Guidance for Industry

Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Revision 1

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Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of direct-acting antiviral (DAA) drugs for the treatment of chronic hepatitis C (CHC) from the initial pre-investigational new drug application (pre-IND) through the new drug application (NDA) and postmarketing stages.[2] For the purpose of this guidance, we define direct-acting hepatitis C virus (HCV) antivirals as drugs that interfere with specific steps in the HCV replication cycle through a direct interaction with the HCV genome, polyprotein, or its polyprotein cleavage products. Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs to support DAA drugs. This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public.[3]

This guidance does not address the development of drugs that target host functions necessary for viral replication or immune-based drugs for the treatment of HCV infection such as new interferon (IFN) drugs. Therapeutics without antiviral mechanisms intended to mitigate or reverse clinical or pathophysiological outcomes of CHC, such as prevention of hepatocellular carcinoma (HCC), reversal of fibrosis, or treatment of acute hepatitis C, are not addressed in this

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated in CDER unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of DAAs.

guidance. This guidance discusses development of DAAs with and without IFN, but the main focus of this guidance is on development of DAAs as part of IFN-free regimens.

Additionally, general issues of statistical analyses or clinical trial design are not addressed in this guidance. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4] This guidance also does not contain details regarding nonclinical safety and toxicology studies unless specific to HCV drug development. Such studies for direct-acting HCV antivirals generally should be conducted in standard animal models as described in the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

This guidance revises the draft guidance for industry *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment* issued in September 2010. Significant changes in this revision include:

- Details on phase 2 and phase 3 trial design options for the evaluation of IFN-free and IFN-containing regimens in treatment-naïve and treatment-experienced populations, including DAA-experienced populations

- Revised primary endpoint to sustained virologic response at 12 weeks post-treatment cessation

- Greater emphasis on DAA drug development in specific populations including trial design options for human immunodeficiency virus (HIV)/HCV co-infected subjects, subjects with decompensated cirrhosis, and subjects pre- or post-liver transplant

- More details on clinical virology considerations for DAA drugs

Development of treatments for hepatitis C is a rapidly evolving field with substantial scientific advances announced at every major liver disease meeting. Therefore, sponsors are strongly encouraged to contact the DAVP regarding scientific advances that affect their DAA drug development program.

Sponsors considering development of antiviral drugs for the treatment of CHC are encouraged to communicate with the FDA through the pre-IND consultation program.[5] Pre-IND consultation with the FDA is optional, although it may be particularly helpful for sponsors with limited experience in the IND process or with unusual drugs or treatment approaches.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family (Kim, Chang, et al. 2013). At least six viral HCV genotypes are identified, numbered 1 to 6; most genotypes have been divided into multiple subtypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70 to 80 percent), followed by genotypes 2 and 3. The remaining genotypes occur uncommonly in the United States, but may predominate in other parts of the world (Bostan and Mahmood 2010).

In the United States, approximately 3 million people have chronic HCV infection (Armstrong, Wasley, et al. 2006; Klevens, Dale, et al. 2012). CHC causes cirrhosis and hepatocellular carcinoma and is currently the most common reason for liver transplantation in the United States. By 2007 there were more yearly deaths in the United States related to HCV than HIV (Ly, Xing, et al. 2012) and, without effective treatment interventions, significant increases in CHC-associated morbidity, mortality, and health care costs are predicted (Kim 2002).

The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation, and HCC. However, because progression of liver disease occurs over a long period of time, clinicians use sustained virologic response (SVR), defined as lack of detection of HCV RNA in blood several months after completing a course of treatment, to determine treatment success. SVR is considered a virologic cure (Shiratori, Ioto, et al. 2005; Singal, Volk, et al. 2010).

Current treatment of CHC is rapidly evolving. Total duration of treatment and choice of regimen may depend on HCV genotype or subtype and host genotype. For many years, the standard of care for treatment of CHC had been a combination of pegylated interferon alpha-2 (peg-IFN) and ribavirin (RBV) administered for 24 (genotypes 2 and 3) or 48 weeks (genotype 1 and others). Evaluation of SVR at 24 weeks (SVR24) post-treatment cessation has been the universally accepted time point to assess virologic response. With peg-IFN- and RBV-based therapy, viral relapse usually occurs within the first few weeks following treatment cessation and measurement of SVR at an earlier time point could yield greater trial efficiency (Chen, Florian, et al. 2013).

The addition of a DAA (e.g., HCV protease inhibitor) to peg-IFN and RBV has substantially increased SVR (Casey and Lee 2013). In addition, proof of concept for achieving SVR using only DAAs (without IFN) has been established. It is expected that IFN-free regimens will be the future of CHC treatment for the majority of patients (Zeuzem, Soriano, et al. 2012).

Key on-treatment virologic response milestones that have been used to guide treatment duration are also evolving. On-treatment responses to peg-IFN/RBV and peg-IFN/RBV/DAA regimens have included:

1. Rapid virologic response (RVR; an HCV RNA not detected at week 4 of treatment)

2. Complete early virologic response (HCV RNA not detected at week 12 of treatment)

3. Extended rapid virologic response (HCV RNA not detected at week 4 through week 12 of treatment)

Additional on-treatment response criteria to guide treatment duration (i.e., response-guided therapy (RGT)) are included in the package inserts of HCV NS3/4A protease inhibitors used in combination with peg-IFN and RBV. It is expected that criteria for treatment duration and early discontinuation will change over time depending on the regimen. Because on-treatment virologic responses by themselves are not expected to provide a sustained clinical benefit, it is important to distinguish between on-treatment antiviral activity and treatment efficacy. Throughout this guidance, antiviral treatment *efficacy* refers to SVR, whereas antiviral *activity* refers to treatment-associated reductions in HCV RNA levels such as 1, 2, and 3 above.

Host factors (e.g., genetic polymorphisms and metabolic parameters) and viral factors (e.g., HCV genotype and resistance-associated amino acid substitutions) are being investigated for their roles in predicting response to treatments for CHC. In particular, certain host genetic polymorphisms near the interleukin 28B (IL28B) gene, encoding IFN-λ-3 (IFN-λ-3), have been shown in several studies to predict an approximately two-fold increase in treatment efficacy for peg-IFN/RBV in subjects of African-American and European ancestries (Ge, Fellay, et al. 2009). These genetic polymorphisms can affect the efficacy of DAA + peg-IFN/RBV regimens (Poordad, Bronowicki, et al. 2012), and also may affect the efficacy of peg-IFN-free, combination DAA regimens (Zeuzem, Soriano, et al. 2012).

III. DEVELOPMENT PROGRAM

A. General Considerations

Information about pre-investigational new drug testing and information regarding appropriate nonclinical assays is available from the FDA.[6] Virology development for HCV DAAs should follow existing guidance for drug development.[7] Additional recommendations for nonclinical

[6] See the FDA Web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm.

[7] See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency.*

and clinical virology specific to the development of HCV DAAs are summarized throughout this guidance.

1. Pharmacology/Toxicology Development Considerations

Pharmacology/toxicology development for single direct-acting HCV antivirals should follow existing guidances for drug development.[8]

The ICH guidance for industry referenced above, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, recommends nonclinical combination studies to support clinical trials of combination drugs for entities in early stages of development. Section I.C., Scope of the Guidance, states, "Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimize and expedite drug development."

For new HCV drug combinations (consisting of two or more investigational drugs) that are not expected to represent an advantage (in terms of efficacy, tolerability, safety, use in specific populations or ease of administration) over approved combination therapies, combination toxicology studies usually should be submitted as part of an IND to conduct combination clinical trials. However, usually no more than two drugs should be tested simultaneously in a particular arm of a toxicology study. The design of such studies should be discussed with the DAVP. For DAA combinations that are expected to treat patients with limited or no treatment options or to improve response rates in patients at risk of serious morbidity or expected to be a substantial improvement over approved therapies, the FDA may conclude that the benefits of these combinations outweigh the potential risks of foregoing the combination toxicology studies when all of the following apply:

- Mechanisms of action or in vitro data of potential off-target effects of the individual drugs do not suggest a potential for additive or synergistic toxicity of a serious nature.

- Studies in animals or humans of absorption, distribution, metabolism, and excretion of the individual drugs show no potential for an unmanageable interaction (one that cannot be addressed with dose adjustments) or serious toxicity for the combination.

- Toxicology studies (of at least 3 months duration) of the individual drugs show a substantial safety margin for the intended clinical dose(s) or exposures.

[8] See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

- Phase 1 clinical data in healthy volunteers or HCV-infected subjects receiving the individual drugs show no substantial or unmanageable safety concerns. Phase 1 data should include single- and multiple-dose pharmacokinetic (PK) and safety trials, at minimum. Additional safety data from phase 1 and phase 2 trials are encouraged and may be needed if one or more of the drugs demonstrate a potential serious safety risk.

- There are no concerning overlapping toxicities for the individual drugs based on animal toxicology studies and phase 1 or phase 2 clinical data.

- Clinically significant PK-based drug interactions are considered unlikely or can be reliably managed with dose adjustments such that safety margins based on individual drug exposures are not exceeded.

After considering the above points, sponsors can first evaluate (in phase 1 and phase 2) drug combinations in HCV-infected subjects who are treatment naïve or have remaining treatment options. After initial trials in treatment-naïve subjects (or in subjects who have remaining approved treatment options) have helped to define the most active doses, subjects with few or no remaining options can be studied. This approach helps to ensure that subjects with no remaining treatment options are not exposed to suboptimal doses or combinations that could severely jeopardize their chance for achieving SVR. However, combination trials in healthy volunteers or subjects with early stage CHC should not be the first-in-human trials unless the drugs cannot be administered separately and unless combination toxicology studies have been completed. We recommend referring to ICH guidance (i.e., *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*) in designing such studies.

