Guidance for Industry

Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents 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DRAFT GUIDANCE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)

September 2010
Clinical Antimicrobial

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

This guidance provides recommendations for the development of direct-acting antiviral agents (DAAs) regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of chronic hepatitis C (CHC) infection. For the purpose of this guidance, we define direct-acting hepatitis C virus (HCV) antivirals as agents that interfere with specific steps in the HCV replication cycle through a direct interaction with the HCV polyprotein and its cleavage products. This guidance is intended to serve as a focus for continued discussions among the review divisions, pharmaceutical sponsors, the academic community, and the public.[2] The organization of the guidance parallels the development plan for a particular drug or biologic.[3]

This guidance does not address the development of immune-based agents for the treatment of HCV infection such as new interferon products. 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 guidance.

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

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

Additionally, general issues of clinical trial design or statistical analyses for HCV trials 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*.[4] This guidance also does not contain details regarding nonclinical safety and toxicology studies. 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.*

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 RNA virus in the Flaviviridae family. Six viral genotypes, numbered 1 to 6, have been identified; some 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 90 percent), followed by genotypes 2 and 3. Other genotypes occur uncommonly in the United States, but may predominate in other parts of the world.

In the United States, HCV infection causes 20 percent of all cases of acute viral hepatitis and 70 to 90 percent of all cases of HCC. Estimates show nearly 3.2 million Americans are chronically infected with HCV. CHC is currently the leading indication in the United States for liver transplantation, and predictive modeling suggests that without effective treatment interventions significant increases in CHC-associated liver morbidity, mortality, and health care costs are likely (Kim 2002).

Current treatment of CHC typically is a pegylated interferon administered in combination with ribavirin (Peg-Interferon/RBV), often referred to in hepatitis C clinical trials as standard of care (SOC). The goal of treatment is sustained virologic response (SVR), defined as undetectable plasma HCV RNA at week 24 following treatment cessation (SVR24). Total duration of current treatment depends on genotype, with longer treatment durations needed to achieve SVR for genotypes 1 and 4 and shorter treatment durations needed for genotypes 2 and 3. SVR rates in treatment-naive patients receiving Peg-Interferon/RBV typically are in the range of 40 percent to 45 percent for viral genotype 1 and are 70 percent to 80 percent for genotypes 2 and 3 (Ghany, Stradler, et al.

[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.

2009).[5] SVR rates for blacks and HIV co-infected patients with genotype 1 HCV are in the range of 20 percent to 30 percent (in some studies less than 20 percent), which is substantially lower than rates for whites and patients who are not co-infected.

On-treatment virologic measurements at early time points can predict the likelihood of SVR and are often used to guide treatment duration. When treating with interferon-based regimens, health care providers generally stop treatment if patients do not have at least a 2 $\log_{10}$ drop from baseline in HCV RNA at week 12 or do not have an undetectable HCV RNA by week 24, because not meeting these interim virologic response criteria results in a low likelihood of SVR. Three terms relating to on-treatment responses used in clinical trials include: (1) rapid virologic response (RVR), meaning an undetectable HCV RNA at 4 weeks of treatment; (2) complete early virologic response, meaning an undetectable HCV RNA at week 12 of treatment; and (3) extended RVR, meaning an undetectable HCV RNA at week 4 that persists through week 12. These measurements are sometimes used to guide treatment duration strategies in clinical trials.

Even among patients who achieve SVR, liver injury may persist and hepatic complications may occur; although the likelihood of hepatic complications appears to be substantially reduced compared to patients who do not achieve SVR. Multiple observational cohorts show correlations between SVR and improvements in clinical outcomes of interest, 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). Evaluating clinical outcomes from prospective, randomized controlled clinical trials is challenging because of the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events such as HCC.

Pegylated interferons and RBV are difficult to tolerate and have significant adverse event profiles that limit treatment in many patients or result in substantial morbidity. Therefore, new drugs are needed that increase SVR rates when added to current therapy, that shorten the duration of interferon-based regimens, or that replace components of current therapy in patients who cannot tolerate interferon or RBV. New drugs are also needed to construct regimens in patients with decompensated cirrhosis and in patients undergoing liver transplant.

Host factors, such as genetic polymorphisms, metabolic parameters, and viral factors (i.e., genomic mutations), are being investigated for their roles in predicting response to treatments for CHC. Recently, a genetic polymorphism near the IL-28B gene, encoding interferon-l-3 (IFN-l-3), has been shown in several studies to predict an approximately two-fold change in response to interferon-based treatment regimens in patients of

[5] See also labeling information for PegIntron and Pegasys at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?CFID=42688251&CFTOKEN=cea143f9dc49c115-37E6D01E-0AF3-6971-CCAA04EECE6DE6A7.

