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

Guidance for Industry

**DRAFT GUIDANCE**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)

May 2016
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Revision 2
Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry

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U.S. Department of Health and Human Services
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Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 pre-investigational new drug application (pre-IND) through the new drug application (NDA) and postmarketing stages. For the purposes 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 This draft guidance is intended to serve as a focus for continued discussions among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and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. The organization of the guidance parallels the development plan for a particular drug or biologic.

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. Treatment of acute hepatitis C or therapeutics without antiviral mechanisms intended to mitigate or reverse clinical or pathophysiological outcomes of CHC, such as prevention of hepatocellular carcinoma (HCC) or reversal of fibrosis, are also not addressed in this guidance. The main focus of this guidance is on development of DAAs as part of IFN-free regimens. Because there are currently safe and highly effective FDA-approved IFN-

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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.
Contains Nonbinding Recommendations
Draft — Not for Implementation

free treatment options, the DAVP recommends against studying an IFN-containing regimen in a DAA treatment-naive population.

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. 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 revised draft guidance for industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment issued in October 2013. Significant changes in this revision include:

- Modification of several sections to focus on IFN-free DAA regimens.
- Additional details on phase 2 and phase 3 trial design options for the evaluation of IFN-free regimens in treatment-naive and treatment-experienced populations, including DAA-experienced populations. Specifically, this guidance recommends that each marketing application contain at least one active-controlled comparative trial.
- Additional clarification on DAA drug development in specific populations including trial design options for human immunodeficiency virus-1 (HIV-1)/HCV co-infected patients, patients with advanced chronic kidney disease (CKD), patients with decompensated cirrhosis, patients either pre- or postliver transplantation, and patients who failed to respond to a prior DAA-based regimen.

Sponsors considering development of antiviral drugs for the treatment of CHC are encouraged to communicate with the FDA through the pre-IND consultation program. 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.

In general, FDA’s guidance documents 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.

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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.

II. BACKGROUND

HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family. There are at least seven different HCV genotypes, numbered 1 to 7; most genotypes have been divided into multiple subtypes (e.g., genotype 1 subtypes 1a and 1b) (Smith, Bukh, et al. 2014). 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 (Gower, Estes, et al. 2014).

In the United States, approximately 3 million people have chronic HCV infection (i.e., CHC) (Armstrong, Wasley, et al. 2006; Klevens, Dale, et al. 2012). CHC causes cirrhosis and HCC 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).

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, Ito, et al. 2005; Singal, Volk, et al. 2010).

Total duration of treatment and choice of regimen may depend on HCV genotype or subtype and disease factors such as the HCV RNA level or the presence or absence of cirrhosis. 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). The addition of a DAA (e.g., HCV protease inhibitor) to peg-IFN and RBV substantially increased SVR (Casey and Lee 2013). Currently, the ability to achieve SVR rates exceeding 90 percent using only DAAs (without IFN) in many populations of HCV-infected patients has been well established. Throughout this guidance, antiviral treatment efficacy refers to SVR assessed 12 weeks following cessation of treatment (SVR12).

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

In addition to nonclinical development and early phase drug development, an overall drug development approach with respect to target population, efficacy, and safety is addressed in the following sections.
1. **Nonclinical Virology Development 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 and clinical virology specific to the development of HCV DAAs are summarized throughout this guidance.

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 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 an investigational drug should be characterized in cell culture to demonstrate activity and identify a preliminary target concentration for evaluation in HCV-infected patients. Antiviral activity of candidate drugs targeting nonstructural components should be assessed using HCV replicon systems, and 50 and 90 percent effective concentrations (EC\textsubscript{50} and EC\textsubscript{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\textsubscript{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 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.

c. **Cytotoxicity and mitochondrial toxicity**

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\textsubscript{50}) and therapeutic index should be

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\(^7\) See the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency.*
calculated (CC\textsubscript{50}/EC\textsubscript{50}). Cytotoxicity also should be assessed using various cell lines and primary cells cultured under proliferating and nonproliferating conditions. Nucleos(t)ide analog polymerase inhibitors should be assessed for bone marrow precursor cell toxicity with appropriate controls. Mitochondrial toxicity should be assessed in glucose-containing and in galactose-containing medium (i.e., Crabtree effect; Marroquin, Hynes, et al. 2007). Mitochondrial assessments include assessments of mitochondrial toxicity, viability, function, structure, and apoptosis in multiple cell types (e.g., assessing mitochondria copy number, mitochondrial DNA, cell growth, cell protein, adenosine triphosphate content, oxidative phosphorylation, lactase release). Inhibition of mitochondrial RNA polymerase also should be evaluated for nucleos(t)ide analogs (Arnold, Sharma, et al. 2012). Positive controls for mitochondrial toxicity studies should be relevant to the class of the investigational drug whenever possible.

d. Antiviral activity in animal models

In general, studies of anti-HCV activity in an animal model are 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.

e. 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 investigational 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\textsubscript{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-1/HCV co-infected patients.

