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Guideline on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis

Draft

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Guideline on the clinical evaluation of direct acting antivirals for the treatment of chronic hepatitis

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Executive summary

This draft guideline replaces the CHMP's *Guideline on the clinical evaluation of direct acting antiviral agents intended for treatment of chronic hepatitis C (EMEA/CHMP/EWP/30039/2008)*.

There have been considerable developments in the field of hepatitis C virus (HCV) therapy since the adoption of *EMEA/CHMP/EWP/30039/2008*. Since 2013 direct acting antivirals (DAAs) have been approved for the treatment of chronic HCV infections within interferon-free combination regimens. Therefore this revision of the prior guidance concerns the development of DAA-only regimens.

The mechanism of action of each new agent should be elucidated. In-vitro activity against different HCV genotypes and subtypes should be characterised. The selection of resistance should be studied *in vitro* for each genotype and the impact of mutations from wild-type on viral susceptibility should be investigated. The viral drug target should be sequenced at baseline in clinical studies; furthermore, genotypic resistance testing should be performed on samples from patients with virological failure and phenotypic resistance testing should be performed if the impact of individual mutational events on susceptibility remains uncharacterised or if no emerging mutations are detected.

The drug-drug interaction profile (DDI) of a new DAA or fixed dose combination (FDC) should be adequately characterised, with focus on co-medications of crucial relevance for the target HIV infection (e.g. including drugs used for the treatment of HIV, for management of liver transplantation and for opiate substitution)

The primary endpoint in clinical trials aiming at viral clearance should be sustained virological response defined as plasma HCV RNA below the lower limit of quantification of the assay (LLOQ) 12 weeks after the planned end of therapy (SVR12). There should be further follow-up to confirm the durability of response for novel drug regimens.

The sponsor should design the clinical development programme (pre- and post-initial licensure) so that the efficacy and safety of the new DAA within one or more combination regimens is documented for the full range of patients in whom beneficial effects and clinical use may be anticipated. The patient and viral characteristics that should determine eligibility for each clinical trial will be selected accordingly. As applicable, these characteristics may include viral genotype, level of liver damage (degree of fibrosis, Child-Pugh classification category and any clinical features of decompensation) and prior DAA regimen treatment history.

In general, randomized controlled trials with an active comparator, considered standard of care for the study population, is the most informative study design for pivotal trials. This should be considered in all cases. In case a DAA is developed as an add-on to an established combination (to increase efficacy or to shorten treatment duration) or as a substitute for a component in such a combination, randomized controlled trials against an active comparator are generally necessary to document efficacy.

If the sponsor is developing a wholly new combination regimen, and phase II data are indicative that very high SVR rates are anticipated, it may not be essential to conduct randomised controlled studies to describe efficacy. Since the spontaneous resolution rate of chronic HCV infection is negligible, and key baseline demographic and disease factors that impact response are well described, it is possible to assess the efficacy of a treatment regimen in uncontrolled trials in which the point estimate and its precision (based on 95% confidence intervals) are documented. To document the safety profile, it is recommended that at least one study in the program be of double-blind design vs. an active control or placebo for the duration of the active treatment period(s), after which those assigned to placebo could switch to open-label active treatment. Such a comparison is considered most valuable if performed in patients with compensated cirrhosis.

For studies in patients with decompensated liver disease, an active standard-of-care comparator arm is recommended.

1. Introduction (background)

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.

2. Scope

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

The scope of this guideline reflects the 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 and relevant guidelines

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.

- Choice of a Non-Inferiority Margin - CPMP/EWP/2158/99
- Pharmacokinetic studies in man – CHMP/EWP/147013/04
- Investigation of drug interactions – CPMP/EWP/560/95
- Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - EMA/CHMP/37646/2009
- Evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function - CPMP/EWP/225/02
- Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH11)
- Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/04

- Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02)
- Non-clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).
- Fixed Combination Medicinal Products CPMP/EWP/240/95
- Note for guidance on studies in support of special populations : Geriatrics (CPMP/ICH/379/95)

4. Pharmacodynamics and pharmacokinetics

4.1. Nonclinical virology studies

The preliminary in-vitro investigation of a new agent for the treatment of hepatitis C virus (HCV) should include the following:

1. A characterization of the mechanism of action of the new agent.
2. A determination of the antiviral activity (IC50) in enzymatic assays (if such are available given the mechanism of action).
3. Determination of EC50/90 in cell based assays representing the different HCV genotypes and subtypes. Primarily, use of the sub-genomic replicon assay is anticipated to determine viral drug susceptibility. The choice of replicon representing each viral genotype/subtype (e.g., full length versus chimeric replicons) should be justified.
4. Determination of the impact of protein binding on EC50/90.
5. Determination of the cytotoxicity and of the therapeutic index of the drug against the same cell line in which antiviral activity is determined.
6. For each viral genotype/subtype, an assessment of the in-vitro selection of resistant variants and characterisation of their phenotypic and genotypic properties. Selection experiments should be performed with a range of drug concentrations in relation to the EC50, to characterize the concentration-dependency of the selection of resistant variants.
7. Characterization of the activity of the new agent against viruses/replicons (which may include clinical isolates or site directed mutants) harbouring a range of resistance associated mutations.
8. Studies of the activity of the new drug against other viruses (e.g. in particular HBV and HIV). If activity that might exert selective pressure against such viruses is detected, this should prompt further investigations to evaluate the potential for this to occur when using the agent to treat HCV in co-infected patients.
9. Studies of the potential for additive/synergistic or antagonistic effects to occur when the new agent is co-administered with other antiviral agents active against HCV. If the new agent is active against other viruses then further studies could be needed as appropriate to its spectrum.
10. If the new agent requires intracellular modification to form the active moiety (e.g. serial phosphorylation as for nucleoside/nucleotide analogues) it is important to assess the possible effects of co-incubation with other drugs that may compete for the activation pathway resulting in modification of antiviral activity.

When presenting in-vitro data, the assays and prototype strains used should be clearly defined and justified. It is preferable that the same methods should be used throughout the development programme to enable comparisons between studies. If methods are changed (e.g. due to modifications of or advances in assays over time) appropriate controls should be included to enable comparisons between studies.

4.2. Clinical virology studies

4.2.1. Viral drug resistance

The viral drug target gene should be sequenced at baseline for viruses obtained from all patients entering clinical trials, unless otherwise justified. Naturally occurring polymorphisms associated with differential drug efficacy should be identified. For example, the impact on drug susceptibility of common polymorphisms should be analysed *in vitro* (see section 4.1) and trials should explore correlations between baseline polymorphisms and viral response on-treatment and post-treatment.

Genotypic studies should be performed on samples obtained from patients at the time of documenting lack of response, whether this is non-response or a loss of initial response. Any genotypic change that has emerged since baseline should preliminarily be assumed to be due to the selective pressure of the drug regimen, and should be explored for correlation with a phenotypic change if this has not previously been established for the specific mutation(s) detected. If no genotypic change since baseline is found then the isolate should undergo phenotypic analysis.

There are several different methods for the analysis of genotypic resistance. Population sequencing is the standard method, but only detects variants with a frequency of about 20% (a figure that varies depending on viral load). Clonal sequencing is more sensitive, and can provide additional information about the linkage of mutations and the frequency of different quasispecies. Next generation sequencing methods may provide a further understanding of on-treatment and post-treatment (in case of failure to reach SVR) quasispecies dynamics. The sponsor should justify the methods used at each stage of investigation, and should closely follow the scientific discussion and development of methods within the field. Within clinical trials, samples should be stored to enable further analysis with different methods, if required.

4.2.2. Determination of HCV genotype and subtype

The reference method for HCV genotype and subtype determination is direct sequencing and phylogenetic analysis with either CE-marked or validated in-house techniques. Unless otherwise justified, the target gene should be sequenced for all patients in the clinical investigation program (see also above). Alternatively, one may use a CE-marked second generation line probe assay. Outside of genotype 1, however, this is not sufficient for the determination of subtype; therefore, direct sequencing is necessary. If other methods are used, this should be fully justified. Techniques based solely on the analysis of the 5' non coding region are not recommended, as a too high incidence of erroneous determination of the subtype has been reported.

4.2.3. Determination of plasma HCV-RNA levels

HCV RNA levels should 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. Levels of viremia below the lower limit of quantification (LLOQ), should be reported as "target detected" or "target not detected" . The choice of assay should be appropriate for 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.