Nonclinical combination studies of an investigational DAA plus an approved DAA or IFN and RBV generally are not needed. Therefore, unless data from nonclinical studies of an investigational DAA suggest a potential for serious synergistic toxicity with an approved therapeutic drug, combination toxicology studies are not anticipated.

Applicants can choose to submit carcinogenicity studies with an initial NDA. Applicants who do not choose to do so may be required to submit carcinogenicity studies as postmarketing studies under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[9]

2. Nonclinical Virology Development Considerations

a. Mechanism of action

The mechanism by which a DAA exhibits anti-HCV activity should be investigated in studies that include evaluation of the effect of the drug on relevant stages of the virus life cycle. Mechanism-of-action investigations should include appropriate controls for assessing the

[9] See also the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*.

specificity of anti-HCV activity, which may include assessments of activity against unintended HCV target proteins, related host proteins, or other viruses.

b. Antiviral activity in cell culture

The antiviral activity of a new drug should be characterized in cell culture to demonstrate activity and identify a target plasma concentration for evaluation in HCV-infected subjects. Antiviral activity of candidate drugs targeting nonstructural components should be assessed using HCV replicon systems, and 50 and 90 percent effective concentrations (EC_{50} and EC_{90}) determined. We recommend evaluation of the drug's antiviral activity at different concentrations of human serum and extrapolation to a 100 percent human serum-adjusted EC_{50} value. The antiviral activity of drugs that target HCV entry functions can be evaluated using HCV pseudoparticle systems. Assessments of antiviral activity against HCV grown in cell culture are recommended for any anti-HCV drug when appropriate.

Cell culture antiviral activity studies should include assessments of antiviral activity against the major U.S. HCV genotypes and subtypes and those for which an indication will be sought. We also recommend assessments of antiviral activity against replication models using HCV components derived from multiple clinical isolates because antiviral activity can vary for strains within each subtype. If sponsors observe differences in susceptibility for different clinical isolates within the same viral genotype or subtype, they should conduct additional genotypic and phenotypic characterizations to identify genetic polymorphisms that may affect HCV susceptibility to the drug.

The cytotoxic effects of the drug should be quantified directly in the cells used for assessing anti-HCV activity, and a 50 percent cytotoxic concentration (CC_{50}) and therapeutic index should be calculated (CC_{50}/EC_{50}). Cytotoxicity also should be assessed using various cell lines and primary cells cultured under proliferating and nonproliferating conditions. Mitochondrial toxicity should be assessed under proliferating conditions for nucleos(t)ide analog polymerase inhibitors. Positive controls should be included for these assessments.

c. Antiviral activity in animal models

Demonstration of anti-HCV activity in an animal model is not critical. However, if such studies are conducted and provided in support of an anti-HCV therapy program, reported data should include the HCV genotype/subtype used, time course plots of viral load data for each animal, and an assessment of resistance development that includes monitoring the persistence of resistant virus in the absence of anti-HCV treatment.

d. Combination antiviral activity

Most, if not all, HCV DAAs will be used to treat CHC in combination with other anti-HCV drugs. Early in development, cell culture combination antiviral activity relationships of the new drug and other drugs anticipated to be used in combination should be characterized to determine whether or not the combination antiviral activity is antagonistic. For all combination antiviral activity assessments, sponsors should provide combination index values when the two drugs are

combined at or near their individual EC_{50} values, and studies should include controls for cytotoxicity and antagonism (Coelmont, Paeshuyse, et al. 2006). Combination antiviral activity relationships for HIV and HCV drugs with similar mechanisms of action (e.g., HIV nucleos(t)ide analogue reverse-transcriptase inhibitors and HCV nucleos(t)ide analogue NS5B polymerase inhibitors) also should be assessed before testing combinations of the drugs in HIV/HCV co-infected subjects.

e. Resistance and cross-resistance

The ability of HCV to develop resistance to a DAA when subjected to drug selection should be examined in appropriate cell culture models. Amino acid or nucleotide substitutions associated with the development of resistance to the candidate drug should be determined and validated by introducing the changes into the HCV genome and determining the conferred fold-shift in susceptibility using cell culture and/or biochemical assays. Results from these studies should be used to: (1) characterize the genetic barrier for resistance; (2) predict whether a clinically achievable concentration of the new drug can reduce the enrichment of drug-resistant viral populations; (3) identify potential resistance pathways; and (4) support the drug's hypothesized mechanism of action. The *resistance barrier* for an HCV DAA depends on many factors, and usually is defined as it relates to other drugs that are approved or in development (Kwong, Najera, et al. 2011).[10]

Resistance studies should include evaluation of the potential for cross-resistance, both to approved drugs and to drugs in development (when possible), particularly focusing on those in the same drug class and other classes with the same viral target. Although the mechanism of action for RBV remains unclear, RBV should be included in assessments of cross-resistance for inhibitors that target the NS5B RNA-dependent RNA polymerase.

3. Drug Development Population

Drug development programs should include as broad a population as appropriate for the characteristics of the antiviral drug. However, a DAA may have differential activity against different HCV genotypes or subtypes; therefore, development can be targeted to a specific genotype (e.g., genotype 1 versus genotype 2 or 3) or subtype (e.g., genotype 1a versus genotype 1b). We recommend including subjects diagnosed with compensated cirrhosis in phase 2 and phase 3 trials. Also, we encourage the study of combinations of DAA HCV antivirals in subjects with the greatest need for new drugs, such as subjects who cannot tolerate IFN, subjects for whom IFN is contraindicated, subjects with bleeding disorders, transplant subjects, and subjects with decompensated cirrhosis.

Similarly, subjects on opioid maintenance therapy should be studied after the potential for drug-drug interactions between the investigational drug and medications used for opioid maintenance therapy is understood. DAAs can be studied in combination with other DAAs, with or without

[10] For the purpose of this guidance, a drug is generally defined as having a low resistance barrier when one or two specific nucleotide changes from the wild-type consensus sequence are adequate to confer HCV resistance to a clinically relevant concentration of the drug.

RBV, and with or without peg-IFN in HIV co-infected subjects as soon as appropriate based on the availability of data to choose an appropriate dose and rule out or manage important drug-drug interactions. Supportive data may be needed before trials in the above-mentioned subgroups to define safety and pharmacokinetics, such as hepatic impairment trials and drug-drug interaction trials (e.g., antiretrovirals for HIV, immunosuppressants for transplant).

CHC is a disease that is present worldwide and clinical trials typically are conducted internationally. However, trials should include adequate U.S. subject representation to ensure applicability of trial results to the U.S. population. An adequate representation of males and females, races, ages, and weights is recommended during drug development, especially in phase 3 trials. Because race (e.g., Black, Asian) and ethnicity (e.g., Latino) affect response rates to anti-HCV treatment, the ability to ensure sufficient diversity in clinical trial demographics to conduct meaningful analyses of such groups is important (Hepburn M, Hepburn L, et al. 2004). In addition we encourage sponsors to include investigators and sites who have experience treating CHC patients who use intravenous drugs so that the clinical trial data can reflect the spectrum of patients who will use CHC treatments after approval. Sponsors should share with the FDA their pretrial initiation work to ensure the sites selected have sufficient numbers of subjects from these populations (e.g., women, Black/African Americans, Hispanic/Latinos, subjects with cirrhosis, subjects with bleeding disorders, and subjects using intravenous drugs) to enroll in phase 2 and phase 3 clinical trials.

4. Early Phase Clinical Development Considerations

a. General considerations for phase 1 and phase 2 development

Early clinical evaluation of HCV DAAs should follow a rational approach to provide sufficient data to establish safety, antiviral activity, and antiviral efficacy to support phase 3 trials. In general, phase 1 trials should be conducted to assess safety, pharmacokinetics, and initial antiviral activity of the DAA. Phase 2 trials should characterize the optimal dose and treatment duration of the DAA(s) as part of combination regimens with regard to both antiviral activity and safety.

Based on HCV replication dynamics in infected subjects (Rong, Dehari, et al. 2010), the error-prone nature of HCV genome replication, and the fact that the activity of a DAA is often reduced by a single amino acid substitution in the drug target, multiple anti-HCV drugs with non-overlapping resistance pathways generally are needed to suppress pre-existing and emerging drug-resistant variants for most patients to achieve SVR. Sponsors can choose to develop a DAA for dosing in combination with other DAAs (with or without RBV), or in regimens that include peg-IFN. The overall design of a phase 2 clinical development program should attempt to demonstrate the contribution of individual drugs in the regimen (as described in section III.A.5., Efficacy Considerations).

Sponsors should provide the following information to support phase 2 trials of multiple DAAs:

- Mechanism of action for each drug in combination.
- Resistance and cross-resistance patterns for each drug in the combination.
- Combination antiviral activity data from cell culture studies.
- Anti-HCV activity data from clinical trials (e.g., short-term monotherapy trials, or dose-finding trials in combination with peg-IFN/RBV or other antiviral drugs).
- Human safety data on each drug.
- Data from clinical trials or other sources that indicate chosen doses and duration of dosing provide anti-HCV activity. Dose selection should take into consideration potential for overlapping toxicities with the individual components.
- Drug-drug interaction data if the metabolism profiles suggest an interaction potential between drugs in the combination regimen.

A primary objective of a phase 2 program should be demonstration of proof of concept of efficacy (i.e., SVR) for DAA-containing regimens that are planned for study in phase 3. Early on-treatment virologic responses and end-of-treatment responses often are not predictive of SVR for DAA-containing regimens. Therefore, off-treatment responses (such as undetectable virus at weeks 4 or 12; also called SVR4 or SVR12, respectively) should be available before progression to phase 3.

Phase 2 studies also should be designed to include a representative population of subjects with chronic HCV infection. These populations include, but are not limited to, Blacks/African Americans, Hispanics, prior peg-IFN/RBV treatment failures, and subjects with compensated cirrhosis. Inclusion of these groups in phase 2 will assist in sample size calculations and estimations of expected SVR rates in phase 3.

