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Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C.

Draft

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Guideline on clinical evaluation of medicinal products for the treatment of chronic hepatitis C.

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EXECUTIVE SUMMARY

This guideline provides guidance on the clinical development of compounds for the treatment of Chronic Hepatitis C (CHC), including directly acting antivirals (DAAs) as well as host targeting antivirals (HTA). It should be read in conjunction with updated and recognised clinical treatment guidelines. Various combination regimens, including a DAA or HTA together with peginterferon (pegIFN) and ribavirin, regimens with more than one DAA/HTA in combination with pegIFN + ribavirin, as well as regimens excluding either or both of these agents, are considered.

While the primary investigation of new DAA/HTA in combination with pegIFN + ribavirin in patients with genotype (GT) 1 remains important, it is recognised that other paths of drug development, focussing on wider or alternative populations, or other drug combinations (such as more than one DAA/HTA with or without ribavirin, or 2 DAA/HTAs in combination with pegIFN+ribavirin) are warranted and ongoing.

The guidelines emphasize the importance of new DAA/HTA for usage in special populations including patients with decompensated liver disease, patients pre/post transplantation, HCV/HIV co-infected patients, patients intolerant to pegIFN and/or ribavirin and patients with prior DAA experience.

When studying novel agents in combination with pegIFN and ribavirin, the comparator in pivotal trials should be a licensed first line recommended regimen; notwithstanding this, European regulators recognise the need for licensed DAA/HTAs from several classes, with different side effects profiles and resistance patterns, which is seen as a benefit per se. When studying novel drug combinations without pegIFN, it is recommended that patients previously failing therapy with pegIFN+ribavirin that do not have an immediate treatment need be avoided prior to obtaining proof-of-concept of sustained virological response (SVR), as the consequences of acquired drug resistance in terms of retreatment success has still not been investigated. For drugs to be used in combinations eschewing pegIFN, it is recognised that patients that do not tolerate pegIFN have no presently licensed therapeutic options and a probability of viral clearance close to zero. Thus, for licensure, response rates would be weighed in relation to this fact. Regarding special populations, the need to start trials as early as can safely be done for groups with an important unmet medical need (e.g., patients with decompensated liver disease or HCV/HIV coinfection) is emphasised,

Since the previous guidelines were adapted, host IL-28B genotype has emerged as a very important predictor of the efficacy of pegIFN, and it is recommended that stratification by IL28B genotype be employed whenever the studied drug regimen includes this drug.

Regarding future developments, proof-of-concept of SVR with treatment combination excluding pegIFN, as well as data on retreatment of patients that have failed therapy that has selected for DAA-resistant variants, but whose dominant population has subsequently reverted to wild-type, are eagerly awaited. Such data are likely to greatly impact regulatory considerations within the field. It is recognised that this is a rapidly moving therapeutic area, and that a further revision of these guidelines may be mandated within the foreseeable future.

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. HCV therapy

The general aim of therapy is to achieve sustained viral response (SVR), defined as the absence of detectable virus 24 weeks after the planned end of therapy. This ends the progression of HCV-related hepatic injury, Despite SVR however, the risk of cirrhosis-related complications, including hepatocellular carcinoma, still remains in patients that have developed significant liver injury due to the infection.

Over approximately 15 years, HCV therapy has evolved from the use of a standard (non-pegylated) interferon alone, via combination therapy with a standard interferon + ribavirin, to the combination of a pegylated interferon and ribavirin. For GT 1 virus, SVR rates in treatment naive patients with GT1 virus with 48 weeks of standard interferon therapy were approximately 10 percent, whereas with combination therapy of an unpegylated interferon and ribavirin for 48 weeks, SVR rates were about 30-35%. With the combination of pegIFN 2a or 2b and ribavirin for 48 weeks, which remains the present standard of care pending the approval of the first DAAs, response rates in GT1 or 4 have been approximately 40-50% in the pivotal trials. Lower SVR rates, however, are seen in some sub-populations such as those with HCV/HIV co-infection. In contrast, around 70-85% of treatment naive patients infected with HCV GT 2 and 3 achieve SVR after a 6-month treatment course with pegIFN and ribavirin. The first generation of directly acting antivirals (DAA, see below) has been developed for use with PegIFN and ribavirin in patients with GT1, showing response rates of around 70% in treatment naïve patients. The response rate to a first generation DAA added to pegIFN+ribavirin is even higher when re-treating the selected patient group that achieved an end-of-treatment response with pegIFN+ribavirin therapy, but subsequently relapsed. Also in patients with prior non- or null response to pegIFN+ribavirin, SVR rates are substantially increased with the addition of a first generation DAA. Still, even after the approval of the first generation DAAs there will remain a need for development of new treatment approaches for numerous patient categories, including those that do not tolerate PegIFN or ribavirin or those in whom the background regimen of PegIFN and ribavirin has limited activity, and therefore gives insufficient support to the DAA.

1.4. Direct acting antivirals

A large number of direct acting antivirals (DAAs) from different drug classes are currently under investigation. The life-cycle of HCV offers several molecular targets for inhibition. Among these, inhibitors of the N3/4A protease, the NS5B polymerase, and the NS5A co-factor are presently furthest in development, with the marketing approval of the first NS3/4A inhibitors expected in 2011. 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 to a varying degree under drug pressure, both *in vitro* and by non-suppressive therapy *in vivo*. Available data indicate that the barrier to resistance varies greatly between drugs in the DAA category. Within class cross-resistance is likely, e.g. among hitherto investigated NS3/4A inhibitors and among non-nucleoside inhibitors of NS5B binding to the same allosteric site. Resistant variants, rather than wild type HCV, have usually been recovered from patients with virological failure or who relapsed after achieving an end-of-treatment response (ETR) following treatment with an NS3/4A inhibitor in combination with PegIFN and ribavirin. The impact of resistance on subsequent treatment attempts remains unknown. 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.