4.3. Clinical pharmacokinetics

The clinical pharmacokinetic study programme should follow the relevant CHMP guidelines (Pharmacokinetic studies in man – CHMP/EWP/147013/04). In order to reduce the risk of selection of drug resistant variants, the initial pharmacokinetic studies should be performed in healthy volunteers. Studies of pharmacokinetics in patients with hepatic and renal impairment should be conducted in accordance with the principles described in the relevant CHMP guidelines (CPMP/EWP/2339/02 and CPMP/EWP/225/02). If it is known that the test agent has a high barrier to resistance, and selection of resistance is unlikely, studies in patients with hepatic impairment may be performed in patients with HCV infection.

4.4. Drug-drug interactions

The general principles described in CHMP guidance on the investigation of drug-drug interactions should be followed (CPMP/EWP/560/95/Rev.1Corr*). In designing the mechanistically driven drug-drug interaction programme, priority should be given to studies of oral contraceptives, as well as drugs used in the management of 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.

Sufficient data to guide the safe use of the drug(s) in the target population is expected to be available at the time of the initial marketing authorisation. If the possibility of a relevant interaction with an important co-treating agent 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.

5. Assessment of efficacy

5.1. General considerations for clinical trials

Randomised, active-controlled studies with a standard-of-care regimen for the target population, is generally considered the most informative design for confirmatory trials. In case such designs are not used, a scientific justification is necessary. Further, unless specifically justified, randomised controlled studies should be double-blind.

Due to the dynamics of the field, the appropriate design in terms of, e.g., genotypes and populations to be studied, as well as in terms of appropriate comparator regimens, prior to commencing confirmatory studies may change over time. A generally recommended standard of care regimen for the particular target population would usually be considered the appropriate reference treatment in a pivotal trial. However, spontaneous resolution of chronic HCV infection in the absence of therapy is a very rare event Therefore, studies without an active, prospective randomised control constituting an approved and recommended regimen may be sufficiently informative if SVR12 rates are anticipated to be very high (e.g., around 95%).

Possible alternative designs include a placebo control arm with delayed treatment, comparisons of different regimens (doses, durations, number of drugs) including the new agent(s), or single arm studies. If a pivotal study does not have a standard-of-care comparator arm, it is crucial that the sponsor can justify that the demographic and disease characteristics of the patients included cover a

range that is relevant to the proposed recommended uses of the regimen. Enrichment of studies with patients that have characteristics that may be associated with lower SVR12 rates, such as prior treatment failure or advanced liver disease, may be considered in order to ascertain that SVR12 rates are not driven by the selection of “easy to cure” patients.

It is notable that studies that do not randomise to a control arm may not be straightforward in their interpretation if anticipated SVR rates turn out substantially lower than assumed at the planning stage; from a scientific point randomised, active control trials remain the preferred option.

It is acknowledged that the pre-licensure clinical development programme may often include pivotal trials with different study designs. In general, the applicant is encouraged to include at least one study in which the test regimen is compared to placebo (deferred treatment), or to an active comparator, in order to further the understanding of the safety profile of the regimen. Such comparative safety data may be most informative in patients with cirrhosis.

5.2. Subject characteristics and the definition of patient populations

5.2.1. Viral genotypes

The patterns of activity (EC50 as well as barrier to resistance) of many DAAs are genotype- and subtype dependent, with some agents showing *in vitro* and clinical activity only against certain genotypes.

The range of genotypes for which clinical studies are relevant for a certain drug will be inferred initially on the basis of in-vitro antiviral activity data. The results of early clinical studies (e.g. using monotherapy against a range of genotypes) should be used to select the genotypes/sub-genotypes for later studies.

The rationale for studying different genotypes and subtypes in separate studies or within the same study should take into account which drug combinations, doses and treatment durations might be optimal for each genotype. Such considerations may also include whether the same comparator regimen is relevant for each genotype/subtype. If several genotypes/subtypes are studied within the same trials in a development program, genotype or subtype may be an important stratification and/or capping factor. The totality of evidence, from *in vitro* virological findings to clinical outcomes, must be sufficient to enable a sound assessment of the benefit-risk relationship for each particular genotype/subtype for which the use of a drug regimen is recommended. Concerning genotype/subtype determination, see section 4.2.