f. 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 investigational drug should be determined and validated by introducing the changes into the HCV genome and determining the conferred fold-shift in susceptibility (based on EC\textsubscript{50} and EC\textsubscript{90} values) using cell culture 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 investigational 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
205 DAA depends on many factors, and usually is defined as it relates to other drugs that are
206 approved or in development (Kwong, Najera, et al. 2011).8
207
208 Resistance studies should include evaluation of the potential for cross-resistance with approved
209 drugs, particularly focusing on those in the same drug class and other classes with the same viral
210 target. If a sponsor intends to develop a drug to be used in patients previously treated with drugs
211 in the same class, the activity of the investigational drug should be evaluated against HCV
212 variants that emerge in patients treated with other drugs in the class. In addition, the activity of
213 other representative approved drugs in the class should be evaluated against HCV variants
214 associated with resistance to the investigational drug.
215
216 2. General Considerations for Phase 1 and Phase 2 Development
217
218 Early clinical evaluation of HCV DAAs should follow a rational approach to provide sufficient
219 data to establish safety, antiviral activity, and antiviral efficacy to support phase 3 trials. In
220 general, phase 1 trials should be conducted to assess safety, pharmacokinetics, and initial
221 antiviral activity of the DAA. Phase 2 trials should characterize the optimal dose and treatment
222 duration of the DAA(s) as part of combination regimens with regard to both antiviral activity and
223 safety.
224
225 Based on HCV replication dynamics in infected patients (Rong, Dehari, et al. 2010), the error-
226 prone nature of HCV genome replication, and the fact that the activity of a DAA is often reduced
227 by a single amino acid substitution in the drug target, multiple anti-HCV drugs with non-
228 overlapping resistance pathways generally are needed to suppress preexisting and emerging
229 drug-resistant variants for most patients to achieve SVR. Sponsors can choose to develop a
230 DAA for dosing in combination with other DAAs, and/or in regimens that include RBV. The
231 overall design of a phase 2 clinical development program should attempt to demonstrate the
232 contribution of individual drugs in the regimen (as described in section III.A.4., Efficacy
233 Considerations).
234
235 The following information is recommended to support phase 2 trials of multiple DAAs:
236
237 • Mechanism of action for each drug in the combination
238
239 • Resistance and cross-resistance patterns for each drug in the combination
240
241 • Combination antiviral activity data from cell culture studies
242
243 • Anti-HCV activity data from clinical trials (e.g., short-term monotherapy trials, or dose-
244 finding trials in combination with other antiviral drugs)
245
246 • Phase 1 human safety data on each drug
247
8 For the purposes 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.
• Dose selection rationale that considers 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 SVR12 for DAA-containing regimens. Therefore, off-treatment responses such as SVR at post-treatment weeks 4 and 12 (SVR4 and SVR12, respectively) should be available before progression to phase 3. Specifically, for an end-of-phase 2 meeting, SVR4 data from all enrolled patients in key supporting phase 2 trials, and all available SVR12 (or longer) data from phase 2 trials should be submitted 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 patient populations for study in phase 3.

Phase 2 studies should include a representative population of patients with chronic HCV infection. These populations can include, but are not limited to, Blacks/African Americans, Hispanics, prior peg-IFN/RBV treatment failures, prior DAA treatment failures and patients 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 following recommendations and examples are provided for potential phase 1 and phase 2 trial designs for HCV DAAs based on the current state of the field.

a. Phase 1a/first-in-human trials

In general, we recommend single- and/or multiple-ascending-dose trials in healthy adult patients to assess safety and pharmacokinetics for the first-in-human trials. Single-dose and short-duration multiple-dose pharmacokinetic (PK) trials (see below) also can be conducted in HCV-infected patients.

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

The first proof-of-concept antiviral activity trial in HCV-infected patients 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 EC50 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 patients with CHC who are naïve to previous anti-CHC therapy (including the investigational drug), and who have minimal fibrosis and no significant comorbidities. Following demonstration of safety and antiviral activity in treatment-naïve patients, sponsors can plan additional trials in treatment-experienced patients, 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 patients.

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 plasma concentrations. 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.

c. Phase 2 trials with combination DAA regimens

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 several different DAA combinations (all investigational or approved plus investigational) at various doses and treatment durations. The number of DAAAs in a regimen depends on individual drug potency and estimated resistance barriers as determined in earlier stages of drug development. RBV can be included in some or all of the treatment arms depending on the DAAs, the HCV genotype/subtype and the patient population being evaluated. SVR12 is the recommended primary endpoint. Patients should be followed through week 24 post-treatment cessation to further confirm the reliability of SVR12 as a marker of virologic success. Trial randomization should be stratified according to genotype/subtype or other key baseline characteristics predicted to have a significant effect on treatment outcome.

Initial trials should include frequent HCV RNA monitoring and both patient- and treatment arm-specific stopping rules for poor virologic outcomes (e.g., virologic breakthrough or relapse). When feasible, protocols should include opportunities for patients with virologic failure to receive appropriate alternative therapeutic regimens that could consist of investigational and/or approved drugs. Final SVR12 and SVR24 efficacy outcome data from patients who received protocol-specified re-treatment (approved and/or investigational) 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.
We anticipate that the number of single- and multiple-class DAA treatment-experienced patients 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 combination regimen may be particularly difficult to treat. Many of the host and viral factors that contributed to treatment failure with the prior DAA combination regimen(s) will remain, such as cirrhosis, advanced liver disease, poor immune clearance of HCV replication complexes and infected cells, high baseline HCV RNA levels, suboptimal exposures, poor adherence, poor tolerability, or drug resistance (i.e., enrichment of HCV viral populations that are resistant to one or multiple HCV DAA classes).

Multiple rounds of DAA treatment failure may severely limit treatment options for patients; therefore, initial trials in DAA-experienced patients should include regimens and treatment durations that are predicted to provide patients with the best chance of achieving SVR. For example, exploration of relatively short treatment durations should be considered only after preliminary evidence of SVR has first been demonstrated for longer treatment durations. Also, because of the number of promising DAA classes approved or 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 and drug resistance characteristics, we are not able to provide detailed guidance on appropriate trial designs for all possible circumstances. The need for drug resistance screening depends on the specific drug classes in the regimen, emerging data from other trials in DAA-experienced populations, and the characteristics of the patient population, including HCV DAA exposure history, peg-IFN/RBV treatment history, and eligibility for a treatment regimen containing peg-IFN/RBV.

