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

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

**November 2017
Clinical/Antimicrobial**

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

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

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

**November 2017
Clinical/Antimicrobial**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	DEVELOPMENT PROGRAM.....	3
A.	General Drug Development Considerations.....	3
	<i>1. Nonclinical Virology Development Considerations</i>	<i>3</i>
	a. Mechanism of action.....	3
	b. Antiviral activity in cell culture	3
	c. Cytotoxicity and mitochondrial toxicity	4
	d. Antiviral activity in animal models.....	4
	e. Combination antiviral activity.....	5
	f. Resistance and cross-resistance	5
	<i>2. General Considerations for Phase 1 and Phase 2 Development.....</i>	<i>5</i>
	a. Phase 1a/first-in-human trials.....	7
	b. Phase 1b (proof-of-concept) trials.....	7
	c. Phase 2 trials with combination DAA regimens	8
	<i>3. Drug Development Population</i>	<i>9</i>
	<i>4. Efficacy Considerations.....</i>	<i>10</i>
	<i>5. Safety Considerations</i>	<i>11</i>
B.	Phase 3 Efficacy Trial Considerations	11
	<i>1. Trial Design</i>	<i>11</i>
	a. Treatment-naïve and non-DAA treatment-experienced populations	12
	b. DAA treatment-experienced population	12
	<i>2. Trial Population.....</i>	<i>13</i>
	<i>3. Entry Criteria.....</i>	<i>13</i>
	a. Assessment of cirrhosis.....	13
	b. HCV genotype considerations	13
	c. DAA treatment experience.....	14
	<i>4. Randomization, Stratification, and Blinding.....</i>	<i>14</i>
	<i>5. Specific Populations.....</i>	<i>14</i>
	a. HIV-1/HCV coinfecting patients.....	14
	b. Patients with decompensated cirrhosis and pre- or post-transplant	15
	c. Pediatric populations.....	16
	d. Patients with advanced chronic kidney disease	18
	<i>6. Dose Selection.....</i>	<i>18</i>
	<i>7. Efficacy Endpoints.....</i>	<i>19</i>
	<i>8. Trial Procedures and Timing of Assessments.....</i>	<i>20</i>
	<i>9. Statistical Considerations</i>	<i>20</i>
	a. Analysis populations	21
	b. Efficacy analyses	21
	c. Noninferiority comparison	22
	d. Handling of missing data	22
	<i>10. Accelerated Approval (Subpart H) Considerations</i>	<i>22</i>
C.	Other Considerations.....	23
	<i>1. Relevant Nonclinical Safety Considerations.....</i>	<i>23</i>
	<i>2. Pharmacokinetic Considerations.....</i>	<i>25</i>

a. Pharmacokinetic assessments.....	25
b. Specific pharmacokinetic evaluation	25
3. <i>Clinical Virology Considerations</i>	26
a. HCV RNA assessments and data reporting.....	26
b. HCV genotype or subtype determination.....	26
c. Resistance analyses	27
4. <i>Expanded Access Considerations</i>	28
GLOSSARY OF ACRONYMS	30
REFERENCES	31
APPENDIX: STUDY POPULATION TERMS AND TREATMENT RESPONSE	
DEFINITIONS	35

Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry¹

This guidance represents 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 office 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) stage through the new drug application (NDA) and postmarketing stages.² For the purposes of this guidance, the Food and Drug Administration (FDA) defines direct-acting hepatitis C virus (HCV) antivirals as drugs that interfere with specific steps in the HCV replication cycle through direct interaction with the HCV genome, polyprotein, or 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. The organization of this guidance parallels the drug development plan.

This guidance does not address the development of drugs that target host functions necessary for viral replication or of immune-based drugs for the treatment of HCV infection such as new interferon (IFN) drugs. This guidance also does not address treatment of acute hepatitis C or the use of 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. The main focus of this guidance is on development of DAAs as part of IFN-free regimens. Because safe and highly effective FDA-approved IFN-free treatment options are available, the Division of Antiviral Products (DAVP) recommends against studying an IFN-containing regimen in a DAA treatment-naïve population.

¹ This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research 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.

Contains Nonbinding Recommendations

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. 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.³ 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*.

We encourage sponsors considering development of antiviral drugs for the treatment of CHC to communicate with the FDA through the pre-IND consultation program.⁴ 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.

II. BACKGROUND

HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family. There are at least seven 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). Because reported HCV genotype 7 is extremely rare, this guidance will only focus on HCV genotypes 1-6. In the United States, genotype 1 is the most common (70 to 80 percent of HCV infections), followed by genotypes 2 and 3. The remaining genotypes occur less commonly in the United States but may predominate in other parts of the world (Gower, Estes, et al. 2014).

In the United States, about 3 million people have CHC (Armstrong, Wasley, et al. 2006; Klevens, Dale, et al. 2012). CHC causes cirrhosis and HCC and is the most common reason for liver transplantation in the United States. By 2007, there were more annual deaths in the United States related to HCV than human immunodeficiency virus (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. Clinicians use sustained virologic response (SVR) — defined as no detectable HCV RNA in blood several months after completing a course of treatment — to determine if treatment is a success and is

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁴ See the FDA Pre-IND Consultation Program web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>.

Contains Nonbinding Recommendations

considered a virologic cure (Shiratori, Ito, et al. 2005; Singal, Volk, et al. 2010). Achieving a virologic cure is associated with a substantial decrease, but not elimination, in the risk of HCC.

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. The ability to achieve SVR rates greater than 90 percent using only DAAs (with and without ribavirin (RBV)) 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 appropriate nonclinical assays is available on the FDA website.⁵ Sponsors with virology development for HCV DAAs should consider the guidance for industry *Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency*. Additional recommendations for nonclinical and clinical virology specific to the development of HCV DAAs are summarized throughout this guidance.

a. Mechanism of action

A sponsor should investigate the mechanism by which a DAA exhibits anti-HCV activity through evaluations 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

A sponsor should characterize in cell culture the antiviral activity of an investigational drug to demonstrate its activity and identify a preliminary target concentration for evaluation in HCV-infected patients. Sponsors should use HCV replicon systems to assess antiviral activity of investigational drugs targeting nonstructural components, and 50 and 90 percent effective

⁵ See the FDA Getting Started With the Division of Antiviral Products Pre-IND Process web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077546.htm>.

Contains Nonbinding Recommendations

concentrations (EC_{50} and EC_{90}) should be determined. We recommend evaluating the drug's antiviral activity at different concentrations of human serum and extrapolating a 100 percent human serum-adjusted EC_{50} value. Sponsors can evaluate the antiviral activity of drugs that target HCV entry functions using HCV pseudoparticle systems. For any anti-HCV drug, we recommend assessments of antiviral activity against HCV grown in cell culture, when appropriate.