5.2.2. Host IL28B genotype

Host IL28B genotype was first described as a major predictor of response to interferon-based regimens in patients with genotype 1 (GT1) infection. It has subsequently emerged as a predictor of response also to interferon-free regimens in GT1 when these are not optimized in terms of potency, barrier to resistance and/or treatment duration. Furthermore, there are data to support the impact of IL28B genotype on response to treatment of other viral genotypes too; however, this impact has tended to be less consistent and smaller than in GT1. Therefore, categorisation of patients on the basis of a favourable or non-favourable genotype (e.g., rs12979860 C/C vs C/T, T/T) is of potential importance at several levels of drug development, and it is recommended that this parameter be recorded in all patients participating in clinical trials within a drug development program for hepatitis C, regardless of viral genotype/subtype. A sufficient number of patients with each IL28B genotype should be

investigated for inferences on the claimed treatment effect to be made for both C/C and non-C/C genotypes.

5.2.3. Treatment history

It is recommended that peginterferon (pegIFN) +ribavirin treatment experience and prior response be documented, as this is helpful in understanding the relationship of interferon response and response to the interferon-free regimen. Furthermore, a targeted enrichment of treatment experienced patients (particularly prior non/null responders) may be valuable in defining the optimal regimen (e.g., treatment duration) in those patients that have the lowest interferon response/host immunity to HCV. The crucial issue is that the drug development program should provide the basis for the identification of an appropriate regimen based on the known baseline characteristics of the individual patient.

For classifying prior response to pegIFN and ribavirin in genotype 1 infection, the following terms are recommended:

- Null-response is defined as less than 2 $\log_{10}$ decline in viral load at week 12.
- Partial-response is defined as at least 2 $\log_{10}$ decline in viral load at week 12, but never achieving an unquantifiable viral load
- Relapse is defined as unquantifiable virus at end of treatment but subsequent re-emergence of quantifiable HCV-RNA.
- Breakthrough indicates the re-emergence of quantifiable virus while on treatment after previously being unquantifiable or a confirmed increase of at least 1 $\log_{10}$ in HCV-RNA during treatment.

Emerging categories of patients, in terms of treatment experience, include those that have failed treatment with pegIFN+ribavirin in combination with a DAA, as well as patients that have failed therapy with DAA only regimens. This issue is further discussed below, in section 5.7.4.

5.2.4. Assessment of liver fibrosis

The impact of cirrhosis on PK, efficacy and safety should be determined. The role of liver fibrosis assessment within clinical trials may be to exclude patients with advanced fibrosis/cirrhosis from early clinical trials, or, conversely, to correctly identify patients with cirrhosis, e.g., to enable stratification and subgroup analysis of drug effect in such patients.

A number of different techniques for non-invasive assessment of liver histology are available. The choice of method should be justified on the basis of the operating characteristics of the methods, in view of the predictive value to include or exclude advanced fibrosis/cirrhosis, as relevant for the particular purpose.

For patients in whom baseline histology is available through routine clinical care (liver biopsy performed within 2 years prior to study entry), biopsy data should be collected and the relation between baseline histology and efficacy and safety reported.

5.3. Methods to evaluate efficacy

The recommended primary endpoint for studies aiming at defining cure rate is sustained virological response (SVR), defined as HCV-RNA < LLOQ 12 weeks after the *planned* completion of therapy (SVR12), regardless of the actual duration of treatment. Patients with missing data should be

accounted as failures; the exception being that SVR12 may be imputed in patients for whom SVR has been shown to be reached at a later date (e.g., SVR24).

SVR24 data should also be collected, and all available SVR24 data should be submitted at the time of licensure, followed by submission of the remaining data as they emerge. Preferably the main study protocols should follow patients up to one year after the planned end of treatment (EOT). Concerning the long term follow up of patients, see section 5.5.6.

Apart from SVR, the kinetics of on-treatment viral response should be fully investigated and reported in the drug development program,

Due to the approximate 90% predictive value of SVR4 for SVR12, it is reasonable to make decisions within a clinical development program (e.g., going from phase II to phase III) on the basis of such data.

5.4. Dose finding studies

5.4.1. Monotherapy studies

An adequate range of doses should be studied, based on protein binding-adjusted EC50 values *in vitro* and on available dose-related drug exposure data from healthy volunteers. EC50 values of both wild-type 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 pre-existing variants with reduced drug susceptibility, if this is feasible.

It is expected that monotherapy studies will initially be performed in chronic HCV-infected patients without advanced fibrosis. Currently, 3 days of monotherapy, covering the first phase of viral decay, is considered sufficient to assess the antiviral effect of a dose regimen in the general case. If in vitro data and available knowledge of the drug class are strongly suggestive of a high barrier to resistance, longer term monotherapy studies could be considered.