The appropriate scale (e.g., number of subjects and treatment arms) and specific design aspects of an early phase development program for a new HCV DAA depend on many factors. Possible phase 2 trial designs can vary greatly depending on whether a DAA is intended to be used in combination with a peg-IFN, or if the DAA will be developed only for use with other oral antiviral drugs. Also, as more safe, tolerable, and effective drug regimens become available, we anticipate the risk-benefit considerations for many subject populations will evolve. In turn, the availability of additional treatment options for subjects can affect both early phase trial design as well as the amount of preliminary safety and efficacy data needed for progression to phase 3.

For an end-of-phase 2 meeting, SVR4 data from all enrolled subjects and any SVR12 (or longer) data from phase 2 trials should be available to support progression to phase 3. All available SVR data from all regimens under study in the drug development program should be used to select appropriate drug regimens and subject populations chosen for study in phase 3.

The following subsections provide recommendations and examples for potential phase 1 and phase 2 trial designs for HCV DAAs based on the current state of the field.

b. Phase 1a/First-in-human trials

In general, we recommend single- and/or multiple-ascending-dose trials in healthy adult subjects to assess safety and pharmacokinetics for the first-in-human trials. Single-dose and short-duration multiple-dose PK trials (see below) also can be conducted in HCV-infected subjects; testing should be done in HCV-infected subjects if nonclinical data indicate a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers.

c. Phase 1b (proof-of-concept) trials

The first proof-of-concept antiviral activity trial in HCV-infected subjects should be a repeat-dose, randomized, dose-ranging, monotherapy trial with collection of intensive PK, safety, and HCV RNA data. Doses selected for phase 1b should be predicted to provide plasma and/or liver tissue drug exposures that exceed by several-fold the protein binding-adjusted, cell culture EC_{50} value of the drug for the relevant HCV genotype/subtype. The doses evaluated also should take into account any safety margins previously identified in animal toxicology studies and in any trials conducted in healthy volunteers. We generally recommend initial antiviral activity phase 1b trials be conducted in subjects with CHC who are naïve to previous anti-CHC therapy (including the drug under investigation), and who have minimal fibrosis and no significant comorbidities. Following demonstration of safety and antiviral activity in treatment-naïve subjects, sponsors can plan additional trials in treatment-experienced subjects, as appropriate.

The maximum recommended duration of DAA monotherapy for an initial phase 1b trial depends on several factors, such as the drug's mechanism of action, pharmacokinetics, expected resistance barrier, study population, and availability of other drugs within and outside of the drug class. For example, for an NS3/4A protease inhibitor or NS5A inhibitor with a low resistance barrier and overlapping resistance pathways with other drugs in the class, the recommended maximum duration of monotherapy is approximately 3 days. In this example, monotherapy exceeding 3 days is not recommended because previous data with these DAA classes indicate resistant virus is rapidly selected during monotherapy, and prolonged selection of resistance may reduce the efficacy of other treatments and limit future treatment options for study subjects.

On the other hand, a dosing duration of 3 to 7 days may be justified for a DAA that represents a novel DAA class, has a relatively higher predicted resistance barrier, or requires several days of dosing before achieving steady state. Additionally, multiple weeks of monotherapy could be appropriate for a drug that does not specifically target intracellular HCV replication, for which demonstration of an HCV RNA decline would require loss of infected cells. All DAA monotherapy trial protocols should include justification for the proposed duration of treatment. Additionally, monotherapy trials of a drug with an unusually long half-life that could lead to resistance should include plans to minimize risk to patients.

Results from proof-of-concept antiviral activity trials can be used to guide dose selection for subsequent phase 2 trials in which DAAs are studied for longer durations as part of a combination regimen. We recommend sponsors conduct mechanistic modeling of the concentration-viral kinetics and the concentration-safety profile from phase 1 monotherapy trials to predict the most active and tolerable doses for study in phase 2. The mechanistic viral kinetic model should describe time-dependent changes in HCV RNA and the effect of drug concentrations (Snoeck, Chanu, et al. 2010). Results from subjects infected with different HCV genotypes and subtypes should be analyzed independently, as sample size permits, to begin to evaluate dose response relationships for relevant subpopulations. The model also should include components to describe virologic breakthrough or relapse and may be used to inform dose selection and treatment duration based on predictions of SVR. Additionally, the model should be used to identify the appropriate population for treatment, and to reduce the risk of selecting for resistant virus caused by subtherapeutic exposure.

For optimizing the regimen with respect to dose and treatment duration for multiple investigational drugs, one possible approach is to use drug effectiveness parameters and mechanisms of action identified for each individual drug from phase 1 and phase 2 data and combine these observations within a single model. Such models should be evaluated against on-treatment data of the drug combination and drug effectiveness parameter estimates and mechanisms of action should be refined as necessary. Optimal doses identified based on single drug results may not be optimal for combination treatment, and the sponsor is encouraged to evaluate a range of doses in subsequent trials if available data support changes to one or more of the drugs in the combination treatment.

d. Phase 2 trials of IFN-free regimens in DAA-naïve subjects

Specific phase 2 trial designs for all oral, combination DAA regimens can vary greatly depending on the drug class(es), intended patient population(s), HCV genotype, currently available treatment options, and emerging data from other HCV DAA development programs. In general, phase 2 trial designs should be randomized comparisons of subjects with several different combinations of DAAs (all investigational or approved plus investigational) at various doses and treatment durations in IFN-naïve or -experienced subjects. The number of DAAs in a regimen depends on individual drug potency and estimated resistance barriers as determined in earlier stages of drug development. Depending on the DAAs being evaluated, RBV can be included in some or all of the treatment arms. An active-controlled arm including IFN is not needed; however, if an IFN-free DAA drug regimen is approved in the future and becomes a clinically accepted standard of care, then inclusion of that regimen as an active control is recommended. SVR12 is the recommended primary endpoint. Subjects should be followed through week 24 post-treatment cessation to further confirm the reliability of SVR12 as a predictor of virologic success. Trial randomization should be stratified according to HCV genotype/subtype, viral load, IL28B genotype, or other baseline characteristics predicted to have a significant effect on treatment outcome.

Initial trials should include frequent HCV RNA monitoring and both subject- and treatment arm-specific stopping rules for poor virologic outcomes (e.g., virologic breakthrough or relapse). When feasible, protocols should include opportunities for subjects with virologic failure to

receive appropriate alternative therapeutic regimens that could consist of investigational and approved drugs. Final SVR12 and SVR24 efficacy outcome data from subjects who received therapeutic rescue should be collected and reported in final trial reports or other relevant regulatory submissions, because these data could be informative for future clinical trial design as well as for clinical practice.

e. Phase 2 trials; IFN-containing regimens, DAA naïve

Phase 2 trials evaluating HCV DAA(s) dosed in combination with peg-IFN and RBV should explore various dose levels and treatment durations of the DAA(s), possibly with additional treatment duration exploration of the peg-IFN/RBV components. SVR12 is the recommended primary endpoint. RGT, where early virologic response criteria are used to determine the treatment duration, has been used in IFN-containing regimens with the goal of reducing the treatment duration and toxicity of IFN in subjects who appear to be responding well. Examples of approaches for evaluating RGT include:

1. Randomizing subjects to RGT and fixed duration treatment arms

2. Having a second randomization point in one or more treatment arms where *early responders* (e.g., those with RVR) receive either an abbreviated or standard duration of treatment

3. Conducting retrospective analyses of different fixed duration treatment arms to identify subpopulations that may benefit from longer or shorter durations of treatment

The need for further confirmation of an RGT approach in phase 3 depends upon available data from phase 2 trials and emerging data from other trials. Additional guidance on HCV RNA cutoffs for RGT is provided in section III.C.1., Clinical Virology Considerations.

We recommend the first phase 2 trial for dose-finding of a new single DAA plus peg-IFN/RBV regimen be conducted in treatment-naïve subjects. Analyses of on-treatment safety and antiviral activity data from an initial proof-of-concept combination trial with peg-IFN/RBV in treatment-naïve subjects can be used to design larger phase 2b trials to further characterize optimal dosing and treatment duration in broader populations, including both treatment-naïve and treatment-experienced subjects. Host genotypes are emerging as correlates of clinical response to antivirals and may partially explain differences in response rates by race; therefore, collection of subject DNA is an important consideration (Hepburn M, Hepburn L, et al. 2004). Randomization in phase 2 DAA plus peg-IFN/RBV trials should be stratified by IL28B genotype, HCV genotype/subtype, or other baseline characteristics that are predicted to have a significant effect on treatment outcome.

Initial trials of multiple DAAs dosed in combination with peg-IFN/RBV can be conducted in either treatment-naïve or peg-IFN/RBV treatment-experienced subjects. Such trial designs can be supported by antiviral activity data for each individual drug dosed as monotherapy or in combination with peg-IFN/RBV or other anti-HCV drugs. For trials conducted in prior peg-IFN/RBV null responders and other difficult-to-treat populations, proof-of-concept efficacy

should be demonstrated with a treatment duration of approximately 24 weeks (or longer) before exploring shorter durations of treatment.

Other designs may be appropriate in some circumstances and will be considered on a case-by-case basis.

f. Phase 2 trials in DAA-experienced populations

We anticipate the number of single- and multiple-class DAA treatment-experienced subjects will increase as more HCV DAAs are studied in clinical trials and used in practice. Sponsors are encouraged to develop and evaluate new treatment regimens to address the treatment challenges for this population. Patients who did not achieve SVR with a full therapeutic duration of a DAA-containing regimen may be particularly difficult to treat. Many of the host and viral factors that contributed to treatment failure with the prior DAA-containing regimen(s) will still exist, such as advanced liver disease, poor responsiveness to peg-IFN or RBV, poor immune clearance of HCV replication complexes and infected cells, high baseline HCV RNA levels, poor drug pharmacokinetics, poor adherence, poor tolerability, or drug resistance (i.e., enrichment of HCV viral populations that are resistant to one or multiple HCV DAA classes).