Cell culture studies should include assessments of antiviral activity against those HCV genotypes and subtypes most common in the United States and those types 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, sponsors should conduct additional genotypic and phenotypic characterizations to identify genetic polymorphisms that may affect HCV susceptibility to the drug.

c. Cytotoxicity and mitochondrial toxicity

Sponsors should quantify directly the cytotoxic effects of the drug in the cells used for assessing anti-HCV activity and should calculate a 50 percent cytotoxic concentration (CC_{50}) and therapeutic index (CC_{50}/EC_{50}). Sponsors should assess cytotoxicity using various cell lines and primary cells cultured under proliferating and nonproliferating conditions. Sponsors should also assess, with appropriate controls, nucleos(t)ide analog polymerase inhibitors for bone marrow precursor cell toxicity.

Sponsors should assess mitochondrial toxicity for all investigational nucleos(t)ide analogs and other drug classes as appropriate based on mechanism of action or any signals of mitochondrial toxicity in nonclinical studies or clinical trials. Mitochondrial toxicity assessments should include evaluation of cytotoxicity in glucose- versus galactose-containing medium (Crabtree effect) (Marroquin, Hynes, et al. 2007). Sponsors should also evaluate the inhibition of mitochondrial RNA polymerase for nucleos(t)ide analogs (Arnold, Sharma, et al. 2012). Positive controls for mitochondrial toxicity studies should be included in the nonclinical studies and 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 sponsors conduct such studies to support an anti-HCV therapy program, the sponsors should provide a detailed description of the animal model. Reported data from animal model studies should include the HCV genotype or 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.

Contains Nonbinding Recommendations

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, sponsors should characterize cell culture combination antiviral activity relationships of the investigational drug and other drugs anticipated to be used in combination to determine whether 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 EC₅₀ values, and studies should include controls for cytotoxicity and antagonism (Coelmont, Paeshuysse, 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, HCV nucleos(t)ide analogue NS5B polymerase inhibitors) should be assessed before testing combinations of the drugs in HIV-1/HCV co-infected patients.

f. Resistance and cross-resistance

Sponsors should examine in cell culture models the ability of HCV to develop resistance to a DAA when the virus is subjected to drug selection. Sponsors should determine the amino acid or nucleotide substitutions associated with the development of resistance to the investigational drug and validate the substitutions by introducing the changes into the HCV genome and determining the conferred fold shift in susceptibility (based on EC₅₀ and EC₉₀ values) using cell culture or biochemical assays. Sponsors should use the results from these studies 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 DAA refers to the capacity of the drug to retain its antiviral activity when the virus acquires genetic changes in the drug target (Kwong, Najera, et al. 2011).⁶

Resistance studies should include evaluation of the potential for cross-resistance with approved drugs, particularly focusing on those in the same drug class and other classes with the same viral target. If a sponsor intends to develop a drug to be used in patients previously treated with drugs in the same class, the sponsor should evaluate the activity of the investigational drug against HCV variants that emerge in patients treated with other drugs in the class. In addition, sponsors should evaluate the activity of other representative approved drugs in the class against HCV variants associated with resistance to the investigational drug.

2. *General Considerations for Phase 1 and Phase 2 Development*

In addition to assessing safety and pharmacokinetics, phase 1 trials should provide an initial assessment of antiviral activity of the DAA. Phase 2 trials should characterize the effects of dose and treatment duration of the DAA or DAAs as part of combination regimens with regard to both antiviral activity and safety.

⁶ 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 virus consensus sequence are adequate to confer HCV resistance to a clinically relevant concentration of the drug.

Contains Nonbinding Recommendations

Based on HCV replication dynamics in infected patients (Rong, Dahari, et al. 2010), the error-prone nature of HCV genome replication, and the fact that the activity of a DAA is often reduced by a single amino acid substitution in the drug target, multiple anti-HCV drugs with nonoverlapping resistance pathways generally are needed to suppress preexisting and emerging drug-resistant variants for most patients to achieve SVR. Sponsors can develop a DAA for dosing in combination with other DAAs and/or in regimens that include RBV. The overall design of a phase 2 clinical development program should attempt to demonstrate the contribution of individual drugs in the regimen (as described in section III.A.4., Efficacy Considerations).

We recommend that sponsors have the following information before conducting phase 2 trials of combinations of DAAs:

- Mechanism of action for each drug in the combination
- Resistance and cross-resistance patterns for each drug in the combination
- Combination antiviral activity data from cell culture studies
- Anti-HCV activity data from clinical trials (e.g., short-term monotherapy trials, dose-finding trials in combination with other antiviral drugs)
- Phase 1 human safety data on each 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 investigational combination regimen and comedications potentially administered by HCV-infected patients enrolled in the trial or trials

A primary objective of a phase 2 program should be demonstration of proof of concept of efficacy (i.e., SVR) with appropriate safety and tolerability 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, post-treatment response data, such as SVR4 and SVR12, 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 trials should include a representative population of patients with chronic HCV infection. These populations can include, but are not limited to, relevant racial and ethnic subgroups (e.g., blacks/African Americans, Hispanics/Latinos), patients with prior pegylated- (peg-) IFN/RBV treatment failures, patients with prior DAA treatment failures, and patients with compensated

Contains Nonbinding Recommendations

cirrhosis. Inclusion of these groups in phase 2 will assist in sample size calculations and estimations of expected SVR rates in phase 3.

We have provided the following recommendations and examples 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 subjects to assess safety and pharmacokinetics for the first-in-human trials. Sponsors also can conduct single-dose and short-duration multiple-dose pharmacokinetic (PK) trials 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 severalfold the protein binding-adjusted, cell culture EC₅₀ value of the drug for the relevant HCV genotype or 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 subjects. We generally recommend that sponsors conduct initial antiviral activity phase 1b trials 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, trial 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 about 3 days. In this example, we do not recommend that monotherapy exceeds 3 days because 3 days is usually sufficient to demonstrate proof-of-concept antiviral activity and to identify drug doses for evaluation in phase 2 trials, and previous data with these DAA classes indicate resistant virus is rapidly selected during monotherapy. Prolonged selection of resistance may reduce the efficacy of other treatments and limit future treatment options for trial 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 clearance of infected cells. All DAA monotherapy trial protocols should include justification for the

Contains Nonbinding Recommendations

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 or classes, intended patient population, HCV genotype, 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 drugs or approved drugs plus investigational drugs) at various doses and treatment durations. The number of DAAs 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 or subtype, and the patient population being evaluated. We recommend SVR12 as the primary endpoint. Patients should be followed through week 24 following treatment cessation to further confirm the reliability of SVR12 as a marker of virologic success. Sponsors should stratify trial randomization according to genotype or 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 retreatment (approved and/or investigational) should be collected and included in final reports or other relevant regulatory submissions because these data could be informative for future clinical trial design and for clinical practice.

We anticipate that the number of single- and multiple-class DAA treatment-experienced patients will increase as more HCV DAAs are used in practice. We encourage sponsors 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 or regimens 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 with reduced susceptibility 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 been demonstrated for longer treatment durations. Also, because of the number of promising DAA classes approved or in development that would be

Contains Nonbinding Recommendations

appropriate to test in DAA-experienced populations, we strongly encourage cross-company collaboration when needed to construct a scientifically justified regimen.