African-American and European ancestries (Ge, Fellay, et al. 2009). At least one test for the IL-28B polymorphism is now available to physicians and for use in clinical protocols.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Pharmacology/Toxicology Development Considerations

Pharmacology/toxicology development for single direct-acting HCV antivirals should follow existing guidances for drug development.[6]

Guidance suggests conducting nonclinical combination studies to support clinical trials for combination drugs.[7] However, similar to the approach used for HIV and oncology drugs, we do not recommend that these nonclinical studies be conducted routinely for the following reasons:

- In clinical practice, DAAs are likely to be used with multiple hepatitis C drugs, including interferon and RBV and other DAAs, in multiple different combinations; it would not be feasible to conduct animal studies for all potentially relevant combinations

- Given the difficulty of conducting combination toxicologic studies that may require multiple different drugs and multiple dose combinations, we believe that nonclinical studies would be more interpretable and may offer more useful data by looking at individual agents at multiple and higher doses

- Single- and multiple-dose drug-interaction trials in humans and in vitro metabolic studies can screen for potential pharmacokinetic (PK) drug interactions that may lead to safety issues

To support clinical trials evaluating 2 or more investigational DAAs for up to 90 days, we recommend a minimum of 3 months repeat-dose nonclinical toxicity studies in a rodent and nonrodent species for each individual agent. Longer term data on individual agents (6-month rodent, 9-month nonrodent) can support longer duration combination clinical trials, depending on the toxicity profile (see ICH M3(R2)).

Nonclinical combination studies of an investigational antiviral plus approved SOC (e.g., Peg-Interferon/RBV) may not be needed unless data from nonclinical studies of an

[6] 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.*

[7] See the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations.*

investigational antiviral drug suggest a potential for increased or synergistic toxicity with the approved therapeutic agents.

2. Nonclinical Virology Development Considerations

DAAs for the treatment of CHC should be tested in cell culture for antiviral activity before submission of an initial investigational new drug application (IND). Information about pre-investigational new drug testing and information regarding appropriate nonclinical assays is available from the FDA.[8] Additional recommendations for general antiviral drug development can be found in the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*.

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 agent on relevant stages of the virus life cycle. Mechanism of action investigations should include appropriate controls for assessing the specificity of anti-HCV activity, which may include assessments of activity against HCV proteins that are not targeted by the candidate agent, relevant host proteins, or other viruses.

b. Antiviral activity in cell culture

The antiviral activity of a new agent should be characterized in cell culture to identify a target plasma concentration for evaluation in HCV-infected patients. Antiviral activity of candidate agents targeting nonstructural components should be assessed using HCV genotype 1a- and 1b-derived replicon systems, and a 50 percent effective concentration (EC_{50}) determined. Nonclinical studies should include assessments of antiviral activity against the major HCV genotypes and subtypes. Assessments of antiviral activity against replication models using HCV components derived from multiple clinical isolates are also recommended, because antiviral activity can vary for strains within each subtype. If differences in susceptibility are observed for different clinical isolates within the same viral genotype or subtype, additional genotypic and phenotypic characterizations should be conducted to identify genetic polymorphisms that may affect HCV susceptibility to the new agent.

The antiviral activity of agents 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 agent when appropriate. The cytotoxic effects of the agent should be quantified directly in the cells used for assessing anti-HCV activity, and a 50 percent cytotoxic concentration (CC_{50}) and a therapeutic index should be calculated. Cytotoxicity should also be assessed using various cell lines and primary cells cultured under proliferating and nonproliferating conditions. Sequestration of the

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

agent by serum proteins should also be assessed and a serum-adjusted EC_{50} value determined. We recommend evaluation of the agent's antiviral activity at different concentrations of human serum and extrapolation to a 100 percent human serum EC_{50} value.

c. Resistance and cross-resistance

The ability of HCV to develop resistance to a DAA when subjected to drug pressure should be examined in appropriate cell culture models. Amino acid or nucleotide substitutions associated with the development of resistance to the candidate agent should be determined and validated by introducing the changes into the HCV genome and determining the conferred fold-shift in susceptibility using appropriate cell culture and/or biochemical assays. Results from these studies should be used to: (1) determine whether the genetic barrier for resistance development is high or low; (2) predict whether the genetic barrier for resistance may vary as a function of concentration of the new agent; (3) reveal potential resistance pathways and the potential for cross-resistance with other anti-HCV agents; and (4) support the agent's hypothesized mechanism of action.

Resistance studies should include evaluation of the potential for cross-resistance, both to approved agents and to agents in development, particularly focusing on those in the same drug class. 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.

d. Combination antiviral activity

Most, if not all, DAAs for HCV will be used to treat CHC in combination with other approved drugs. Early in development, cell culture combination antiviral activity relationships of the new agent and pegylated interferons and the new agent and RBV should be characterized to determine whether the combination antiviral activity is additive, synergistic, or antagonistic. Additional combination antiviral activity studies with other candidate anti-HCV agents should be conducted if future combination therapy with other agents is anticipated. For all combination antiviral activity assessments, sponsors should provide combination index values when the two agents are combined at or near their individual EC_{50} values, and studies should include controls for cytotoxicity. Combination antiviral activity relationships for HIV and HCV agents with similar mechanisms of action (e.g., nucleoside analogue polymerase/reverse-transcriptase inhibitors, protease inhibitors) should also be assessed before testing combinations of the agents in HIV/HCV co-infected patients.

e. Activity in animal models

Demonstration of anti-HCV activity in an animal model is not needed. 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.