Available data indicate that reversion to wild-type virus by population sequencing is frequent but not universal after the discontinuation of unsuccessful DAA treatment. Retreatment studies of such patients, with an optimized regimen (e.g., a higher dose if relevant, or a regimen including an additional DAA) are strongly encouraged and would be of great value to the understanding of the clinical consequences of selection of viral resistace to DAAs, and for understanding of the risks involved in participation in early clinical trials of DAAs (see also section 4.5.5.).

1.5. Host targeting antivirals

Apart from the DAAs, numerous host targeting antivirals (HTA) are presently also under development. These drugs have different mechanisms of action and presently include, e.g., lambda interferons, cyclophilin inhibitors and toll-like receptor agonists. Since such drugs do not directly bind to viral targets, the barrier to acquired viral drug resistance of HTA is generally expected to be higher than for many DAAs, if indeed they select for viral resistance mutations at all. For this reason, HTAs are anticipated not only to be developed in combination with peginterferon and ribavirin, if appropriate, but also to be useful as substitutes for peginterferon, and perhaps also ribavirin, in combination with one or more DAA, or other HTAs. As drugs from this category are heterogeneous, including both biologicals and small molecules, and to a varying degree being immunomodulators, particular preclinical and clinical concerns may pertain to different drugs within this class.

2. SCOPE

Guidance is provided on the design of exploratory and confirmatory clinical studies considered to be of relevance for the evaluation of DAA and HTA compounds.

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).
- Guideline on missing data in confirmatory clinical trials (EMA/CPMP/EWP/1776/99 Rev. 1.)

4. MAIN GUIDELINE TEXT

4.1. Subject characteristics and the definition of patient populations

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.

The first generation DAAs have been developed for use in combination with pegIFN and ribavirin. The effect has initially been characterised in treatment-naive and –experienced patients with genotype 1 infection that have compensated liver disease. Subsequent and ongoing trials are targeting other populations, such as patients infected with other genotypes and patients with HCV/HIV co-infection. Though several ongoing development programmes for DAAs and HTAs are still following this pattern, this sequence of investigations can no longer be held as a general rule within the field. It is foreseen that DAAs or HTAs may primarily be investigated for use in other combinations than with pegIFN and ribavirin, or, in some cases, for other genotypes than GT1.

4.1.1. Viral genotypes

The patterns of activity of many DAAs are genotype-dependent, with some agents showing *in vitro* and clinical activity only against certain genotypes. Also, the activity of HTAs may vary depending on genotype, as does that of pegIFN. Furthermore, potency and/or barrier to resistance for a given agent may differ between GT1 subtypes 1a and 1b, and perhaps between subtypes of other genotypes.

As regards the genotypes prevalent in the EU (1, 2 and 3), it is still expected that efficacy against genotypes 1 and 2/3 respectively be studied in separate trials, regardless of the relative activity of the investigational agent against the respective genotypes, as the efficacy of pegIFN+ribavirin in patients

with GT 2/3 is considerably higher than in GT1 (see section 1.3). For the latter reason, GT1 has been the primary focus in the developmental programs for DAA/HTAs, and it is anticipated that this, in most cases, will remain so within the foreseeable future.

As regards GT2 and -3, the most urgent medical need is, arguably, in patients having failed prior therapy, and in patients that do not tolerate pegIFN/ribavirin, though the general need for therapies with less side effects and shorter duration is also recognised. As some agents do not have activity against both GT 2 and 3, the appropriateness of including both genotypes (and in some case perhaps also subtypes) needs to be justified case by case, based on the similarity of the activity of the investigational compound against these genotypes. For treatment experienced patients with genotype 2/3, randomised clinical trials against a pegIFN+ribavirin regimen would primarily be anticipated prior to licensure. However, the relative scarcity of treatment experienced patients with these genotypes is recognised, and if a sponsor considers other approaches (e.g., single arm studies), European regulatory advice should be sought. Pending licensed treatment options, and given that reasonably safe and effective doses has been identified, single arm studies of pegIFN sparing regimens would be appropriate in patients with GT 2/3 that are intolerant to pegIFN. The sample size of confirmatory should be large enough to confidently determine benefit-risk in this population, though it is likely that in many cases the safety database at the time of licensure will include a larger experience in patients with GT1 infection.

The activity of pegIFN+ribavirin against GT4 is considered of similar magnitude as against GT1. GT4 may be studied in trials together with GT1, provided that the in vitro activity of the investigational compound against these genotypes is roughly similar. For an investigational compound used in combination with pegIFN and ribavirin, a specific demonstration of efficacy against GT4 would not be necessary for labelling, given that in vitro activity and available viral response data, including early viral kinetics and SVR rates, show adequate consistency between GT1 and GT4.

The reference *method for HCV genotype determination* is direct sequence analysis with either CE-marked or validated in-house techniques. If used, 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 which has been validated for correct subtyping of at least subtypes 1a and 1b, and ideally also others, should be used. An alternative to this is to use a CE-marked second generation line probe assay. If other methods are used, this should be fully justified. Techniques based 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.

4.1.2. Host IL28B genotype

The recent emergence of host IL28B genetic polymorphisms as major determinants of pegIFN response, at least in GT1, is impacting the definition of populations for clinical trials. Categorisation of patients with GT1 infection on the basis of a favourable or non-favourable genotype (e.g., rs12979860 C/C vs C/T, T/T) is of putative importance at several levels of drug development. When dose-ranging a DAA or HTA in a combination including pegIFN, it is recommended to stratify by IL28B genotype, as this not only reduces variability, but the optimal dose of the investigational agent may vary depending on genotype. Since IL28B genotype may also determine the optimal duration of therapy, similar stratification is valuable also later in drug development, including confirmatory trials. Finally, when conducting dose ranging and proof-of-concept trials of DAA-only combinations where failure may result in multiple class resistance, restricting the population to those with a favourable IL28B genotype would provide a high likelihood for successful salvage with a pegIFN based regimen, if needed. Thus, this should be considered, though it is recognised that the ultimate target population for such novel combination therapies may be different, and furthermore that, theoretically, IL28B genotype may

impact the response also to treatment regimens not containing pegIFN. The dose selection should be based on the worst case scenario regarding IL28B genotype (in combination with GT1 subtype, if relevant). Dose-ranging trials in parallel in clinical trials, investigating the dose need in the respective populations should be considered. A sufficient number of patients with each genotype should be investigated for inferences on treatment effect to be made for both C/C and non-C/C genotypes.

