed. Ribavirin presents a specific problem from this perspective, since the *in vivo* activity of this drug cannot be fully accounted for by its *in vitro* antiviral effects.

Cell-free functional assays (such as polymerase or protease assays) and the HCV-replicon system are used in the study of anti-HCV activity *in vitro*, including the assessment of phenotypic resistance. Modifications of these systems are used by different developers and academic centres, and there are presently no standardised methodologies for these investigations.

It is expected that applicants will provide a full justification for the range of studies performed, and the methods used, with adequate use of controls where possible. For genotype 1 virus, subtype should also be determined (1a vs. 1b), and putative differences in antiviral response according to subtype should be explored.

Although quite useful during drug development, the results obtained *in vitro* (e.g., fold-change in inhibitory concentrations associated with specific mutations) may show poor correlation to in-vivo efficacy.

“Genotypic resistance” should be analysed by means of direct sequence analyses (population sequencing) or clonal analysis (20-30 clones to be tested). Different prototype HCV-strains are used, and at present gold standard strains cannot be defined.

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.

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. It is

foreseen that a higher degree of standardisation will be possible, in line with upcoming discussions and decisions of international meetings regarding HCV resistance. Therefore the sponsor should closely follow the scientific discussion on these matters.

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.

4.4. Clinical efficacy studies

Studies are expected to be randomised and, whenever possible, double-blinded.

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).

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 of a market authorisation application submission, but could be reported subsequently.

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.

4.4.1. Exploratory studies

Dose finding monotherapy studies

These studies can provide a preliminary identification of appropriate dose regimens. An adequate range of doses should be studied, based on (protein binding-adjusted) IC50 values *in vitro* and on PK data.

IC50 values of both wildtype virus and viruses with mutations (single and in combination) derived during drug pressure *in vitro* should be taken into account, so that selected doses for combination studies will be likely to provide sufficient exposure for activity also against variants with reduced sensitivity, if this is feasible.

Currently, 5-(7) days duration of monotherapy is considered acceptable. If there is a strong scientific rationale to prolong this period of monotherapy, and if the compound is foreseen to have a high genetic barrier to resistance, 10-14 days might be acceptable. In this context (i.e., when no *in vivo* data are available), a high genetic barrier may be defined as the need for more than 2 mutations to produce IC50 values higher than the expected free drug exposure *in vivo*.

It is expected that these studies would initially be performed in patients who are naïve to HCV therapy or that have relapsed after ETR with SOC treatment, who do not have advanced fibrosis and who are not co-infected with HIV Depending on the degree of cross resistance, as evident from *in vitro* studies, it could, in the future, also be appropriate to study patients with viruses that show reduced susceptibility to an approved DAA of the same class as the experimental DAA.

Early exploratory studies of combination therapy (new Agent + SOC)

In these studies, it is anticipated that regimens with different dosages and treatment durations of the new DAA will be added to SOC, and compared to SOC alone in treatment naive patients/relapsers without severe fibrosis. If both treatment-naïve patients and relapsers are included in the same study, they should be stratified by treatment-group at randomisation. It is advised that neither group (naive patients or relapsers) constitute less than 40% of the study population, if this includes both categories. Stringent stopping criteria should be applied, and sampling should be sufficiently frequent to adequately describe viral kinetics, pharmacokinetics and the possible evolution of resistance.

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 review of the data from the first studies, with knowledge of the properties of the DAA in question and other DAA under development or licensed. Issues to be addressed include:

- Is there a need for further exploratory studies in order to optimise the dose and/or duration of DAA treatment?
- Have proper stopping criteria been identified for the experimental regimen?
- Is the use of more than one DAA as add-on likely to be needed to optimise benefit – risk, taking resistance development into account?

European regulatory discussion is advisable prior to the initiation of confirmatory studies.