3. Drug Development Population

Overall drug development programs should include a broad population as appropriate for the characteristics of the antiviral agent. 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). We recommend including patients diagnosed with compensated cirrhosis in phase 2 and phase 3 trials. Also, we encourage the study of combinations of direct-acting HCV antivirals in patients with the greatest need for new agents, such as patients who cannot tolerate interferon, patients for whom interferon is contraindicated, transplant patients, and patients with decompensated cirrhosis. DAAs can be studied in combination with other DAAs and with or without SOC in HIV co-infected patients as soon as appropriate based on the availability of data. Trials in the above-mentioned subgroups may need to be supported by preliminary data from trials to define safety and pharmacokinetics, such as hepatic impairment trials and drug-drug interaction trials (e.g., antiretrovirals for HIV, immunosuppresants for transplant).

CHC is a disease that is present worldwide and clinical trials typically are conducted internationally. However, trials should include adequate U.S. patient 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 interferon-based regimens, it is important to ensure that there is sufficient diversity in clinical trial demographics to conduct meaningful analyses of such groups. Furthermore, in addition to viral genotypes, host genotypes are emerging as correlates of clinical response to antivirals and may partially explain differences in response rates by race; therefore, collection of patient DNA is an important consideration.[9]

4. Early Phase Clinical Development Considerations

The early clinical evaluation of new DAAs should follow a rational plan to provide sufficient data to establish preliminary safety and activity to support phase 3 trials.

a. 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. However, single-dose and short multiple-dose PK trials (see below) can also be conducted in HCV-infected patients, particularly if nonclinical data suggest a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers.

[9] See the guidance for industry *Pharmacogenomic Data Submissions*.

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

The first proof-of-concept trial (meaning a trial in HCV-infected patients that demonstrates initial activity as measured by reductions in HCV RNA from baseline levels) should be a repeat-dose, randomized, dose-ranging, monotherapy trial, of approximately 3 days duration, with collection of intensive PK, safety, and HCV RNA decay data. Doses selected for phase 1b should be predicted to provide plasma drug exposures expected to exceed, by several-fold, the protein binding-adjusted, cell culture EC_{50} value of the agent for the relevant HCV genotype/subtype. Choice of doses should also take into account safety margins identified in animal toxicology studies and in any trials conducted in healthy volunteers.

Monotherapy exceeding 3 days is not recommended because data indicate resistant virus is rapidly selected during monotherapy dosing with some DAA drug classes. Furthermore, 3 days of monotherapy with a directly targeting anti-HCV agent is usually sufficient for establishing proof of concept and for initial dose exploration. Selection of resistance may limit the future utility of the new agent as well as other agents with similar resistance pathways. In most cases, longer durations of monotherapy with directly targeting anti-HCV agents are not appropriate because of resistance concerns, but can be considered on a case-by-case basis depending on the characteristics of the individual agent. In addition to limiting the duration of monotherapy, we recommend that phase 1 trials of initial activity be conducted in patients with CHC who are naïve to previous anti-CHC therapy (including the agent under investigation), and who have minimal fibrosis and no significant co-morbidities. Following demonstration of safety and antiviral activity in treatment-naïve patients, sponsors can plan additional trials in treatment-experienced patients.

Results from proof-of-concept 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 that sponsors conduct mechanistic modeling of the concentration-viral kinetics and the concentration-safety profile from phase 1 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 infection and the effect of drug concentrations (Neumann, Lam, et al. 1998). The model should also include components to describe virologic breakthrough, relapse, and long-term viral response (e.g., SVR) to inform dose selection and treatment duration. In general, the model should be used to inform dose selection and to reduce the risk of selecting for resistant virus because of subtherapeutic exposure.

c. Phase 2 trials and dose-finding

A goal of early phase 2 trials is to begin to characterize the optimal dose and duration of the DAA as part of combination regimens with regard to both activity and safety.

The most straight-forward design for early phase 2 is a randomized controlled trial of several doses of a DAA added to Peg-Interferon/RBV compared to a standard-of-care regimen (consisting of Peg-Interferon/RBV). In general, trial patients should receive a full course of treatment with the Peg-Interferon/RBV component (24 to 48 weeks depending on early treatment responses); however, the DAA component can be administered for shorter durations (e.g., 12 weeks, depending on results from phase 1b). The dosing duration of the investigational agent in phase 2 trials should be based on scientific and clinical rationale and not limited in duration only because long-term animal toxicology studies have not been completed.

The U.S.-approved Peg-Interferon/RBV labels for treatment of HCV genotype 1 HCV recommend 48 weeks of therapy; although in practice many clinicians shorten the course for patients who have HCV RNA levels below the limit of detection at week 4 of treatment. At present, the optimal duration of dosing a third drug in combination with Peg-Interferon/RBV is not known and is likely to vary depending on characteristics of the investigational agent and treatment population. Thus, various durations of treatment can be evaluated in clinical trials. However, we generally recommend that phase 2 trials include at least one treatment arm that evaluates 48 weeks of treatment with all components of a regimen unless antiviral activity or safety data support a rationale for shorter durations of the DAA component of the regimen. Evaluating shorter durations of a regimen or a component of the regimen can also be accomplished by incorporating a second randomization to assess treatment duration in those patients who have demonstrated early virologic suppression. For example, one treatment strategy can allow patients who reach undetectable HCV RNA by week 4 (RVR) and maintain undetectable HCV RNA level at week 12 (extended RVR) to be re-randomized to receive a regimen of 24 versus 48 weeks in duration. Patients who do not attain extended RVR would receive 48 weeks of therapy in this example.