Patients 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 patients 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 preliminary evidence of SVR in DAA-naïve patients.

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 development can be targeted to regimens that are optimized for specific subtypes. We recommend including patients diagnosed with compensated cirrhosis in phase 2 and phase 3 trials. Also, we encourage the study of combinations of DAA HCV antivirals in patients with the greatest need for new drugs, such as patients with bleeding disorders, transplant patients, patients with advanced CKD, patients with decompensated cirrhosis, and patients who have previously failed DAA-based treatment.
Similarly, patients 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
RBV in HIV-1/HCV co-infected patients as soon as appropriate based on the availability of data
to choose an appropriate dose and rule out or manage important drug-drug interactions (see
section III.B.5.a., HIV-1/HCV co-infected patients). Supportive data may be needed such as
hepatic impairment trials and drug-drug interaction trials (e.g., antiretrovirals for HIV,
immunosuppressants for transplant) before trials in the above-mentioned subgroups are
conducted to define safety and pharmacokinetics.

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) may 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, Hepburn, 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 patients from these
populations (e.g., women, Black/African Americans, Hispanic/Latinos, patients with cirrhosis,
patients with bleeding disorders, and patients using intravenous drugs) to enroll in phase 2 and
phase 3 clinical trials.

4. Efficacy Considerations

Dose- and duration-finding should be performed in phase 2 trials to select optimal dose(s) and
treatment duration(s) for further evaluation in phase 3 trials. See section III.B.6., Dose Selection,
for additional considerations. For more detailed guidance on phase 3 trial design issues, see
section III.B.1., Trial Design.

Efficacy should be established in key subpopulations, including patients:

- With and without cirrhosis
- With compensated and decompensated liver disease
- With HCV genotypes (e.g., 1, 2, 3, 4, 5, and 6, depending on susceptibility)
- Who are DAA-naïve and DAA-experienced

Sponsors can submit an NDA to gain approval of a drug in a single population. 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. In this case, 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 (see section III.B., Phase 3 Efficacy Trial Considerations).
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 patients 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

- Early phase 2 clinical trial data showing that the addition of a drug to a DAA combination improves SVR or reduces the emergence of viral variants with resistance-associated substitutions

- Data demonstrating improved efficacy of a combination regimen relative to historical results with one or more components of the combination regimen

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. HCV treatment drugs also may be eligible for fast track, breakthrough,9 and priority review designation if the specifics of the relevant criteria are met.10,11

5. 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 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

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10 See the guidance for industry Expedited Programs for Serious Conditions — Drugs and Biologics for information regarding fast track, breakthrough, and priority review designation.

11 Accelerated approval, which can rely on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit, does not apply to drug development for hepatitis C because the endpoint used in clinical trials for full approval is considered a validated surrogate endpoint (SVR12) that is known to predict clinical benefit.
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 safety compared to currently available therapeutic options.

Data from randomized, controlled, and comparative trials are recommended to assess the safety
of the investigational drug. Ideally, to obtain comparative safety data, an active comparator in a
phase 3, controlled trial should be an antiviral drug that is recommended for treatment of chronic
HCV infection by authoritative scientific bodies based on clinical evidence that also reflects
current practice. In some cases, use of an immediate versus deferred trial design to obtain
comparative safety data may be appropriate (see section III.B., Phase 3 Efficacy Trial
Considerations).

B. Phase 3 Efficacy Trial Considerations

1. Trial Design

The benefit-risk profile of the investigational drug and the available approved treatment options
for the indicated population are important factors to determine an appropriate trial design. We
recommend that at least one of the pivotal efficacy trials is designed as a randomized trial with
an active-control arm. The active comparator in a phase 3, controlled trial should be an antiviral
drug that is recommended for treatment of chronic HCV infection by authoritative scientific
bodies based on clinical evidence that also reflects current practice at the time of trial initiation.
A randomized, active-controlled design allows for a direct comparison of the safety and efficacy
of the study regimen to an FDA-approved, recommended treatment option. We recommend
sponsors discuss with the FDA regarding the choice of an active control and choice of study
population before trial initiation. Although randomized, controlled, comparative trials are
preferable, in some situations (e.g., when no IFN-free recommended treatment option exists for
the population under study), 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. Treatment-naïve and non-DAA treatment-experienced populations

A randomized, active-controlled noninferiority (NI) or superiority trial design is preferred over a
single-arm design, and at least one of the pivotal trials should be designed as such. The active
comparator in a phase 3, controlled trial should be an antiviral drug that is recommended for
treatment of chronic HCV infection by authoritative scientific bodies based on clinical evidence
that also reflects current practice. Sponsors considering an NI trial design should discuss in
advance their justification of the NI margin, trial designs, and the data analysis plans.

12 See the HCV treatment guidelines provided by the American Association for the Study of Liver Diseases for the

13 Ibid.

14 Ibid.
In addition to a randomized, active-controlled trial or in situations where a randomized, active-controlled trial is not feasible, and a single-arm trial is under consideration, we recommend an immediate versus deferred placebo-controlled trial design in patients who are not considered to need immediate treatment. In this design, patients should be randomized to the DAA-based regimen or placebo for the intended treatment duration. At the end of treatment, patients randomized to the placebo arm can receive the DAA-based regimen. The purpose of the deferred treatment design is to collect comparative safety data and the primary efficacy comparison is to a historical reference of a recommended HCV treatment regimen at the time of trial initiation rather than to compare virologic response between trial arms. It is expected that no patient will respond virologically while receiving placebo. Sponsors should include sufficient information in the protocol to support the historical control used. Sponsors should also make adequate provisions in the trial to maintain the trial blind and should minimize the potential for patients in the placebo arm to drop out.