Exploratory studies in specific patient populations

In order further to document the safety and efficacy of the experimental compound, additional exploratory studies should be considered in the following groups of patients:

- *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.
- *SOC non-responders:* Currently available data indicate that a single DAA as add-on to SOC still results in high numbers of patients not being cured. These patients may harbour virus resistant to the DAA, likely to be cross-resistant to other agents in its class. Exploratory studies are therefore needed in order to inform the design of confirmatory studies to be undertaken in this group of patients. Such studies can be started once preliminary data on efficacy (including e.g. RVR, EVR and/or ETR rates in phase 2b trials) and safety are available, and an appropriate dose has been selected, by way of dose-ranging studies in combination with SOC, performed in treatment naïve patients/relapsers (section above). Though the characterisation of optimal dose in treatment naive patients is expected prior to starting studies in more vulnerable patient groups, it is recognised that a higher dose may turn out to be appropriate in difficult-to-treat populations.
- *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
- *Patients that have failed therapy with the experimental agent:* Efforts should be undertaken by the sponsor to study the consequences of treatment failure and resistance development for patients treated with the experimental DAA. Patients who have failed therapy with an experimental agent (A), could, if feasible, be included in a subsequent study including a DAA of different class (B).
- *Patients with genotype 2/3*: As SVR rates to SOC are very high in patients with GT 2/3 infection, it is anticipated that initial studies would mainly target previous non-responders/relapsers to SOC, or aim at investigating a shorter treatment course.
- *Patients with genotype 4*: Response rates with SOC in this genotype are of the same magnitude as those seen in patients with genotype 1. Therefore, though rare in many parts of the world, the unmet needs for this group are similar to those in patients with genotype 1. Since efficacy against genotype 4 cannot a priori be assumed for a DAA effective against genotype 1, patients with genotype 4 should be studied in separate trials.

Exploratory studies of SOC-sparing regimens

SOC carries substantial side effects, and is contraindicated in some patients. Furthermore, a number of patients show non-response to this treatment. Hence, there is a need for SOC-sparing regimens, both for patients with GT 1 and GT 2/3 infection. Such studies are encouraged, though the optimal design is presently unclear.

Until now, the results of ribavirin-sparing regimens have been disappointing. At present, PEG-IFN sparing regimens have scarcely been studied. It may be that for a PEG-IFN sparing regimen to have satisfying efficacy, the use of more than one DAA in combination would be required, given the very low intrinsic antiviral activity of ribavirin. In the following, however, the term "SOC-sparing regimen" refers to drug combinations including neither PEG-IFN nor ribavirin.

It is anticipated that a SOC sparing regimen will require DAAs in combination. The main concern particular for such a regimen is that treatment failure will be accompanied by multiple class resistance. For this reason, an appropriate dose for each antiviral compound per se should be characterized prior to the SOC-saving approach. It is suggested that dose selection for compounds in the SOC-saving study should not be done before early safety and reassuring response (RVR, EVR) data are available from dose-ranging studies with SOC for each of the respective agents. Furthermore, interaction data for the selected doses should be available, as well as toxicology studies with the combination for at least the same duration as that planned for the exploratory study.

It is recommended that the initial DAA combination study be performed in treatment naïve patients and/or relapsers without advanced fibrosis. The design should attempt to minimize the risk for resistance development. Presently available experience does not allow for more detailed recommendations on the design of trials of SOC-sparing regimens. Outstanding issues include, e.g., endpoints in short-term exploratory trials, appropriate stopping criteria, as well as appropriate control arms when SOC-sparing regimens are studied in patients where randomization to SOC is not considered an option. European regulatory discussion is advisable prior to initiating studies of SOC-sparing regimens with DAAs in combination.

4.4.2. Confirmatory studies

The objective of add-on trials would be to demonstrate enhanced efficacy and/or an overall reduction in the duration of therapy in relation to SOC. A shorter duration of treatment might increase the tolerability of a regimen; ultimately, however, the enhanced efficacy of a new regimen would be weighed in the light of its safety profile. A shorter duration of a given regimen might not be considered appropriate if this results in a net loss of efficacy, taking the risk of failure-associated drug resistance into account.

In most cases, it is foreseen that first confirmatory studies will be initiated in HCV genotype 1-infected patients that are treatment naïve patients and/or that have relapsed after ETR with SOC, The range of patients to be included in further confirmatory studies must be decided on a case by case basis depending on accumulated data with the new DAA. Target populations may include different groups, as detailed in section 4.1 of this guideline.

Prior to the initiation of confirmatory trials, preliminary stopping rules for insufficient viral response for DAA containing study arm(s) should have been identified.

The various scenarios envisaged for the design of confirmatory studies include:

- A comparison with SOC in order to demonstrate superiority of the DAA+SOC regimen over the SOC regimen. If both forms of PEG-IFN (2a and 2b) are used within a study, stratification is recommended.