We recommend that sponsors conduct their first phase 2 combination trials with Peg-Interferon/RBV in treatment-naïve patients as opposed to starting dose-finding in treatment-experienced patients. Giving suboptimal doses to treatment-experienced patients can further increase emergence of resistance and incomplete virologic response to a DAA in combination with Peg-Interferon/RBV and this could jeopardize future treatment regimens for those individuals.

Sustained virologic response should be the primary endpoint of the phase 2 trials; however, analyses of 12 weeks of safety and antiviral activity data from the first combination trial with Peg-Interferon/RBV in treatment-naïve patients can be used to design larger phase 2b dose comparison trials to further characterize optimal dosing in broader populations, including both treatment-naïve and treatment-experienced patients.

To provide the most meaningful comparisons for further development of a DAA, we recommend phase 2 trial designs allow for direct comparisons between treatment arms with respect to dose, strategy, and duration. For example, if two doses are evaluated, both treatment doses should be evaluated for the same duration of therapy.

Because the presence of an IL-28B genetic polymorphism has been shown to predict substantial treatment response differences among patients receiving Peg-Interferon/RBV, an effort should be made to collect samples for IL-28B testing at baseline to reduce the potential for confounding in trial analyses. For example, in smaller dose-finding trials, treatment arm imbalances in patients with the IL-28B polymorphism can confound interpretation of trial results if sponsors do not consider the potential effect of this predictive marker on treatment outcome. Sponsors should consider stratifying based on IL-28B when DAAs are combined with Peg-Interferon/RBV in phase 2 and phase 3 trials.

d. Combination therapy with multiple DAAs

We encourage trials of DAAs with and without Peg-Interferon/RBV, depending on the patient population. Trials of combinations of DAAs in patients who cannot tolerate interferon or for whom interferon is contraindicated may address an unmet medical need. Based on HCV replication dynamics in infected patients (Perelson 2009), 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 DAAs are needed to suppress all pre-existing and emerging drug resistant variants to achieve SVR. At present it is not known whether regimens that do not include interferon can produce SVR.

Ideally, agents with different mechanisms of action should be considered for combination use. The information recommended to support combination trials using DAAs without interferon and RBV includes:

- Combination antiviral activity data from cell culture
- Resistance and cross-resistance patterns for each agent in the combination
- Anti-HCV activity data from clinical trials (from short-term monotherapy trials or from dose-finding in combination with Peg-Interferon/RBV)
- Some human safety data on each agent
- Justification for proposed doses based on clinical trials or other sources to indicate doses chosen are likely to provide reasonable anti-HCV activity
- Drug-drug interaction data if the metabolism profiles suggest an interaction potential between agents in the combination regimen

Some examples of potential designs for initial trials of combinations of DAAs include but are not limited to the following:

- Randomized, controlled trials that compare short durations (less than 2 weeks) of multiple DAAs in treatment-naïve patients followed by a full course of Peg-Interferon/RBV either with or without one or more of the DAAs evaluated in the

first 2 weeks. An approved Peg-Interferon/RBV regimen can be used as a control arm.

- Randomized, controlled trials that compare several different dosing combinations of multiple DAAs given for longer durations in treatment-naïve or -experienced patients. This type of design includes frequent HCV RNA monitoring and stopping rules for loss or lack of antiviral response. When enrolling treatment-naïve patients or treatment-experienced patients who can tolerate interferon and RBV, protocols can specify adding interferon and RBV to the DAA regimen after a specified time point (e.g., 6 weeks) or at any other time if virologic rebound or lack of complete virologic response is determined.

- A single-arm trial evaluating multiple doses of combination therapy before liver transplant to study the overall antiviral effect before liver transplant and potentially the effect on preventing infection of the transplanted liver. Response rates can be compared to historical controls because transmission of HCV to a transplanted liver in this setting is universal (Gane 2008), such that demonstrating lack of infection in a substantial proportion of allograft recipients is meaningful.

Sponsors are encouraged to discuss with the FDA proposed development plans for combination therapy of two or more DAAs.

e. Other phase 2 trial design considerations

Phase 2 trials can also be used to explore alternative dosing strategies of a DAA in combination with other agents before confirmation of alternative dosing strategies in larger phase 3 trials. Detailed rationale for an alternative dosing strategy should be included with a phase 2 protocol submission. One example of an alternative dosing strategy is a lead-in period with Peg-Interferon/RBV (before initiation of the new agent as part of a three-drug therapy). One arm containing a lead-in period with Peg-Interferon/RBV can be compared to another arm in which all drugs in the regimen were started simultaneously. In theory, a lead-in strategy may be beneficial before starting a DAA with a low genetic barrier to resistance because Peg-Interferon/RBV may reach a steady-state by the time the new agent is added, reducing the possibility of combining the agent in the setting of subtherapeutic Peg-Interferon/RBV exposures. The effects of variations in dosing of a combination regimen, such as lead-in periods, can be explored in phase 2 and confirmed in phase 3.