Before evaluating DAA-experienced subjects, sponsors should collect data demonstrating proof-of-concept efficacy of the DAAs in DAA-naïve subjects, and ideally in peg-IFN/RBV null responders or other difficult-to-treat populations. Proof-of-concept efficacy in DAA-naïve subjects could be based on trial results of a combination regimen in a small trial or could be extrapolated from efficacy trials of the individual components in combination with other drugs. For example, proceeding with a trial evaluating a regimen of peg-IFN/RBV plus two DAAs from different classes could be supported by SVR data from trials of the individual DAAs dosed with peg-IFN/RBV.

Multiple rounds of DAA treatment failure may severely limit treatment options for subjects; therefore, initial trials in DAA-experienced subjects should include regimens and treatment durations (e.g., at least 24 weeks) that are predicted to provide subjects with the best chance of achieving SVR. For example, exploration of relatively short treatment durations should be considered only after proof-of-concept efficacy has first been demonstrated for longer treatment durations. Also, because of the number of promising DAA classes in development that would be appropriate to test in DAA-experienced populations, we strongly encourage cross-company collaboration when needed to construct a scientifically justified regimen.

Because re-treatment regimens may need to be individualized based on many factors such as prior DAA treatment history, peg-IFN tolerance, and drug resistance characteristics, we are not able to provide detailed guidance on appropriate trial designs for all possible circumstances. Below are examples of appropriate types of investigational regimens for specific subject populations that could be studied in single-arm, historically controlled trials or in dose or treatment duration comparison trials. Alternatives to these investigational regimens will be considered on a case-by-case basis.

1. For subjects who did not achieve SVR with an NS3/4A protease inhibitor plus peg-IFN/RBV regimen:

   - Drug regimen consisting of peg-IFN/RBV and at least two classes of HCV DAAs for which the subject has never been exposed.

   - Drug regimen consisting of peg-IFN/RBV, at least one class of HCV DAAs for which the subject has never been exposed, and one NS3/4A protease inhibitor. The first cohort of subjects should be screened to exclude those with key NS3/4A protease inhibitor resistance-associated substitutions. The need for resistance screening of subsequently enrolled subjects depends on efficacy results from the first cohort.

   - Peg-IFN-free, combination DAA (+/- RBV) regimen with demonstrated efficacy in peg-IFN/RBV null responders or other difficult-to-treat populations without the use of an NS3/4A protease inhibitor. An NS3/4A protease inhibitor could be added to the regimen if hypothesized to provide an efficacy benefit.

2. For subjects who did not achieve SVR with a peg-IFN-free, combination DAA regimen:

   - Drug regimen consisting of peg-IFN/RBV and at least two classes of HCV DAAs, for at least one of which the subject has never been exposed

   - Peg-IFN-free, combination DAA (+/- RBV) regimen with demonstrated efficacy in peg-IFN/RBV null responders or other difficult-to-treat populations

   For example 2, the need for drug resistance screening depends on the specific drug classes in the regimen and the characteristics of the subject population, including HCV DAA exposure history, peg-IFN/RBV treatment history, and peg-IFN/RBV treatment eligibility.

Subjects who were exposed to short, nontherapeutic treatment durations of one or more DAAs, such as in short course monotherapy trials, but otherwise have never failed treatment with a regimen intended to result in SVR, or subjects who were responding virologically but discontinued prior treatment early for reasons unrelated to efficacy, may be eligible for later phase 2 trials (or phase 3 trials) of regimens that have demonstrated proof-of-concept efficacy in DAA-naïve subjects.

Sponsors should identify DAA-experienced subjects in efficacy, clinical virology, and drug resistance datasets for all reports submitted for review. For trials of re-treatment regimens that include one or more HCV DAA classes for which subjects have been exposed, retrospective analyses should be conducted to assess the relationship between re-treatment efficacy and (1) prior treatment response (e.g., breakthrough, nonresponse, relapse); (2) time since prior DAA exposure; and (3) the detection of DAA-resistant HCV populations at baseline using a next generation sequencing assay that can detect and quantify minority variants. Results from these retrospective analyses should be used to guide the design of subsequent trials (e.g., whether inclusion should be based on a certain threshold of detection for drug-resistant HCV populations). See section III.C.1.c., Resistance analyses.

5. Efficacy Considerations

We recommend that sponsors analyze and provide summaries of SVR outcome data (SVR4 data from all enrolled subjects and any SVR12 (or longer) data) from phase 2 to demonstrate that treatment responses are durable and to allow for sample size calculations for phase 3 trials.

Sponsors can submit an NDA to gain approval of a drug in a single population (e.g., treatment-naïve or treatment-experienced subjects). Such an application should include at least two adequate and well-controlled trials conducted in the proposed population intended for labeling. Alternatively, sponsors can choose to pursue an indication for different populations (e.g., treatment-naïve and -experienced subjects). In this circumstance, the NDA should contain at least one adequate and well-controlled phase 3 trial in each subject population, with adequate supporting data from phase 2 trials.

Trial designs for combinations of investigational DAAs with or without RBV should include provisions for demonstrating that each component of the combination therapy contributes to the desired effect. Establishing the contribution of each component can be accomplished using factorial designs or modified factorial designs; however, we acknowledge that factorial designs in which subjects are randomized to only one new DAA may not be appropriate because of concerns of suboptimal efficacy and emergence of resistance. As an alternative to factorial designs, sponsors can show a DAA's contribution toward efficacy of a multiple DAA combination regimen using other types of data. Examples of data supporting contribution of efficacy include but are not limited to the following:

- Cell culture data showing that DAA combinations slow or prevent the emergence of resistance compared to single drugs.

- Clinical trial data showing the efficacy of each new DAA in combination with peg-IFN and RBV.

- Comparisons of HCV RNA reductions in short-term monotherapy trials (e.g., 3-day trials) with HCV RNA reductions with combination therapy in the same trial or across other short-term trials. In this example, the slopes of short-term HCV reductions in subjects given combination therapy with two DAAs should be substantially greater than those observed in subjects given the single drugs.

- Early phase 2 clinical trial data showing that DAA combinations prevent or reduce the emergence of viral variants with resistance-associated substitutions.

Sponsors should consult 21 CFR 300.50 regarding combining drug products in a single dosage form. Additional recommendations for codevelopment of two investigational drugs can be found in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

HCV treatment development plans may be eligible for consideration under 21 CFR part 312, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses, for fast track,[11] breakthrough,[12] or priority review if the specifics of the development plan justify such an approach. See the FD&C Act, 21 U.S.C. § 356 (2012) (as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144, 126 Stat. 993 (2012)).

6. Safety Considerations

In general, we recommend that initial marketing applications for drugs intended to treat CHC in subjects without decompensated cirrhosis contain a safety database of approximately 1,000 to 1,500 subjects exposed to the proposed dose and duration of treatment. However, if significant safety signals emerge during drug development, the safety database may need to be increased or specific safety studies may need to be conducted. Flexibility in the recommended safety database may be considered for investigational drugs that demonstrate substantial improvement in efficacy and improvement in safety profile compared to the currently available therapeutic options. For example, a safety database of 500 to 1,000 subjects may be adequate for an initial marketing application for an IFN-free regimen that is more efficacious, shorter in duration, and better tolerated than currently available treatment.

If the initial NDA is for decompensated cirrhosis or subjects who have a high risk of morbidity or few if any treatment options, a safety database of approximately 300 subjects given the DAA(s) for the proposed dose and duration may be sufficient for filing an application. See section III.C.3., Comorbidities, for more information on safety database recommendations. We encourage sponsors to discuss their proposed safety database before phase 3. On occasion, specific findings in nonclinical or clinical development may indicate the need for a safety database that is larger to adequately evaluate potential drug toxicity.

We strongly recommend sponsors engage in early discussions with the DAVP on the trial designs for subjects who fail to respond to DAA-containing regimens. The subject database size for an indication for re-treatment of DAA failure subjects depends on other available safety and efficacy data for the individual drugs in the regimen, as well as the availability of other treatments for the population. A sole indication for DAA treatment-experienced subjects should be supported by a safety database of at least 300 subjects.

Safety data from randomized controlled and comparative trials is recommended to assess the safety of the investigational drug. Until IFN-free regimens are available, we prefer the immediate versus deferred trial design (see section III.B.1.a., IFN-free regimen in treatment-naïve and treatment-experienced populations) to obtain comparative safety data. In some

[11] See the guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*.

[12] See the FDA fact sheet for breakthrough therapies at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm.

situations, uncontrolled or historically controlled data may be appropriate for marketing applications for the first IFN-free regimens. If IFN-free DAA combination regimens become approved and become the clinically accepted standard of care, we recommend sponsors provide comparative study data using such regimens.

B. Specific Efficacy Trial Considerations

1. Trial Design

The risk-benefit profile of the investigational drug and the available approved treatment options for the indicated population are important factors to determine an appropriate trial design. Although randomized controlled comparative trials are preferable, in some situations, single-arm trials using a historical control may be appropriate. Trial design considerations by type of regimen and intended population are discussed in more detail below.

a. IFN-free regimen in treatment-naïve and treatment-experienced populations

We recommend an immediate versus deferred placebo-controlled trial design in subjects who are not considered to need immediate treatment. In this design, subjects should be randomized to the DAA-based regimen or placebo for the intended treatment duration. At the end of treatment, subjects randomized to the placebo arm can receive the DAA-based regimen. The purpose of the deferred treatment design is to collect comparative safety data rather than to compare virologic response between trial arms. It is expected that no subject will respond virologically while receiving placebo. The primary efficacy comparison will be between immediate treatment and a historical reference of an IFN-based regimen. Sponsors should make adequate provisions in the trial to maintain the trial blind and should also minimize the potential for subjects in the placebo arm to drop out.

