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DRAFT

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

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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) and 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 clinical development of DAAs, this guideline is focussed 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.

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 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. 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 of adding on a DAA is well described in these types of patients later studies could evaluate efficacy in specific groups such as those with other genotypes, HIV co-infected patients and null responders to SOC.

Advice is provided regarding 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. Such information is important for the assessment of the potential significance of resistance for the likely success of any 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 time frame.

1. INTRODUCTION

1.1. Epidemiology

Hepatitis C virus (HCV) infection is the most common infection causing chronic liver disease in Europe, and globally second only to Hepatitis B virus infection. Worldwide around 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 CHC in the vast majority of cases is reported among patients with past blood transfusion (before 1991) and ongoing or previous intravenous drug abuse, the prevalence varies by geographic region from about 0.5% in Northern countries to 2% and higher in Mediterranean countries and in Eastern Europe. HCV of genotype 1 (GT 1) is the predominant genotype globally and in most European regions. In Europe and the US around 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 infected individuals become chronic carriers. Studies in patients who acquired CHC by blood transfusion before HCV-screening was available, indicate that after about 20 years, around 20–30% of them had progressed to cirrhosis, 5–10% had end stage liver disease and 4–8% had died of liver-related causes. In patients with cirrhosis, the 5-year risk of hepatic decompensation is around 15-20% and that of hepatocellular carcinoma around 10%.

The prognosis of HIV infection is now much improved due to modern antiretroviral therapy. Among those co-infected with HIV and HCV, however, liver failure due to CHC has become a leading cause of mortality. In co-infected patients, progression of liver disease also seems to be faster, at least for 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 with individuals of 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 absence of recurrence of detectable virus at 6 months after end of therapy. In practice this means cure of the viral disease, even though there is a remaining risk of cirrhosis-related complications, including hepatocellular carcinoma.

With current standard-of-care (SOC), i.e., pegylated interferon-alpha 2a or 2b (PEG-IFN) and ribavirin, around 70-85% of patients infected with HCV genotype (GT) 2 and 3 achieve SVR after a 6-month treatment course. In contrast, only half of 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 that can improve on these SVR rates. Tolerability and safety is also a concern with current SOC and a shortened duration of SOC is a worthwhile objective 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 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 is likely to 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 SOC for optimal treatment of CHC.

The impact of resistance on subsequent treatment attempts is unknown. It is also not known how long resistant variants may persist after stopping therapy in cases of virological failure. However, resistant variants, and not wild type HCV were 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.

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 as add-on to SOC in different target populations.

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 taking the risk of selecting for resistant variants into account 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 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 before commencement of 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 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 recommended.

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.

Thus, it is anticipated that later studies (which may precede or follow an initial approval for use in the above mentioned patients) 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.
- 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.
- 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 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.

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.

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.

4.2.2. 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.

4.2.3. Secondary endpoints

End-of-treatment response (ETR) and time to confirmed undetectable viral load should be reported.

Rapid viral response (RVR) 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.

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

4.2.4. 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 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.

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, or hepatic safety issues make this necessary.

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 an extensive drug interaction potential. As 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 pre- or post-initial approval) should take into account the possible mechanisms of interactions and the clinical need for co-administration of specific agents with the DAA.

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 without reasonable therapeutic alternatives and a potential for interaction should be prioritised for study and the aim should be to provide sufficient data to support recommendations for adjustment of dose and/or dose intervals as necessary for the experimental compound and for essential drugs.

For DAAs that are nucleoside analogues, the potential for interaction to occur at the level of intracellular activation by phosphorylation should be explored. 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*, then *in vivo* studies should be undertaken with an appropriate range of compounds measuring possible effects on activated compounds.

This guidance document foresees that DAAs are used as add-on to SOC which includes the nucleoside analogue ribavirin. The very long T1/2 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 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.

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. The results need to be cautiously interpreted, however, and the full spectrum of mechanisms of activity for anti-HCV activity *in vivo* should be known.

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 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. 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" is analysed by means of direct sequence analyses (population sequencing). Different prototype HCV-strains are used and at present gold standard strains cannot be defined.

It is expected that detailed virological studies of clinical isolates recovered from those who fail to respond or relapse will be performed.

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.

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. The sponsor should therefore closely follow the scientific discussion on these matters.

It is acknowledged that the predictive value of viral fitness analyses conducted *in vitro* is poorly defined, but it is advised that such studies are undertaken.

4.4. Clinical efficacy studies

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

Adherence to therapy is of vital importance for treatment outcome and major efforts to encourage and document compliance should be undertaken.

Patients included in efficacy studies and achieving SVR should be followed for at least one year post treatment. Any late post-treatment relapses (or re-infection) should be carefully documented.

Patients exposed to DAA(s) and not achieving SVR should be monitored with frequent sampling of HCV-RNA (e.g., every three months) and assessment of genotypic and phenotypic resistance for at least one year. Reversion to wild type virus and long-term persistence of drug-resistant variants should be documented.