5.4.2. Early combination dose ranging studies (phase 2a)

As combination therapy is generally anticipated, such studies should be performed with the aim of characterising appropriate doses, regimens and treatment durations for further investigation in phase 3. It is anticipated that such studies will initially be performed in patients without advanced liver disease, and subsequently in patients with more advanced disease. When including patients with a more urgent need of treatment in experimental protocols, remaining options for treatment aiming at viral clearance in case of failure should be considered. In particular, allocating cirrhotic patients to regimens of short duration for which efficacy has not yet been established in patients with less advanced disease should be avoided unless a likely effective salvage regimen would be available in case of virological failure with the selection of drug resistant virus.

5.5. Phase IIb studies and confirmatory studies

5.5.1. Study populations

Sponsors are generally encouraged to study the widest relevant range of patients in confirmatory phase III studies, and particularly patients with advanced fibrosis. Unless there are specific

pharmacokinetic or safety concerns, it is expected that patients with compensated cirrhosis be included in phase IIb/III studies.

Which subpopulations in terms of, e.g., viral (sub)genotype, IL28B genotype, cirrhosis/non-cirrhosis and treatment experience are appropriate to study under the same protocol or under different protocols may vary from case to case. This may depend on the known qualities of the regimen (e.g., the anticipated required potency and treatment duration), as well as on the availability of licensed and recommended comparator regimens for the particular population. A specific concern is patients with advanced fibrosis, who may require longer treatment duration for maximizing SVR rates.

5.5.2. Selection of the study regimen

Presently all clinically useful regimens for the treatment of HCV are combination regimens. An investigational agent may be added to one or more previously approved drugs, or a test agent may be substituted for a component of a recommended regimen, or the test regimen may exclusively consist of two or more investigational drugs. As an increasing number of DAAs are approved, the sponsor should carefully consider the respective value of add-on or substitution studies based on previously approved drugs and regimens, versus the investigation of an entirely novel drug combination.

5.5.3. Add-on and substitution studies

In some cases, an active comparator arm is generally necessary. If the investigational drug is used as an add-on or substitution to an approved regimen, that regimen should primarily be considered for comparison, unless other designs can be justified. In the case of a substitution study, or an add-on trial where the aim is to shorten treatment duration, a non-inferiority design would be relevant. If the intent of the add-on study is to increase efficacy, a superiority design is required.

5.5.4. Studies aiming at a shortened treatment duration

Drug development may aim at documenting the efficacy of regimens shorter than those presently generally recommended (i.e. <12 weeks). When including patients in trials with a shortened treatment duration, patients in relatively urgent need of therapy (e.g., cirrhotic patients) should only be included if there is a clear interferon-free treatment option in case of failure, taking anticipated cross-resistance with approved agents into account. These considerations apply also to situations where the recommended standard of care in a target population has a longer duration than the maximal duration studied in the development program of the test agent.

5.5.5. Fixed dose combinations

Sponsors may develop single drugs or drugs formulated in FDCs. The latter may combine previously approved drug(s) with new compounds, or only contain new compounds. The present guideline concerns all these scenarios.

The specific guidelines for the development of fixed dose combination medicinal products should be consulted and applied as relevant (EMEA/CHMP/SWP/258498/2005).

5.5.6. Follow-up after the primary endpoint

The primary endpoint in confirmatory trials should be SVR (for further details, see above, section 5.3.). A representative subset of patients achieving, as well as not achieving, SVR should be monitored after determination of SVR12. For those that achieve SVR12, a total of one year follow up post EOT for

durability of response is requested (though not necessary at the time of the MAA). For patients not reaching SVR12, a total of 3 year follow up post EOT with assessment of genotypic resistance is requested. The aim of the latter is to understand the kinetics of reversion to wild-type and/or long-term persistence of drug-resistant variants after the cessation of the selective pressure of the treatment regimen. These follow-up data do not need to be available at the time of a market authorisation application submission, but should be reported subsequently. If relevant, patients in a long term follow up programme could be recruited for a re-treatment study

5.5.7. Combination of medicinal products and the demonstration of the contribution of each component to regimen efficacy

The likely need for combination therapy from Phase 2a onwards is recognised. Given available knowledge of general virological principles, as well as preclinical virology data relevant to the particular regimen, trials that have a full factorial design to directly demonstrate the contribution of each agent to efficacy, are not generally expected. The drug development programme should be designed to provide a reasonable rationale for the need for each drug, given the totality of evidence (see also section 5.5.3 concerning add-on and substitution studies).