Because retreatment 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.

Patients who were exposed to short, nontherapeutic treatment durations of one or more DAAs, such as in short-course monotherapy trials, but otherwise 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, sponsors can target drug development to a specific genotype) or 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 phase 3 studies of combinations of HCV DAA antivirals in patients with the greatest need for new drugs, such as patients with bleeding disorders, transplant patients, patients with advanced chronic kidney disease (CKD), patients with decompensated cirrhosis, and patients who 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. To choose an appropriate dose and rule out or manage important drug-drug interactions, sponsors can study DAAs in combination with other DAAs, with or without RBV in HIV-1/HCV coinfecting patients, as soon as appropriate, based on the availability of data (see section III.B.5.a., HIV-1/HCV coinfecting patients). Supportive data such as hepatic and renal impairment trials and drug-drug interaction trials (e.g., antiretrovirals for HIV, immunosuppressants for transplant) may be needed before sponsors can conduct trials in the above-mentioned subgroups.

CHC is a global disease and clinical trials are typically conducted internationally. However, we recommend that trials include adequate U.S. patient representation to ensure applicability of trial results to the U.S. population. An adequate representation of sexes, 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, including sufficient representation of such groups in clinical trial demographics is important for conducting meaningful analyses (Hepburn, Hepburn, et al. 2004). In addition, we encourage sponsors to include hepatitis B virus (HBV)/HCV coinfecting patients and CHC patients with active illicit

Contains Nonbinding Recommendations

injection drug use 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, blacks/African Americans, Hispanics/Latinos, patients with cirrhosis, patients with bleeding disorders, patients with HBV/HCV coinfection, patients using injection drugs) to enroll in phase 2 and phase 3 clinical trials.

4. Efficacy Considerations

Sponsors should perform phase 2 trials to select an optimal dose or doses and treatment duration or durations 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.

Sponsors should establish efficacy in key subpopulations including patients:

- Who have and do not have cirrhosis
- Who have HCV genotypes (e.g., 1, 2, 3, 4, 5, or 6, depending on susceptibility)
- Who are DAA naïve and DAA experienced

Sponsors can submit an NDA to gain approval for 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 well-controlled 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. It is generally recognized that monotherapy with a DAA does not have sufficient antiviral durability to result in a high rate of SVR12. Therefore, if a novel combination regimen consisting of two DAAs with nonoverlapping resistance pathways demonstrates favorable efficacy, both drugs likely contribute to treatment efficacy. Establishing the contribution of each additional drug in a combination regimen can be accomplished using modified factorial trial designs.

When a factorial design is not used, additional data may be used as supportive evidence of a DAA's contribution to efficacy of a multiple DAA combination regimen. 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

Contains Nonbinding Recommendations

- Data demonstrating strong evidence of 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,⁷ and priority review designation if the specifics of the relevant criteria are met.^{8,9}

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 about 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 sponsor may need to increase the safety database or conduct specific safety studies.

We recommend using data from randomized, controlled trials with an active comparator or a comparison of immediate versus delayed treatment to obtain comparative safety data (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 for determining an appropriate trial design. We recommend that at least one of the pivotal efficacy trials be 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 approved and recommended for treatment of chronic HCV infection by

⁷ See the FDA fact sheet for breakthrough therapies at <https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/fdasia/ucm329491.htm>.

⁸ See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* for information regarding fast track, breakthrough, and priority review designation.

⁹ 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 FDA considers the endpoint used in clinical trials for full approval to be a validated surrogate endpoint (SVR12) that is known to predict clinical benefit.

Contains Nonbinding Recommendations

authoritative scientific bodies based on clinical evidence that also reflects current practice at the time of trial initiation.¹⁰ 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 their choice of an active control and choice of study population before trial initiation. Although randomized, controlled, comparative trials are preferable, in some situations single-arm trials using a historical control may be acceptable. However, historical controls have limitations including the difficulty to establish patient comparability at baseline for many potential prognostic factors. We discuss trial design considerations by type of regimen and intended population in more detail below.

a. Treatment-naïve and non-DAA treatment-experienced populations

We prefer a randomized, active-controlled noninferiority (NI) or superiority trial design over a single-arm design, and at least one of the pivotal trials should be designed as such. Sponsors considering an NI trial design should discuss in advance their justification for the proposed NI margin based on historical control effect, trial designs, and the data analysis plans.

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 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. The primary efficacy comparison (either superiority or noninferiority depending on regimen studied) should be to a historical reference of a recommended HCV treatment regimen rather than a comparison to those receiving placebo (in the deferred treatment arm) because 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 deferred 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. 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.

¹⁰ See the HCV treatment guidelines provided by the AASLD for the current HCV treatment recommendations available at <https://www.hcvguidelines.org>.

Contains Nonbinding Recommendations

Sponsors should engage in early discussions with the DAVP regarding development plans in DAA treatment-experienced patients.

2. Trial Population

Sponsors should ensure that patients enrolled in a trial have CHC as confirmed by at least 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 anti-HCV antibody and HCV RNA at the time of screening
- They are positive for anti-HCV antibody and HCV RNA at the time of screening with clinical or laboratory evidence of CHC disease, such as the presence of fibrosis by biopsy or noninvasive tests

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 statuses remains critical for making correlations between the presence of cirrhosis and efficacy, safety, and pharmacokinetics. Sponsors should evaluate 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 want to seek an indication for HCV treatment in several genotypes. Sponsors should establish efficacy 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 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 or 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 or DAAs 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

Contains Nonbinding Recommendations

Considerations, for recommendations regarding HCV genotype or 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 or DAAs. In such cases, efficacy should be specifically demonstrated in patients with drug resistance-associated substitutions that emerged from prior therapy with the same DAA class or classes as the investigational DAA or DAAs; sponsors should consider conducting resistance analyses at screening to enrich for these patients.

4. *Randomization, Stratification, and Blinding*

We encourage sponsors to conduct double-blinded trials whenever feasible to minimize any potential biases. 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 patients different levels of encouragement to continue in the trial.

Sponsors can consider stratification of patients by important baseline factors that are predictive of SVR. Stratification factors depend on the regimen and population studied but could include one or more of the following: HCV genotype or subtype, key baseline viral polymorphisms or resistance-associated substitutions, prior treatment history, baseline HCV RNA, or presence or absence of cirrhosis. In international trials, patients should be stratified by geographic area (inside versus outside the United States).