Patients exposed to SOC only, and not achieving SVR should be managed according to clinical practise.

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-adjusted) IC50 values *in vitro* and from PK data.

IC50 values of both wildtype virus and from virus with mutations (single and in combination) derived during drug pressure *in vitro* should be taken into account so that selected doses for combination studies provide sufficient exposure to be likely active also for variants with reduced sensitivity, if at all 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 > 2 likely key mutations to achieve IC50 values higher than expected free drug exposure *in vivo*.

It is expected that these studies initially would be performed in patients naïve to SOC, without co-infection and without advanced fibrosis. Depending on degree of cross resistance, as evident from *in vitro* studies, it could 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

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.

Consideration could be given to employing a lead-in-phase of SOC before randomisation to identify those patients that might derive most benefit from addition of another agent to SOC. In this way patients with detectable HCV-RNA, but with e.g., ≥ 1 log HCV-RNA decrease after 4 weeks of SOC may be randomised to remain on SOC or to receive DAA + SOC. At the same time the lead-in phase could serve to avoid randomisation of the following groups of patients:

1. Null-responders to SOC (e.g., < 1 log decrease at week 4). If randomised, these patients might in practise receive functional monotherapy with the DAA, with a high risk of treatment failure and selection of resistant variants.
2. Rapid virological responders (HCV non-detectable at week 4). These patients have a high chance of SVR using SOC. Excluding these patients in early trials enriches the population for patients likely to benefit from add-on therapy to SOC.

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.

It is also acknowledged that reduced viral load at initiation of DAA add-on might reduce the possibility to detect dose/exposure related differences in viral kinetics while enrichment increases the possibility.

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 and 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?
- Is shortened duration of SOC meaningful to study in identifiable groups of patients, e.g., rapid virological responders to lead in SOC, or SOC + DAA?
- Have proper stopping criteria been identified for the experimental regimen?
- Is a lead in phase with SOC likely to be overall beneficial?

- Is the use of more than one DAA as add-on likely to be needed to optimise benefit – risk taking resistance development into account?
- Is an exploratory trial warranted in patients with documented responsiveness to prior SOC, but without SVR despite proper adherence with respect to dosages and duration?

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 are likely to be needed and should be considered in the following groups of patient:

- *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 null-responders:* Currently available data indicate that a single DAA as add-on to SOC results in poor SVR and the benefit of SOC as part of combination regimens is considered unproven. Exploratory studies are therefore needed in order to inform the design of confirmatory studies to be undertaken in this group of patients.
- *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 who 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), should, if feasible, be included in a subsequent study including a DAA of different class (B). Alternative designs are foreseeable, but include a randomised trial comparing A + B + SOC with B + SOC. Whether confirmatory studies are warranted should be decided on a case-by-case basis.

4.4.2. Confirmatory studies

The objectives of add-on trials would be to demonstrate enhanced efficacy and/or an overall reduction in the duration of therapy that might confer improved tolerance of a treatment regimen compared to SOC. The final risk-benefit analysis would have to take into account the degree of enhancement of efficacy in the light of the safety profile of the regimen and the risk of selecting for drug-resistant variants, with implications for the possible success of further therapeutic regimens.

In most cases, it is foreseen that first confirmatory studies are conducted in treatment naïve patients infected with HCV genotype 1. 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 encompass patient populations 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 demonstrating superiority of the DAA+SOC regimen over the SOC regimen.
- When at least one DAA has been approved, consideration will need to be given to comparison of the new DAA with an approved DAA, each added to SOC, in a study intended to demonstrate at least non-inferiority of the experimental agent.
- 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 and so reduce the number of treatment arms.

In HIV/HCV co-infected patients, the activity of SOC, including use of weight-based ribavirin dosing, is currently poorly documented with respect to effect size. Therefore randomised SOC comparative trials are considered necessary in order to document the add-on activity of DAA.

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, cannot be viewed as a proper reference regimen. It is foreseen that dual or triple DAA constitute putative treatment options.

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 patients relevant for this target population from a virological perspective, single arm studies designed to provide pharmacokinetics, safety and viral response data, including SVR may be sufficient to support a claim provided that the anti-viral activity is of similar magnitude to that in non-transplant patients.

Patients with decompensated liver disease and where 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 as 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 anticipated that clinical efficacy and safety studies in children will be performed until comprehensive safety and efficacy data have been accumulated 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 and of relevance for the development of new DAAs relate to impaired liver function at baseline, the known toxicity of current SOC and the potential for this 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 and the impact on glucose transport for protease inhibitors) 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 agents
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
RVR:	Rapid virological response: undetectable HCV-RNA at week 4 of SOC.
SOC:	Standard of care: Pegylated interferon alpha 2a or 2b, plusribavirin.

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.
Null-responders to SOC:	Patients with, for example, <1 $\log_{10}$ reduction of HCV-RNA at week 4 (or later) of SOC.