  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.

- If exploratory studies indicate a need for combination therapy including more than one DAA (licensed or under development), the most informative design is SOC vs. SOC+A vs. SOC+B

vs. SOC+AB. However, data from exploratory studies may indicate that one or both of SOC+A or SOC+B would be sub-optimal; if so, these regimens should not be included in the trial.

In HIV/HCV co-infected patients, the activity of SOC is currently poorly documented with respect to effect size. 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.

Patients with non-response to SOC constitute a group for whom no evidence-based guidance can currently be provided, as regards the proper design of confirmatory studies. SOC, however, could be considered as an appropriate reference treatment at this moment, on the condition that stringent stopping rules are in place to avoid unnecessary treatment burden for patients both in the SOC and the DAA+SOC arm. For patients in whom previous SOC has shown virtually no antiviral activity, however, alternative study designs excluding SOC should be considered. In order to avoid functional monotherapy, the use of more than one DAA may be warranted in these population, including combinations of unlicensed DAAs (see section 4.4.1).

Concomitant therapy

Concomitant therapy and supportive measures should be detailed in the study report. In case clinical data suggests that specific supportive measures are needed, e.g. use of erythropoeisis stimulating agents, this should be justified and detailed in the study protocol of confirmatory studies to ensure consistent use across study sites.

4.5. Studies in special populations

4.5.1. Transplant patients

If a favourable benefit – risk for a DAA containing regimen has been demonstrated in non-transplant patients with relevant genotype and degree of liver injury, single arm studies in transplant patients, designed to provide pharmacokinetics, safety and viral response data, including SVR, may be sufficient to support an indication, provided that the anti-viral activity is of similar magnitude as that seen in non-transplant patients.

Patients with decompensated liver disease in whom SOC cannot be used, constitute an important target population for DAAs, whether in a pre-transplantation phase or not. At least dual therapy with DAAs is foreseen to be warranted.

4.5.2. Studies in children

Due to the rather low prevalence of CHC in children and, more importantly, the slow progression rate of liver injury, it is currently not generally anticipated that clinical efficacy and safety studies in children will be performed until comprehensive safety and efficacy data have been accumulated in adults. However, as off-label usage in the paediatric populations may be anticipated if data from adult trials are encouraging, consideration should be given to initiating pharmacokinetic and safety studies in paediatric populations after completion of phase III studies in adults. It is foreseen that this section will be expanded in forthcoming updates of this guideline.

4.6. Clinical safety evaluation

Specific safety concerns related to CHC that are of relevance for the development of new DAAs include impaired liver function at baseline, the known toxicity of current SOC, the potential for SOC toxicity to be enhanced by the DAA, PK interactions and development of drug resistance. In addition, the association between CHC and fatty liver and insulin resistance is of importance, with implications for safety monitoring practises during studies

It is expected that mechanism-related toxicities (such as mitochondrial toxicity for nucleoside analogues) will have been well characterised in non-clinical and clinical studies. Any signals that emerge from the non-clinical studies should be followed in the clinical development programme.

DEFINITIONS AND ABBREVIATIONS

CHC:	chronic hepatitis C
DAA:	direct acting antiviral agent
EVR:	Early virological response: undetectable HCV-RNA at week 12 of SOC or at least $2\log_{10}$ reduction from baseline HCV RNA.
ETR:	End of treatment response: undetectable HCV-RNA at time point of planned treatment cessation.
GT:	genotype
HCV:	hepatitis C virus
Non-responders:	Patients that have not reached undetectable HCV-RNA levels during SOC, including patients with $< 2\ \log_{10}$ reduction of HCV-RNA at week 12.
PEG-IFN	Pegylated interferon
Relapsers:	Patients that have achieved ETR on SOC, but subsequently relapsed, failing to achieve SVR
RVR:	Rapid virological response: undetectable HCV-RNA at week 4 of SOC.
SOC:	Standard of care: Pegylated interferon alpha 2a or 2b, plus ribavirin. Either form of pegylated interferon alpha may be used as SOC.
SVR:	Sustained virological response: undetectable HCV-RNA 24 weeks after treatment cessation.
Treatment naïve patients:	Patients never exposed to any HCV therapy, including IFN monotherapy.