5.5.8. The extrapolation of efficacy between viral genotypes

The different HCV genotypes show a different geographic distribution. Genotypes 1 and 3 dominate in the EU, followed by genotypes 2 and 4. Genotypes 5 and 6 remain uncommon in areas where clinical trials are generally performed. From a drug efficacy perspective, the genotypes differ in several respects. First, it is well-known that the difficulty of achieving viral clearance with interferon-based immune therapy differs between genotypes, e.g., with SVR rates despite longer treatment duration and higher ribavirin dose in genotype 1 compared to genotypes 3 and -2. This may reflect intrinsic differences in the host's ability to clear the different genotypes. Further, the activity of a particular direct acting antiviral may differ between genotypes or subtypes for reasons that may be more or less understood. This difference in activity may be due to different EC50s of the most common variant(s), but may also be due to different barriers to resistance in different (sub)genotypes, due to the frequency of resistant quasispecies. Moreover, the frequency of detectable, polymorphic variants may differ between genotypes or subtypes (e.g., the NS3/4A Q80K polymorphism or the NS5A L31M polymorphism). Furthermore, available evidence indicates that genotype 3 infections may intrinsically be somewhat more difficult to cure with DAA therapy compared to other genotypes, even though viral susceptibility may be similar. The reason for this is not fully understood.

Subject to the in-vitro virological data, it may be possible to use clinical efficacy data obtained against one genotype to support a conclusion of efficacy against another genotype for which clinical data are relatively limited. For example, efficacy against genotype 1 may support a conclusion on efficacy against genotypes 4, 5 and 6. This approach may make it possible to give dose regimen recommendations in section 4.2. of the SmPC for less commonly encountered genotypes (see section 7). In such a bridging exercise, available data are used to address relevant aspects concerning the sum antiviral efficacy of the drug/regimen against the dominant quasispecies or most common subtypes/variants and against detectable minor quasispecies. In order to support bridging of efficacy, the following elements need to be taken into account.

First, there should be clear indications that the genotype to which the bridge is created, is not intrinsically more difficult to clear than the genotype from which the bridge is built (e.g., a bridge from genotype 2 to genotype 3 would not be accepted). It is anticipated that clinical efficacy data from genotype 1 would generally be used for bridging.

Second, all available clinical and virological data must be taken into account when considering the appropriateness of the bridging exercise. For example, there may be clinical efficacy data for individual components of a regimen against the genotype(s) for which bridging is proposed. If there are no or very few such the bridging exercise must be adequately supported by other evidence such as on-treatment viral kinetics, including any available monotherapy data.

Third, the presumed similarity of on-treatment antiviral potency between genotypes must be supported by similar replicon EC50s.

Fourth, the sponsor must provide an analysis of the genetic heterogeneity of the genotype to which efficacy is bridged, with particular focus on the frequency of potentially relevant polymorphisms in the gene coding for the molecular target. The case must be made that resistant variants or quasispecies are not more common in the genotype(s) to which efficacy assumptions are bridged, than in the genotype(s) from which assumptions are bridged.

5.6. Studies in special patient populations

5.6.1. Treatment of patients with decompensated liver disease

While the term “decompensated liver disease” often denotes those with present or past clinical decompensation events such as variceal haemorrhage, ascites, serious bacterial infections or encephalopathy, and the term “hepatic impairment” usually refers to a functional classification as Child-Pugh B or C, these terms are here used interchangeably to denote either or both of these states.

Once there is sufficient evidence of an appropriate dosing regimen capable of delivering high rates of SVR, as well as PK data in patients with hepatic impairment and a reasonable and acceptable safety database in patients with less advanced disease, trials in patients with very advanced liver disease may commence. Trials in this population are particularly encouraged for genotypes where there is limited evidence for available treatment options or where the efficacy of these may be suboptimal. Available general evidence concerning required treatment duration and the need for ribavirin to optimize outcomes in patients with decompensated liver disease should be taken into account when selecting regimens for study.

SVR is considered an appropriate primary endpoint also in studies of patients with decompensated liver disease, along with prevention of graft infection in case of transplantation. In order to describe the clinical benefit of SVR 12 in this population, it is recommended that patients be further followed up to capture data on mortality, need for transplantation, hepatic function (e.g., MELD score), incidence of hepatocellular carcinoma and reversal of fibrosis.