As an alternative to an immediate versus delayed treatment design, a dose or treatment duration comparison trial could also be used. Consistent with the immediate versus delayed treatment design, the primary efficacy comparison should be between each of the trial arms and a historical reference of a recommended HCV treatment regimen at the time of trial initiation.

b. DAA treatment-experienced population

Patients failing DAA-containing regimens constitute an emerging population in need of effective HCV therapies. Because of the limited available efficacy data 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 patients. In general, we anticipate phase 3 trials will be based on phase 2 proof-of-concept efficacy data. Trial designs and the number of patients needed to support an indication in patients who have failed treatment with DAA-containing regimens depend on the specific characteristics of the patient population and the availability of other treatment regimens.

2. Trial Population

Sponsors should ensure that patients enrolled in a trial have CHC as confirmed by one of the following:

- They are 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

- They are 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)
3. Entry Criteria

a. Assessment of cirrhosis

Even in the era of highly effective DAA combination therapy, cirrhosis has been demonstrated to be a significant factor affecting treatment outcomes (Afdhal, Reddy, et al. 2014). Determining trial patients’ baseline cirrhosis status remains critical for making correlations between the presence of cirrhosis and efficacy, safety, and pharmacokinetics. Sponsors should have a sufficient number of trial patients with documented cirrhosis throughout the course of drug development to explore safety and efficacy correlations between cirrhosis and outcomes.

To define presence or absence of cirrhosis, the 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 patients with cirrhosis.

b. HCV genotype considerations

Certain DAAs demonstrate antiviral activity against multiple HCV genotypes, and sponsors may wish to seek an indication for HCV treatment in several genotypes. Efficacy should be established for each HCV genotype independently, and as seen with HCV genotype 1, some DAA regimens may provide different efficacy for different subtypes. Enrollment of enough patients 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 because of the low prevalence of these genotypes 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 patient isolates from the major subtypes represented in the United States. See also section III.C.3., Clinical Virology Considerations, for recommendations regarding HCV genotype/subtype determination in clinical trials.

c. DAA treatment experience

All clinical trial protocols should describe entry criteria related to prior DAA treatment experience. If DAA treatment-experienced patients are eligible, the protocol should indicate the specific DAA drug or class experience that is eligible or exclusionary. To support a broad indication for DAA treatment-experienced patients, efficacy should be demonstrated in study populations previously exposed to a variety of DAA classes, including those that are shared with the investigational DAA(s). In such cases, efficacy should be specifically demonstrated in patients who have predominant HCV populations with drug resistance-associated substitutions that emerged from prior therapy with the same DAA class(es) as the investigational DAA(s); sponsors should consider conducting resistance analyses at screening to enrich for this population.
4. Randomization, Stratification, and Blinding

We encourage sponsors to conduct double-blinded 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, 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 can consider stratification of patients by important baseline factors that are predictive of SVR. The ideal stratification factors depend on the regimen and population studied, but could include one or more of the following: HCV genotype/subtype, key baseline viral polymorphisms or resistance-associated substitutions, prior treatment history, baseline HCV RNA, or presence/absence of cirrhosis. In international trials, patients should be stratified by geographic area (U.S. versus non-U.S.).

5. Specific Populations

Patients with hepatic impairment or pre- or post-transplant patients, patients with advanced CKD, 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. This section also includes information on HIV-1/HCV co-infected patients; although we no longer consider this population as having an unmet medical need.

a. HIV-1/HCV co-infected patients

Approximately 30 percent of patients infected with HIV-1 are co-infected with HCV (Sulkowski 2008). Patients with HIV-1/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. The SVR rates in HIV-1/HCV co-infected patients receiving all oral antiviral drugs are similar to HCV mono-infected patients. As a result, both HIV-1/HCV co-infected patients and HCV mono-infected patients can enroll into the same clinical trial, and we strongly encourage sponsors to have data on HIV-1/HCV co-infected patients at the time of submission of an original NDA. See section III.B., Phase 3 Efficacy Trial Considerations.

HIV-1/HCV co-infected patients should be included in trials with HCV mono-infected patients or in a separate trial to obtain efficacy and safety data at the proposed dose(s) and treatment duration. The number of patients needed may depend on the effect of drug interactions on exposures of the DAA. More patients may be needed if an increase or decrease in DAA is expected because of drug interactions.

The NDA should also include the following data:

- 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-1/HCV co-infected patients taking antiretrovirals that are expected to have interactions with investigational DAA(s).

- Safety data including HIV RNA data to assess loss of HIV efficacy (rebound in HIV RNA viral load) and changes in CD4 cell counts.

b. Patients with decompensated cirrhosis and pre- or post-transplants

IFN-based regimens are not considered safe for patients with decompensated cirrhosis and may be difficult to administer postliver transplant. As compared to compensated disease, treatment with multiple investigational DAAs, with more drugs or for longer durations, may be needed to achieve viral suppression.

We encourage active-controlled trials when feasible. However, safety and efficacy data can be derived from dose or treatment duration comparison or single-arm, historical control trials. The number of decompensated patients needed to support labeling claims should be discussed in advance with the DAVP. The minimum acceptable safety database for this population will be determined by the demonstrated safety profile of the regimen in other populations. 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 patients are initiated to support concomitant dosing of a DAA regimen and immunosuppressive drugs.

We strongly recommend that an original NDA submission for the treatment of HCV with a combination of DAAs contain some clinical data from patients with decompensated cirrhosis, as well as pre- and post-transplant patients. 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 patients with decompensated cirrhosis and pre- or post-transplant recipients who received the drug for the recommended treatment duration

The safety evaluation of populations with advanced liver disease may need to incorporate additional safety analyses to assess the safety of the investigational drug in this unique population. Specific hepatic safety monitoring and treatment discontinuation criteria should be discussed with the DAVP during the protocol development phase to incorporate case selection criteria and laboratory cut-off values specific to the population.