II-28 genotyping is rapidly becoming available in routine clinical practice. This should be considered, when performing single arm confirmatory studies in populations where that is appropriate; the sponsor need to ensure that a particular IL28B genotype is not inappropriately selected for when recruiting for the study, e.g., by recruitment capping.

4.1.3. Treatment history

Patients should be classified as treatment naive or -experienced. The response pattern of patients that have failed therapy with the combination of pegIFN +ribavirin may be classified as prior null-response, non-response, relapse or breakthrough:

- Null-response is defined as less than 2 log10 decline in viral load at week 12.
- Non-response is defined as at least 2 log10 decline in viral load at week 12, but never reaching undetectable virus.
- Relapse is defined as undetectable virus at end of treatment but subsequent re-emergence of detectable HCV-RNA.
- Breakthrough indicates the re-emergence of detectable virus while on treatment after previously being undetectable or a confirmed increase of at least 1 log10 in HCV-RNA during treatment.

Thus, these terms are primarily defined in relation to the response to pegIFN+ribavirin therapy, and so used unless otherwise specified. A further emerging class in terms of treatment history are patients with prior failure on treatment with a DAA, that may or may not harbour resistant virus.

4.1.4. Special populations

Important special populations are discussed in section 4.5, and include:

- Patients with decompensated liver disease, including the pre-transplant setting
- Patients post transplantation
- HCV/HIV co-infected
- Patients intolerant to pegIFN and/or ribavirin
- Patients with prior DAA experience
- Pediatric patients

4.1.5. Assessment of liver histology

The role of liver histology assessment within clinical trials may be to exclude patients with advanced fibrosis/cirrhosis from early clinical trials, or to enable stratification and subgroup analysis of drug effect in patients with cirrhosis. Liver biopsies will not be required for clinical trials aiming at viral RNA clearance (i.e. SVR).

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. Since non-invasive methods have replaced liver biopsy for the routine management of HCV patients in large parts of Europe, it is recognised that the availability of biopsy data will decrease over time.

If a new treatment is developed as maintenance rather than curative therapy, European regulatory advice should be sought on the need for liver biopsy.

4.2. Methods to evaluate efficacy

4.2.1. Determination of 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. Outcomes, including levels of viremia below the lower limit of quantification, should be reported according to the operating manual of the assay. 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.

4.2.2. Endpoints

In principle, treatment outcome in clinical trials should be measured at the same time-point for all patients in all treatment arms, regardless of the actual duration of therapy. However, given the accumulated experience in HCV therapeutics, and the problems posed by loss to follow up, for treatment regimens containing pegIFN, the recommended primary endpoint for studies aiming at defining cure rate is sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after completion of therapy (SVR24), regardless of the scheduled duration of treatment. In the primary efficacy analysis in confirmatory studies, all missing SVR24 data should be considered as non-response

Though the primary endpoint for practical reasons is defined as above, virological response data should also be collected for all patients at a time-point equalling 24 weeks after the longest scheduled duration of therapy within the study, as this would be the formally correct time-point for comparison. The use of the former as primary endpoint is based on the confidence in the predictive value of such data for long term outcome, and the concern that loss to follow-up might be substantial in the shorter treatment arms, as the duration of therapy might differ with six months or more, depending on treatment arm and virological response. For regimens not including PegIFN, the pattern of relapse following undetectable viremia at end of treatment is presently unknown. For this reason, further long term follow up is expected, at least from a subset of patients (e.g., those included in preliminary trials) in order to provide sufficient confirmation of the ability of SVR24 to reliably predict long-term cure, though full long term follow up of the patients in the pivotal trials would not be required at the time oflicensure. Due to present lack of data, these considerations may be subject to revision as data are forthcoming from studies of different drug combinations.

On-treatment virological response have traditionally focused on week 4 (e.g., proportion with undetectable HCV-RNA at week 4) and week 12, based on experiences with pegIFN and ribavirin

combination therapy. However, for novel drug combinations, depending on the sum potency and barrier to resistance, response at other timepoints may be more predictive of continued virological efficacy and SVR. Thus, the kinetics of on-treatment viral response should be fully investigated and reported, as appropriate for the drug and regimen under investigation. It is expected that the kinetics of viral response be intensely monitored during exploratory trials, in order to find appropriate time-points for describing viral kinetics, to be reported as secondary endpoints in confirmatory studies. Furthermore, monitoring of viral kinetics during early trials should aim at defining appropriate stopping rules for later, larger studies, in order to avoid futile therapy as well as continued exposure to non-suppressive regimens, thus selecting for more fit resistant variants that may be more likely to persist. The stopping rules applied in confirmatory trials should be thoroughly justified on the basis of viral kinetics, and investigators are encouraged to pursue rules of decision based on the earliest possible point of measurement. Also, within a drug development program, early viral responses should be investigated in relation to the required duration of therapy, as regards all components of a drug regimen (e.g., both for the DAA/HTA and for pegIFN+ribavirin). The use of response-guided therapy is generally anticipated.

4.3. Clinical pharmacology, virology and toxicology studies

4.3.1. Pharmacokinetics and drug drug interactions

The general principles laid down in current CHMP guidelines on pharmacokinetics are applicable. Studies on the pharmacokinetics in patients with cirrhosis should be performed, as well as in patients with decompensated liver disease, if this is an intended target population.