5. *Specific Populations*

Patients with hepatic impairment, pre- or post-transplant patients, patients with advanced CKD, and patients with decompensated cirrhosis are populations with unmet medical needs. Early in drug development, we strongly encourage sponsors to discuss the process to determine appropriate timing for initiating trials in these populations. This section also includes information on HIV-1/HCV coinfecting patients although we no longer consider this population as having an unmet medical need.

a. HIV-1/HCV coinfecting patients

About 30 percent of patients infected with HIV-1 are coinfecting with HCV (Sulkowski 2008). Patients with HIV-1/HCV coinfection 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 coinfecting patients receiving all oral antiviral

Contains Nonbinding Recommendations

drugs are similar to HCV mono-infected patients; therefore, both HIV-1/HCV coinfecting patients and HCV mono-infected patients can enroll into the same clinical trial. Sponsors can also study HIV-1/HCV coinfecting patients in a separate trial to obtain efficacy and safety data at the proposed dose or doses 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. We strongly encourage sponsors to have data on HIV-1/HCV coinfecting patients at the time of submission of an original NDA. See section III.B., Phase 3 Efficacy Trial Considerations.

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 coinfecting patients taking antiretrovirals that are expected to have interactions with an investigational DAA or DAAs.
- 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-transplant

As compared to compensated disease, decompensated disease may require treatment with more drugs and/or longer durations to achieve viral suppression.

We encourage active-controlled trials when possible; however, safety and efficacy data can be derived from dose or treatment duration comparisons or single-arm trials with a historical reference. Sponsors should discuss in advance with the DAVP the number of decompensated patients needed to support labeling claims. The demonstrated safety profile of the regimen in phase 2 and phase 3 clinical trials in patients with compensated liver disease would determine the minimum acceptable safety database for the decompensated patient population.

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 to support concomitant dosing of a DAA regimen and immunosuppressive drugs in post-transplant patients. These data should be available before sponsors begin trials in post-transplant patients.

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 the following:

- 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 patients who received the drug for the recommended treatment duration

Contains Nonbinding Recommendations

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 cutoff values specific to the population.

Evaluation by an independent adjudication committee is encouraged to review all serious hepatic events, deaths, liver transplantations, and changes in prespecified alanine transaminase, aspartate transaminase, and bilirubin parameters in this cohort of patients with decompensated liver disease and/or those patients listed for liver transplantation.

The NDA should include assessments based on the Model for End Stage Liver Disease and Child Pugh Turcotte scores at 12 weeks following cessation of treatment (SVR12 time point) compared to the patient's baseline values. We recommend long-term follow-up to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation.

Plans for expanded access trials or safety trials also should be considered for this population early in development. See section III.C.4., Expanded Access Considerations.

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 formulations and clinical development plans 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,”¹¹ unless the FDA waives or defers those assessments.¹² A sponsor is required to submit a pediatric study plan — which includes 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.¹³ In the absence of a serious safety signal in adults, we recommend sponsors enroll adolescents

¹¹ See section 505B(a)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(a)(1)(A). Section 505B(a)(1)(B) of the FD&C Act also requires that “an original (drug or biological product) application for a new active ingredient with an adult oncology indication” that is “(i) intended for the treatment of an adult cancer; and (ii) directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer” must “submit with the application reports on the investigation described in (section 505B(a)(3) of the FD&C Act).”

¹² See section 505B(a)(4) and (a)(5) of the FD&C Act.

¹³ 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 Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

Contains Nonbinding Recommendations

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.¹⁴

In addition to requiring pediatric assessments of certain drugs, PREA also requires that when conducting those assessments sponsors use a formulation of the drug that is appropriate for each age group being studied.¹⁵ 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 (about 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 studies can be initiated after phase 2 adult data characterizing the safety profile and preliminary evidence of efficacy (SVR) are available. Initial pediatric PK data and results of available modeling and simulation should be discussed with the DAVP before dose selection for pediatric treatment studies. Pediatric extrapolation of efficacy is acceptable for HCV DAA 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 (although not statistically powered for efficacy comparisons).

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 studies should provide confirmatory PK data and a safety database of about 100 patients receiving the proposed dose for the proposed duration of treatment, which would adequately be distributed across the age range groups for which studies are required and would not be 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 clinically indicated biopsies are performed, sponsors should provide biopsy data at the time of the NDA submission.

¹⁴ 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)(5)(i) and section 505B(a)(5)(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 birth to 3 years of age range that studies are “impossible or highly impracticable,” any required assessments in children younger than 3 will be waived.

¹⁵ See section 505B(a)(2)A) of the FD&C Act.

Contains Nonbinding Recommendations

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 more than 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, Martin, 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 patients in each of the important CKD subgroups (e.g., CKD Stage 4/5, hemodialysis, peritoneal dialysis). Trials should be stratified based on the degree of CKD severity (and dialysis status) because these factors may affect drug clearance. We encourage sponsors who are considering trials in this population to engage in early discussions with the DAVP.

6. *Dose Selection*

Sponsors can use results from proof-of-concept antiviral activity monotherapy trials 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 models of the concentration-viral kinetics and concentration safety using all available drug exposure, viral kinetic, and safety data from studies to predict the most active and tolerable doses to be evaluated in phase 2 trials. Mechanistic concentration-viral kinetic models, if developed, should include an appropriate targeted drug effect, components to describe virologic breakthrough, relapse, and long-term viral response (i.e., SVR), and relevant covariates for describing differences in response between HCV genotypes and subtypes or viral populations with or without drug resistance-associated polymorphisms or substitutions. Sponsors should analyze independently results from patients infected with different HCV genotypes and subtypes, as

Contains Nonbinding Recommendations

sample sizes permit, 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.

Sponsors should use the model 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 treatments, and we recommend that the sponsor evaluate a range of doses in subsequent trials.

To optimize the regimen with respect to dose and treatment duration in phase 3 trials, sponsors can combine drug efficacy data from phase 1 and phase 2 trials in a single model to predict SVR in the planned trials. Sponsors should evaluate such a model against on-treatment data of the regimen and refine drug efficacy parameter estimates as necessary.

7. Efficacy Endpoints

As mentioned, the recommended primary endpoint for approval in trials evaluating CHC treatments is SVR12. Sponsors should measure viral RNA clearance (SVR12) 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.¹⁶ 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; in subsequent analyses of trials of IFN-free regimens, similar concordance between SVR12 and SVR24 was shown. Therefore, the FDA considers SVR12 a suitable primary endpoint for registrational trials for both IFN-based and IFN-free regimens to support approval.

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

¹⁶ Yoshida, Shiratori, et al. 1999; Yoshida, Arakawa, et al. 2002; Shiratori, Ito, et al. 2005; Okanoue, Itoh, et al. 1999; Imai, Kawata, et al. 1998; Arase, Ikeda, et al. 2007; Veldt, Heathcote, et al. 2007; Braks, Ganne-Carrie, et al. 2007; Bruno, Stroffolini, et al. 2007; Manos, Zhao, et al. 2009; Singal, Volk, et al. 2010; Backus, Boothroyd, et al. 2011; Simmons, Saleem, et al. 2015

Contains Nonbinding Recommendations

combination drug regimens. Additional post-treatment follow-up (e.g., 1 year or longer) may be necessary if one or more drugs in the regimen has a long plasma or intracellular half-life or prolonged antiviral activity. At the time of NDA submission, sponsors should have analyzed all available SVR12 and SVR24 data (and longer term follow-up data as applicable) from phase 2 and phase 3 trials to assess concordance of these results and the results of the analyses included in the application package. If the drug or drugs are approved, the FDA will generally request any additional follow-up data from phase 3 registrational trials as a postmarketing commitment.