For treatment-experienced subjects, the appropriateness of the trial design also should take into consideration the intended treatment-experienced subpopulation (e.g., null responders, partial responders, responder relapsers, DAA-experienced) along with currently approved regimens. See section III.A.4.d., Phase 2 trials of IFN-free regimens in DAA-naïve subjects, and section III.A.4.f., Phase 2 trials in DAA-experienced populations.

Alternatively, for either treatment-naïve or treatment-experienced subjects, a dose or treatment duration comparison or single-arm, historical control trial could be used. Sponsors should include sufficient information in the protocol to support the historical control used.

If IFN-free DAA combination regimens become available, an active-controlled superiority or noninferiority trial design may be feasible and preferred over a single-arm design. Sponsors considering a noninferiority trial design should discuss in advance their justification of the noninferiority margin, trial designs, and the data analysis plans.

b. IFN-containing regimen in a treatment-naïve population

For IFN-containing regimens, appropriate trial designs in the treatment-naïve population include:

- A superiority design in which an investigational DAA is compared to an approved DAA both given in combination with peg-IFN and RBV
- A noninferiority design in which an investigational DAA is compared to an approved DAA both given in combination with peg-IFN and RBV
- Dose-response or duration comparison designs
- An immediate versus deferred placebo-controlled trial design, or single-arm trial with a historical control as discussed above, when an active-controlled trial cannot be conducted

c. IFN-containing regimen in a treatment-experienced population

When designing trials for the IFN-experienced population with a new regimen containing IFN, sponsors should consider the available phase 2 data to determine if an active control is feasible for each IFN-experienced subpopulation (e.g., partial responders, responder relapsers, null responders, and DAA-experienced). If an active-controlled design is not feasible, then an immediate versus deferred placebo-controlled trial design, a dose or treatment duration comparison, or single-arm trial with a historical control as discussed above may be appropriate. Also see section III.A.4.d., Phase 2 trials of IFN-free regimens in DAA-naïve subjects, and section III.A.4.f., Phase 2 trials in DAA-experienced populations.

Subjects failing DAA-containing regimens constitute an emerging population in need of effective HCV therapies, and section III.A.4.f., Phase 2 trials in DAA-experienced populations, provides recommendations and examples for phase 2 trial designs for these subjects. Because of lack of adequate proof-of-concept efficacy in this population, detailed guidance for phase 3 trial design cannot be provided at this time. Sponsors should engage in early discussions with the DAVP regarding development plans in prior DAA treatment-experienced subjects. In general, we anticipate phase 3 trials to be based upon phase 2 proof-of-concept efficacy data. Trial designs and the number of subjects needed to support an indication in patients failing treatment with DAA-containing regimens depends on the specific characteristics of the patient population and the availability of other treatment regimens.

2. Trial Population

a. Subject enrollment definition

To be enrolled in a trial, there should be adequate assurance that subjects have CHC as confirmed by one of the following:

- Positive for anti-HCV antibody, HCV RNA, or an HCV genotype at least 6 months before screening, and positive for HCV RNA and anti-HCV antibody at the time of screening

or

- Positive for anti-HCV antibody and HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrollment with evidence of CHC disease, such as the presence of fibrosis)

In trials of treatment-experienced subjects, the ability to understand a subject's virologic response to his or her prior therapeutic regimen is important to guide future treatment decisions including dose and treatment duration of the investigational drug(s). Historically, the definitions of naïve, null, partial responder, and relapser characterize categories of peg-IFN responsiveness (see Appendix A). In trials of treatment-experienced subjects, an adequate representation of these prior treatment response populations should be included for analysis until sufficient data from DAA trials are available to document similar responses between groups regardless of prior IFN responsiveness. These subjects should have well-documented prior response status to allow appropriate outcome analyses.

b. Subject enrollment biopsy considerations

Baseline biopsies can help to establish CHC diagnosis and can be useful for making correlations between the stage of baseline fibrosis (specifically cirrhosis versus no cirrhosis) and efficacy, safety, and pharmacokinetics. Correlations between presence or absence of cirrhosis and efficacy or safety outcomes can provide useful information in labeling. Sponsors should have a sufficient number of trial subjects with baseline biopsies throughout the course of drug development to explore safety and efficacy correlations between fibrosis and outcomes. Biopsies can be waived for subjects who would be placed at risk from the procedure, such as subjects with bleeding disorders. Inability to perform a liver biopsy should not exclude subjects from a trial. In situations where biopsies are not available or appropriate (e.g., bleeding disorders), use of noninvasive diagnostic modalities may be appropriate for determining whether a subject has cirrhosis or not, but may not be able to adequately distinguish between lower grades of fibrosis (F1 to F3). Use of a noninvasive modality in a protocol should be supported by references that summarize performance characteristics and sensitivity and specificity of the modality for identifying subjects with cirrhosis or varying levels of fibrosis.

c. HCV genotype considerations

Certain DAAs demonstrate antiviral activity against multiple HCV genotypes, and sponsors may want to seek an indication for HCV treatment in several genotypes (e.g., HCV genotype 1, 4, 5, and 6). As seen with HCV genotype 1, some DAA regimens may provide different efficacy for different subtypes, and we anticipate some subtype-specific differences within other genotypes as well. Enrollment of enough subjects with genotypes 4, 5, or 6 into trials to fully characterize efficacy for all the major subtypes may not be feasible for trials conducted only in the United States. Clinical trial data should be sufficient to inform differences in response between each of

the most common subtypes and identify whether any subtypes have decreased efficacy to the proposed regimens. The total population size for each genotype/subtype should be discussed with the DAVP before phase 3 trial initiation. The nonclinical virology data should characterize the anti-HCV activity and resistance barrier of the individual DAA(s) for HCV replicons (or other appropriate cell culture system) derived from subject isolates from the various subtypes.

3. Randomization, Stratification, and Blinding

We encourage sponsors to conduct double-blind trials whenever feasible. The primary endpoint (SVR12) is an objective endpoint; however, other aspects of the trial can be influenced by knowledge of treatment assignment. In open-label protocols, subjects may be more likely to drop out of the trial if they know they are not receiving the new treatment, or investigators could provide different levels of encouragement to continue.

Sponsors should consider stratification of subjects by important baseline factors that are predictive of SVR to ensure adequate balance across different treatment arms. The ideal stratification factors depend on the regimen and population studied, but could include one or more of the following: HCV genotype/subtype, IL28B genotype, prior treatment history, baseline HCV RNA, or cirrhosis. In international trials, subjects should be stratified by geographic area (U.S. versus non-U.S.).

4. Efficacy Endpoints

The recommended primary endpoint is SVR12. Viral RNA clearance (SVR12) should be measured using an FDA-approved sensitive and specific quantitative HCV RNA assay. Use of unapproved assays should be discussed in advance with the FDA.

Evaluating clinical outcomes in prospective, randomized controlled clinical trials of CHC is challenging because of the difficulty of maintaining subjects on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events such as HCC or need for liver transplantation. However, multiple observational cohorts show correlations between SVR24 and improvements in clinical outcomes such as development of HCC, hepatic events, fibrosis, and all-cause mortality (Yoshida, Shiratori, et al. 1999; Yoshida, Arakawa, et al. 2002; Shiratori, Ito, et al. 2005; Okanoue, Itoh, et al. 1999; Imai, Kawata, et al. 1998; Arase, Ikeda, et al. 2007; Veldt, Heathcote, et al. 2007; Braks, Ganne-Carrie, et al. 2007; Bruno, Stroffolini, et al. 2007; Manos, Zhao, et al. 2009; Singal, Volk, et al. 2010; Backus, Boothroyd, et al. 2011). These observational data support the use of SVR as a validated surrogate of HCV disease progression and, therefore, use of SVR is the recommended primary efficacy endpoint for traditional approval in trials evaluating CHC treatments.

In a previous version of this guidance, SVR24 was the recommended endpoint for CHC clinical trials. Currently, SVR12 (SVR at 12 weeks after completion of a scheduled course of therapy) is recommended to be the primary endpoint. The FDA examined whether assessing SVR12 could be used as a primary efficacy endpoint by examining the correlation between SVR12 and SVR24 in more than 13,000 subjects pooled from multiple clinical trials of peg-IFN-based regimens (Chen, Florian, et al. 2013). In brief, there was a high rate of concordance between SVR12 and

SVR24. Sensitivity and specificity for SVR12 was 99 percent and 98 percent, respectively; therefore, SVR12 is considered a suitable primary endpoint for registrational trials for both IFN-based and IFN-free regimens.

Although SVR12 has been shown to predict SVR24 based on analyses of data in subjects receiving IFN-based regimens with and without DAAs, the concordance of SVR12 and SVR24 results should continue to be assessed, particularly for new DAA classes and combination drug regimens. At the time of NDA submission, all available SVR12 and SVR24 data from phase 2 and phase 3 trials should be analyzed to assess concordance of these results, and the results of the analyses included in the application package. If the drug(s) is approved, any additional emerging SVR24 data from phase 3 registrational trials can be submitted as a postmarketing commitment.

5. Trial Procedures and Timing of Assessments

Recommended key time points for measuring HCV RNA depend on the drug regimen and subject population. For peg-IFN/RBV plus single DAA regimens, key on-treatment measurements can include weeks 1, 2, 4, 8, 12, 24, and 48 or at the end of therapy. For all regimens, additional visits for HCV RNA monitoring should be included as appropriate to ensure virologic breakthrough or other treatment futility is detected in a timely manner.