It is foreseen that some new DAAs will have a significant drug interaction potential. Since an important subpopulation 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, as well as oral contraceptives. Within these areas, essential drugs (for which reasonable therapeutic alternatives are lacking) that have a foreseen potential for interaction, should be prioritised for study. Such data is expected to be available at the time of the marketing authorisation. 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). Still it is recognised that in some cases certain antiretroviral drugs (e.g. ritonavir-boosted protease inhibitors) may not be possible to use in combination with a certain DAA or HTA.

Pilot trials of a DAA/HTA in HIV/HCV co-infected patients may proceed prior to the completion of a full drug interaction programme. In such cases, the use of antiretroviral agents may be limited by protocol, if preclinical data and studies with probe compound suggest likely clinically relevant drug interactions.

For DAAs that are nucleoside analogues, the potential for drug interactions at the level of intracellular activation by phosphorylation should be considered, considering that the guanosine analogue ribavirin may be part of the projected regimen. 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.

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 and drug resistance

It is anticipated that an initial application dossier should contain an extensive evaluation of the *in vitro* activity of a new DAA or HTA, 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. In vitro studies of resistance are expected also for HTAs, followed by clinical investigations as appropriate.

The *in vitro* antiviral activity of a new agent should also be investigated in combination with interferon, ribavirin and other potential agents for use in combination. 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 cell-based assays such as the subgenomic HCV-replicon system are most often 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). As for many agents there are differences in antiviral activity and barrier to resistance according to subtype, this should be thoroughly investigated.

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 testing should be performed at baseline and on samples from patients at virological non-response, breakthrough or relapse. Naturally occurring polymorphisms associated with differential drug efficacy should be identified. Any changes from baseline in samples on treatment or at relapse should be assumed to be due to the selective pressure of the drug regimen. Variants not previously described in the preclinical investigations of drug resistance should undergo phenotypic studies.

There are several different methods for the analysis of genotypic resistance. Populations sequencing is the standard methods, but only detects variants with a frequency of about 20% (a figure that varies depending on viral load). Clonal sequencing is more cumbersome but more sensitive, and can provide additional information about the linkage of mutations and the frequency of different quasispecies. Ultra-deep sequencing methods are under development and applicants are advised to follow the development of such. 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.

While population sequencing presently remains the standard, routine assay for the monitoring of drug resistance within protocols, other methods should be used when appropriate (see above). Importantly, within clinical trials samples should be stored to enable further analysis with more sensitive methods, if required.

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. 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.

To what extent acquired drug resistance in patients failing therapy with DAA regimens will emerge as an important problem affecting future drug development and treatment options is presently not fully known, as previously mentioned. However, if further experience would indicate that acquired resistance to DAA/HTAs will be an important clinical problem, sponsors are highly encouraged to co-operate (with other sponsors as well as with academia) in its investigation, e.g., by sharing raw data suitable for the clinical assessment of drug resistance.

4.3.3. Toxicology studies

General guidelines for preclinical toxicology studies including the SWP guideline on combination (EMEA/CHMP/SWP/258498/2005) and ICH M3(R2) should be followed. It is anticipated that combination drug regimens will generally be pursued. Combination toxicology studies may be required if there are specific concerns about additive or synergistic toxicity. In case of unexpected toxicities with the combination in clinical trials, further preclinical studies may be warranted to elucidate the mechanism of toxicity.

4.4. Clinical efficacy studies

Whereas the first DAAs will initially be approved for use in combination with pegIFN and ribavirin, and other programmes will continue to study the combination of a DAA or a HTA with these drugs, there are numerous other possible drug combination, for which proof-of concept may or may not be available, and for which the challenges of drug development varies. These include e.g.:

DAA/HTA + DAA/HTA + PegIFN + ribavirin

DAA/HTA + DAA/HTA

DAA/HTA + DAA/HTA + ribavirin

DAA/HTA + HTA + pegIFN

DAA/HTA+DAA/HTA+DAA/HTA

Comparative studies are expected to be randomised and, whenever possible, double-blinded. In some circumstances (e.g., in the study of certain special populations, see below) single arm studies may be justified.

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).

Stringent stopping criteria should be applied, and sampling should be sufficiently frequent to adequately describe viral kinetics, pharmacokinetics and the possible evolution of resistance. It is expected that stopping criteria and response guided algorithms in later studies be fully justified on the basis of viral kinetics (see also section 4.2.2.)

4.4.1. Dose finding monotherapy studies

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 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 variants with reduced sensitivity, if this is feasible.

Currently, 3 days of monotherapy, covering the first phase of viral decay, is considered sufficient in the general case. A longer period of monotherapy may increase the risk of acquired drug resistance. If there is a strong scientific rationale to prolong this period of monotherapy, longer duration studies could be warranted. In such a decision, the anticipated barrier to resistance of the compound should be taken into account.

It is expected that monotherapy studies would initially be performed in patients without advanced fibrosis, and in whom salvage with a licensed treatment option is likely to succeed (e.g., patients with a favourable IL28B genotype), in case of resistance development.

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

Further dose-ranging studies are expected to be performed in combination with other agents. For studies of regimens including pegIFN viral response at 4 weeks, supported by efficacy and safety data at week 12, usually informs dose selection for phase 2b trials aiming at estimating SVR rates, defining appropriate treatment durations and identifying predictors of response/required treatment duration. For experimental regimens, a longer duration than four weeks may be necessary to assess the relative risk of viral breakthrough between study arms.

If proof-of concept of the drug combination is lacking, the initial combination studies should be performed in patients groups that can readily be salvaged in case of failure (e.g., treatment naive patients without cirrhosis, and with a favourable IL28B genotype), though it is recognised that these may not be the ultimate target population for the regimen.