Secondary endpoints should include the following:

- 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
- SVR24 rates
- Percentage of virologic failure patients with treatment-emergent, resistance-associated changes in their HCV population

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 timely detection of a virologic breakthrough or other treatment futility.

Sponsors can use measurements of viral RNA at earlier time points 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

In general, the sponsor should submit a detailed statistical analysis plan stating the trial hypotheses and analysis methods before trial initiation. For information on statistical analysis topics and issues, see the FDA guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Non-Inferiority Clinical Trials to Establish Effectiveness* and the journal article *Statistical Considerations on Subgroup Analysis in Clinical Trials* (Alosh, Fritsch, et al. 2015).

Contains Nonbinding Recommendations

a. Analysis populations

In general, all randomized patients should be included in the primary efficacy analysis. However, if a substantial proportion of randomized patients do not receive treatment in either or both arms, then additional sensitivity analyses are likely needed.

b. Efficacy analyses

The primary efficacy analysis should compare the proportion of patients who achieve SVR12 across treatment arms. This analysis determines whether effectiveness has been demonstrated.¹⁷

For subgroup analyses, sponsors should analyze SVR12 for patients with important demographic and baseline characteristics (e.g., geographic region, sex, race, age group, HCV genotype/subtype, HCV drug resistance-associated polymorphisms or 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).¹⁸ 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 (superiority or noninferiority depending on regimens studied) 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 demonstrating an effect on the prespecified primary endpoint. The protocol should propose a multiple testing strategy for important secondary endpoints that adjust for multiplicity conditional on demonstrating the primary endpoint.

Patients who experience virologic relapse or who stop treatment because their HCV RNA was not adequately suppressed 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. Sponsors should note this information in the protocol case report forms and capture the information in the electronic dataset. This information can be used to understand reasons for patients' discontinuation and how patients will be included in the analysis.

¹⁷ Patients who discontinue therapy, for whatever reasons, before the protocol-defined treatment duration can still be considered responders if they have confirmed absence of HCV RNA 12 weeks after the originally planned treatment duration.

¹⁸ 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)).

Contains Nonbinding Recommendations

c. Noninferiority comparison

Before initiating NI trials, sponsors should discuss with the DAVP the choice of an NI margin for statistical hypotheses. The sponsor should justify the NI margin based on prior evidence of the quantitative contribution of the active control (substituted part of the drug regimen) to the regimen as a whole (M_1). This contribution should be determined in a similar population with a similar length of follow-up to the proposed trial. 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 SVR rates for approved drugs are all less than 95 percent, sponsors should discuss with the DAVP the size of the NI margin and provide adequate justification. For NI testing, sponsors should employ two-sided 95 percent confidence intervals, and the overall type I error rate should be controlled using adjustments for multiple comparisons or other appropriate testing procedures.

Sponsors can assess both NI and superiority in an NI trial provided that the NI comparison is conducted first, and superiority is conducted only after testing for NI. For additional information regarding NI trials in general, see ICH E10 and the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

d. Handling of missing data

There is no single optimal way to deal with missing data in clinical trials. Sponsors should make every attempt to limit loss of patients from the trial to make the findings interpretable. When a 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.

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, but the patient achieved SVR24. Sponsors should consider a patient as not having 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.

Appropriate sensitivity analyses may be needed to demonstrate that the primary analysis is robust to the assumptions regarding missing data.

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,¹⁹ does not apply to drug

¹⁹ See section 506(c) of the FD&C Act; 21 CFR part 314, subpart H.

Contains Nonbinding Recommendations

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.²⁰

The ICH guidance for industry *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 human immunodeficiency virus (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, ease of administration) over approved combination therapies, sponsors should usually submit combination toxicology studies 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. Sponsors should discuss with the DAVP the design of such a study. For DAA combinations that are expected to treat patients who have limited or no treatment options or to improve response rates in patients who are at risk of serious morbidity or for DAA combinations that are expected to have a substantial improvement over approved therapies, the FDA may conclude that the benefits of these combinations outweigh the potential risks of foregoing the combination toxicology studies when all of the following apply:

- Mechanisms of action or in vitro data of potential off-target effects of the individual drugs do not suggest a potential for additive or synergistic toxicity of a serious nature.
- Animal and human studies on 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-month durations) of the individual drugs show substantial safety margins for the intended clinical dose or doses or exposures.

²⁰ 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*.

Contains Nonbinding Recommendations

- Phase 1 clinical data in healthy subjects or HCV-infected patients receiving the individual drugs show no substantial safety concerns. Phase 1 data should include single- and multiple-dose PK and safety trials, at minimum. We encourage sponsors to have additional safety data from phase 1 and phase 2 trials that may be needed if one or more of the drugs demonstrate a potential serious safety risk.
- No overlapping toxicities of concern exist for the individual drugs based on animal toxicology study findings and phase 1 or phase 2 clinical data.
- Sponsors consider clinically significant PK-based drug interactions unlikely or 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 trials) 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) help to define the most active doses, sponsors can study patients with few or no remaining treatment options. 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 chances for achieving SVR.

Combination trials in healthy subjects 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 were completed. We recommend referring to relevant guidances for industry when designing such trials.²¹

In general, nonclinical combination studies of an investigational DAA plus an approved DAA, IFN, or RBV 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.

Sponsors should submit carcinogenicity studies for HCV products that are expected to be used chronically. The DAVP allows the sponsor of products for serious and life-threatening indications (such as HCV) to begin carcinogenicity studies (with written agreement) before submitting an NDA and to submit the studies during the postmarketing period under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.²² Because of the likelihood of retreatment for patients who fail therapy (an intermittent chronic, recurrent dosing paradigm²³), generally sponsors that have clinical indications for HCV DAAs with treatment durations of 24 or more weeks should conduct carcinogenicity studies.

²¹ See guidances for industry ICH M3(R2) and *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

²² 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*.

²³ See the ICH guidance for industry *S1A The Need for Carcinogenicity Studies of Pharmaceuticals*.

Contains Nonbinding Recommendations

2. *Pharmacokinetic Considerations*

a. Pharmacokinetic assessments

Trials conducted in HCV-infected patients should include an assessment of pharmacokinetics and the relationship between drug exposure (e.g., minimum or maximum plasma concentration (C_{\min} or C_{\max}), 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 investigational drugs. For example, sponsors should implement an intensive sampling schedule in early phase 1 monotherapy trials. In longer term trials, however, an intensive sampling schedule might not be feasible. Alternatively, sponsors can combine sparse sampling from these trials with intensive PK data from earlier trials for analysis. Sponsors should obtain sparse PK samples at the time of key virologic assessments. These data can then be subjected to appropriate population PK analysis. Documenting dosing times and plasma sampling times is important.