Evaluation by an independent adjudication committee is encouraged to identify adverse events of interest in this cohort of patients with decompensated liver disease and/or those listed for liver transplantation. The NDA should include assessments based on the Model for End Stage Liver Disease (MELD) and Child Pugh Turcotte (CPT) scores at 12-week post-treatment (SVR12 time point) compared to the patient’s baseline values.
Plans for expanded access trials or safety trials also should be considered for this population early in development.

c. Pediatric populations

The rapid evolution of HCV drug development and treatment affects pediatric development programs. Therefore, we encourage sponsors to begin discussions about their pediatric formulation and clinical development plan early in development because pediatric assessments are required under the Pediatric Research Equity Act (PREA) as part of the overall drug development program for a “new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration,” unless those assessments are waived or deferred. Sponsors are required to submit pediatric study plans — which would include an outline of the pediatric assessments that the sponsor plans to conduct, or a request for a waiver or deferral of the requirement to submit those assessments — no later than 60 days after an end-of-phase 2 meeting or such other time as may be agreed upon by the FDA and the sponsor. In the absence of a serious safety signal in adults, we recommend sponsors enroll adolescents concurrently with adults in phase 3 trials and make every effort to submit confirmatory PK and safety data from a small cohort in this age group at the time of the original NDA. Note that, because young children with HCV infection rarely have progressive liver disease requiring treatment, evaluation of patients younger than 3 years of age may not be required.

In addition to requiring pediatric assessments of certain drugs, PREA also requires that those assessments be conducted using a formulation of the drug that is appropriate for each age group being studied. Formulation development is expected to be the most challenging aspect of pediatric DAA development because many drug products will contain two or more drugs in a fixed-dose combination. Adult formulations generally will be considered to be appropriate for adolescent patients (approximately 12 to 18 years of age) (Momper, Mulugeta, et al. 2013), but younger children, some of whom may not be able to swallow pills, may require different formulations. Therefore, pediatric formulation development should begin as early as possible to enable the creation of appropriate pediatric formulations of HCV drugs.

In general, pediatric clinical trials can be initiated after phase 2 adult data characterizing the safety profile and preliminary evidence of efficacy (SVR) are available. Initial pediatric PK data

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16 See section 505B(a)(3) and (a)(4) of the FD&C Act.

17 See section 505B(e)(2)(A)(ii) of the FD&C Act; see also the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. When final, this guidance will represent the FDA’s current thinking on this topic.

18 Pediatric assessments will be waived in cases where the FDA finds that “necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed)” (section 505B(a)(4)(i) of the FD&C Act). For drugs that trigger the requirements of PREA, if the FDA finds that there are so few patients with progressive liver disease in the 0 to 3-year age range that studies are “impossible or highly impracticable,” any required assessments in children younger than 3 will be waived.

19 See section 505B(a)(2)A of the FD&C Act.
and results of available modeling and simulation should be discussed with DAVP before dose selection for pediatric treatment trials. Pediatric extrapolation of efficacy is acceptable for HCV drugs because the course of HCV infection and the effects of DAAs are sufficiently similar between adult and pediatric populations. Therefore, after critical PK parameters for a drug are identified from adult data, pediatric development programs can rely on matching the relevant pediatric and adult exposure parameters to demonstrate effectiveness in pediatric populations. Additional data should be submitted to support safety in pediatric populations and to assess whether SVR rates are comparable to those observed in adult trials.

Because the number of pediatric patients available for enrolling in HCV clinical trials may be limited, we recommend that sponsors focus pediatric development on their best available regimen that is expected to be highly effective based on adult data. We encourage sponsors to work collaboratively to identify such regimens. In general, pediatric trials should provide confirmatory PK data and a safety database of about 100 patients receiving the proposed dose for the proposed duration of treatment and adequately distributed across the age range groups for which studies are required and not waived or deferred. If clinical trials in adults have demonstrated differences in safety profile or treatment regimen based on fibrosis stage, pediatric patients should be assessed for presence or absence of cirrhosis using the most appropriate modality for each study location. If biopsies are performed because they are clinically indicated, biopsy data should be provided at the time of submission.

d. Patients with advanced chronic kidney disease

HCV infection is a common comorbidity in hemodialysis patients. The prevalence rate of HCV among patients undergoing hemodialysis within a U.S. hemodialysis network was reported as 7.8 percent (range: 5.5 to 9.8 percent) (Finelli, Miller, et al. 2005), and it is estimated that over 60,000 HCV-infected patients will require hemodialysis by 2020 (Butt, Wang, et al. 2011). A significant relationship has been observed between HCV infection and increased mortality among patients on long-term dialysis (Fabrizi, Dixit, et al. 2012).

HCV infection can also negatively affect renal transplantation. Compared to non-HCV-infected CKD Stage 4/5 patients, HCV-infected CKD Stage 4/5 patients have poor graft survival and higher overall mortality outcomes following renal transplantation (Fabrizi, Martin, et al. 2005; Terrault and Adey 2007).

Peg-IFN-based regimens have been evaluated in advanced CKD patients, and dosing recommendations are available for patients receiving dialysis. However, SVR rates are poor (56 percent), and tolerability is low (Fabrizi, Marti, et al. 2011). Therefore, the achievement of optimal SVR rates in this population will likely require treatment with IFN- and RBV-free combination DAA regimens.