4.4.3. Further development of regimens containing one DAA or HTA in combination with pegIFN and ribavirin

Phase 2b trials of a DAA or a HTA in combination with pegIFN and ribavirin are expected to be performed with one or a few selected dosing regimens, and to have SVR (see section 4.2.2) as primary efficacy endpoint. In such trials a control group not receiving the investigational agent is required. The sponsor should closely follow the scientific discussion and evolving treatment guidelines to select appropriate control regimens. It is expected that phase 2b studies aim at defining appropriate treatment durations for the DAA or HTA as well as for pegIFN + ribavirin. If a DAA is investigated, a maximal DAA treatment duration may be rationally imputed based on the likely persistence of sensitive viral quasispecies. Furthermore, baseline characteristics and early viral response parameters (also prior to week 4) should be investigated aiming at eventual response guided therapeutic regimens.

Studies in GT1 are expected to include patients with subtypes 1a and 1b, unless virologically inappropriate. If virologically rational, patients with GT4 may be studied within the GT1 programme (see also section 4.1.1). GT 2 and 3 may be studied in common or separately, depending on the virological rationale (see also section 4.1.1). In most cases, stratification by GT1 subtype and by genotype is likely to be appropriate, at least in confirmatory studies. Also, it is expected that patients be stratified by IL28B genotype.

Treatment naive patients on the one hand, and prior non-responders to pegIFN+ribavirin therapy on the other (for definition, see section 4.1.3), should be studied in separate trials. Patients with prior relapse have traditionally been studied together with non-responders. However, based on anticipated treatment response and required duration of therapy in the prior relapse population, separate studies or inclusion in trials with the treatment naive may be more appropriate. In the latter case, studies

should be stratified by treatment experience and prior response. Sufficient patients of each category of prior response should be included to support the indication claimed

Null responders to pegIFN+ribavirin should not be randomised to repeat therapy with that treatment modality. However, study designs may include a lead-in with pegIFN + ribavirin for 1 month, for characterisation of response, which may be incorporated in a study design also investigating the *virological* merits of a lead in phase (see below). In case of no approved treatment for null responders, apart from pegIFN and ribavirin, single arm studies of a DAA/HTA + pegIFN and ribavirin would be appropriate, and a lower 95% confidence interval bracket above 20% SVR would be considered indicative of a regimen having increased activity over pegIFN+ribavirin in well-characterised null responders. If the control regimen has been approved for the use in prior null responders, such patients may be studied in the same trials as prior non-responders. As the use of a DAA together with pegIFN +ribavirin in null-responders may de facto approach functional monotherapy, the strength of the virological rationale for any such studies should be carefully considered. If the resistance barrier and/or potency of the DAA are not reassuring, studies including more than one DAA/HTA should be considered at an early stage of drug development.

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

A pegIFN+ribavirin lead in phase may be investigated in one or several treatment arms. Its virological merit would consist in the prevention of breakthrough of DAA-resistant variants, and may depend on the pegIFN used, as well as on the DAA. It may also be of value within the developmental programme to characterise the pegIFN response requirements for efficacy as well as treatment duration, and perhaps also clinically to inform response-guided therapy.

Confirmatory trials should be designed with the abovementioned concerns regarding populations in view. The reference treatment in such trials should be a recommended first-line regimen for the relevant population, based on the most recent clinical guidelines. For novel DAA/HTAs to be licensed in combination with peginterferon and ribavirin, comparative studies with a present state-of-the art regimen would in most cases be necessary. Such studies are anticipated to have non-inferiority designs, at least for treatment-naive and prior relapser populations. However, the general need for licensed alternatives within the DAA/HTA groups is recognised. This includes the development and licensure of agents from multiple classes that can putatively be combined in regimens with or without peginterferon. In this context a different and/or improved side effects profile in relation to licensed agents, as well as a different mechanism of action or resistance profile, are considered added values to be considered in the risk/benefit assessment. As the field is expected to advance rapidly, it is recommended that regulatory advice be sought on appropriate study design and comparative regimen, as well as, when appropriate, on the non-inferiority margin, prior to initiating studies.

It is anticipated that response guided therapy be investigated in confirmatory trials.

The primary endpoint in confirmatory trials should be SVR (for further details, see section 4.2.2). A representative subset of patients exposed to DAA(s) and not achieving SVR should be monitored for three years after the documentation of nonresponse, with frequent sampling (e.g., every three months) of HCV-RNA and assessment of genotypic resistance. The aim 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. Where a genotypic correlate of resistance has not been observed, phenotypic resistance should also be assessed (see also section 4.3.2). This follow-up of non-responders would 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.

While SVR rates are similar for both of the presently licensed pegIFNs in combination with ribavirin, the kinetics of viral response differ between agents. Therefore it may be that, when using a DAA or HTA in combination with pegIFN, the mean treatment duration required may differ depending on which pegIFN is used. Also, due to differing PK/PD relations, the rationale for a lead in phase with peginterferon and ribavirin prior to starting DAA therapy may differ between peginterferons. For the reasons given above, and also since the total duration of therapy is anticipated to be guided by early viral response, sponsors are urged to limit the use to a single pegIFN within confirmatory studies. Such a limitation facilitates the elucidation of the relation of early viral kinetics to response, including the many subgroups in which efficacy would need to be inferred, and increases the ability to properly define algorithms for response guided therapies. For licensure in combination with both pegIFNs, indications of similar SVR rates and benefit-risk would be required.

4.4.4. Studies of 2 DAA/HTAs in combination with pegIFN and ribavirin

It is anticipated that the use of more than one DAA and/or HTA in combination with pegIFN and ribavirin might further increase SVR rates in patients with suboptimal pegIFN response, such as those with prior non/null response or an unfavourable IL28B genotype.

Prior to efficacy studies of such drug combinations, at least one of the DAA/HTAs should have been dose ranged through phase 2a, and the other should at least have undergone at least preliminary monotherapy studies (see section 4.4.1). Furthermore, appropriate drug interaction studies should have been performed.