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. For these analyses, sponsors should consider virologic relapse and the development of resistance to the investigational drug when assessing differences between treatment regimens. When applicable, sponsors should use the developed exposure-response relationships 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_{\min} , area under curve) can be used to support evidence of effectiveness and justify dose selection

In exposure-response safety analyses, sponsors should consider the toxicities that are related to the investigational drug, and infrequent but severe safety events in order to inform dose selection and dose adjustments. 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, we recommend that sponsors conduct these trials with the final regimen rather than the individual components separately.

Contains Nonbinding Recommendations

Sponsors can find specific recommendations related to trial design and data analysis in the relevant FDA clinical pharmacology guidances.

3. *Clinical Virology Considerations*

a. HCV RNA assessments and data reporting

For antiviral activity and efficacy trials, sponsors should measure HCV RNA levels using a sensitive and specific quantitative assay. Clinical trial protocols should describe the HCV RNA assay or assays to be used, including a brief description of assay performance characteristics. Protocols or final reports should include the names and addresses of the laboratories conducting HCV RNA assessments (e.g., central laboratory, assay vendor).

In clinical trial protocols, final reports, and HCV RNA datasets, sponsors should use clear and consistent language 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 detected but less than the lower limit of quantification (LLOQ) should be reported as “< {LLOQ value in IU/mL} Detected,” and HCV RNA not detected should be reported as “Target Not Detected” or “HCV RNA Not Detected.” We do not recommend using terms such as *undetectable* or *greater than the limit of detection* or *less than the limit of detection* (LOD) (“> LOD” or “< LOD,” respectively), even if the validated assay LOD and LLOQ are equal, because HCV RNA levels can still be detected at a certain rate depending on the actual HCV RNA concentration.

A detected or not detected HCV RNA cutoff can be problematic for trial 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, we encourage sponsors to use the assay LLOQ (or other quantitative HCV RNA threshold as appropriate) as the HCV RNA cutoff for treatment futility rules and trial endpoints including SVR, virologic relapse, and virologic breakthrough. See also Appendix: Study Population Terms and Treatment Response Definitions for recommended terms and definitions related to virologic response and treatment history.

b. HCV genotype or subtype determination

A validated assay with accuracy that is comparable to HCV genotyping or subtyping reference methods (Smith, Bukh, et al. 2014) should be used for HCV genotype or subtype screening and randomization of patients; we also recommend using an FDA-approved assay. Clinical trial protocols should describe the HCV genotype or subtype assay or assays to be used, and include a brief description of assay performance characteristics. Genotyping or 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 or subtype determination may not resolve HCV subtypes other than 1a and 1b. Therefore, in patients with nongenotype 1 HCV infections, sponsors should perform

Contains Nonbinding Recommendations

retrospective analyses to identify HCV subtypes based on reference methods (Smith, Bukh, et al. 2014) or phylogenetic analyses of the drug target sequence or sequences.

c. Resistance analyses

For efficacy trials, sponsors should perform treatment-emergent resistance testing 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 sponsors should analyze the first available follow-up sample with adequate HCV RNA. 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. Sponsors should conduct similar treatment-emergent resistance analyses for all patients in early-phase monotherapy trials.

Sponsors should analyze pretreatment samples from clinical trial patients to identify HCV genetic polymorphisms in DAA target genes, and sponsors should also evaluate the effect of HCV polymorphisms on treatment response. These analyses should consider both the investigational DAA or DAAs and any background DAA or DAAs evaluated in combination. Sponsors should determine the prevalence of HCV populations carrying detectable resistance-associated polymorphisms, both in the full trial population and in the U.S. trial patient population specifically.

Sponsors should follow patients who have detectable resistance-associated substitutions at treatment cessation or follow-up 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 a wild-type virus.

Clinical trials of DAA regimens for patients previously exposed to a DAA or DAAs of the same class or classes 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, we encourage sponsors to use sensitive and quantitative genotypic resistance assays to characterize the relative and absolute quantity of DAA-resistant variants at baseline and to relate these findings to treatment outcome. Sponsors should use results from these analyses to guide the design of subsequent trials (e.g., whether to include patients 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

Contains Nonbinding Recommendations

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. Sponsors should report fold changes in antiviral activity based on EC₅₀ and EC₉₀ (or EC₉₅) 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 or drugs are 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 sponsors fully enroll patients in phase 3 trials or have the trials 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, and submitted by the sponsor and reviewed by the FDA. Alternatively, individual patient and intermediate-size patient population expanded access may be possible. In contrast to treatment INDs or 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 the following:

- 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

Contains Nonbinding Recommendations

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

GLOSSARY OF ACRONYMS

CC	cytotoxic concentration
CHC	chronic hepatitis C
CKD	chronic kidney disease
DAA	direct-acting antiviral
EC	effective concentration
HBV	hepatitis B virus
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 quantification
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

Contains Nonbinding Recommendations

REFERENCES

- Afdhal, N, KR Reddy, DR Nelson, E Lawitz, SC Gordon, E Schiff, R Nahass, R Ghalib, N Gitlin, R Herring, J Lalezari, ZH Younes, PJ Pockros, AM Di Bisceglie, S Arora, GM Subramanian, Y Zhu, H Dvory-Sobol, JC Yang, PS Pang, WT Symonds, JG McHutchison, AJ Muir, M Sulkowski, and P Kwo, 2014, Ledipasvir and Sofosbuvir for Previously Treated HCV Genotype 1 Infection, *N Engl J Med*, 370(16):1483–93.
- Alosh, M, K Fritsch, M Huque, K Mahjoob, G Pennello, M Rothmann, E Russek-Cohen, F Smith, S Wilson, and L Yue, 2015, Statistical Considerations on Subgroup Analysis in Clinical Trials, *Stat Biopharm Res*, 7:286–304.
- Arase, Y, K Ikeda, F Suzuki, Y Suzuki, S Saitoh, M Kobayashi, N Akuta, T Someya, R Koyama, T Hosaka, H Sezaki, M Kobayashi, and H Kumada, 2007, Long-Term Outcome After Interferon Therapy in Elderly Patients With Chronic Hepatitis C, *Intervirology*, 50(1):16–23.
- Armstrong, GL, A Wasley, EP Simard, GM McQuillan, WL Kuhnert, and MJ Alter, 2006, The Prevalence of Hepatitis C Virus Infection in the United States, 1999 Through 2002, *Ann Intern Med*, 144(10):705–14.
- Arnold, JJ, SD Sharma, JY Feng, AS Ray, ED Smidansky, ML Kireeva, A Cho, J Perry, JE Vela, Y Park, Y Xu, Y Tian, D Babusis, O Barauskus, BR Peterson, A Gnatt, M Kashlev, W Zhong, and CE Cameron, 2012, Sensitivity of Mitochondrial Transcription and Resistance of RNA Polymerase II Dependent Nuclear Transcription to Antiviral Ribonucleosides, *PLoS Pathog*, 8(11):e1003030.
- Backus, LI, D Boothroyd, B Phillips, P Belperio, J Halloran, and L Mole, 2011, A Sustained Virologic Response Reduces Risk of All-Cause Mortality in Patients With Hepatitis C, *Clin Gastroenterol Hepatol*, 9(6):509–16.
- Braks, RE, N Ganne-Carrie, H Fontaine, J Paries, V Grando-Lemaire, M Beaugrand, S Pol, and JC Trinchet, 2007, Effect of Sustained Virological Response on Long-Term Clinical Outcome in 113 Patients With Compensated Hepatitis C-Related Cirrhosis Treated by Interferon Alpha and Ribavirin, *World J Gastroenterol*, 13(42):5648–53.
- Bruno, S, T Stroffolini, M Colombo, S Bollani, L Benvegnù, G Mazzella, A Ascione, T Santantonio, F Piccinino, P Andreone, A Mangia, GB Gaeta, M Persico, S Fagioli, PL Almasio, and Italian Association of the Study of the Liver Disease, 2007, Sustained Virological Response to Interferon-Alpha Is Associated With Improved Outcome in HCV-Related Cirrhosis: A Retrospective Study, *Hepatology*, 45(3):579–87.
- Butt, AA, X Wang, and LF Fried, 2011, HCV Infection and the Incidence of CKD, *Am J Kidney Dis*, 57(3):396–402.
- Casey, L and W Lee, 2013, Hepatitis C Virus Therapy Update 2012, *Curr Opin Gastroenterol*, 29(3): 243–49.