Prior to initiating clinical trials in patients with decompensated liver disease, pharmacokinetics and short term safety should be investigated in patients over the relevant functional range (e.g., Child-Pugh B and C). If the drug(s) do not have a high barrier to resistance, pharmacokinetic studies should be performed in patients that are not infected with HCV. It is recommended that an established treatment regimen for the target population (in terms of the viral genotypes included for study) is used as an active comparator in order to appropriately characterise the safety and efficacy of the new drug or regimen relative to the existing standard of care. An immediate versus deferred (placebo-controlled) design may be less feasible in these patients with an urgent medical need.

It is crucial that the safety of study participants is appropriately monitored when testing new compounds in the population with decompensated liver disease.

5.6.2. Post-transplant treatment

Reinfection of the liver graft is inevitable in patients with detectable HCV-RNA prior to transplantation. Progress to cirrhosis is rapid, and the prognosis of patients transplanted due to HCV is worse than when transplanted for other indications. The tolerability of ribavirin is compromised in this group, and several studies of interferon-free combinations have initiated patients on lower than standard doses of ribavirin. Furthermore, ensuring that potential drug interactions with immunosuppressive agents can be appropriately managed is an important goal of studies in this population. It is recognised that formal drug interaction studies with some immunosuppressive agents may not readily be conducted in healthy volunteers, except on a single dose basis, and that close monitoring of pharmacokinetics may be required during trials. It is presently not entirely clear whether post-transplant status, including the impact of immunosuppression, impacts response to DAA therapy independently of other factors such as fibrosis status; e.g., most available data are on regimens containing ribavirin, and it has not been clarified whether this is needed in the general case. Therefore, clinical efficacy studies in this population are encouraged.

5.6.3. HCV/HIV co-infected patients

The progression of liver disease may be more rapid in patients co-infected with HIV, at least in those with low CD4+ cell counts. Response rates to pegIFN+ribavirin has historically been lower than in mono-infected patients; this however, has generally not been the case when direct acting antivirals are used. Furthermore, based on emerging data and the DDI profile of a given regimen, the inclusion of HCV/HIV co-infected patients in general confirmatory trials may be considered, provided that similar treatment regimens are studied regardless of co-infection status. In such a case, stratification and/or capping for co-infected patients may be relevant. It is of particular importance that a majority of the patients studied are receiving antiretroviral therapy, to confirm that recommendations concerning the management of drug interactions provided in section 4.5 of the SmPC, are in fact useful in providing efficacious and safe co-therapy against HIV and hepatitis C. Population pharmacokinetic studies should be part of these trials, to confirm that the expected exposures are yielded (for new agents and antiretrovirals with proven/potential interactions).

5.6.4. Patients with prior DAA experience

This patient population is of considerable heterogeneity. For instance:

- The prior DAA class and compound(s) tried differ(s).
- The reason for unsuccessful treatment with a DAA regimen may be virological failure or lack of tolerance including adherence issues.
- Patients may or may not have evidence of persistent viral resistance.

The most important *scientific* question pertaining to patients with prior virologic failure and/or selection of variants resistant to DAAs, may be to understand its impact on the contribution of the same agent or a cross resistant agent as a component in a more potent regimen (e.g., including more drugs, a longer treatment duration and/or higher doses). However, the *clinically* most relevant retreatment scenario in most cases may be with a potent combination of drugs of classes to which the patient has not been exposed or to which cross-resistance is not anticipated, with or without ribavirin.

Much remains unknown concerning the impact of emergent drug resistance on subsequent therapy with a partially or potentially cross-resistant compound. It is clear, however, that virtually all patients that fail virologically when treated with DAAs while adhering to therapy are intrinsically “difficult to

cure". This should be taken into account when designing studies for patients that have experienced virological failure on DAA-containing regimens. The virological rationale for regimens used in studies of retreatment of patients with prior failure on DAA regimens should be carefully considered (e.g., the anticipated potency and barrier to resistance of the experimental regimen), and emerging data should be taken into account. It is anticipated that drug pressure (sum potency, treatment duration) will need to be increased compared to the previous treatment attempt, in order to optimise responses in patients with prior virological treatment failure.

If the investigational regimen includes a DAA to which the patients have been exposed, or a potentially cross-resistant agent, baseline drug resistance should be thoroughly investigated so that firm conclusions can be drawn about its impact on treatment response. Retreatment studies of patients with DAA experience that have reverted to wild-type after the selection of resistance during therapy are considered of particular importance for understanding the impact of acquired drug resistance.