Principally, the most appropriate comparator for a combination of 2 DAA/HTA + pegIFN and ribavirin would be either or both of the DAA/HTA as a sole addition to pegIFN and ribavirin, in order to demonstrate the positive benefit-risk of adding the further drug. However, scenarios could arise where a clinically recommended combination of another DAA + pegIFN and ribavirin could be considered as reference treatment (e.g. if early data indicate that a single DAA in the investigational arm might not reach sufficient efficacy in the target population). If this is considered, regulatory advice should be sought.

4.4.5. Studies of 2 or more DAA/HTA without pegIFN, with or without ribavirin

PegIFN and ribavirin are both associated with substantial side effects, and are contraindicated in some patients. Furthermore, a number of patients show null response to pegIFN. Hence, there is a need for potent combination regimens without these agents, both for patients with GT 1/4 and GT 2/3 infection. An important problem in drug development is the risk of dual class resistance in case of failure of such a regimen. Therefore a virological rationale, including indications of a sufficiently high sum barrier to resistance, is an important prerequisite for their study. It may be that at least one agent in the combination should be a HTA or a DAA with a high barrier to resistance (e.g. a nucleoside analogue). Appropriate stopping criteria and adequate monitoring for virological breakthrough are crucial.

Prior to combination therapy, each agent should be dose ranged in monotherapy studies, and results from appropriate drug interaction studies should be at hand. The need for these should be evaluated on the basis of preclinical and probe compound data (see section 4.3.1). Concerning the need for combination toxicology studies, see section 4.3.2. It seems most prudent to perform the first dose ranging studies of novel drug combinations in patient populations that can readily be salvaged with licensed therapeutic options in case of failure (e.g., treatment naive patients without advanced liver injury, and with a favourable IL28B genotype; see also section 4.1.2). The initial duration of such studies may be short (2-4 weeks) and the patients offered to continue with a licensed treatment alternative, or the addition of pegIFN and ribavirin . However, it may be that a longer duration of

therapy may be appropriate already in early trials, to estimate the risk of viral breakthrough. Thus, initial trials with protocols up to 12 weeks of duration may be considered, provided that there is intense real-time monitoring. In a protocol of this duration, patients with end-of-treatment response could undergo viral monitoring after the end of therapy, with the follow-up regimen only being started if virus again becomes detectable when previously undetectable. This would allow for the detection of a putative SVR . Finally, regarding treatment duration in early trials,, protocols may be adapted based on interim analysis, allowing for increasing treatment duration.

As providing proof-of-concept for a novel drug combination (that is, demonstrating its ability to produce SVR) in most cases would likely require treatment and observation of patients for at least one year, there are two possible study populations in which these investigations may be pursued (these approaches are not mutually exclusive). The first is to continue in a population that might readily be salvaged with licensed therapeutic options, as described in the preceding paragraph. An alternative would be to investigate such combinations in patients with an immediate medical need that are deemed not to tolerate existing treatment options (i.e patients with very advanced cirrhosis and some signs of decompensation). From an ethical perspective, this requires that the patients be fully informed about the lack of proof-of-concept. Patients on a transplantation waiting list may provide a bridging population to the general decompensated group (see section 4.5.1).

A population that should not be subjected to experimental regimens prior to obtaining proof-of-concept, and where drug resistance in case of failure is a risk, are patients that may not respond to licensed therapeutic options, but are not considered in immediate need of therapy (e.g., pegIFN null responders without advanced fibrosis).

Available experience has shown that regimens without ribavirin are associated with unacceptable relapse rates, and show higher rates of on-treatment virological breakthrough. Therefore it is presently recommended that studies aiming at proof-of-concept for regimens without pegIFN include at least one treatment arm with ribavirin added to the experimental combination, unless its absence be specifically justified (e.g., in case of the use of an interacting nucleoside analogue).

As regards confirmatory trials of pegIFN sparing regimens, a licensed therapeutic option would be the most appropriate reference treatment in confirmatory trials of pegIFN sparing regimens, provided that this is relevant for the target population. In case licensed therapeutic options are not appropriate or are contraindicated in the intended target population, other control groups or single arm studies may be appropriate (see section 4.5). European regulators recognize that there are presently no licenced therapeutic options available for patients intolerant to pegIFN, or where this is contraindicated. The efficacy (SVR rates) required for licensure of a pegIFN sparing regimen would be weighed in relation to this fact.

When the clinical activity of 3 DAA/HTA agents are investigated, it is considered likely that at least one of the agents would be characterised as to its activity together with presently licensed drugs. Also, proof-of-concept, or at least a characterisation of SVR responses with dual DAA/HTA +/- ribavirin, may exist prior to the addition of a further agent to enhance efficacy. The above considerations concerning the prior study of the individual agents apply also to this sort of regimen. The need for drug interaction studies would be dependent on the qualities of the individual components. As there is presently no experience of such regimens, regulatory advice is recommended prior to initiating clinical trials.

4.4.6. Specific concerns regarding immunomodulating agents

Investigational agents against HCV that are expected to exert their antiviral effect through modulation of host immune function include, e.g., lambda interferons and toll-like receptor agonists. These are presently in early drug development; thus data on their efficacy and safety are limited. However, it is

clear that major safety concerns related to such agents will include the risk of autoimmune events and the like. Though it is recognised that such agents might be used in various drug combinations, some of these agents may primarily be aimed as a substitute for pegIFN within drug regimens, e.g., if additive or synergistic effects with pegIFN be considered unlikely, their co-administration be considered unsafe, and/or the major rationale for the drug be increased tolerability rather than higher efficacy compared to pegIFN. In such cases, the most straightforward way to investigate risk/benefit would be a head-to-head comparison with a pegIFN, each in combination with a DAA + ribavirin.

4.4.7. The use of erythropoesis stimulating agents (ESA) in confirmatory trials

Anemia is the main dose-limiting side effect of ribavirin, and this should primarily be managed according to the product labelling. If it emerges that a DAA/HTA causes anemia, it may interact in an additive or synergistic manner with ribavirin in this respect, and it may be foreseen that the maintenance of DAA/HTA exposures necessary for optimal antiviral activity could be problematic. In clinical care, as well as in some clinical trials, ESA have been used (off-label) to augment the tolerability of CHC treatment. The risks and benefits of this practice, however, are presently not fully investigated. If the use of ESA is to be permitted within confirmatory trials, this should be protocol-specified and fully justified.