Contains Nonbinding Recommendations

Chen, J, J Florian, W Carter, RD Fleischer, TS Hammerstrom, PR Jadhav, W Zeng, J Murray, and D Birnkrant, 2013, Earlier Sustained Virologic Response End Points for Regulatory Approval and Dose Selection of Hepatitis C Therapies, *Gastroenterology*, published online ahead of print March 5, 2013: doi: 10.1053/j.gastro.2013.02.039.

Chevaliez, S, M Bouvier-Alias, R Brillet, and JM Pawlotsky, 2009, Hepatitis C Virus (HCV) Genotype 1 Subtype Identification in New HCV Drug Development and Future Clinical Practice, *PLoS One*, 4(12):e8209.

Coelmont, L, J Paeshuysse, MP Windisch, E De Clercq, R Bartenschlager, and J Neyts, 2006, Ribavirin Antagonizes the In Vitro Anti-Hepatitis C Virus Activity of 2'-C-methylcytidine, the Active Component of Valopicitabine, *Antimicrob Agents Chemother*, 50(10):3444–46.

Fabrizi, F, V Dixit, and P Messa, 2012, Impact of Hepatitis C on Survival in Dialysis Patients: A Link With Cardiovascular Mortality?, *J Viral Hepat*, 19(9):601–7.

Fabrizi, F, P Martin, V Dixit, S Bunnapradist, and G Dulai, 2005, Hepatitis C Virus Antibody Status and Survival After Renal Transplantation: Meta-Analysis of Observational Studies, *Am J Transplant*, 5(6):1452–61.

Fabrizi, F, P Martin, V Dixit, and P Messa, 2011, Combined Antiviral Therapy of Hepatitis C Virus in Dialysis Patients: Meta-Analysis of Clinical Trials, 2011, *J Viral Hepatitis*, 18(7):263–69.

Finelli, L, JT Miller, JI Tokars, MJ Alter, and MJ Arduino, 2005, National Surveillance of Dialysis-Associated Diseases in the United States, *Semin Dialysis*, 18(1):52–61.

Gane, EJ, 2008, The Natural History of Recurrent Hepatitis C and What Influences This, *Liver Transpl*, 14 (Suppl 2): S36–S44.

Ge, D, J Fellay, AJ Thompson, JS Simon, KV Shianna, TJ Urban, EL Heinzen, P Qiu, AH Bertelsen, AJ Muir, M Sulkowski, JG McHutchison, and DB Goldstein, 2009, Genetic Variation in IL28B Predicts Hepatitis C Treatment-Induced Viral Clearance, *Nature*, 461(7262):399–401.

Gower, E, C Estes, S Blach, K Razavi-Shearer, and H Razavi, 2014, Global Epidemiology and Genotype Distribution of the Hepatitis C Virus Infection, *J Hepatol*, 61(1 Suppl):S45–S57.

Harrington, PR, W Zeng, and LK Naeger, 2012, Clinical Relevance of Detectable but Not Quantifiable Hepatitis C Virus RNA During Boceprevir or Telaprevir Treatment, *Hepatology*, 55(4):1048–57.

Hepburn, MJ, LM Hepburn, NS Cantu, MG Lapeer, and EJ Lawitz, 2004, Differences in Treatment Outcome for Hepatitis C Among Ethnic Groups, *Am J Med*, 117(3):163–68.

Contains Nonbinding Recommendations

Imai, Y, S Kawata, S Tamura, I Yabuuchi, S Noda, M Inada, Y Maeda, Y Shirai, T Fukuzaki, I Kaji, H Ishikawa, Y Matsuda, M Nishikawa, K Seki, and Y Matsuzawa, 1998, Relation of Interferon Therapy and Hepatocellular Carcinoma in Patients With Chronic Hepatitis C, Osaka Hepatocellular Carcinoma Prevention Study Group, *Ann Intern Med*, 129(2):94–99.

Klebens, MR, J Dale, RJ Hu, and S Homberg, 2012, Evolving Epidemiology of Hepatitis C Virus in the United States, *Clin Infect Dis*, 55(Suppl 1):S3–S9.

Kwong, AD, I Najera, J Bechtel, et al., 2011, Sequence and Phenotypic Analysis for Resistance Monitoring in Hepatitis C Virus Drug Development: Recommendations From the HCV DRAG, *Gastroenterology*, 140(3):755–60.

Ly, KN, J Xing, RM Klebens, RB Jiles, JW Ward, and SD Holmberg, 2012, The Increasing Burden of Mortality From Viral Hepatitis in the United States Between 1999 and 2007, *Ann Intern Med*, 156(4):271–78.

Manos, MM, WK Zhao, VA Shvachko, N Volkova, CP Quesenberry, Viral Hepatitis Registry, and Kaiser Permanente Division of Research, Oakland, CA, March 2009, Long Term Outcomes in Patients Treated With Peg-Interferon/Ribavirin Therapy for Hepatitis C: The Substantial Effect of Sustained Viral Response (SVR) on Liver Disease, Mortality and Diabetes, 13th International Symposium on Viral Hepatitis and Liver Disease, Abstract PL-3.

Marroquin, LD, J Hynes, JA Dykens, JD Jamieson, and Y Will, 2007, Circumventing the Crabtree Effect: Replacing Media Glucose with Galactose Increases Susceptibility of HepG2 Cells to Mitochondrial Toxicants, *Toxicol Sci*, 97(2):539–47.