5. Efficacy Considerations

We recommend that sponsors analyze and provide summaries of SVR outcome data (SVR12 and SVR24) 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, either treatment-naïve or treatment-experienced patients. 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 both treatment-naïve and -experienced patients. In this circumstance, the NDA should contain at least one adequate and well-controlled phase 3 trial in each patient population, with adequate supporting data from phase 2 trials.

Trial designs for combinations of investigational DAAs without interferon and 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 patients are randomized to only one new DAA may not be appropriate because of 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 agents.

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

- Comparisons of viral load reductions of short-term monotherapy trials (e.g., 3-day trials) with viral load reductions of combination therapy in the same trial or across other short-term trials. In this example, short-term viral load reductions in patients given combination therapy with two DAAs should be substantially greater than that observed in patients given the single agents.

- Early phase 2 clinical trial data showing that DAA combinations prevent or reduce emergence of resistance.

Sponsors should consult 21 CFR 300.50 regarding combining drug products in a single dosage form.

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, fast track,[10] or priority review if the specifics of the development plan justify such an approach.

6. Safety Considerations

In general, we recommend that initial marketing applications for drugs intended to treat CHC in patients without decompensated cirrhosis contain a safety database of

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

approximately 1,000 to 1,500 patients 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.

For an indication in patients with decompensated cirrhosis or in patients who generally have a high risk of morbidity and few if any treatment options, a safety database of approximately 500 patients administered the DAA for the proposed dose and duration may be sufficient for filing an NDA. We encourage sponsors to discuss their proposed safety database before submitting an NDA. On occasion, specific findings in nonclinical or clinical development may indicate the need for a database that is larger or longer in duration to adequately evaluate potential drug toxicity.

We recommend that sponsors provide controlled and comparative safety data. Safety data from uncontrolled protocols or treatment IND protocols may be useful, but often lack the degree of detailed reporting obtained in controlled clinical trials. Moreover, the assessment of causal relationships between a drug and an adverse event is more difficult when relying on uncontrolled safety data and spontaneously occurring events or events related to concurrent treatment or underlying illness may be attributed to the new drug.

B. Specific Efficacy Trial Design Considerations

1. Trial Design

Until the first DAA is approved, the recommended, and most straight-forward, design for initial registration of a DAA is demonstration of superiority as an add-on to SOC, Peg-Interferon/RBV, in a blinded comparison to placebo plus SOC. In the future, a superiority design also can include a new drug as part of a four-agent regimen compared to a three-agent regimen. Alternatively, an active-controlled noninferiority trial design could be appropriate, comparing a new DAA plus Peg-Interferon/RBV to another approved DAA (control) plus Peg-Interferon/RBV. The latter design is dependent on the ability to define the contribution of the new active control to the Peg-Interferon/RBV treatment so that a stringent noninferiority margin can be calculated. Sponsors considering a noninferiority trial design should discuss in advance with the FDA justification of the noninferiority margin, trial design, and the data analysis plan.[11]

Patients 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 provided as part of a postmarketing commitment following the initial application.

[11] For more information, see the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

2. Trial Population

a. Patient enrollment definition

To be enrolled in a trial, patients should have CHC as documented by being tested:

- 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 addition to documentation of CHC, treatment-experienced patients should have complete documentation of prior treatment history (including but not limited to compliance with previous therapy and reasons for discontinuation), because these factors may affect their response to retreatment. For the purpose of trial enrollment, the following definitions are used to define the treatment experience of CHC patients, which are based on previous responses to Peg-Interferon/RBV.[12]

- **Naïve:** received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

- **Null Responder[13]:** less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of a Peg-Interferon/RBV

- **Partial Responder:** greater than or equal to 2 $\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a Peg-Interferon/RBV

- **Responder Relapser:** HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up

  Note that *HCV RNA undetectable* for previous treatment response should have been based on an assay that was considered sensitive at the time of treatment.

[12] Patients who previously received interferon monotherapy or nonpegylated interferons plus RBV will be a diminishing proportion presenting for future trials. These patients can be categorized separately.

[13] Other definitions for null response have been proposed, such as less than 1 $\log_{10}$ IU/mL decline in HCV RNA at week 4 of treatment. However, failure to achieve a greater than 2 $\log_{10}$ IU/mL HCV RNA decline at week 12 has typically been used as a treatment futility criterion and use of a null response definition of viral reduction less than 1 $\log_{10}$ IU/mL at week 4 causes a gap in classification for individuals with a viral load reduction greater than 1 $\log_{10}$ at week 4 but less than 2 $\log_{10}$ reduction at week 12.

b. Patient enrollment biopsy considerations

Baseline biopsies can help to establish CHC diagnosis and can be useful for making correlations between the amount of baseline fibrosis and subsequent treatment outcomes such as SVR and occurrence of treatment-related adverse events. Correlations between baseline fibrosis and efficacy or safety outcomes can provide useful information in labeling. Sponsors should have a sufficient number of baseline biopsies throughout drug development to explore correlations between fibrosis and outcomes. We recommend the following regarding enrollment biopsies throughout drug development:

- For phase 1 trials in CHC patients and early phase 2 trials intended to evaluate pharmacokinetics/pharmacodynamics (PK/PD) or initial efficacy and safety, a liver biopsy may not be needed as long as patients fulfill the criteria for CHC infection as described in the section above.