Measurements of viral RNA at earlier time points may be used in protocol decision making for determining duration of DAA dosing or appropriate futility rules for stopping treatment depending on an individual's response.

After completion of treatment, viral RNA should be measured at weeks 4, 12, and 24 of follow-up.

Additional long-term follow-up to assess durability of SVR and characterize the persistence of drug-resistant variants also is recommended (see section III.C.1.c., Resistance analyses). Subjects who achieve SVR should be followed for at least 3 years in larger phase 2 or phase 3 trials to: (1) ensure durability of response; (2) determine whether subsequent detection of HCV RNA represents outgrowth of pre-existing virus versus re-infection; and (3) evaluate development of progressive liver disease and/or HCC. Long-term follow-up can be conducted through a separate observational protocol, and the data provided as part of a postmarketing commitment following the initial application.

6. Statistical Considerations

a. Analysis populations

All subjects who are randomized and receive at least one dose of assigned therapy during the trial should be included in the primary efficacy analysis unless the FDA agrees in advance that certain subjects are not pertinent to the safety and effectiveness review. However, if a substantial proportion of randomized subjects do not receive treatment in either or both arms then sensitivity analyses also may be needed.

b. Efficacy analyses

The primary analysis endpoint should be a comparison of the proportion of subjects who achieve SVR12 across trial treatment arms. This analysis determines whether effectiveness has been demonstrated.[13]

For subgroup analyses, the analysis of SVR12 should be performed within important demographic and baseline characteristics (e.g., geographic region (U.S., non-U.S.), sex, race, age group, HCV genotype/subtype, screening serum HCV RNA, IL28B status, baseline weight, baseline body mass index, baseline alanine aminotransferase (ALT), baseline liver histology, baseline fibrosis, and prior response to IFN/RBV- or DAA-based regimens). The purpose of these analyses is to evaluate the consistency of the SVR12 endpoint result across these subgroups. Of note, simply by chance a homogeneous overall effect in a trial population will almost invariably show statistically significant effects in some subgroups and not in others in any given trial. Therefore, such subgroup results should be interpreted with caution.

For meaningful subgroup analyses in peg-IFN treatment-experienced trials there should be adequate representation from null responders, partial responders, and relapsers, as appropriate for each drug based on activity observed in phase 2 data.

Single-arm trial designs where the SVR12 is compared to historical rates should prespecify the historical rate in the protocol for efficacy comparisons. The historical rate should be based on the intended regimen and subject population. For example, for IFN-free regimens, the historic rate can be based on rates expected with peg-IFN/RBV regimens or no treatment. Estimated SVR calculations using data from previous trials also should account for trial-to-trial variability of historic rates and therefore use the upper bound of the 95 percent confidence interval of historical rates for comparative purposes. Sponsors can choose the larger of two SVR rates to guard against variations in population, environment, or other factors.

SVR rates can vary greatly depending on the trial population. Rates for HCV genotype 1 subjects may be much higher in a trial consisting primarily of IL28B CC (the genotype correlated with a more favorable response to IFN-based therapy) subjects than in a trial with non-CC or cirrhotic subjects. For peg-IFN/RBV therapy, SVR rates generally are less than 50 percent for genotype 1 treatment-naïve subjects but may be 80 percent in genotype 2 and 3 or genotype 1 IL28B CC subjects. Rates for treatment-experienced populations may vary greatly depending on the percentage of null responders, relapsers, and partial responders. All these factors should be taken into consideration when proposing a historical rate for efficacy comparison in trials and should be discussed with the DAVP.

[13] Patients who discontinue therapy, for whatever reason, before the protocol-defined treatment duration can still be considered a responder if they have confirmed absence of HCV RNA 12 weeks after the originally planned treatment duration.

Secondary endpoints can include:

- Normalization of ALT levels
- Relapse rates at 4, 12, and 24 weeks after the end of treatment to confirm SVR12

However, effects on secondary endpoints are not sufficient to support efficacy in the absence of an effect on the primary endpoint. The protocol should propose a multiple testing strategy for secondary endpoints that adjust for multiplicity to be applied after the result for the primary endpoint is significant.

Subjects who experience virologic relapse or who stop treatment because they did not adequately suppress HCV RNA should be regarded as failures in all analyses. For other subjects who discontinue treatment early, investigators should determine if these subjects switched treatments or added additional therapy. This information should be noted in the protocol case report forms and captured in the electronic dataset. This information can be used to understand reasons for discontinuation and how subjects will be included in the analysis.

c. Handling of missing data

For the primary analysis, sponsors should consider a subject not to have achieved an SVR if he or she discontinues from a trial before having an HCV RNA measurement at 12 weeks of follow-up and if the subject has missing HCV RNA values at the end of the scheduled 12- and 24-week follow-up period.

Sponsors should make every attempt to limit loss of subjects from the trial. When the loss is unavoidable, sponsors should explain the causes of missing data and attempt to determine the final status of a subject who does not complete the protocol. Analyses excluding subjects with missing data or other post-treatment outcomes can be biased because subjects who do not complete the trial may differ substantially in both measured and unmeasured ways from subjects who remain in the trial.

A range of sensitivity analyses should be performed to demonstrate that the primary analysis is robust to discontinuation and missing data. Sensitivity analyses can be performed using various methods for imputing missing post-treatment virologic results at 12 weeks of follow-up. Examples include but are not limited to using results from any available last post-treatment week in place of the 12-week follow-up visit or treating a percentage of missing data as successes or failures based on the overall results in which post-treatment data are available.

We recommend that sponsors collect detailed data on confirmation of reasons for discontinuation (e.g., opportunity to enter another trial offering a promising new treatment, death or events leading to death, disease progression, adverse events, loss to follow-up, withdrawal of consent, noncompliance, pregnancy, protocol violations, not discontinued or not known to be discontinued but data were missing at the final visit). The underlying reasons for discontinuation should be interpreted. For example, the statistical analysis should include the number of subjects who withdrew consent or were lost to follow-up, or who discontinued because of adverse events.

d. Interim analyses and data monitoring committees

If interim (or futility) analyses are performed, these analyses should be specified in the statistical analysis plan (SAP). The purpose of the interim analysis should be stated in the SAP.

The SAP should include provisions that ensure the interim analysis does not compromise trial integrity. Sponsors should refer to ICH E9 when considering the use of interim analyses in clinical trials.

Sponsors should consider using a data monitoring committee for phase 3 trials evaluating treatments for CHC, particularly if there are potential safety issues with one or more treatment arms. A detailed charter with the composition of the committee members and the operational details should be provided for review.[14]

e. Statistical analysis plan

For any phase 2b trial (larger phase 2 trial intended to be supportive of efficacy for registration) or phase 3 trial, we recommend sponsors provide a detailed SAP. The SAP can be either a separate document or be within the protocol. The SAP should be submitted as soon as possible after the protocol is finalized and before unblinding (when applicable) or conducting any analysis. The SAP should have details on endpoint ordering, the analysis population, the structure of statistical hypotheses to be tested, methods and statistical models of analyses including the mathematical formulas, level of significance or alpha-level, alpha adjustments for multiple comparisons and interim analyses, and any planned covariates for the analyses. Sponsors can modify an SAP as long as the trial remains blinded, but sponsors should recognize that a detailed discussion may be needed concerning data access and appropriate operating procedures for maintaining the integrity of the blind.

The SAP should prospectively identify the covariates to be used in the analysis. Additionally, the number of covariates should be kept to a minimum and limited to those that are expected to strongly influence outcome.

Treatment-by-region and treatment-by-HCV genotype/subtype interaction should be investigated and reported to assess consistency of the efficacy results.

C. Other Considerations

1. Clinical Virology Considerations

a. HCV RNA assessments and cutoffs for response-guided therapy

[14] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

For antiviral activity and efficacy trials, HCV RNA levels should be measured using a sensitive and specific quantitative assay. Clinical trial protocols should describe the HCV RNA assay(s) to be used, including a brief description of assay performance characteristics. Protocols also should include the names and addresses of the laboratories conducting HCV RNA assessments (e.g., central laboratory or assay vendor). Sponsors are encouraged to compare HCV RNA results obtained using different quantitative HCV RNA assays, either prospectively or retrospectively, particularly if treatment duration decisions (e.g., RGT) are being made based on HCV RNA cutoffs that are near or below the assay lower limit of quantitation (LLOQ).

HCV RNA levels reported as detected but less than LLOQ are not equivalent to HCV RNA levels reported as less than LLOQ "Target Not Detected," and can be clinically relevant during DAA-based treatment of HCV (Harrington, Zeng, et al. 2012). On the other hand, a detected/not detected HCV RNA cutoff can be problematic for treatment decision making because it is inherently less reproducible compared to an HCV RNA cutoff that is within the validated quantitative range of the assay. Therefore, for early phase clinical trial protocols, sponsors are encouraged to use the assay LLOQ or other quantitative HCV RNA threshold to guide treatment decision making (e.g., RGT, virologic futility). Analyses of HCV RNA results from completed trials should be performed to determine if use of a different HCV RNA cutoff (e.g., detected/not detected) should be considered for treatment decisions in subsequent clinical trials or in clinical practice.