We encourage active-controlled trials when feasible; however, at a minimum a delayed-treatment, placebo-controlled group should be employed in clinical trials in this population. This will facilitate interpretation of the safety data given the anticipated increased rate of adverse events in the CKD population compared to those without CKD.
The minimum acceptable safety database for this population will be determined by the demonstrated safety profile of the regimen in other populations. We encourage sponsors to study an adequate number of patients in each of the important CKD subgroups (e.g., CKD Stage 4/5, hemodialysis, and peritoneal dialysis). Trials should be stratified based on the degree of CKD severity (and dialysis status) because drug clearance may be affected by these factors. We encourage sponsors who are considering trials in this population to engage in early discussions with the DAVP.

6. Dose Selection

Results from proof-of-concept antiviral activity monotherapy 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 develop a mechanistic model of the concentration-viral kinetics and the concentration safety using all available exposure, viral kinetic, and safety data from previous studies to predict the most active and tolerable doses to be evaluated in phase 2 trials. 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 or viral populations with or without drug resistance-associated polymorphisms/substitutions. Results from patients 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. When applicable, these mechanistic modeling approaches can use viral kinetic model structures and the corresponding disease progression parameter values from the literature.

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. 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.

To optimize the regimen with respect to dose and treatment duration in phase 3 trials, drug efficacy data from phase 1 and phase 2 studies can be combined in a single model to predict SVR in the planned trials. Such a model should be evaluated against on-treatment data of the regimen and drug efficacy parameter estimates should be refined as necessary.

7. Efficacy Endpoints

As mentioned, the recommended primary endpoint for approval in trials evaluating CHC treatments is SVR12 (SVR at 12 weeks after completion of a scheduled course of therapy). 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 patients 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. These observational data support the use of SVR as a validated surrogate of HCV disease progression.

In a previous version of this guidance, SVR24 was the recommended endpoint for CHC clinical trials. However, 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 patients 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. Subsequently, FDA reviews of clinical trials of IFN-free combination DAA regimens have similarly demonstrated concordance of SVR12 and SVR24.

Although SVR12 has been shown to predict SVR24, the concordance of SVR12 and SVR24 results should continue to be assessed in clinical trials, 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 generally will be requested as a postmarketing commitment.

Secondary endpoints should include:

- Virologic failure rate (relapse after end of treatment and virologic breakthrough on-treatment) to aid in the optimization of a dosage regimen and treatment duration
- SVR4 and SVR24 rates (i.e., virologic response at post-treatment week 4 or 24, respectively)
- End-of-treatment response rate
- Rate of drug resistance emergence in patients who experience virologic failure

8. **Trial Procedures and Timing of Assessments**

Recommended key time points for measuring HCV RNA depend on the drug regimen and patient population. Key on-treatment measurements can include weeks 1, 2, 4, 8, 12, and 24, 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.

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Measurements of viral RNA at earlier time points can be used in protocol decision making for determining 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.

9. 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 unless the FDA agrees in advance that certain patients are not pertinent to the safety and effectiveness evaluation. However, if a substantial proportion of randomized patients do not receive treatment in either or both arms then sensitivity analyses also may be needed.

b. Efficacy analyses

The primary efficacy analysis should be a comparison of the proportion of patients who achieve SVR12 across trial treatment arms. This analysis determines whether effectiveness has been demonstrated.21

For subgroup analyses, the analysis of SVR12 should be performed for patients with important demographic and baseline characteristics (e.g., geographic region, sex, race, age group, HCV genotype/subtype, HCV drug resistance-associated polymorphisms/substitutions, screening serum HCV RNA, baseline weight, baseline body mass index, baseline alanine aminotransferase, baseline fibrosis/cirrhosis, and, if applicable, prior response to DAA-based regimens).22 The purpose of these analyses is to evaluate the consistency of the SVR12 endpoint result across these subgroups.

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 patient population.

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 important secondary endpoints that adjust for multiplicity to be applied after the result for the primary endpoint is significant.

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21 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.

22 Subgroup analyses by age, race, and sex are required as well as an analysis of whether modifications of dose or dosage intervals are needed for these subgroups (21 CFR 314.50(d)(5)(v) and (vi)(a)).

21
Patients who experience virologic relapse or who stop treatment because they did not adequately suppress HCV RNA should be regarded as virologic failures in all analyses. For other patients who discontinue treatment early, investigators should determine if these patients 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 patients will be included in the analysis.

c. Noninferiority margin

In NI trials, the choice of an NI margin for statistical hypotheses should be discussed with the DAVP before study initiation because one margin is not appropriate for all study designs. The sponsor should justify a margin ($M_1$) based on prior knowledge of the quantitative contribution of the active control (substituted part of the drug regimen) to the regimen as a whole. This contribution should be determined in a similar population with a similar length of follow-up to the proposed study. In addition, the NI margin ($M_2$) generally should be smaller than $M_1$ to preserve a clinically important effect compared to an active control. If approved drugs have response rates that are 95 percent or higher, a clinically acceptable NI margin ($M_2$) is 5 percent or less; otherwise if the SVRs for approved drugs are all less than 95 percent, sponsors should discuss the size of the NI margin with the DAVP. For NI testing, sponsors should employ two-sided 95 percent confidence intervals adjusted for multiple comparisons or other appropriate testing procedures.

Both NI and superiority can be assessed in an NI study provided that the NI comparison is conducted first and superiority is conducted only after NI is met. For additional information regarding NI studies in general, see ICH E10 and the draft guidance for industry Non-Inferiority Clinical Trials.23

d. Handling of missing data

For the primary analysis, sponsors can consider a patient as having achieved SVR12 if the patient’s week 12 follow-up HCV RNA measurement is missing and the patient achieved SVR24. Sponsors should consider a patient not to have achieved SVR12 if he or she discontinues from a trial before having an HCV RNA measurement at 12 weeks of follow-up or if the patient has missing HCV RNA values at the end of the scheduled 12- and 24-week follow-up periods.