Patients that have failed DAA based regimens due to lack of tolerability, and that do not have evidence of drug resistance, should be evaluated on a case to case basis as regards re-treatment, and are not considered a well-defined target population for clinical trials.

5.6.5. Studies in paediatric patients

It is currently not generally anticipated that clinical efficacy and safety studies in children will be performed until after completion of Phase 3 studies in adults. However, PK studies in adolescents anticipated to require the adult dose regimen may begin earlier and these patients may be included in adult confirmatory trials.

Suitable age-appropriate formulations should be developed, palatability being of particular concern.

Similar to the case with HIV, it is considered that efficacy data may be bridged from adults to children, provided that similar drug exposure is reached in plasma at the recommended doses. Studies primarily aiming at characterising PK and selecting appropriate doses should cover an appropriate range of ages (generally from 3 years and upwards), and should aim at achieving adult plasma drug exposures. Treatment should be continued for a duration that is sufficient to reach SVR to provide clinical benefit for study participants and to generate some safety and efficacy data. Such studies could include the full range of patients (e.g., in terms of viral genotypes and other disease characteristics) for whom the use of the drug/regimen is recommended in adults. It is recognised that the number of children and adolescents with chronic hepatitis C eligible for clinical trials is limited. If there are no specific safety concerns relevant to the paediatric population, pre-authorisation studies could be limited in size to 30-40 patients distributed across the age range from 3 to less than 18 years old. As stated above, these studies could primarily focus on the determination of PK, but would also collect, albeit in a rather limited fashion, data on safety and efficacy. After authorisation, additional safety data would need to be collected, possibly in form of a registry.

3.6.6 Studies in older patients

Hitherto pivotal studies have included relatively few elderly people. While the elderly are not considered a special population in the sense of the abovementioned categories, the inclusion of elderly subjects in clinical trials is generally encouraged.

6. Safety aspects

Specific safety concerns related to the treatment of chronic hepatitis C that are of relevance for the development of new DAAs include impaired liver function at baseline, the known toxicity of currently licensed drugs such as ribavirin, the potential for additive or synergistic toxicities of co-treating agents, PK interactions and development of drug resistance. 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.

A particular problem concerns the investigation of the safety profile might arise when two or more DAAs are investigated in combination, without either agent having previously characterised as to its individual safety profile. Sponsors studying combinations of novel drugs are urged to consider this problem. One way to address this issue is to also investigate one or both DAAs in combination with agents with a previously described safety profile, where the safety profile of the individual investigational agent can be characterised.

If the drug is subject to an expanded access program in patients outside criteria of clinical trial population, safety data should be collected, as appropriate.

7. Information in the Summary of the Product Characteristics

In the general case, the indication (section 4.1. of the SmPC) for DAAs against HCV infection should be as follows:

"[*TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2., 4.4. and 5.1.)*

for genotype specific activity, see sections 4.4 and 5.1."

For fixed dose combinations that may constitute a full regimen, a similar indication, excluding the statement "in combination with other agents" is appropriate in the general case.

Section 4.4. should contain information on lack of data in clinically relevant subpopulations, and thus reflect the potential absence of data to underlie a regimen recommendation, as well as any relevant uncertainty concerning the optimal regimen in different clinical situations. This section may contain recommendations for non-use in case of certain viral genotypes, viral polymorphisms, clinical situations or certain prior DAA experience.

The efficacy data underlying regimen recommendations should be cited in section 5.1., as well as other efficacy data considered of relevance to the prescriber and clinically relevant information on drug resistance. Furthermore, this section should contain a summary of the in vitro potency against each genotype, resistance pathways on in vitro selection and short term monotherapy activity against each genotype. Any molecular understanding of genotype specific activity, such as conserved baseline viral polymorphisms that might impact the activity of the drug, should be highlighted.

Definitions

CE	European Conformity
CHC	Chronic Hepatitis C
DAA	Direct acting antiviral
DDI	Drug-drug interactions
EC50	Median Effective Concentration to induce a 50% effect
EOT	End of treatment
FDC	Fixed dose combination
GT	Genotype
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IL28	Interleukin 28B
LLOQ	Lower limit of quantification
MELD	Model End Stage Liver Disease
pegIFN	Peginterferon alfa
RNA	Ribonucleic acid
SVR	Sustained virological response