4.5. Studies in special populations

4.5.1. Treatment of patients with decompensated liver disease and/or pre-transplant

PegIFN and ribavirin are contraindicated in patients with decompensated liver disease. Therefore, DAA and/or HTA in combination are anticipated for use in this population. Prior to initiating clinical trials, pharmacokinetics and short term safety should be investigated in patients over the relevant functional range (e.g., Child-Pugh B and C).

Populations include the wide population, as well as the subgroup that are on a waiting list for transplantation (pre-transplant). In most cases, SVR would be the most relevant endpoint for studies in a decompensated population (for exceptions, see below). In the subgroup of pre-transplant patients, however, on-treatment virological response and frequency of graft reinfection are more relevant endpoints.

The very first short-term studies of novel combinations lacking proof-of-concept should be performed in patients with compensated liver disease that can likely be salvaged in case of failure, as stated in section 4.4.5. However, following this, single arm studies of such regimens might be initiated in patients with decompensated liver disease prior to obtaining proof-of-concept in the form of SVR in compensated patients. One option would be to study the novel combination in the pre-transplant population, where safety data could be generated and patients might have a palpable clinical gain in the form of prevention of graft reinfection, even if the regimen would not deliver SVR. The other option would be to enroll well-informed patients with advanced liver disease that cannot use existing options, in whom the putative benefit of SVR is considered to outweigh the risk that the regimen proves inefficient or toxic. While it is recognised that this option requires that patients are well-informed, it is considered preferable that early access to novel combination regimens be delivered in the form of clinical trials, rather than in a form that is not readily evaluable. Also, if the aim of treatment is SVR, proof of concept for the combo would be expected to have been generated in patients with compensated liver disease.

In general, in a patient population with decompensated liver disease, single arm studies are anticipated when the primary endpoint is SVR. A sample size of approximately 100 might be sufficient for the evaluation of risk-benefit prior to putative labelling.

Apart from DAA/HTA only combinations, notwithstanding the present labelling, studies of DAA/HTA containing regimens including the experimental use of ribavirin, or pegIFN at lower doses or shortened duration, might be feasible in some patients with decompensated cirrhosis, if conducted at specialist centres with intense monitoring.

It is also possible that a single or combinations of HTAs and/or DAAs with high barriers to resistance may be studied as maintenance therapy in patients with decompensated liver disease. In such trials primary endpoints might include time to death and/or liver transplantation, as well as improvement in hepatic function (e.g., Child Pugh classification, MELD score). Virological endpoints would be secondary in this setting, Putative targets include SVR, but perhaps also functional improvement or time to transplant/death. Such studies should be comparative and, at present, placebo controlled.

As graft reinfection with HCV is almost universal post transplantation, studies aiming at on treatment virological response prior to transplant, with a primary aim of preventing graft infection, are welcomed. Again approximately 100 patients in a single arms study (prior to the labelling of drugs for this indication) might be an adequate target sample size.

In all the above, it is anticipated that DAA/HTA for use in the decompensated patient group are also developed for the use in patients without decompensated liver disease. If a DAA/HTA is developed solely for use in the decompensated population, regulatory scientific advice should be sought.

4.5.2. Post transplant treatment

As stated above, reinfection of the liver graft is almost 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 for many other indications. The tolerability of pegIFN and ribavirin is compromised in this group, and the overall efficacy of pegIFN and ribavirin is low, particularly in patients with GT1 infection. Thus there is an urgent need for new therapies, both as add-on to pegIFN + ribavirin, as well as regimens without these components. It would be expected that proof-of-concept for the drug combination be obtained in non-transplanted patients prior to studies. Also, drug interactions with immunosuppressive agents and other drugs used in this setting should be considered. It is recognised that formal drug interaction studies with some immunosuppressive agents may not readily be conducted in healthy volunteers, and that close monitoring of pharmacokinetics may be required during trials. Single arm studies are presently anticipated for labelling; however, as drug combinations are licensed for treatment in the post transplant setting, comparative trials may become more appropriate.

4.5.3. HCV/HIV coinfected patients

The progression of liver disease is more rapid in patients co-infected with HIV, at least in those with low CD4+ cell counts. Also, in clinical trials, the efficacy of pegIFN and ribavirin in co-infected patients has been considerably lower than in mono-infected patients. If this is only due to the impact of HIV on the immune system, or perhaps also to patient selection and traditional baseline risk factors, is not fully known. Nevertheless, there is an urgent medical need for improved therapies in this patient group. This includes combination regimens with one or two DAA/HTAs and pegIFN+ribavirin, as well as combinations excluding these components. As the development of cirrhosis is accelerated in patients with co-infection, expanded access programs are encouraged for co-infected patients, particularly those with more advanced fibrosis.

It is recognised that the co-infected population is not homogenous. It varies not only in terms of HCV genotype, treatment experience and degree of hepatic injury, from mild to decompensated, but also to the degree of HIV-related immunosuppression (e.g., CD4+ cell counts). Furthermore, drug interactions may present a formidable problem, particularly in patients treated with CYP3A-inhibiting pharmacoenhancers such as ritonavir. It is expected that appropriate drug interaction studies be performed prior to the study and use of investigational DAA/HTA in patients receiving antiretroviral therapy. Such studies, in so far as mechanistically motivated, may be crucial for the safe and efficacious use of novel DAA/HTA in the co-infected population. However, there is no need for a full panel of drug interaction studies prior to trials in co-infected populations, which may contain restrictions regarding permitted antiretroviral medications (e.g., no use of ritonavir and/or certain nucleoside analogues: see also section 4.3.1.)