For clinical study reports and HCV RNA datasets, clear and consistent language should be used to describe low-level HCV RNA results. Specifically, sponsors should follow guidelines for reporting HCV RNA levels as described in FDA-approved assay package inserts. Specifically, HCV RNA levels that are detected but less than LLOQ should be reported as "<{LLOQ value in IU/mL} Detected," and HCV RNA levels that are not detected should be reported as "Target Not Detected" or "HCV RNA Not Detected." Use of terms such as greater than or less than the limit of detection (">LOD" or "<LOD," respectively) is not recommended, even if the validated assay limit of detection (LOD) and LLOQ are equal, because HCV RNA levels less than LOD can still be detected at a certain rate depending on the actual HCV RNA concentration.

b. HCV genotype/subtype determination

Because HCV genotype or subtype can have a major effect on the efficacy of DAA regimens, it is important that HCV genotype and subtype are accurately identified in clinical trials. Nucleotide sequence analysis of the NS5B gene is the reference method for HCV genotype/subtype determination. A validated assay with accuracy that is comparable to the NS5B sequence analysis reference method should be used for screening and randomization of subjects. Assays based only on nucleotide sequence analysis of the 5' (5 prime) noncoding region of the HCV genome should be avoided because of poor performance in distinguishing between HCV subtypes (Chevaliez, Bouvier-Alias, et al. 2009). Retrospective confirmation of HCV genotype and subtype based on phylogenetic analysis of the drug target coding sequence(s) is also recommended.

c. Resistance analyses

Proof-of-concept antiviral activity and efficacy trials should assess the development of HCV genotypic resistance to the investigational drug. For efficacy trials, resistance testing should be performed for subjects who do not achieve SVR. Treatment-emergent genotypic and phenotypic resistance analyses should focus on samples collected while subjects are on the investigational drug; if on-treatment HCV RNA levels are not adequate for analysis, then the first available follow-up sample with adequate HCV RNA should be analyzed. Any changes, including mixtures, in the amino acid coding sequence of the targeted genome region present in on-treatment or follow-up samples, but not in the baseline sample, should be reported as having developed during therapy. In addition, baseline samples should be analyzed to identify HCV genetic polymorphisms that are potentially associated with virologic failure with the new drug.

Viral resistance-associated polymorphisms or substitutions observed in clinical trials should be evaluated phenotypically by introducing the changes into the HCV genome, and determining the conferred fold-shift in susceptibility to the drug using appropriate cell culture and/or biochemical assays. Because resistance pathways can be complex, and a variety of factors can affect drug resistance in treated subjects, the lack of an observed phenotypic reduction in HCV susceptibility conferred by a specific amino acid substitution does not necessarily preclude a role for the substitution in HCV drug resistance. Sponsors also should consider performing phenotypic analyses of HCV replicons or viruses derived from treated subjects, particularly if resistance is suspected but treatment-emergent genotypic resistance patterns are unclear. The performance of population-based phenotypic resistance assays should be evaluated to determine the sensitivity to detect reductions in HCV drug susceptibility based on fold-changes in EC_{50} and EC_{90} values, as these assays often have poor sensitivity to detect drug-resistant variants that are present as a mixture with drug-susceptible variants. Sponsors are encouraged to report fold-changes in EC_{90} (or EC_{95}) values or dose-response slopes for population-based phenotypic resistance results, which may improve assay sensitivity relative to fold-changes in EC_{50} values.

Emerging data with new DAAs indicate that certain resistance-associated substitutions may persist for long periods of time in the absence of drug selection. Because DAAs within the same drug class typically have overlapping resistance profiles, the persistence of resistance-associated substitutions may significantly limit a subject's future treatment options. Therefore, subjects who have detectable resistance-associated substitutions at treatment cessation or follow-up should be followed for an extended period, at least 1 year after treatment cessation or until the initiation of alternative HCV therapies, to assess the persistence of resistance-associated substitutions. The potential persistence of resistance-associated substitutions should be characterized for subjects enrolled in phase 1 and phase 2 clinical trials so that preliminary long-term follow-up data are obtained by the time of completion of phase 3 trials. Genotyping methodology should be capable of assessing the quantity of resistant viruses during the outgrowth of wild-type virus.

Observations from long-term resistance analyses should be considered when designing protocols to study the efficacy of new DAA regimens in DAA treatment-experienced subject populations. Clinical trials of DAA regimens for subjects previously exposed to DAA(s) of the same class(es) or other classes with the same viral target should include plans to explore the efficacy effect of

prior DAA exposure, considering the duration of prior DAA exposure, time since prior DAA exposure, and resistance characteristics. For initial proof-of-concept studies in these subject populations, sponsors are encouraged to use sensitive and quantitative genotypic resistance assays to characterize the relative and absolute quantity of DAA-resistant variants at baseline, and relate these findings to treatment outcome.

Sponsors should consult with the DAVP before submitting HCV drug resistance data.

2. Clinical Pharmacology Considerations

a. Pharmacokinetic/Pharmacodynamic assessments

Trials conducted in HCV-infected subjects should include assessment of pharmacokinetics and the relationship between drug exposure (e.g., C_{min}, C_{max}, or area under curve) and virologic success and toxicity in all subjects.

Sponsors can use a combination of intensive and sparse sampling throughout development to characterize the pharmacokinetics of the investigational drug. For example, intensive sampling schedule should be implemented in early phase monotherapy trials. In longer term trials, however, intensive sampling schedule might not be feasible. Alternatively, sparse sampling from these trials can be combined with intensive PK data from earlier trials for analysis. Sparse PK samples should be obtained at the time of key virologic assessments, such as weeks 4, 12, 24, and 48. Earlier PK sampling may be needed in cases where key virologic assessments occur earlier during treatment (e.g., week 1 or week 2). These data can then be subjected to appropriate population PK analysis. PK samples for evaluation of peg-IFN/RBV or any other drug in the regimen also should be collected in trials of combination therapy to assist in exposure-response analyses. It is important to document dosing times and plasma sampling times.

Sponsors can use the following two broad approaches to characterize the relationship between exposure and viral kinetics or virologic success of the investigational drug, depending on the development stage and purpose of the analysis. Both approaches should account for differences in response between relevant viral subtypes and allow for exploration of relevant covariates. These analyses should consider virologic relapse and the development of resistance to the investigational drug when assessing differences between treatment regimens. When applicable, the developed exposure-response relationships should be used to support proposed dosing and treatment duration for subsequent trials.

1. To aid the design of phase 2b or phase 3 trials, with respect to dose, duration, regimen choice, and population, a mechanistic approach relating drug concentrations and viral kinetics is most appropriate. Specifically, sponsors should develop a viral kinetic model that describes time-dependent changes in HCV infection during treatment using all available exposure and viral kinetic data from previous studies. Such a model should include a mechanistically appropriate targeted drug effect, components to describe virologic breakthrough, relapse, and long-term viral response (i.e., SVR), and contain relevant covariates for describing differences in response between HCV genotypes and

subtypes. When applicable, these mechanistic modeling approaches can use viral kinetic model structures and the corresponding disease progression parameter values from the literature.

2. When sufficient SVR12 data are available, a simplified analysis relating the proportion of subjects with virologic success and the appropriate exposure variable (e.g., C_{min} or area under curve) can be used to support evidence of effectiveness and justify dose selection.

Exposure-response safety analyses should consider the common adverse events, toxicities that are unique to the investigational drug, and infrequent but severe events to determine whether the drug is safe. The appropriate exposure parameter and modeling approach depends on the investigational drug and toxicity.

These exposure-response analyses, modeling codes, and scripts for both efficacy and safety should be provided at the time of an NDA submission and also should be part of the submission package for meetings during the course of the development program (e.g., end-of-phase 2a, end-of-phase 2). In addition to these analyses, a voluntary data submission project, termed the Antiviral Information Management System (AIMS), seeks to inform dose selection for proposed trials using viral kinetic modeling and to archive clinical study data across multiple hepatitis C drug development programs. Providing datasets for the AIMS project assists in the review and recommendation process for early phase meetings. Submission of these materials is encouraged when new safety and efficacy protocols and meeting packages for early development meetings are provided.

b. Specific populations

We strongly encourage PK evaluation in subjects with renal impairment and hepatic impairment early in drug development so these subjects can be enrolled into phase 2 and 3 trials as appropriate. The following is general guidance for PK evaluation in these populations.

- **PK evaluation in subjects with renal impairment**

For drugs primarily eliminated through the renal route, PK studies in subjects with different degrees of renal impairment can provide useful information on dosing recommendations. However, impaired kidney function also has been shown to affect the absorption and disposition of drugs that are primarily metabolized or excreted through the biliary route. Therefore, PK studies in subjects with renal impairment should be considered for all DAAs during drug development. Specific recommendations related to trial design and data analysis can be found in the draft guidance for industry *Pharmacokinetics in Patients With Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*.[15]

[15] When final, this guidance will represent the FDA's current thinking on this topic.

- **PK evaluation in subjects with hepatic impairment**

A hepatic impairment trial to inform the need for dose modifications should be conducted early in development so that subjects with different degrees of hepatic impairment can be included in phase 2 and phase 3 trials, as appropriate. These data also can support use in pre- or post-transplant subjects.[16]

3. Comorbidities

Patients with hepatic impairment or pre- or post-transplant patients, patients co-infected with HIV and HCV, and patients with decompensated cirrhosis are populations with unmet medical needs. We strongly encourage sponsors to discuss early in development the process to determine appropriate timing for initiating trials in these populations.

a. HIV/HCV co-infected subjects

Approximately 30 percent of patients infected with HIV are co-infected with HCV (Sulkowski 2008). Patients with HIV/HCV co-infection are at higher risk of more rapid progression of liver disease and higher rates of liver-related morbidity and mortality compared to HCV mono-infected patients. In addition, SVR rates in HIV/HCV co-infected patients treated with peg-IFN/RBV generally are lower than in patients with HCV infection alone.

We recommend that a sponsor submitting an original NDA for a DAA, as part of an IFN-containing or IFN-free regimen, include data on HIV/HCV co-infected subjects. These data should include, at a minimum:

- As needed, based on the investigational drug's potential for drug interactions, drug interaction data with the most commonly used HIV drugs. The drug interaction data should be available before trial initiation in HIV/HCV co-infected subjects taking antiretrovirals that are expected to have interactions with an investigational DAA(s).

- Safety data including HIV RNA data to assess loss of HIV efficacy, on a cohort of HIV/HCV co-infected subjects receiving the proposed regimen for the recommended treatment duration.