Sponsors should make every attempt to limit loss of patients 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 patient who does not complete the protocol. 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.

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23 When final, this guidance will represent the FDA’s current thinking on this topic.
Appropriate 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 patients who withdrew consent or were lost to follow-up, or who discontinued because of adverse events.

e. 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.24

f. 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, and alpha adjustments for multiple comparisons and interim analyses. Sponsors can modify an SAP as long as the trial remains blinded, but sponsors should recognize that a detailed discussion with the DAVP may be needed concerning data access and appropriate operating procedures for maintaining the integrity of the blind.

24 See the guidance for clinical trial sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees.
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. If multiple genotypes are included in a single trial then efficacy analyses should be conducted separately within each genotype and there should be enough patients to have sufficient power for the primary efficacy analysis within each genotype.

10. Accelerated Approval (Subpart H) Considerations

Accelerated approval, which can rely on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit, does not apply to drug development for hepatitis C because the endpoint used in clinical trials for full approval is considered a validated surrogate endpoint (SVR12) that is known to predict clinical benefit.

C. Other Considerations

1. Relevant Nonclinical Safety Considerations

Pharmacology/toxicology development for single HCV DAAs should follow existing guidances for drug development. 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

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25 See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H.

26 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(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. 

24
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.
- Phase 1 clinical data in healthy volunteers or HCV-infected patients receiving the
individual drugs show no substantial or unmanageable safety concerns. Phase 1 data
should include single- and multiple-dose 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 patients who are treatment-naïve or have remaining treatment
options. After initial trials in treatment-naïve patients (or in patients who have remaining
approved treatment options) have helped to define the most active doses, patients with few or no
remaining options can be studied. This approach helps to ensure that patients with no remaining
treatment options are not exposed to suboptimal doses or combinations that could severely
jeopardize their chance for achieving SVR.

Combination trials in healthy volunteers or patients 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., ICH
M3(R2)) when designing such studies.

Nonclinical combination studies of an investigational DAA plus an approved DAA, IFN, or
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. It is generally accepted that applicants who have clinical indications for HCV DAAs that have a treatment duration for 24 or more weeks should conduct carcinogenicity studies.

2. Pharmacokinetic/Pharmacodynamic Considerations

a. Pharmacokinetic/Pharmacodynamic assessments

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

Sponsors can use a combination of intensive and sparse sampling throughout development to characterize the pharmacokinetics of the investigational drug. For example, an intensive sampling schedule should be implemented in early phase monotherapy trials. In longer term trials, however, an 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, and 24. 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. 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.

- To aid the design of phase 2b and phase 3 trials, with respect to dose, duration, regimen choice, and population, a mechanistic approach relating drug concentrations and viral kinetics is most appropriate

- When sufficient SVR12 data are available, a simplified analysis relating the proportion of patients with virologic success and the appropriate exposure variable (e.g., $C_{\text{min}}$ 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

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27 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.
drug is safe. The appropriate exposure parameter and modeling approach depends on the investigational drug and toxicity.

b. Specific pharmacokinetic evaluation

We strongly encourage PK evaluation in patients with renal impairment and hepatic impairment, to inform the need for dose modifications, early in drug development so these patients can be enrolled into phase 2 and phase 3 trials as appropriate. In general, it is recommended that these studies be conducted with the final regimen rather than the individual components separately. Specific recommendations related to trial design and data analysis can be found in the relevant FDA clinical pharmacology guidances.

3. Clinical Virology Considerations

a. HCV RNA assessments and data reporting

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 or study reports should include the names and addresses of the laboratories conducting HCV RNA assessments (e.g., central laboratory or assay vendor).

For clinical trial protocols, study reports, and HCV RNA datasets, clear and consistent language should be used to describe low-level HCV RNA results, following guidelines for reporting HCV RNA levels as described in FDA-approved assay package inserts. Specifically, HCV RNA levels that are detected but less than lower limit of quantitation (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 undetectable or greater than or less than the limit of detection (LOD) (“> LOD” or “< LOD,” respectively) is not recommended, even if the validated assay 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.

A detected/not detected HCV RNA cutoff can be problematic for study endpoints or 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, sponsors are encouraged to use the assay LLOQ (or other quantitative HCV RNA threshold as appropriate) as the HCV RNA cutoff for treatment futility rules and study endpoints including SVR, virologic relapse, and virologic breakthrough. See also Appendix A for recommended terms and definitions related to virologic response and treatment history.

b. HCV genotype/subtype determination

A validated assay with accuracy that is comparable to HCV genotyping/subtyping reference methods (Smith, Bukh, et al. 2014) should be used for HCV genotype or subtype screening and randomization of patients; use of an FDA-approved assay is recommended. Clinical trial
protocols should describe the HCV genotype/subtype assay(s) to be used, including a brief description of assay performance characteristics. Genotyping/subtyping assays (or historical data) based only on nucleotide sequence analysis of the 5'-noncoding region of the HCV genome should be avoided because of poor performance in distinguishing between certain HCV genotypes and subtypes 1a and 1b (Chevaliez, Bouvier-Alias, et al. 2009). Clinical assays used for HCV genotype/subtype determination may not resolve HCV subtypes other than 1a and 1b. Therefore, for patients with nongenotype 1 HCV infection, retrospective analyses should be conducted to identify HCV subtypes based on reference methods (Smith, Bukh, et al. 2014) or phylogenetic analysis of the drug target sequence(s).

c. Resistance analyses

For efficacy trials, treatment-emergent resistance testing should be performed for patients who do not achieve SVR. Treatment-emergent genotypic and phenotypic resistance analyses should focus on samples collected while patients 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. Enrichment of substitutions from mixtures at baseline should also be reported; how these data are considered in treatment-emergent resistance analyses may depend on clinical trial design and nucleotide sequencing methods. Similar treatment-emergent resistance analyses should be conducted for all patients in early phase monotherapy trials.