- For later phase 2 trials and phase 3 treatment-naïve trials, we recommend biopsies within 2 to 3 years before enrollment. If cirrhosis has been previously demonstrated on a biopsy, then biopsies obtained more than 3 years before enrollment need not be repeated.

- For later phase 2 and 3 trials in treatment-experienced patients, a biopsy within 2 to 3 years may not be needed for trial enrollment; however, documentation of a prior biopsy showing histological evidence of CHC should be available for review.

- Biopsies can be waived for patients who would be placed at risk from the procedure, such as patients with bleeding disorders. Inability to do a liver biopsy should not exclude patients from a trial.

Noninvasive measures of hepatic fibrosis and disease activity assessments using biochemical or scanning measurements are not considered validated and should not be a substitute for the histological information yielded by liver biopsy.

3. Randomization, Stratification, and Blinding

We encourage sponsors to conduct double-blind trials whenever feasible. For add-on superiority trials of a new DAA plus SOC compared to SOC alone, patients randomized to SOC should receive a matching DAA placebo. It is appreciated that endpoints in these trials are objective, but other aspects of the trial can be influenced by knowledge of treatment assignment. In open-label protocols, patients 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 patients by important baseline factors such as IL-28B polymorphisms, viral load (high or low), HCV genotype/subtype, and cirrhosis,

because these baseline factors are predictive of SVR depending on the regimen and population studied. In international trials, patients should be stratified by geographic area.

4. Efficacy Endpoints

The primary endpoint for phase 3 studies should be SVR at 24 weeks after completion of a scheduled course of therapy (SVR24). Viral RNA clearance should be measured using a sensitive and specific quantitative assay. Before initiation of clinical trials, sponsors should provide in their development plans the name and performance data for the assay proposed for measuring HCV RNA viral load.

5. Trial Procedures and Timing of Assessments

Recommended key time points for measuring viral RNA are at weeks 4, 12, 24, and 48 or at the end of therapy (which may occur at 24 or 48 weeks). Viral measurements at week 12 and 24 have been critical for deciding whether a full course of interferon/RBV is justified. Week 4 and 12 measurements can be used in protocol decision making for determining duration of a DAA or a regimen.

6. Statistical Considerations

a. Analysis populations

All patients who are randomized and receive at least one dose of assigned therapy during the trial should be included in the primary efficacy analysis. If a substantial proportion of patients exit the trial after randomization but before receiving treatment or if there is an imbalance between treatment arms in the number of such patients, then sensitivity analyses can be conducted imputing all or a proportion of those who exited as treatment failures.

b. Efficacy analyses

The primary analysis endpoint should be SVR24, which measures the presence or absence of viral RNA 24 weeks after completing a protocol-defined treatment course, and this analysis determines whether effectiveness has been demonstrated.[14] The primary analysis should be adjusted for at least one or two of the most important covariates (e.g., baseline HCV genotype, screening HCV RNA or IL-28B polymorphism). The covariates that will be included in the primary analysis should be prespecified in the protocol.

For subgroup analyses, the analysis of SVR24 should be performed within important demographic and baseline characteristics (e.g., geographic region (U.S., non-U.S.), sex, race, age group, HCV genotype, screening serum HCV RNA, IL-28B status, baseline

[14] 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 24 weeks after the originally planned treatment duration.

weight, baseline body mass index, baseline alanine aminotransferase (ALT), baseline liver histology, baseline fibrosis, and prior response to interferon/RBV-based regimens). The purpose of these subgroup analyses basically is to evaluate the consistency of the SVR24 endpoint result across these subgroups. It is important to recognize, however, that simply by chance a hypothetical drug that has 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 treatment-experienced trials there should be adequate representation from null responders, partial responders, and responder relapsers, as appropriate for each drug based on activity observed in phase 2 data (phase 2 data may suggest that it is futile to study certain categories of nonresponders in phase 3).

Secondary endpoints can include:

- Normalization of ALT levels
- The proportion of patients with RVR (undetectable HCV RNA after 4 weeks of treatment)
- The proportion of patients with complete early virologic response (undetectable HCV RNA after 12 weeks of treatment)
- The proportion of patients with undetectable levels of HCV RNA at the end of treatment and 12 weeks after the end of treatment
- Relapse rates at 12 and 24 weeks after the end of treatment

However, 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.