With the above-mentioned data, labeling describing the results of drug-interaction trials and safety concerns may be appropriate. In general, to expand the patient population to HIV/HCV co-infected patients, efficacy and safety data at the proposed dose(s) and duration in 300 co-infected subjects is recommended. Alternative proposals for the total number of co-infected subjects may be appropriate; however, sponsors should discuss their development plans with the DAVP in advance.

[16] See the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.

We prefer an immediate versus deferred trial design with respect to evaluation of the HCV regimen for co-infected subjects (see section III.B.1.a., IFN-free regimen in treatment-naïve and treatment-experienced populations). Alternatively, a dose or treatment duration comparison or single-arm, historical control trial could be used.

After IFN-free DAA combination regimens become available, an active-controlled superiority or noninferiority trial design may be feasible and preferred over a single-arm design. Sponsors considering a noninferiority trial design should discuss in advance with the DAVP their choice of noninferiority margin, trial design, and data analysis plans.

The primary endpoint in co-infected subjects should be SVR12. As part of the safety evaluation, loss of HIV efficacy (rebound in HIV RNA viral load) should be assessed.

b. Patients with decompensated cirrhosis and pre-/post-transplant

IFN-based regimens are not considered appropriate for patients with decompensated cirrhosis or for most patients pre- or post-liver transplant; therefore, treatment with multiple investigational DAAs is likely needed to achieve viral suppression. Until a DAA-based regimen is approved in patients with decompensated cirrhosis, safety and efficacy data may be derived from dose or treatment duration comparison or single-arm, historical control trials.

If supportive safety data showing robust efficacy findings are available in other populations, a safety database of approximately 100 subjects with decompensated cirrhosis may be considered adequate for a supplemental NDA. Although SVR12 is considered the primary efficacy endpoint, other important endpoints can include progression of liver disease, transplantation, and mortality. The effectiveness of a combination regimen in preventing HCV recurrence post-liver transplant should be evaluated through long-term follow-up.

As needed, and based on a particular investigational drug's metabolic profile, sponsors should conduct drug interaction trials with the most commonly used immunosuppressive drugs. These data should be available before trials in post-transplant subjects are initiated to support concomitant dosing of a DAA regimen and immunosuppressive drugs.

We strongly suggest that an original NDA submission for the treatment of HCV with a combination of DAAs contain some clinical data from subjects with decompensated cirrhosis, as well as pre- and post-transplant subjects. Such data should include:

- As relevant, based on the investigational drug's potential for drug interactions, drug interaction data with the most commonly used immunosuppressive drugs

- Safety data from a cohort or cohorts of subjects with decompensated cirrhosis and pre- or post-transplant recipients who received the drug for the recommended treatment duration

Plans for expanded access trials or safety trials also should be considered for this population early in development.

4. Pediatric populations

Early trials of DAAs should enroll adult subjects only, deferring pediatric exposure until the pharmacokinetics, pharmacodynamics, and safety of the drug are reasonably well defined. Sponsors are encouraged to begin discussions about their pediatric formulation and clinical development plan early in development because pediatric clinical trials are a required part of the overall drug development program and sponsors should submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting. See the Pediatric Research Equity Act, 21 U.S.C. 355c (2013), as amended by FDASIA (Public Law 112-144, 126 Stat. 993 (2012)). In general, pediatric clinical trials can be initiated after phase 2 adult data characterizing the safety profile and initial antiviral efficacy are available. Initial pediatric PK data and results of available modeling and simulation should be discussed with the DAVP before dose selection for pediatric treatment trials. Depending on results of the adult clinical trials, either comparative or single-arm trials may be appropriate in pediatric subjects. If clinical trials in adults have demonstrated no safety concern specific to a histologic stage, liver biopsies are not recommended for routine entry criteria into pediatric trials. If biopsies are performed because they are clinically indicated, biopsy data should be provided at the time of submission.

5. Expanded Access

Some HCV-infected subjects who are unable to take or who have not responded to approved treatments and who are at substantial risk of liver disease progression may be eligible under 21 CFR 312.310, 312.15, or 312.20 to receive new therapeutic options before their approval. Treatment INDs or treatment protocols for DAAs may be appropriate when sufficient clinical trial data have been generated to characterize a reasonably safe and active dose of an investigational drug(s). Ideally, submission of a treatment IND or protocol should occur after phase 3 trials are fully enrolled or well underway so as not to interfere with phase 3 drug development. A treatment IND or protocol can provide access to an investigational drug while phase 3 trials are being completed, analyzed, submitted, and reviewed by the FDA. Alternatively, individual patient and intermediate-size patient population expanded access may be possible. In contrast to treatment INDs/protocols for larger populations during or after phase 3 trials, expanded access for intermediate size patient populations can occur earlier in drug development.

Historically, expanded access programs for the treatment of HIV infection allowed many patients to gain access to lifesaving drugs. However, for some individuals, expanded access to an investigational drug resulted in what amounted to sequential monotherapy and the emergence of multidrug resistance. Because treatment of CHC requires multiple drugs to achieve SVR and to reduce the emergence of drug resistance to single drugs or drug classes, expanded access programs that include two or more investigational drugs or that allow co-enrollment in several expanded access programs simultaneously are desirable, particularly for difficult-to-treat populations or for subjects who cannot take IFN-based regimens. However, treatment use through expanded access of multiple investigational drugs should be supported by:

- Data and rationale that characterize the potential for PK-based drug interactions and potential for overlapping toxicity; data to support dose modifications if needed

- Information suggesting the potential for additive or synergistic activity and no or minimal overlapping resistance profiles

See section III.A.4.d., Phase 2 trials of IFN-free regimens in DAA-naïve subjects, for the data needed to support treatment use through expanded access of multiple investigational drugs in a treatment regimen.

GLOSSARY OF ACRONYMS

CC	cytotoxic concentration
CHC	chronic hepatitis C
DAA	direct-acting antiviral
EC	effective concentration
EVR	early virologic response
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
IFN	interferon
IL	interleukin
LLOQ	lower limit of quantitation
LOD	limit of detection
Peg	pegylated
PK/PD	pharmacokinetic/pharmacodynamic
RBV	ribavirin
RGT	response-guided therapy
RNA	ribonucleic acid
RVR	rapid virologic response
SAP	statistical analysis plan
SVR	sustained virologic response
SVR4	sustained virologic response 4 weeks after stopping treatment
SVR12	sustained virologic response 12 weeks after stopping treatment
SVR24	sustained virologic response 24 weeks after stopping treatment

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APPENDIX A: STUDY POPULATION TERMS AND DEFINITIONS

Points to Consider

- The terms in Table A can be used for documentation of prior treatment responses (i.e., for trial inclusion criteria) or for responses observed in clinical trials. For prior treatment responses, some flexibility in the definitions may be appropriate, particularly when the level of detail indicated in the table is not typically available.

- Other protocol-defined or retrospectively defined responses will be considered, but should be discussed in advance with the DAVP.

- Peg-IFN refers to a pegylated interferon product.

- For DAA-containing treatment regimens, breakthrough should take precedence. Exceptions to this guideline should be discussed in advance with the DAVP.

- Ideally, only one term should be used for each patient per round of treatment, with the most recent DAA-based treatment taking precedence. However, multiple terms can be considered as appropriate to document responses to multiple rounds of treatment.

- Specific details regarding drug/class experience should be noted as part of protocol-specified data collection. Also, when possible the following additional detail should be included in line-item datasets:

  – P/R Partial Responder: distinguish between P/R partial responders and those who experienced virologic breakthrough during P/R

  – P/R+DAA Breakthrough: distinguish between breakthrough during P/R+DAA treatment period versus P/R tail treatment period

Table A: Recommended Terms and Definitions

NAÏVE-ALL	Naïve to all anti-HCV treatment
P/R* NULL RESPONDER	<2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 of a peg-IFN/RBV regimen
P/R PARTIAL RESPONDER	≥2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable (target not detected) at end of treatment with a peg-IFN/RBV regimen; also can include those who experienced virologic breakthrough during treatment with a peg-IFN/RBV regimen that never included dosing with an HCV DAA

continued

Table A, continued

P/R RELAPSER	HCV RNA undetectable (target not detected) at end of treatment with a peg-IFN/RBV regimen, but HCV RNA quantifiable (≥LLOQ) during follow-up
P/R+DAA NONRESPONDER	HCV RNA detected at end of treatment with a regimen that included one or more HCV DAAs dosed in combination with peg-IFN/RBV. Can include patients who met protocol-defined virologic futility rule (except for breakthrough, which is captured elsewhere).
P/R+DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Could have occurred either: (a) during the DAA dosing period with a regimen that included one or more HCV DAAs dosed in combination with peg-IFN/RBV; or (b) during peg-IFN/RBV tail dosing period that followed a peg-IFN/RBV/DAA(s) dosing period.
P/R+DAA RELAPSER	HCV RNA undetectable (target not detected) at end of treatment with a regimen that included one or more HCV DAAs dosed in combination with peg-IFN/RBV, but HCV RNA quantifiable (≥LLOQ) during follow-up
DAA NONRESPONDER	HCV RNA detected at end of treatment with a regimen that included only HCV DAAs (also can include RBV, but not IFNs). Can include patients who met protocol-defined virologic futility rule (except for breakthrough, which is captured elsewhere).
DAA BREAKTHROUGH	Confirmed ≥1 $\log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA ≥LLOQ if HCV RNA previously declined to <LLOQ (detected or not detected). Occurred during treatment with a regimen that included only HCV DAAs (also can include RBV, but not IFNs).
DAA RELAPSER	HCV RNA undetectable (target not detected) at end of treatment with a regimen that included only HCV DAAs (also can include RBV, but not IFNs), but HCV RNA quantifiable (≥LLOQ) during follow-up

* P/R = peg-IFN/RBV