Pretreatment samples from clinical trial patients should be analyzed to identify HCV genetic polymorphisms in DAA target genes, and the effect of HCV polymorphisms on treatment response should be evaluated. These analyses should consider both the investigational DAA(s) as well as any background DAA(s) evaluated in combination. The prevalence of HCV populations carrying detectable resistance-associated polymorphisms should be determined, both in the full study population and in U.S. study patients specifically.

Patients 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 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.

Clinical trials of DAA regimens for patients 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 the detection of DAA resistance-associated substitutions. For initial proof-of-concept studies in these patient 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. Results from these analyses should be used to guide the design of subsequent trials; for example, whether inclusion should be based on the detection of DAA-resistant viral populations.

Drug 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 or biochemical assays. Sponsors should perform phenotypic analyses of HCV replicons or viruses derived from treated patients if resistance is suspected but treatment-emergent genotypic resistance patterns are unclear. Fold-changes in antiviral activity should be reported based on EC\textsubscript{50} and EC\textsubscript{90} (or EC\textsubscript{95}) values. Because resistance pathways can be complex, and a variety of factors can affect drug resistance in treated patients, 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.

Because nucleotide sequencing technologies and data standards are evolving, sponsors should consult with the DAVP for current recommendations regarding the organization and submission of drug resistance datasets.

4. Expanded Access Considerations

Some HCV-infected patients 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 able to seek treatment with an investigational drug or drugs, before the drug(s) is approved, through expanded access under 21 CFR 312.310, 312.315, or 312.320. Treatment INDs or treatment protocols for DAAs may be appropriate when sufficient clinical trial data have been generated to develop a treatment protocol (including planned dosing) that meets the requirements of 21 CFR 312.320. Ideally, submission of a treatment IND or protocol should occur after phase 3 trials are fully enrolled or well underway so as to avoid interference 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 individual patient and 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. 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.2., General Considerations for Phase 1 and Phase 2 Development, for the data needed to support treatment use through expanded access of multiple investigational drugs in a treatment regimen.
Contains Nonbinding Recommendations
Draft — Not for Implementation

GLOSSARY OF ACRONYMS

CC  cytotoxic concentration
CHC  chronic hepatitis C
CKD  chronic kidney disease
DAA  direct-acting antiviral
DNA  deoxyribonucleic acid
EC   effective concentration
HCC  hepatocellular carcinoma
HCV  hepatitis C virus
HCV RNA  hepatitis C virus ribonucleic acid
HIV  human immunodeficiency virus
IFN  interferon
IU   international unit
LLOQ lower limit of quantitation
LOD  limit of detection
mL   milliliter
NI   noninferiority
Peg  pegylated
PK   pharmacokinetic
RBV  ribavirin
RNA  ribonucleic acid
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 TREATMENT RESPONSE DEFINITIONS

Points to Consider

Table A includes recommended terms and definitions for documentation of prior treatment history and responses (i.e., for trial inclusion criteria).

- Some flexibility in the definitions may be appropriate, particularly when the level of detail indicated in the table is not typically available.

- Peg-IFN refers to a pegylated interferon product.

- For prior treatment history, multiple terms can be considered as appropriate to document responses to multiple rounds of treatment. If only one term is used per patient, the most recent DAA-based treatment should take precedence.

- Specific details regarding all prior drug/class experience should be noted as part of protocol-specified data collection.

Table A: Recommended Terms and Definitions for Treatment History

<table>
<thead>
<tr>
<th>TREATMENT-NAÏVE</th>
<th>Naïve to all anti-HCV treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/R-ONLY EXPERIENCED*</td>
<td>Did not achieve SVR with previous P/R treatment, and never received an HCV DAA.</td>
</tr>
<tr>
<td>DAA-EXPERIENCED</td>
<td>Previously treated with an HCV DAA in any context (e.g., IFN-free or IFN-containing treatment). Patients can be further subcategorized according to specific DAA or DAA class experience, or by type of prior response (e.g., virologic breakthrough or relapse).</td>
</tr>
</tbody>
</table>

* P/R = peg-IFN/RBV
Table B includes recommendations for protocol definitions of response/nonresponse to investigational regimens.

**Table B: Recommended Protocol Definitions for Response/Nonresponse**

<table>
<thead>
<tr>
<th>SVR(X)</th>
<th>HCV RNA &lt; LLOQ at X weeks following cessation of treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-Treatment Virologic Failure</strong></td>
<td>HCV RNA ≥ LLOQ at the end of treatment. For example, can include patients who experienced virologic breakthrough (confirmed or unconfirmed) or met an on-treatment virologic futility rule.</td>
</tr>
<tr>
<td><strong>Virologic Breakthrough</strong></td>
<td>Subcategory of On-Treatment Virologic Failure. 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 &lt; LLOQ (detected or not detected).</td>
</tr>
<tr>
<td><strong>Virologic Relapse</strong></td>
<td>HCV RNA &lt; LLOQ at end of treatment, but HCV RNA quantifiable (≥ LLOQ) during follow-up; can include patients who experienced late virologic relapse who also achieved primary SVR endpoint.</td>
</tr>
<tr>
<td><strong>Nonvirologic Failure</strong></td>
<td>Did not achieve SVR and did not meet any virologic failure criteria (e.g., adverse event, lost to follow-up).</td>
</tr>
</tbody>
</table>