Momper, JD, Y Mulugeta, and DJ Green, 2013, Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007, *JAMA Pediatr*, 167(10):926–32.

Okanoue, T, Y Itoh, M Minami, S Sakamoto, K Yasui, M Sakamoto, K Nishioji, Y Murakami, and K Kashima, 1999, Interferon Therapy Lowers the Rate of Progression to Hepatocellular Carcinoma in Chronic Hepatitis C but Not Significantly in an Advanced Stage: A Retrospective Study in 1148 Patients, Viral Hepatitis Therapy Study Group, *J Hepatol*, 30(4):653–59.

Poordad, F, JP Bronowicki, SC Gordon, S Zeuzem, IM Jacobson, MS Sulkowski, T Poynard, TR Morgan, C Molony, LD Pedicone, HL Sings, MH Burroughs, V Sniukiene, N Boparai, VS Goteti, CA Brass, JK Albrecht, BR Bacon, and SPRINT-2 AND RESPOND-2 Investigators, 2012, Factors That Predict Response of Patients With HCV Infection to Boceprevir, *Gastroenterology*, published online ahead of print May 21, 2012: doi: 10.1053/j.gastro.2012.05.011.

Rong, L, H Dahari, RM Ribeiro, and AS Perelson, 2010, Rapid Emergence of Protease Inhibitor Resistance in Hepatitis C Virus, *Sci Transl Med*, 2(30):30ra32.

Contains Nonbinding Recommendations

Shiratori, Y, Y Ito, O Yokosuka, F Imazeki, R Nakata, N Tanaka, Y Arakawa, E Hashimoto, K Hirota, H Yoshida, Y Ohashi, M Omata, and Tokyo-Chiba Hepatitis Research Group, 2005, Antiviral Therapy for Cirrhotic Hepatitis C: Association With Reduced Hepatocellular Carcinoma Development and Improved Survival, *Ann Intern Med*, 142(2):105–14.

Simmons, B, J Saleem, K Heath, G Cooke, and A Hill, 2015, Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-Analysis of the Survival Benefit of Achieving a Sustained Virologic Response, *Clin Infect Dis*, 61(5):730–40.

Singal, AG, M Volk, D Jensen, et al., 2010, A Sustained Viral Response Is Associated with Reduced Liver Related Morbidity and Mortality in Patients With Hepatitis C Virus, *Clin Gastroenterol Hepatol*, 8(3):280–88.

Smith, DB, J Bukh, C Kuiken, AS Muerhoff, CM Rice, JT Stapleton, and P Simmonds, 2014, Expanded Classification of Hepatitis C Virus into 7 Genotypes and 67 Subtypes: Updated Criteria and Genotype Assignment Web Resource, *Hepatology*, 59(1):318–27.

Snoeck, E, P Chanu, M Lavielle, P Jacqmin, EN Jonsson, K Jorga, T Goggin, J Grippo, NL Jumbe, and N Frey, 2010, A Comprehensive Hepatitis C Viral Kinetic Model Explaining Cure, *Clin Pharmacol Ther*, 87(6):706–13.

Sulkowski, MS, 2008, Viral Hepatitis and HIV Coinfection, *J Hepatol*, 48(2):353–67.

Terrault, NA and DB Adey, 2007, The Kidney Transplant Recipient With Hepatitis C Infection: Pre- and Posttransplantation Treatment, *Clin J Soc Nephrol*, 2(3):563–75.

Veldt, BJ, EJ Heathcote, H Wedemeyer, J Reichen, WP Hofmann, S Zeuzem, MP Manns, BE Hansen, SW Schalm, and HL Janssen, 2007, Sustained Virologic Response and Clinical Outcomes in Patients With Chronic Hepatitis C and Advanced Fibrosis, *Ann Intern Med*, 147(10):677–84.

Yoshida, H, Y Arakawa, M Sata, S Nishiguchi, M Yano, S Fujiyama, G Yamada, O Yokosuka, Y Shiratori, and M Omata, 2002, Interferon Therapy Prolonged Life Expectancy Among Chronic Hepatitis C Patients, *Gastroenterology*, 123(2):483–91.

Yoshida, H, Y Shiratori, M Moriyama et al., 1999, Interferon Therapy Reduces the Risk for Hepatocellular Carcinoma: National Surveillance Program of Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C in Japan, IHIT Study Group, Inhibition of Hepatocarcinogenesis by Interferon Therapy, *Ann Intern Med*, 131(3):174–81.

Zeuzem, S, V Soriano, T Asselah, JP Bronowicki, AW Lohse, B Mullhaupt, M Schuchmann, M Bourliere, M Buti, S Roberts, E Gane, JO Stern, G Kukulj, L Dai, WO Bocher, and FJ Mensa, 2012, SVR4 and SVR12 With an Interferon-Free Regimen of BI 201335 and BI 207127, +/- Ribavirin, in Treatment-Naïve Patients With Chronic Genotype-1 HCV Infection: Interim Results of SOUND-C2, EASL International Liver Congress, Abstract 101.

Contains Nonbinding Recommendations

**APPENDIX:
STUDY POPULATION TERMS AND TREATMENT RESPONSE DEFINITIONS**

Table A includes recommended terms and definitions for documentation of prior hepatitis C virus (HCV) 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 direct-acting antiviral (DAA) based treatment should take precedence.
- Specific details regarding all prior drug or class experience should be noted as part of collecting protocol-specified data.

Table A: Recommended Terms and Definitions for HCV Treatment History

TREATMENT-NAÏVE	Naïve to all anti-HCV treatment.
P/R-ONLY EXPERIENCED*	Did not achieve sustained virologic response (SVR) with previous P/R treatment, and never received an HCV DAA.
DAA-EXPERIENCED	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).

* P/R = peg-IFN/RBV (ribavirin)

Contains Nonbinding Recommendations

Table B includes recommendations for protocol definitions of response or nonresponse to investigational regimens for HCV.

Table B: Recommended Protocol Definitions for Response or Nonresponse

SVR(X)	HCV RNA < LLOQ* at X weeks following cessation of treatment.
On-Treatment Virologic Failure	HCV RNA \geq 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.
Virologic Breakthrough	Subcategory of On-Treatment Virologic Failure. Confirmed $\geq 1 \log_{10}$ IU/mL HCV RNA on-treatment increase from nadir, or confirmed increase in HCV RNA \geq LLOQ if HCV RNA previously declined to < LLOQ (detected or not detected).
Virologic Relapse	HCV RNA < LLOQ at end of treatment, but HCV RNA quantifiable (\geq LLOQ) during follow-up; can include patients who experienced late virologic relapse who also achieved primary SVR endpoint.
Nonvirologic Failure	Did not achieve SVR and did not meet any virologic failure criteria (e.g., adverse event, lost to follow-up).

* RNA = ribonucleic acid; LLOQ = lower limit of quantification