Patients who stop treatment because they did not completely suppress HCV RNA or had rebound of HCV RNA after complete suppression should be regarded as failures in all analyses. For patients who discontinue treatment early, sponsors should collect information to determine if these patients switched treatments or added additional therapy. This information can be used to understand reasons for discontinuation and how patients will be included in the analysis.

c. Handling of missing data

For the primary analysis, sponsors should consider patients not to have achieved an SVR if the patients discontinue from a trial before the end of the scheduled 24 week follow-up

period and if the patients have missing HCV RNA values at the end of the scheduled 24 week follow-up period.

Sponsors should make every attempt to limit loss of patients from the trial, and when the loss is unavoidable, to collect information that can help explain the cause of the loss and the final status of the patient. Analyses excluding patients with missing data or other post-treatment outcomes can be biased because patients who do not complete the trial may differ substantially in both measured and unmeasured ways from patients who remain in the trial.

A range of sensitivity analyses should be performed to demonstrate that the primary analysis is robust to discontinuation and noncompliance. Sensitivity analyses can be performed using various methods for imputing missing post-treatment virologic results at 24 weeks of follow-up. Examples include but are not limited to using results from any available last post-treatment week in place of the 24-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 drug-adherence and 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 patients who withdrew consent or were lost to follow-up, or who had adverse events (e.g., nausea and diarrhea) that could have been related to the treatment they were taking.

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.[15]

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

e. Statistical analysis plan

Before initiation of 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 considered as part of the protocol and ideally should be finalized together with the protocol before patient enrollment. 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 formulations, level of significance or alpha-level, alpha adjustments for multiple comparisons and interim analyses, and any planned covariates for the analyses. It is possible to 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 *firewalls* for maintaining the integrity of the blind.

It is important that the SAP prospectively identify the covariates to be used in the analysis. It is also important that the number of covariates be kept to a minimum and limited to those that are expected to strongly influence outcome.

Center-by-treatment interaction should be investigated and reported to assess consistency of the efficacy results.

C. Other Considerations

1. Clinical Virology Considerations

Proof-of-concept and efficacy trials should assess the development of HCV genotypic resistance to the investigational agent. Resistance testing should be performed for patients who demonstrate virologic breakthrough (defined as a greater than or equal to 1 $\log_{10}$ increase in HCV RNA above nadir, or detectable HCV RNA, while on treatment, after an initial drop to below detection), an incomplete antiviral response (e.g., detectable HCV RNA at end of treatment), a slow or plateau viral load decay phase, or virologic relapse after treatment cessation. 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 associated with differential antiviral activity with the new agent.

Viral resistance-associated polymorphisms or substitutions observed in clinical trials but not identified and characterized in nonclinical virology experiments should be evaluated phenotypically by introducing the changes into the HCV genome, and determining the conferred fold-shift in susceptibility to the agent using appropriate cell culture and/or biochemical assays. In addition, phenotypic analyses should be performed using baseline and on-treatment clinical isolates from a subset of trial patients representative of the HCV genetic diversity and virologic responses observed in clinical trials.

Emerging data with new DAAs suggest 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 can significantly limit a patient's future treatment options. Therefore, patients who have detectable resistance-associated substitutions at treatment cessation or follow-up should be followed for an extended period, preferably at least 1 year after treatment cessation, to assess the persistence of resistance-associated substitutions. The potential persistence of resistance-associated substitutions should be characterized for patients 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.

Sponsors should consider genotyping regions outside the direct HCV genome target depending on the characteristics of the antiviral agent and interactions of the target with other viral proteins. In cases when resistance is suspected based on viral RNA kinetics, but genotypic evidence of resistance is not detected, sponsors should also consider performing additional genotypic analyses using a method sufficiently sensitive to detect minority variants.[16]

2. PK/PD Considerations

Trials conducted in HCV-infected patients should include assessment of pharmacokinetics and the relationship between exposure and virologic success and toxicity in all patients.

Sponsors can use a combination of dense and sparse sampling throughout development to characterize the pharmacokinetics of the investigational agent. For example, a dense sampling schedule should be implemented in monotherapy trials. In longer term trials, however, a dense sampling schedule might not be feasible. Alternatively, sparse sampling from these trials can be combined with dense 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. These data can then be subjected to appropriate population PK analysis.[17] PK samples for evaluation of Peg-Interferon/RBV or any other agent in the regimen should also be collected in trials of combination therapy to assist in exposure-response analyses.

Sponsors can use the following two broad approaches to characterize the relationship between exposure and viral kinetics or virologic success of the investigational agent, depending on the stage of development and purpose of the analysis. Both approaches

[16] Additional guidance for reporting HCV drug resistance can be found in the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HCV Resistance Data*.

[17] See the guidance for industry *Population Pharmacokinetics*.

allow for exploration of relevant covariates. These analyses should also account for the development of resistance to the investigational agent.

(1) To aid the design of phase 2b or phase 3 trials, with respect to dose and regimen choice, 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, includes a mechanistically appropriate targeted drug effect, and, includes components to describe virologic breakthrough, relapse, and long-term viral response.