Relevant population strata among co-infected patients would include CD4 count in addition to those of general importance for HCV-infected patients (viral genotype, IL28B, treatment experience, degree of hepatic injury, etc). Depending on the characteristics of the particular drug and the extent of available data on the relevant drug combination, inclusion in exploratory and confirmatory trials in co-infected patients may be limited in varying ways, and no general rule for appropriate inclusion and exclusion criteria can be given. It is noted, however, that most patients to receive HCV treatment in clinical practice are likely to receive concomitant antiretroviral therapy. This should be reflected in clinical trial protocols. Regulatory advice should be sought prior to initiating confirmatory trials.

Presently, single arm trials are foreseen in this population, but this may be subject to change as treatment options are licensed. As regards various subgroups of co-infected patients (see above), specific efficacy demonstrations would not be required for each stratum, but the evaluation would take efficacy data in the monoinfected into account. In principle, trials of approximately 100 patients might suffice to establish whether further studies are needed.

4.5.4. PegIFN and ribavirin intolerant patients

This category includes patients with “formal” contraindications to either agents, patients deemed by their physicians not likely to tolerate therapy, as well as patients who have discontinued either drug due to side effects. As patients not tolerating pegIFN presently lack licensed treatment options, the need for new therapies is urgent. However, this patient category is heterogeneous. Some of these patients belong to other groups treated in this document under the label “special populations” (e.g., decompensated liver disease), and should be considered as such. However, there are numerous comorbidities that complicate or contraindicate pegIFN therapy, and there are numerous reasons why patients may not have tolerated pegIFN treatment (e.g., haematological, autoimmune, endocrine or psychiatric side effects). For this reason, while studies of pegIFN sparing regimens are strongly encouraged for such patients, it is difficult to set up a general definition of “pegIFN intolerant”.

The class of agents where study in a general population defined as “pegIFN” intolerant would primarily include agents that could putatively have similar side effects and safety concerns (e.g., lambda interferons and other immune modulators). As long as there is no licensed reference treatment for patients not tolerating pegIFN, single arm studies would be appropriate. However, the full evaluation of the safety of a novel immunomodulator prior to licensure may require a head-to-head comparison with pegIFN (see section 4.4.6).

4.5.5. Patients with prior DAA experience

This patient population is of considerable heterogeneity. Firstly, the DAA class and compound tried differs. Secondly, the reason for an unsuccessful DAA experience may be virological failure or lack of tolerance. Thirdly, patients with prior virological failure may have been exposed to an optimised or to a

suboptimal regimen (e.g., monotherapy or an insufficient dose), and may or may not have evidence of persistent viral resistance. If lack of tolerance was the cause of failure, the culprit might have been the DAA or the background therapy.

Much is presently unknown concerning the impact of emergent drug resistance as regards subsequent therapy with a partially cross-resistant compound, with more than one DAA/HTA (including the one previously used), or, if relevant, with more appropriate doses of the same DAA. It is clear that most patients that fail virologically when treated with DAAs in combination with pegIFN and ribavirin, are poor responders to pegIFN. 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. 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. Presently, single arm trials are anticipated, but if combination regimens with more than one DAA/HTA are considered, comparative trials may be appropriate.

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 treatment, and are not considered a well defined target population for clinical trials.

4.5.6. Studies in children

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 pediatric populations may be anticipated if data from adult trials are encouraging, consideration should be given to initiating studies to explore the appropriate dosage, virological response and safety of the new agent in pediatric populations after completion of phase III studies in adults. The major medical need in the pediatric population pertains to GT1 patients, where increased efficacy above that of pegIFN+ribavirn, as well as a shortened treatment duration with these agents, are considered valuable goals.

It is anticipated that the first studies of new agents in the pediatric population will be the combination of a DAA with pegIFN+ribavirin. As regards appropriate ages for inclusion, treatment during the pubertal growth spurt should generally not be expected, as well as in patients below the age of three years (due to their known potential for spontaneous viral clearance) . Depending on adult data, treatment experienced patients might be included in pivotal pediatric trials, if they are likely to benefit based on prior response to pegIFN+ribavirin. Treatment of different genotypes might be studied in the same trial if virologically rational, but stratification should be used; the same holds for patient IL28B genotype. As liver biopsies are still part of the routine management of pediatric HCV infection, such data should be collected at baseline.

Generally, if efficacy and acceptable safety have been convincingly demonstrated in adults, single-arm pediatric trials are anticipated, prior to the licensure of a DAA/HTA option for pediatric patients. The relative increment in treatment effect compared to historical data should be consistent with what is seen in adults. As new treatment options for children are licensed, comparative designs may be appropriate for confirmatory trials.

As regards safety issues particular to the pediatric population, on treatment growth should be evaluated, and patients followed up for at least 5 years after therapy. Pubertal development and

parental heights should be documented, to allow for a full assessment of any impact of therapy on adult stature.

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 currently licensed drugs, and 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 DAA/HTA 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 DAA/HTA in combination with agents with a well known safety profile, such as pegIFN +/- ribavirin, where the safety profile of the individual investigational agent can be characterised.

5. Definitions and Abbreviations:

Breakthrough:	The re-emergence of detectable virus while on treatment after previously being undetectable or a confirmed increase of at least 1 log10 in HCV-RNA during treatment.
CHC:	Chronic Hepatitis C
DAA:	Directly acting antiviral
ETR:	End of Treatment response (undetectable plasma HCV-RNA at the end of therapy)
GT:	Viral genotype
HTA:	Host targeting antiviral
MELD:	Model for End Stage Liver Disease
Non-responder:	at least 2 log10 decline at week 12, but never reaching undetectable virus during pegIFN+ribavirin therapy.
Null-responder:	less than 2 log10 decline at week 12 of pegIFN+ribavirin therapy
PegIFN:	Peginterferon
Relapse:	undetectable virus at end of treatment but subsequent re-emergence of detectable HCV-RNA
SVR:	Sustained virological response (undetectable plasma HCV-RNA 24 weeks after the planned end of therapy)