(2) When sufficient SVR12 or SVR24 data are available, a simplified analysis relating proportion of patients with virologic success and appropriate exposure variable (e.g., C_{min} or area under curve) can be used to support evidence of effectiveness and justify dose selection.[18]

3. Special Populations

Treatments for patients with hepatic impairment or pre- or post-transplant patients, patients co-infected with HIV and HCV, and patients with decompensated cirrhosis are 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. Hepatic impairment

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

b. HIV/HCV co-infected patients

It is estimated that nearly 30 percent of patients 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 than patients with HCV infection alone. In addition, treatment responses (SVR24) with SOC in co-infection are generally less than responses (SVR24) with HCV infection alone.

As needed, and based on a particular investigational drug's metabolic profile, drug-drug interaction trials should be conducted before trials in co-infected patients to support concomitant dosing of a new HCV drug and antiretroviral drugs.

We strongly suggest that an initial NDA for the treatment of HCV contain some clinical data on the HIV/HCV co-infected population at time of filing, including:

[18] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

- Drug-drug interaction data with the most commonly used HIV drugs

- Safety data on a cohort of co-infected patients receiving the drug for the recommended treatment duration

- Preliminary efficacy data characterizing, at minimum, on-treatment responses

With the above-mentioned preliminary data, labeling describing drug interactions and preliminary safety data may be appropriate. For more extensive labeling that expands the indication to the HIV co-infected population or includes a description of efficacy in the co-infected population, a clinical trial demonstrating efficacy and safety in at least 300 co-infected patients may be appropriate. In some cases, single-arm prospective trials (with historical controls) may be appropriate for the co-infected population if trials in the HCV mono-infected population showed robust and substantial efficacy of the new DAA added to SOC. Trials in co-infected patients should evaluate SVR at 24 weeks after end of therapy as the primary efficacy endpoint. As part of the safety evaluation, loss of HIV efficacy (rebounds in HIV viral RNA) should be assessed.

c. Patients with decompensated cirrhosis

SOC, interferon-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 to be needed to achieve viral suppression. Because there are currently no HCV treatments in patients with decompensated cirrhosis and because spontaneous resolution of HCV infection in this population is consistently negligible, dose-response trials or historically controlled efficacy and safety trials showing clinically significant SVRs may be appropriate to expand the labeling for this population. However, as more drugs become available for study in combination regimens, we will encourage comparative trials. SVR24 should be the primary efficacy endpoint, but other important endpoints include progression of liver disease, transplantation, and mortality. SVR24 is an important endpoint notwithstanding disease progression requiring transplantation, because SVR24 will likely translate into prevention of infection of a newly transplanted liver.

The contribution of each agent toward overall efficacy of a regimen should be demonstrated, but can be based on data such as that discussed in section III.B.6, Statistical Considerations. For example, trials showing the efficacy of one new DAA added to Peg-Interferon/RBV in patients with compensated cirrhosis can serve as supportive data for demonstrating contribution toward efficacy in other populations that are more difficult to study.

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

d. Pediatric populations

Early trials of DAAs should enroll adult patients only, reserving pediatric exposure until the pharmacokinetics, pharmacodynamics, and safety of the agent are reasonably well-defined. Sponsors are encouraged to begin discussions of their pediatric formulation and clinical development plan early in development, but pediatric clinical trials should be initiated once phase 2 adult data characterizing the safety profile and initial antiviral efficacy are available. 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 done because they are clinically indicated, biopsy data should be provided.

4. Early Access/Treatment INDs

Some hepatitis C-infected patients who have not responded to approved treatments and/or who are at substantial risk of liver disease progression may benefit from access to new therapeutic options before their approval. Treatment INDs or other access 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 agent. Ideally, the timing of a treatment IND would occur after phase 3 trials were fully enrolled or well underway so as not to interfere with phase 3 drug development. Treatment INDs can provide early access while phase 3 trials are being completed, analyzed, submitted, and reviewed by the FDA. Alternatively, individual patient INDs and treatment access protocols for intermediate size populations may be possible. In contrast to treatment INDs for larger populations during or after phase 3 trials, access for intermediate size populations (approximately 100 patients or fewer), can occur earlier in drug development.

Historically, early access programs with HIV allowed many people to gain access to life-saving drugs. However, for some individuals, early access to a drug resulted in what amounted to sequential monotherapy and the emergence of multidrug resistance. Because treatment of CHC requires multiple agents to achieve SVR and to reduce the emergence of drug resistance to single agents or drug classes, treatment INDs that include two or more investigational agents or that allow co-enrollment in several treatment IND programs simultaneously are desirable, particularly for previous null responders or for patients who cannot take interferon-based regimens. However, treatment use of multiple investigational agents should be supported by:

- Data and rationale that characterize the potential for PK drug interactions and potential for overlapping toxicity. Data to support dose modifications if drug interactions are present.

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

Refer to section III.A.4.d., Combination therapy with multiple DAAs, for the data needed to support treatment use of multiple investigational agents.

GLOSSARY OF ACRONYMS

CHC	chronic hepatitis C
DAA	direct-acting antiviral agent
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCV RNA	hepatitis C virus ribonucleic acid
HIV	human immunodeficiency virus
IFN	interferon
IL	interleukin
Peg	pegylated
RBV	ribavirin
RVR	rapid virologic response
SOC	standard of care
SVR	sustained virologic response
SVR24	sustained virologic response 24 weeks after stopping treatment

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